OL Organic Letters

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α-Iminol Rearrangement Triggered by Pd-Catalyzed C−H Addition to Nitriles Sequences: Synthesis of Functionalized α-Amino Cyclopentanones

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Cite This: *Org. Lett.* 2021, 23, 1021−1025 Read Online

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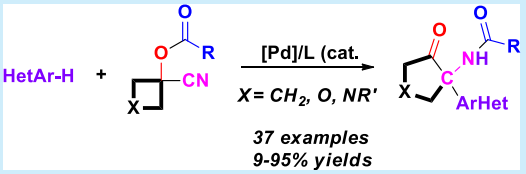
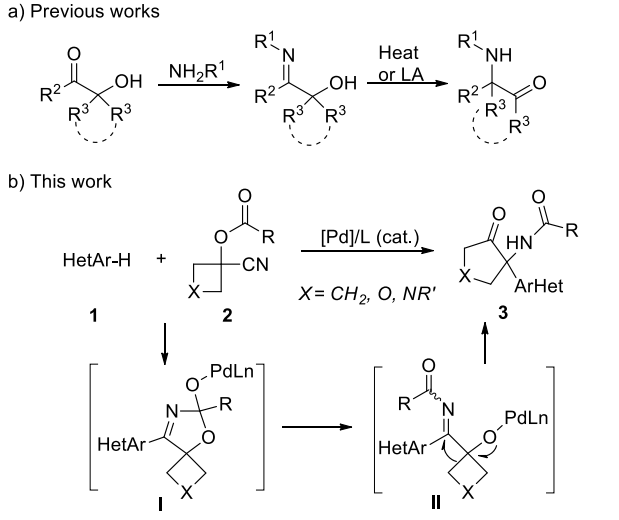
ABSTRACT: A α-iminol rearrangement triggered by Pd-catalyzed C−H addition of electronic-rich heteroarenes to cyclobutanone-derived *O*-acyl cyanohydrins was described, which provided a practical and efficient protocol for the preparation of functionalized α-amino cyclopentanones in an atom- and step-economic fashion. In addition, further synthetic transformations of products have also been demonstrated.



Among fundamental C−C bond formation methods, the skeletal rearrangements involving 1,2-carbon-to-carbon migration constitute a category of efficient and powerful approaches for the construction of organic molecules through molecular reorganization processes,[1] often rendering a practical way to access otherwise inaccessible molecular frameworks. For examples, α-ketol rearrangement, which involves the conversion of α-hydroxy ketones (or aldehydes) into their isomeric forms by a 1,2-alkyl- (aryl) shift, has been well studied and applied to the preparation and structural modification of natural products.[2,3] In contrast, α-iminol rearrangement involving a 1,2-carbon shift has been received less attention,[2b,4] despite the fact that the development of efficient α-iminol rearrangement is of high synthetic value, given the importance of the α-amino ketones in the synthesis of biologically relevant compounds.[5] Thermally driven and acid (Brønsted acid or Lewis acids) catalyzed rearrangements of performed α-iminols constituted the main body of α-iminol rearrangement.[4] Recently, elegant Lewis acid catalyzed asymmetric versions of α-hydroxy aldimines have also been achieved by the Wulff and Feng groups, respectively.[2i,4h] However, extra synthetic steps were required to access α-iminols, which were prepared normally from the condensation between α-hydroxy aldehydes (or ketones) and amines (Scheme 1a),[6] and were liable to hydrolysis generally. To best our knowledge, a straightforward approach combining the formation of α-iminol and subsequent rearrangement from readily available starting materials under the mild reaction conditions is unexploited.

Transition-metal-catalyzed C−H bond additions to nitriles have witnessed remarkable advances for decades.[7,8] In these transformations, organometallic species generated by C−H bond activations attacked the CN bond of nitriles to provide the imine intermediates, which subsequently delivered either aryl ketone products or azaheterocycles, where nitriles served as C-1 building blocks or C−N synthons. As one of the most common functionalized nitriles, *O*-acyl cyanohydrins, readily

Scheme 1. α-Iminol Rearrangement Involving a 1,2-Carbon Shift



prepared from aldehydes and ketones, have displayed considerable synthetic potential as diverse building blocks.[9] Very recently, we employed these scaffolds to prepare various valuable azaheterocycles bearing heteroaromatic units via Pd-catalyzed direct heteroaromatic C−H bond addition to nitriles/cyclization sequences.[8] Given our ongoing interest in the development of efficient catalytic processes to prepare

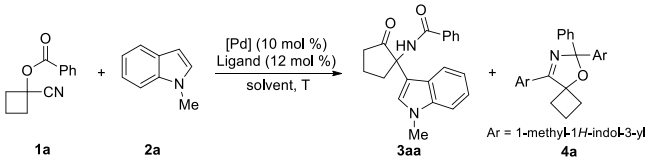
Received: December 22, 2020
Published: January 26, 2021

https://dx.doi.org/10.1021/acs.orglett.0c04214
Org. Lett. 2021, 23, 1021−1025

diverse cyclic frameworks, we envision that a α-iminol rearrangement triggered by Pd-catalyzed C−H addition to cyclobutanone derived *O*-acyl cyanohydrin sequence would be feasible (Scheme 1b), in which the cleavage of C−O bond of resultant tetrahedral intermediate **I** would deliver cyclobutane-based α-iminol intermediate **II** with an activated functional group (*N*-acyl group) and subsequently **II** undergoes 1,2-carbon shift to afford the functionalized α-amino cyclopentanone in an atom- and step-economic fashion. Moreover, the readily availability and manipulation of reaction partners in which heteroarenes are common feedstock chemicals, while cyclobutanone-derived *O*-acyl cyanohydrins are readily prepared from cyclobutanone derivatives, would enable this transformation to access diverse α-fully substituted amino cyclopentanones under redox-neutral and catalytic reaction conditions, in contrast to well-established approaches of α-amination of carbonyl compounds.[10] Herein, we report this preliminary work.

Our investigation commenced with testing the feasibility of this Pd-catalyzed C−H addition to nitrile/α-iminol rearrangement sequences between 1-cyanocyclobutyl benzoate **1a** and *N*-methylindole **2a** (Table 1) under the catalysis of $Pd(OAc)_2$

Table 1. Optimal Reaction Conditions[a]



1a 2a 3aa 4a

entry	[Pd]	solvent	ligand	additive	T (°C)	yield of **3aa**[b] (%)
1[c]	$Pd(OAc)_2$	NMP	bpy	HOAc	80	18
2[c]	$Pd(OAc)_2$	DMA	bpy	HOAc	80	45
3[c,d]	$Pd(OAc)_2$	NMA	bpy	HOAc	80	87
4[c,d]	$Pd(OAc)_2$	THF	bpy	HOAc	80	15
5[c]	$Pd(OAc)_2$	toluene	bpy	HOAc	80	13
6	$Pd(OAc)_2$	NMA	bpy		80	96
7	$Pd(TFA)_2$	NMA	bpy		80	nd
8	$Pd(acac)_2$	NMA	bpy		80	nd
9	$PdCl_2$	NMA	bpy		80	nr
10	$Pd(OAc)_2$	NMA	phen		80	87
11	$Pd(OAc)_2$	NMA	bpy		40	9
12		NMA	bpy		80	nd
13	$Pd(OAc)_2$	NMA			80	nd
14[e,f]	$Pd(OAc)_2$	NMA	bpy		80	95

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), catalyst (10 mol %), and ligand (12 mol %) in solvent (c = 0.2 *M*). [b]Isolated yields. [c]HOAc (40 mol %). [d]**4a** was obtained. [e]$Pd(OAc)_2$ (5 mol %), bpy (6 mol %). [f]**2a** (0.4 mmol). bpy: 2,2′-bipyridine. phen: 1,10-phenanthroline. NMA: *N*-methylacetamide. DMA: *N*, *N*-dimethylacetamide.

(10 mol %)/2,2′-bipyridine (12 mol %) and HOAc (40 mol %) in NMP at 80 °C, and the desired product **3aa** was obtained in 18% yield with low conversion (entry 1). The evaluation on the influence of solvent was examined first (entries 1−5). It turned out that NMA was the most effective solvent for this transformation, while other solvents provided inferior results, along with a small amount of bisindole adduct **4a** as the byproduct. Unlike the previous results in which acid promoted the Pd-catalyzed C−H addition to nitrile/cyclization sequences,[8a−d] this Pd-triggered α-iminol rearrangement sequence proceeded more smoothly in the absence of HOAc and furnished the desired product **3aa** in excellent yield (entry 6). Further screening of Pd(II) catalysts and ligands revealed that $Pd(OAc)_2$/2,2′-bipyridine played a very important role in this reaction, since other Pd(II) catalysts such as $Pd(TFA)_2$, $Pd(acac)_2$, and $PdCl_2$ did not afford any of the desired product **3aa** at all in the presence of 2,2′-bipyridine, while $Pd(OAc)_2$/phen provided the desired product **3aa** in slightly reduced yield (entries 7−10). Decreasing the temperature led to the dramatic reducing production of **3aa** (entry 9). Both catalyst and ligand are essential for this transformation, and removal of either Pd(II) catalyst or ligand completely shut down the reaction (entries 12 and 13) (for details see the Supporting Information). It was noteworthy that further reducing the loading of $Pd(OAc)_2$/2,2′-bipyridine and the amount of *N*-methylindole did not affect the efficiency of this transformation, which provided product **3aa** in the comparable yield with that of $Pd(OAc)_2$ (10 mol %)/2,2′-bipyridine (12 mol %) promoted reaction (entry 14).

With the optimized conditions in hand, the scope of the reaction was investigated by employing various indoles **1** and cyclobutanone-derived cyanohydrins **2** first (Scheme 2). Except for *N*-unsubstituted and *N*-acetal indoles that were ineffective, the benzyl group was compatible with the reaction, providing the corresponding product **3ab** in 94% yield. Then the reactions between a broad range of *N*-methylindoles **2** with 1-cyanocyclobutyl benzoate **1a** were examined. The substitution pattern and electronic nature of substitutions at the benzene ring of the indole core were well tolerated and gave α-indoyl-substituted α-amino cyclopentanones in high to excellent yields (**3af**−**3aj**), except for 4-substituted indole which gave the moderate yield (**3ae**), presumably due to the steric hindered effect. Due to the ready availability and manipulation of cyclobutanone-derived *O*-acyl cyanohydrins, this transformation also can provide an efficient way to prepare α-substituted amino cyclopentanones with diverse *N*-acyl groups (R^3) under the optimized reaction conditions. For example, a range of *N*-acyl groups (R^3) such as electron-rich or electron-poor aromatic groups (**3ba**−**3ha**), heteroaromatic groups (**3ia**−**3ja**), alkenyl (**3ka**), and linear alkyl (**3la**−**3ma**) were well tolerated. However, *O*-branched alkylacyl cyanohydrin did not give the desired products (**3na**−**3oa**). In addition, oxa- and azocyclobutane-based analogues were also examined. It seemed that the reactions were sensitive to heteroatoms in the cyclobutane ring. The reaction between the oxa-analogue and **1a** proceeded sluggishly under the optimized reaction conditions, and an improved yield could be obtained with 10 mol % $Pd(OAc)_2$ (**3pa**). *N*-Boc-substituted azo-analogue can also give the desired product in good yield (**3qa**), while *N*-benzhydryl analogue failed to deliver the desired product (**3ra**).

Next different heteroarenes were surveyed (Scheme 3). When *N*-methyl-2-phenylpyrrole was employed, the addition of the 5- and 4-positions of the C−H bond of pyrrole to 1-cyanocyclobutyl benzoate **1a** was observed in the presence of 10 mmol % $Pd(OAc)_2$ (**6a** and **6a′**). 4-Pyrrolyl-substituted α-amino cyclopentanone **6a′** was obtained in 46% yield as a major product at the higher temperature. The reactions of 2-substituted thiophenes and furan with **1a** proceeded sluggishly with 10 mmol % $Pd(OAc)_2$ and provided 5-substituted thiophenes or furan products in low yields (**6b**, **6c**). No reactions occurred when benzo[*b*]thiophene or benzofuran

https://dx.doi.org/10.1021/acs.orglett.0c04214
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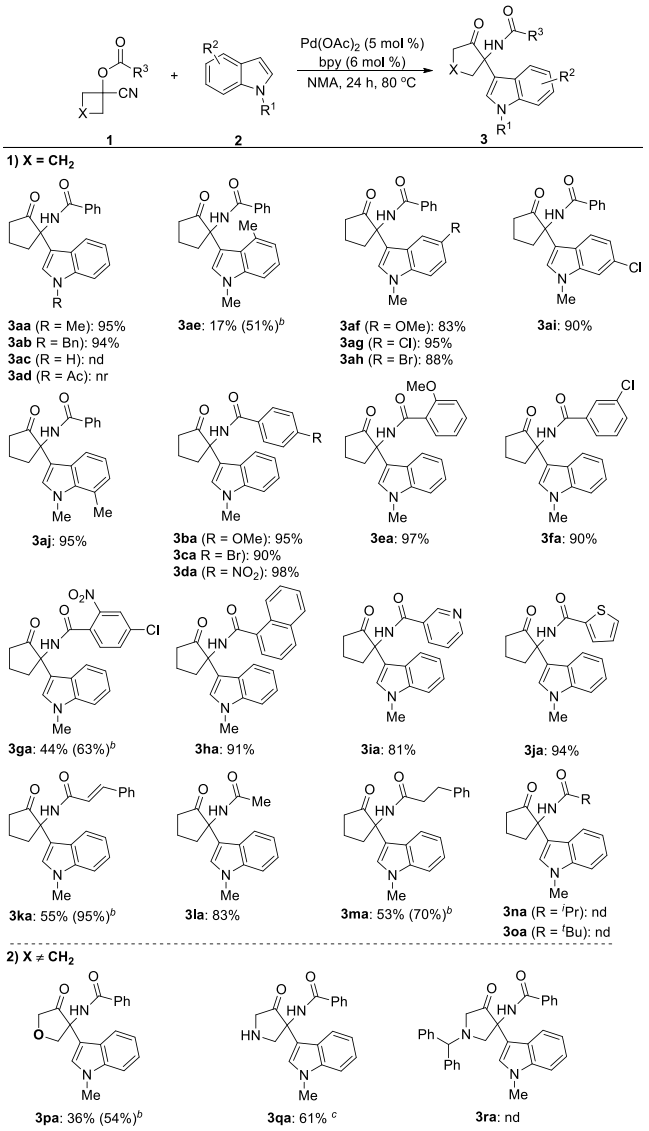
Scheme 2. Substrate Scope for Reaction of Indoles 2 and Cyanohydrins 1[a]

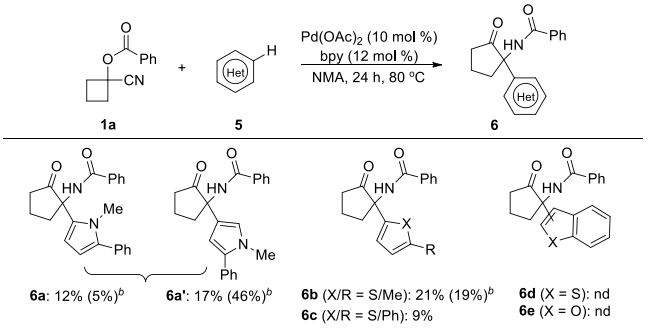


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), and bpy (6 mol %) in NMA (c = 0.2 M). Yields of isolated products. [b]$Pd(OAc)_2$ (10 mol %)/ bpy (12 mol %), 100 °C. [c]Deprotection of the resulting product with TFA led to **3qa** as a single isomer.

were employed, which indicated that the reactivities of heteroarenes is critical to this reaction.

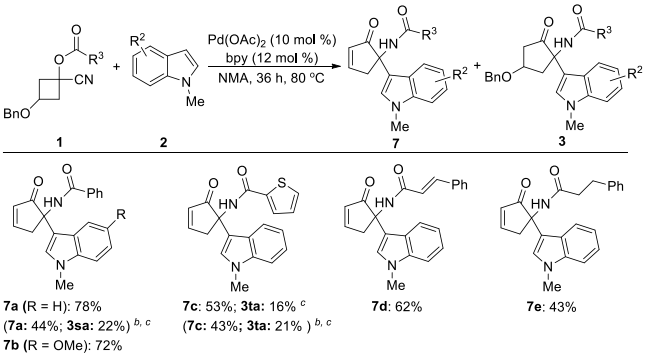
Noteworthily, this approach is also applicable to the constructure of α-fully substituted amino cyclopentenones (Scheme 4). When 3-(benzyloxy)-1-cyanocyclobutyl benzoate was employed, it was found that this reaction afforded not only the desired cyclopentanone **3sa** in 22% yield, but also cyclopentenone **7a** in 44% yield *via* the elimination of a benzyloxy group under the optimized reaction conditions. Further investigations indicated that the production of cyclopentenone **7a** can be improved with 78% yield by increasing the loading of $Pd(OAc)_2$ (10 mol %). The exemplifications of the preparation of α-fully substituted amino cyclopentenones were illustrated in Scheme 4. Several *O*-acyl cyanohydrins bearing benzyloxy **1** and indoles **2** were

Scheme 3. Substrate Scope for Reaction of 5 and 1a[a]



[a]Reaction conditions: **1a** (0.2 mmol), **5** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), and bpy (12 mol %) in NMA (c = 0.2 M). Yields of isolated products. [b]120 °C.

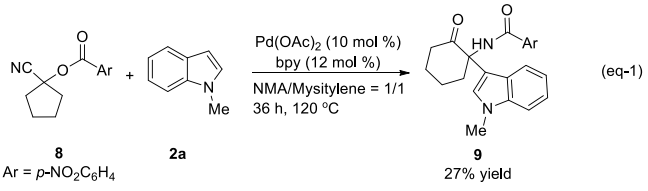
Scheme 4. Substrate Scope for Preparation of Cyclopentenones 7[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), and bpy (12 mol %) in NMA (c = 0.2 M). Yields of isolated products. [b]$Pd(OAc)_2$ (5 mol %)/ bpy (6 mol %), **2** (0.4 mmol), 24 h. [c]**3** was isolated with dr >19/1.

examined and furnished the desired products (**7a**−**7e**) in moderate to good yields.

In addition, Pd-catalyzed tandem sequence between *N*-methylindole **2a** and cyclopentanone-derived *O*-acyl cyanohydrin **8** was also evaluated. No desired product **9** was observed under the standard reaction conditions, while 27% yield of the desired product **9** could be obtained under the modified reaction conditions, which indicated that the inherent strain of the cyclobutyl of cyanohydrins **1** may play an important role in this tandem sequence (eq 1).



To exhibit the practicality of this catalytic tandem sequence, the 2.5 mmol scale synthesis of α-amino cyclopentanone **3ka** was performed, and the desired product was obtained in 83% yield (Scheme 5). Subsequently, synthetic transformations of product **3ka** were conducted. Treatment of compound **3ka** with vinylmagnesium bromide can afford the densely functionalized amino alcohol **10** in 61% yield with high diaster-

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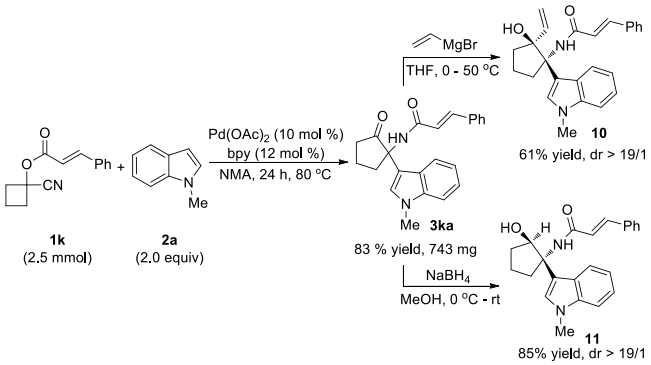
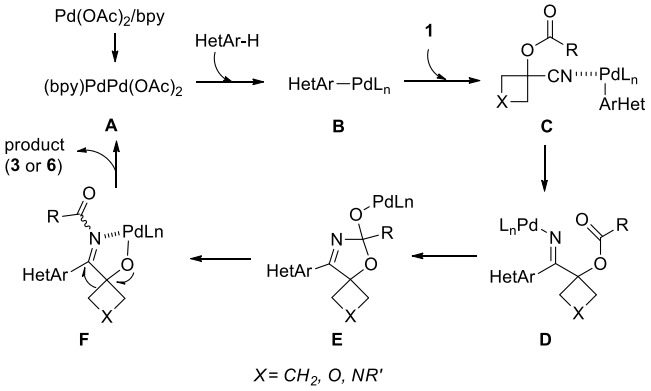
Scheme 5. Synthetic Transformations



eoselectivity, while reduction of the compound **3ka** with $NaBH_4$ delivered compound **11** in 85% yield with >19/1 dr.

On the basis of these results and the previous reports,[4d,h,8c,d] a proposed mechanism was illustrated in Scheme 6. This

Scheme 6. Proposed Mechanism



catalytic sequence may involve a direct palladation at heteroarene with [(bpy)Pd(OAc)$_2$] **A** first, which delivers a palladium complex **B**. The coordination of the cyano group of cyclobutanone-derived *O*-acyl cyanohydrin **1** with complex **B** gives intermediate **C**, which undergoes addition of the heteroarene group to the cyano group followed by a cyclization to form the corresponding tetrahedral intermediate **E**. Subsequently, the cleavage of the C−O bond of the resultant intermediate **E** would deliver cyclobutane-based α-iminol intermediate **F** with an activated *N*-acyl group (RCO−), which undergoes a 1,2-carbon shift to afford the desired product.[11]

In summary, we have demonstrated a Pd-catalyzed tandem sequence in which α-iminol rearrangement triggered by Pd-catalyzed C−H addition to cyclobutanone-derived *O*-acyl cyanohydrins provided a straightforward and efficient protocol for the preparation of functionalized α-amino cyclopentanones in an atom- and step-economic fashion. Furthermore, functionalized α-amino cyclopentenones can also been prepared when 3-benzyloxycyclobutane-based *O*-acyl cyanohydrins were employed. Further investigations on other tandem rearrangement sequences are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04214.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSFC (No. 21772063).

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(11) Pd catalyst facilitated the elimination of benzyloxy group for the formation of product **7** (see the control experiments in Scheme S1 of the SI). The mechanism for the formation of **7** is unclear, and further study would continue in our laboratory.

https://dx.doi.org/10.1021/acs.orglett.0c04214
Org. Lett. 2021, 23, 1021−1025