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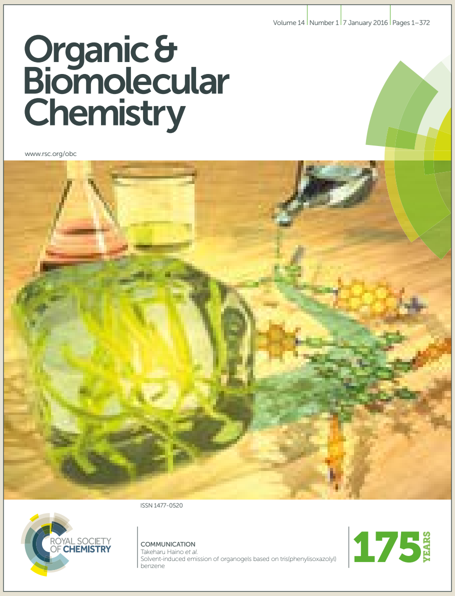

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ARTICLE

Nitrile-Assisted Oxidation over Oxidative-Annulation: Pd-Catalyzed α,β-Dehydrogenation of α-Cinnamyl β-Keto Nitriles

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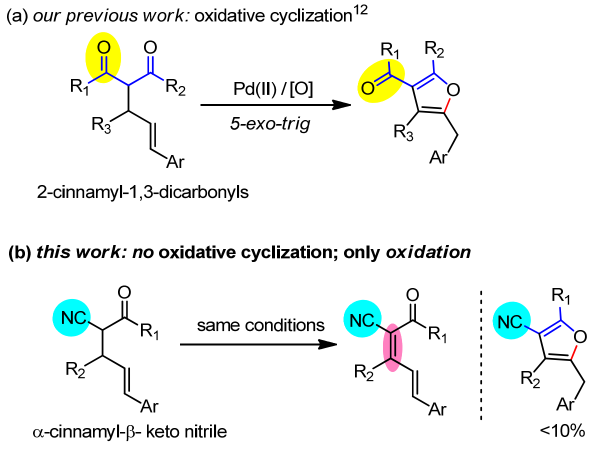
ABSTRACT: A palladium-catalyzed oxidation reaction is disclosed where the nitrile functionality on the substrate simply changes the course of the reaction. Our previous finding showed that using Pd(II)-catalyst in the presence of benzoquinone as an oxidant, 2-cinnamyl-1,3-dicarbonyls provides functionalized furans via oxidative cyclization. When a nitrile group replaces with one of the carbonyl functionality of the same substrate, the oxidative cyclization was completely suppressed; instead, the oxidation at α,β-position occurred to provide α,β,γ,δ-diene containing β-keto nitriles.

α,β,γ,δ-Unsaturated keto nitriles are important precursors in a broad spectrum of chemical transformations. They are also the important synthetic building blocks for the heterocycles such as dihydropyrans, pyridines, pyrroles, etc.[1a-d] Moreover, they are perhaps the most versatile building blocks in organocatalysis.[1d-e] During the past several decades, only a few synthetic methods towards their synthesis have been developed, among which the well-known Knoevenagel condensation of α,β-unsaturated aldehydes with β-ketonitriles is remarkable.[1e] However, these reactions require the presence of relatively strong acidic or basic conditions, producing a significant amount of by-products, suffers from several side reactions, and displays the narrow substrate diversity. Driven by the ever-growing demand for α,β,γ,δ-unsaturated ketonitrile in heterocycle synthesis, new and more efficient approach is still demanding.

The first catalytic homogeneous dehydrogenation of cyclooctane to cyclooctene was discovered by Crabtree and Felkin in 1982.[2a] Tremendous progress has been made in the area of direct dehydrogenation of alkanes to olefins using transition metal catalysis.[2] Recently, Stahl and co-workers have developed oxidative dehydrogenation of cyclohexanone to phenols.[3,4] Similarly, Yoshikai and co-workers also developed the palladium-catalyzed aerobic dehydrogenative aromatization of cyclohexanone imines to arylamines.[5] In the direction of direct oxidation of β-aryl substituted carbonyl compounds, Saegusa oxidation is a convenient and well-established method where transformation of silyl enol ethers to the corresponding α,β-unsaturated carbonyl compounds occurs using Pd(II)-catalysts.[6] Li and coworkers developed a novel amine-$Pd(OAc)_2$ co-catalyzed direct saegusa oxidation of readily available β-aryl aldehyde to α,β-unsaturated aldehydes.[7] Huang and coworkers also established a method for the palladium-catalyzed aerobic dehydrogenation of β-aryl carbonyls to α,β-unsaturated carbonyls.[8] Very recently, Newhouse and coworkers made a report of palladium catalyzed α,β-dehydrogenation of esters, nitriles, and amides.[9,10] In addition to the above advancements, the dehydrogenation of 2-cinnamyl 1,3-dicarbonyls has been developed by Han and co-workers using palladium(II)-catalyst to α,β,γ,δ-unsaturated-1,3-dicarbonyls.[11] Here, in we report a direct oxidation of α-cinnamyl β-ketonitriles to α,β,γ,δ-unsaturated keto nitriles under mild reaction conditions.



Scheme 1: a) Oxidative Annulation of α-Cinnamyl-α,β-diketones. b) Oxidation of α-Cinnamyl-β-Keto Nitriles

Recently, we have developed a novel palladium-catalyzed intramolecular oxidative cycloisomerization of α-cinnamyl-β-dicarbonyls for the creation of structurally diverse 2-benzyl furans (Scheme 1a).[12] During this investigation, we noticed that the replacement of one of the carbonyl group with nitrile functionality, the course of the reaction is dramatically changed. The intramolecular oxidative cycloisomerization is suppressed and only an oxidation at α,β-position occurred to provide α,β,γ,δ-diene containing β-keto nitriles (Scheme 1b). Based on previous literature

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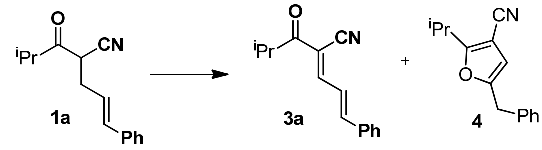
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of products, ^1H and ^{13}C NMR spectra for products, and X-ray crystallographic analysis (CIF file for compound **3l**) CCDC-1444012. See DOI: 10.1039/x0xx00000x reports,[13a-d] we presumed that nitrile functional group has a strong coordination with transition metals and it could act as a successful directing group as well as ligand. Thus, the intramolecular oxidative cycloisomerization phenomenon is suppressed.

We began our studies with a brief optimization of the dehydrogenation of α-cinnamyl-β-keto-nitrile to α,β,γ,δ-unsaturated keto nitrile. α-Cinnamyl-β-ketonitrile (**1a**) was chosen as the model substrate, as shown in Table 1. The catalytic system consisting of $PdCl_2(CH_3CN)_2$ (5 mol%), *p*-toluenesulfonic acid (PTS, 1 equiv), and benzoquinone (BQ, 1 equiv) in THF at 80 °C, which were employed previously,[12] afforded the α,β,γ,δ-unsaturated keto nitrile **3a** in 83% conversion with 78% isolated yield and a small amount of cycloisomerization product **4** (entry 1, Table 1). The requirement of the acid was found to be crucial for the catalytic cycle[13e] (entry 2, Table 1). To further improve the yield as well as the ratio of **3a**:**4**, various acids as additives as well as the solvents, such as CH_3CN, CH_3NO_2, and DMF were screened, however, no improvement was observed (entry 3-7, Table 1).

Table 1: Optimization study of direct oxidation of α-cinnamyl-β-keto nitrile[a, c, d]



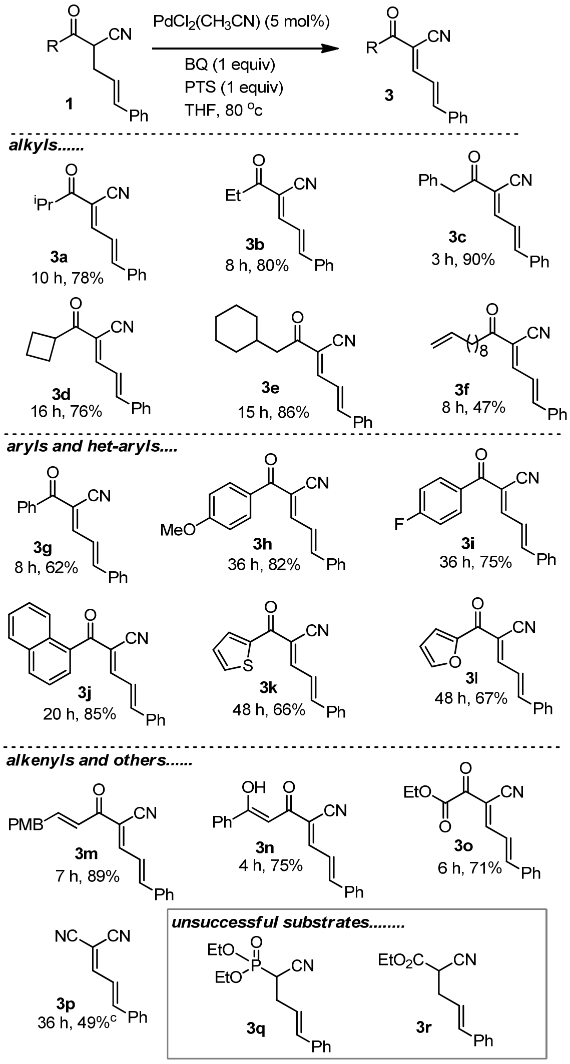
Entry	Catalyst	Additive (1 eq)	[O] (1 eq)	Solvent	3a (%)[b]	3a:4
1	**$PdCl_2(ACN)_2$**	**PTS**	**BQ**	**THF**	**83 (78)[b]**	**94:6**
2	$PdCl_2(ACN)_2$	-	BQ	THF	55	92:8
3	$PdCl_2(ACN)_2$	PivOH	BQ	THF	40	93:7
4	$PdCl_2(ACN)_2$	AcOH	BQ	THF	77	93:7
5	$PdCl_2(ACN)_2$	PTS	BQ	ACN	30	88:12
6	$PdCl_2(ACN)_2$	PTS	BQ	CH_3NO_2	54	69:31
7	$PdCl_2(ACN)_2$	PTS	BQ	DMF	78	90:10
8	$PdCl_2(ACN)_2$	PTS	O_2	THF	trace	-
9	-	PTS	-	THF	-	-

[a]Reaction conditions: α-Cinnamyl-β-keto nitrile **1a** (0.12 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), solvent (1.0 mL), 12 h. [b]The yields were determined based on ^{1}H-NMR data of the reaction mixture using diphenyl acetonitrile as an internal standard. [c] Isolated yield. [d] ACN is acetonitrile.

With the above optimization conditions, we explored the direct dehydrogenation of a series of α-cinnamyl-β-keto-nitriles (Scheme 2). The overall process was shown to be effective in the presence of variously substituted carbonyls (**3a-p**). Various aliphatic moieties, such as ^{i}Pr- (**3a**), Et- (**3b**), benzyl- (**3c**), cyclobutyl- (**3d**), cyclohexyl-methyl- (**3e**), and 9-dacenyl (**3f**) ketones of α-cinnamyl nitriles were tolerated to give the corresponding α,β,γ,δ-unsaturated ketonitrile products, with consistently good yields. Further, aryl-ketones with electron-donating (**3h**) as well as electron-deficient (**3i**) substitutions on the aryl ring were successful. On the other hand, other aryls such as 1-naphthyl-(**3j**) moiety as well as heteroaryls such as 2-thiophenyl-(**3k**) and 2-furyl- (**3l**) groups provided the desired α,β,γ,δ-unsaturated ketonitriles in good yields.

Interestingly, cinnamyl ketone (**3m**), phenyl 1,3-diketone (**3n**), ethyl oxalate (**3o**) and cyano group (**3p**) of α-cinnamyl nitriles could be oxidized to following products, with good yields. To our surprise, α-cinnamyl nitriles having $PO(OEt)_2$, and CO_2Et were ineffective under these reaction conditions. Further, the oxidation product α,β,γ,δ-unsaturated ketonitrile **3l** was confirmed by the X-ray crystallographic analysis (Figure 1).[14]

Scheme 2. Substrate Scope: variations of β-carbonyls-cyano counterpart [a, b]



[a]Reaction conditions: α-cinnamyl-β-keto nitriles **1** (0.12 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), BQ (1.0 equiv), PTS (1.0 equiv), THF (1.0 mL). b Isolated yields after column chromatography. c $PdCl_2(CH_3CN)_2$ (10 mol %).

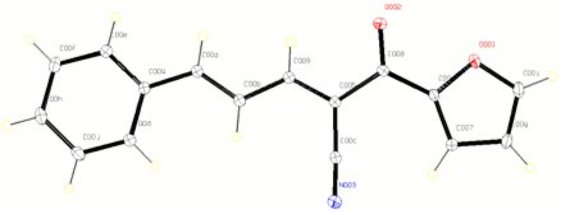


Figure 1: ORTEP diagram of compound **3l** (Ellipsoids: 30% probability) Color code: Carbon (gray), Nitrogen (blue), Oxygen (red) and hydrogens (yellow).[14]

To further expand the substrate scope, we next turned our attention towards testing the feasibility of the substitution on the cinnamyl counterpart (Scheme 3). Different aryls such as phenyl-

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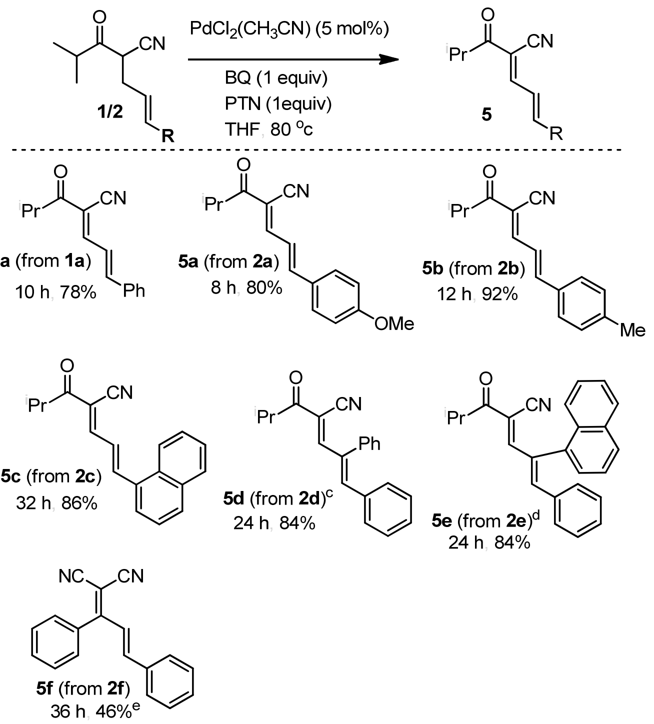
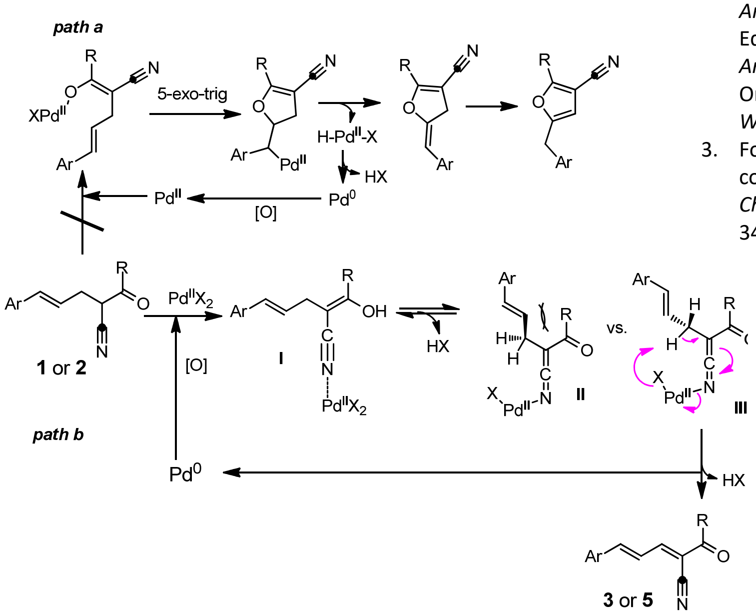
(**3a**), *p*-methoxyphenyl- (**5a**), p-methylphenyl-(**5b**), and α-naphthyl-(**5c**) cinnamyl moiety were well tolerated and provided the corresponding products in 80–92% yields. In addition to the aryl substitution at γ-position on α,β,γ,δ-unsaturated ketonitrile, the aryl substitution at β-position is also well tolerated (**5d-e**). Interestingly, starting with an appropriately designed substrate, α,β,γ,δ-unsaturated ketonitrile with different aryl groups at γ-, δ-, and β-positions could be synthesized as shown in the case of **5d-5f**.

Scheme 3. Substrate Scope: Variations of Cinnamyl Counterpart[a,b]



[a]Reaction conditions: α-cinnamyl-β-keto-nitriles **1** (0.12 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), BQ (1.0 equiv), PTS (1.0 equiv), THF (1.0 mL). [b] Isolated yields after column chromatography. [c] (E: Z = 1:0.1). [d] (E: Z = 1:0.07). [e]$PdCl_2(CH_3CN)_2$ (10 mol %) was used.



Scheme 4. Proposed Mechanism for Current Oxidation

On the basis of the above results, a possible mechanism was proposed in Scheme 4. We envisioned that the strong coordinating ability of nitrile functionality with the transition metals[13] has changed the course of the reaction. Instead of annulation (Scheme 4, path **a**),[12] probably, the coordination of nitrile functionality with Pd^{II} complex (intermediate **I**, path b) occurs, followed by formal elimination of HX to form ketenimine (or keteniminate) intermediates **II** and **III**. Presumably, the presence of acid facilitates such tautomerization. Further, the intermediate **III** undergoes an oxidative β-deprotonation/de-palladation, as shown through the arrow pushing, to produce the α,β,γ,δ-unsaturated ketonitrile. Notably, the conformational stability of **III** over **II** (steric crowding) could be the probable reason for the observed diastereoselectivity. Further, the Pd(0) was reoxidized to Pd(II) with the aid of benzoquinone. The control experiments (see, Supporting Information) also indicate that the nitrile functional group is assisting the direct oxidation of α-cinnamyl-β-ketonitrile to give α,β,γ,δ-unsaturated ketonitriles.

In summary, we have developed a process for the nitrile assisted direct oxidation of readily available α-cinnamyl-β-keto-nitriles into valuable α,β,γ,δ-unsaturated ketonitrile. The disclosed synthetic strategy involves a chemoselective oxidation over the oxidative annulation of α-cinnamyl-β-keto-nitriles, which furnishes α,β,γ,δ-unsaturated ketonitrile in good yield and with broad substrate scope.

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14. Crystallographic data for compound **3l** is available free of charge from the Cambridge Crystallographic Data Centre, accession number **CCDC-1444012** (see, Supporting Information).

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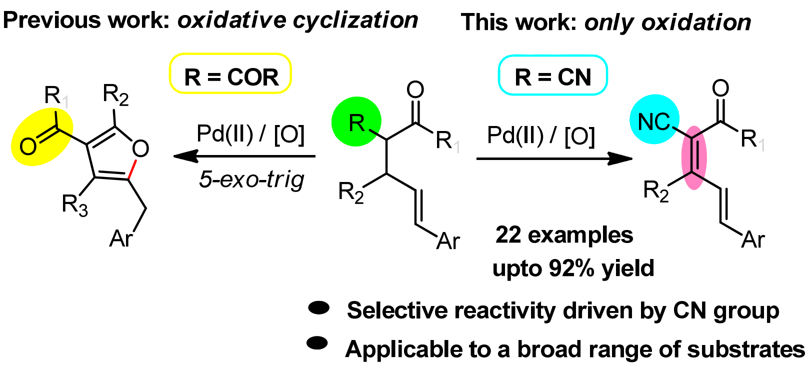

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