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Palladium Catalyzed Intramolecular Acylcyanation of Alkenes Using α-Iminonitriles

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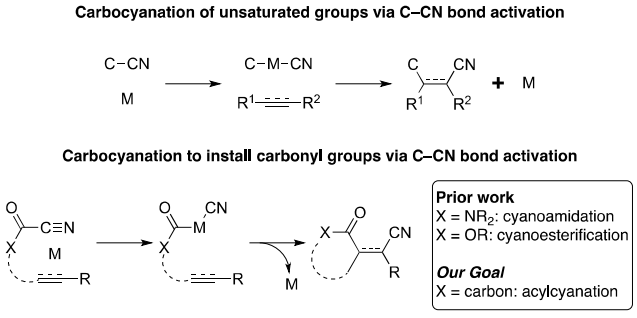
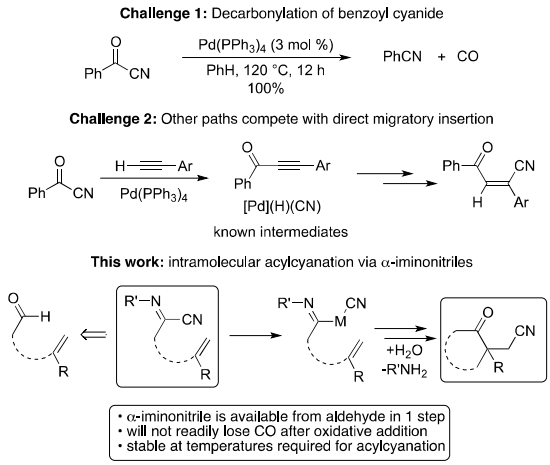
Reported here is a palladium catalyzed intramolecular acylcyanation of alkenes using α-iminonitriles. Through this method, highly functionalized indanones are synthesized in moderate to high yields using $Pd(PPh_3)_4$, without need for any additional ligands, and a common Lewis acid ($ZnCl_2$). Additionally, the reaction tolerates substitution at various positions on the aromatic ring including electron donating, and electron withdrawing groups.

Transition metal catalyzed carbon-carbon (C–C) sigma bond activation and subsequent addition across olefins is a powerful tool in organic synthesis.[1] This process produces highly functionalized products, which can be difficult to synthesize by traditional routes.[2] Among methods involving C–C sigma bond activation, C–CN sigma bond activation and addition across double bonds has emerged as powerful strategy for chemical synthesis (Scheme 1). Recent discoveries include arylcyanation, allyl cyanation, alkylcyanation, cyanoamidation, and cyanoesterification of olefins.[3,4,5,6,7] Although cyanoesterification and cyanoamidation install vicinal cyano and ester or amide groups respectively, the corresponding chemistry to install vicinal cyano and keto groups, acylcyanation, is underdeveloped. Herein we present a method for intramolecular acylcyanation of alkenes.



Scheme 1: Addition Reactions via C–CN Bond Activation

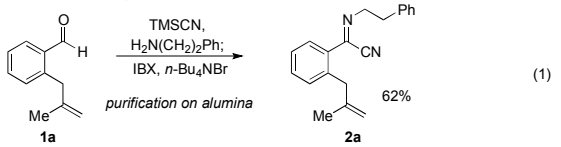
Metal catalyzed C–CN activation of acylnitriles is rare because they have strong tendency to undergo de-carbonylation after activation (Scheme 2, challenge 1).[8] Takaya reported a formal acylcyanation using benzoyl cyanides and terminal alkynes (Scheme 2, challenge 2).[9] Mechanistic studies showed that the reaction occurs via alkyne acylation followed by hydrocyanation of an intermediate ynone and subsequent alkene isomerisation. Due to this pathway, the reaction scope is limited to terminal alkynes and the *E*/*Z* product ratio is determined by the thermodynamic stability of the isomers. These results indicate that direct migratory insertion of an unsaturated moiety into an acyl-palladium nitrile is challenging. At high temperatures (greater than 100 °C), the acylnitrile decomposes. At low temperatures (below 100 °C), direct migratory insertion is not favorable, even with a terminal alkyne. We envisioned that these challenges could be overcome by using α-iminonitriles as an acylnitrile surrogate. Iminonitriles cannot undergo decarbonylation, yet can yield a carbonyl group after hydrolysis upon workup. We chose to examine intramolecular reactions of alkenes, reasoning that intramolecularity would speed migratory insertion. The activation of C–CN bonds is a valuable process as the resulting products retain the nitrile functional group, which is useful in industrial, pharmaceutical and academic research and can be converted to variety of other functional groups like aldehydes, ketones, carboxylic acids and amines.[10]



Scheme 2: Challenges for Direct Acylcyanation

Zhu and co-workers reported the synthesis of α-iminonitriles in one step from the corresponding aldehydes.[11] However, Zhu reports that the α-iminonitriles are acid-sensitive, making it necessary to purify the compounds by chromatography on costly silanized silica gel. In our experience, a modification of Zhu's

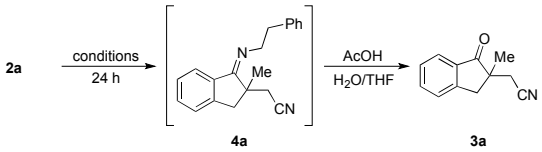
procedure involving treatment of a mixture 2-phenethylamine and benzaldehyde **1a** with TMSCN, followed by *in situ* oxidation of the Strecker product with IBX and tetrabutylammonium bromide produced α-iminonitrile **2a**. We were able to isolate **2a** in 62% yield after chromatography on alumina (equation 1, See SI for additional details).



(1)

Using our optimized procedure, α-iminonitrile **2a** was prepared on preparative scale (>300 mg), allowing us to explore C–CN sigma bond activation and (Table 1).

Table 1: Reaction Conditions for Acylcyanation



	catalyst (mol %)	Lewis acid (mol %)	solvent (0.2 M)	*t* (°C)	**3a** (%)[a]
1	$Pd(PPh_3)_4$(10)	-	*m*-xylene	140	0
2	$Pd(PPh_3)_4$(10)	BPh_3(20)	*m*-xylene	140	55
3	$Pd(PPh_3)_4$(10)	BPh_3(50)	*m*-xylene	140	51
4	$Pd(PPh_3)_4$(10)	$B(C_6F_5)_3$(20)	*m*-xylene	140	0
5	$Pd_2(dba)_3$(5)[b]	BPh_3(20)	*m*-xylene	140	23[c]
6	$Pd(PPh_3)_4$(10)	$ZnCl_2$(20)	*m*-xylene	140	65
7	$Pd(PPh_3)_4$(10)	$Zn(OTf)_2$(20)	*m*-xylene	140	0
8	$Pd(PPh_3)_4$(10)	$ZnCl_2$(20)	1,4-dioxane	120	26[c,d]
9	$Pd(PPh_3)_4$(10)	$ZnCl_2$(20)	*m*-xylene	130	68
10	$Pd(PPh_3)_4$(15)	$ZnCl_2$(20)	PhMe	120	82
11	-	-	PhMe	120	0
12	-	$ZnCl_2$(20)	PhMe	120	0

[a] Isolated yield of indanone **3a**. [b] PPh_3 (20 mol %) was added as ligand. [c] NMR yield of the intermediate imine **4a** calculated using *p*-methoxy acetophenone as internal standard. [d] 65% of starting material detected.

Our investigations into the proposed acylcyanation reaction began using $Pd(PPh_3)_4$ in *m*-xylene at 140 °C (entry 1), however, no desired product was detected under these conditions. We then examined Lewis acid additives, which have been reported to significantly improve the yields in arylcyanation of alkenes via C–CN activation of aryl nitriles.[4] With BPh_3 (20 mol %) as the additive (entry 2), signals attributable to the imine **4a** were assigned in the ^{1}H NMR spectrum of the crude reaction mixture. Subsequent attempts to isolate imine **4a** by chromatographic methods were unsuccessful. Instead, indanone **3a** was isolated in 55% yield. An α-iminonitrile-containing by-product resulting from alkene isomerisation of **2a** was isolated in 23% yield. In subsequent preparative acylcyanation reactions, hydrolysis of the imine to the indanone was performed after a solvent exchange, using acetic acid in a THF/water mixture before purification of the desired indanone. During optimization however, NMR yields of imine **4a** could be measured without hydrolysis to the imine.

Various attempts were made to improve the yield of **3a** and avoid double bond isomerization. Increasing the amount of BPh_3 to 50 mol % (entry 3) did not have a positive effect on the yield and **3a** was isolated in 51% yield. Use of a stronger Lewis acid $B(C_6F_5)_3$ resulted in decomposition of α-iminonitrile **2a** and no product was detected by ^{1}H NMR (entry 4). Changing the source of palladium to $Pd_2(dba)_3$ in the presence of PPh_3 (20 mol %) and BPh_3 (20 mol %) only resulted in a decreased yield of **4a** (as determined by ^{1}H NMR, entry 5). Addition of $ZnCl_2$ (20 mol %) improved the yield of the product to 65% (entry 6). A stronger zinc Lewis acid, $Zn(OTf)_2$, proved ineffective and no **3a** was detected (entry 7). Changing from *m*-xylene to a more polar solvent, 1,4-dioxane, lead to incomplete conversion of the starting material and only 26% of the product observed by ^{1}H NMR (entry 8). Other polar solvents had the same negative effect on reaction yield (not shown). Gratifyingly, lowering the temperature to 130 °C slightly improved the yield of the reaction (entry 9). Further decrease in the temperature in *m*-xylene did not improve the yield (not shown). Lowering the reaction temperature to 120 °C and using toluene, combined with an increase catalyst loading to 15 mol % significantly enhanced the yield of the reaction and indanone **3a** was isolated in 82% yield (entry 10) after hydrolysis of **4a** with acetic acid in THF/H_2O. Control experiments indicated that both $ZnCl_2$ and $Pd(PPh_3)_4$ are necessary for acylcyanation (entries 11 and 12).

With optimized conditions in hand, we studied the scope of the reaction by changing the substitution at various positions of the aromatic ring and olefin (Figure 1). A set of α-iminonitriles **2b-k** was prepared via the corresponding benzaldehydes. In some cases, minor impurities in the α-iminonitrile persisted after chromatography. These were carried into the C–CN bond activation reactions and could be removed afterwards without incident (see SI for details). A low yield of the desired indanone was obtained for *o*-fluoro substrate **3b** at the optimized temperature, but upon increasing the reaction temperature to 130 °C, the reaction proceeded smoothly and the corresponding indanone **3b** was isolated in 73% yield. The 3,5-difluoro-4-trimethylsilyl substrate gave corresponding indanone **3g** in 75% yield, indicating that the reaction also tolerates tri-substitution on the aromatic ring. The reaction proceeds with substitution at *meta* positions with 3,5-difluoro substrate yielding 64% of the corresponding indanone **3c**. Substitution at para position is also allowed with *p*-methyl and *p*-fluoro substrates providing corresponding indanones **3d** and **3e** in 81% and 85% respectively. Interestingly, the reaction also tolerates *p*-chloro substitution on the phenyl ring and the corresponding indanone **3f** was isolated in 79% yield. We also examined the effect different substituents on the aromatic ring with varying electron density have on the efficiency of the reaction. A substrate possessing a strong electron-withdrawing group, such as the *p*-CF_3, allowed the preparation of indanone **3i** in an excellent yield of 90%. Substrates possessing electron-donating groups, such as *p*-^{t}Bu and *p*-OMe, were less reactive and low conversion was observed under the optimized conditions. For these substrates, an increase in the catalyst loading to 20 mol % and an increase in the reaction temperature to 130 °C led to complete conversion and indanones **3j** and **3k** were isolated in 77% and 60% yields respectively. This indicates that electron-withdrawing groups on the aryl ring provide an accelerating effect on the reaction. Next the effect of changing substitution on the double bond was examined. After increasing the reaction temperature from 120 °C to 130 °C, a

non-terminal alkene with an ethyl substitution was fully consumed and the corresponding indanone **3h** was isolated in 76% yield. No indanone was detected when an unsubstituted allyl substrate (R^1 = R^2 = H) was subjected to reaction conditions, possibly due to β–hydride elimination.

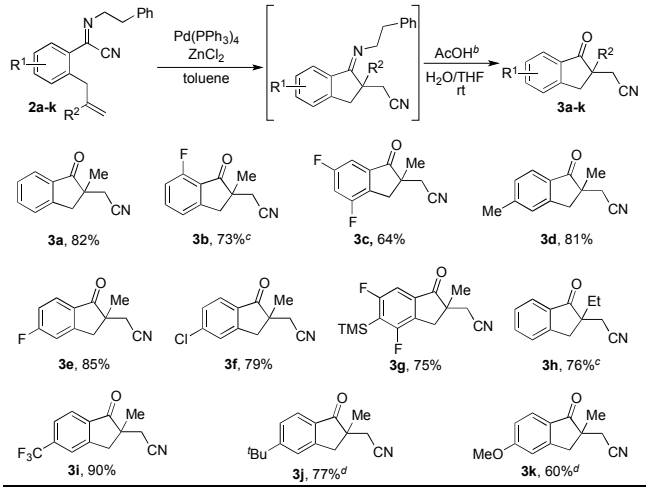
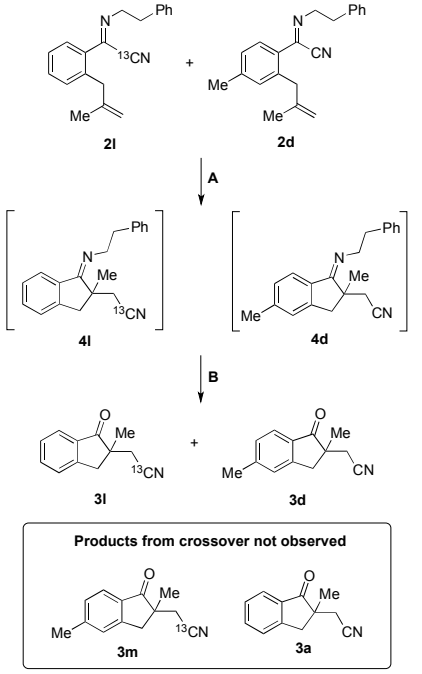


Figure 1: Substrate Scope[a,b]

[a] Isolated yield of indanones after column chromatography on silica gel. Unless otherwise noted, all reactions run at 120 °C with 15 mol % of $Pd(PPh_3)_4$ and 20 mol % of $ZnCl_2$. [b] Please refer to supporting information for the hydrolysis conditions for each substrate. [c] C–CN activation reaction was run at 130 °C. [d] C–CN activation reaction was run at 130 °C with 20 mol % of $Pd(PPh_3)_4$.

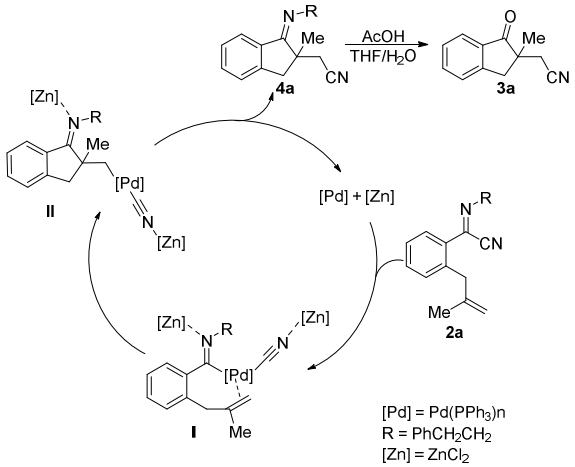
With the presence of Lewis acid being critical to the reaction, we were interested to examine whether binding of $ZnCl_2$ leads to cleavage of the presumptive [Pd]–CN bond during the catalytic cycle. To test this hypothesis, a mixture of ^{13}C labeled α-iminonitrile **2l** and unlabelled α-iminonitrile **2d** were subjected to the optimized reaction conditions. If binding of $ZnCl_2$ leads to cleavage of [Pd]–CN bond during catalytic cycle, crossover products, e.g. **3m** and **3a**, Scheme 3, would be observed. If binding of $ZnCl_2$ solely leads to activation of the bond without cleavage, no crossover products would be observed. For this experiment, only indanones **3l** and **3d** were obtained after hydrolysis and no crossover products (**3m** and **3a**) were observed. This indicates that $ZnCl_2$ likely does not facilitate [Pd]–CN cleavage during catalytic cycle.

Based on the above observations and previous studies[4] of similar systems we believe that the reaction proceeds via the mechanism depicted in Scheme 4. Oxidative addition into the C–CN sigma bond of the α-iminonitrile **2a** by the Pd(0) catalyst is the first step. The Lewis acid $ZnCl_2$ could assist this step by binding to the nitrogen of the nitrile, imine, or both, thereby making the α-iminonitrile more electrophilic and therefore more prone to oxidative addition. Similarly, the effect of electron withdrawing groups on the aryl ring may also increase the rate of oxidative addition. Upon oxidative addition, Pd(II) complex **I** is formed. After coordination of the internal olefin to the metal center, complex **I** would then undergo migratory insertion leading to complex **II**. The higher reaction temperatures necessary for substrate **3h**, which has an ethyl substituent on the olefin, relay the impact of sterics on migratory insertion. In other instances, the reaction temperature needs to be increased due to the presence of an electron-donating group on the phenyl ring, which presumably slows down oxidative addition. These results might indicate that the rate-limiting step is substrate dependant. Similar observations have been made in carboacylation reactions of unstrained C–C bonds with 8-acyl quinoline directing groups.[12] From intermediate **II**, reductive elimination leads to imine **4a** and regeneration of the active Pd(0) catalyst.



A: $Pd(PPh_3)_4$ (15 mol %), $ZnCl_2$ (20 mol %), PhMe, 120 °C, 24 h
B: AcOH, rt, 12 h

Scheme 3: Crossover Experiment



Scheme 4: Mechanistic Hypothesis

In summary we have reported the first metal catalyzed acylcyanation of alkenes. We overcame the challenge of decarbonylation by using α-iminonitriles as a surrogate for acyl

nitriles. These α-iminonitriles are stable to chromatography using alumina and directly prepared from the corresponding benzaldehydes. The C–CN bond activation and alkene addition reaction proceeds in good to excellent yields using a commercially available palladium source ($Pd(PPh_3)_4$) and a common Lewis acid ($ZnCl_2$) and without the use of complex ligands or expensive additives. A crossover experiment gives evidence that the reaction proceeds in an intramolecular fashion, with the nitrile likely bound to the metal during catalytic cycle. Work on an asymmetric version as well as an intermolecular variant of the reaction is currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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