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Palladium-Catalyzed C−CN Activation for Intramolecular Cyanoesterification of Alkynes

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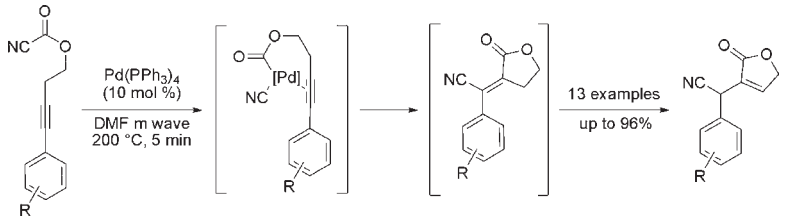
ABSTRACT



Conditions for the C−CN activation and intramolecular cyanoesterification of alkynes to provide butenolides in good to excellent yields are presented. Pd catalysts, high temperatures/short reaction times (microwave irradiation), and Lewis basic solvents minimized competitive decarbonylation. Less sterically encumbered, electron-rich alkynes underwent cyanoesterification with greater ease compared to sterically encumbered, electron-deficient alkynes. The results led to the hypothesis that migratory insertion of the alkyne, rather than C−CN activation, might be the product-determining step.

Carbon−carbon σ bond (C−C) activation and insertion of C−C π bonds have drawn recent attention because highly functionalized products with two new vicinal C−C bonds are formed and with excellent atom economy.[1] Recent work in this area has largely focused upon C−CN activation.[2] Jacobsen[3] and Nakao−Hiyama[4] and their coworkers separately demonstrated the new strategy's potential in organic synthesis with the C−CN activation of aryl nitriles and asymmetric intramolecular addition across alkenes (arylcyanation). Takemoto first reported the C−CN activation of cyanoformamides and subsequent addition across alkynes and alkenes (cyanoamidation) in 2006.[5] Later, Takemoto[6] and our laboratory[7] separately reported highly enantioselective intramolecular cyanoamidation reactions of alkenes to form all-carbon quaternary stereocenters. Our laboratory has utilized asymmetric cyanoamidation to synthesize natural products. Our successes with cyanoformamides motivated us to examine the activation of C−CN bonds of cyanoformate esters.

Intramolecular cyanoesterification of C−C π bonds has not yet been achieved, likely because cyanoformate esters are much more reactive than aryl nitriles and

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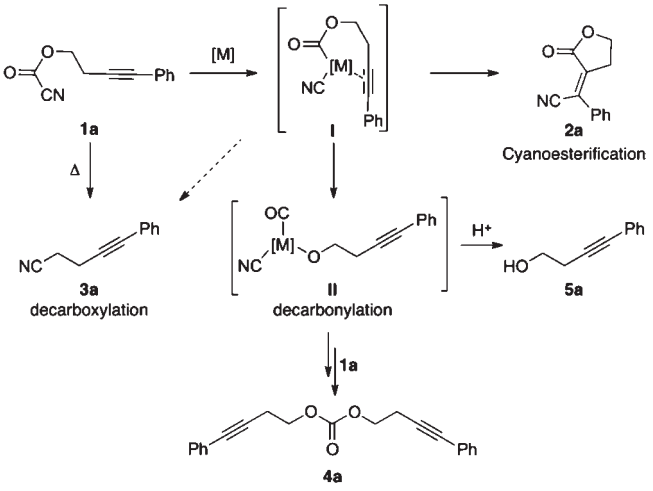
cyanoformamides. They rapidly undergo nucleophilic addition and substitution reactions with mild nucleophiles.[8] Cyanoformate esters **1a** will decarboxylate to form nitriles like **3a** when heated to high temperatures (Scheme 1).[9] Transition metal activation of the C−CN bonds forms **I**, which is also susceptible to various decomposition pathways. We suspect that **I** might undergo a metal-catalyzed decarboxylation, providing nitrile **3a** via a different mechanistic pathway. Decarbonylation of **I** provides **II**, which upon protonation provides alcohol **5a** (vide infra). Nishihara observed that intermediates like **II** can undergo disproportionation in the presence of **1a** to form carbonates like **4a**.[10]

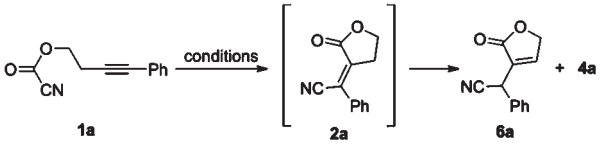
Scheme 1. Potential Reactions of Cyanoformate Esters



Due to a multitude of potential side reactions, very few selective processes involving C−C σ bond activation of cyanoformate esters have been reported. Nishihara reported the first example of Pd-catalyzed intermolecular cyanoesterification of norbornenes and norbornadienes with cyanoformate esters.[10] More recently, Nakao and Hiyama reported a Ni-catalyzed cyanoesterification of allenes[11] and alkynes,[12] also in an intermolecular context.

In this report, we describe an intramolecular cyanoesterification of alkynes with Pd catalysts to produce butenolides by successfully suppressing competitive decarbonylation. We chose cyanoformate ester **1a**, which is readily prepared in one step by treating commercially available 4-phenyl-3-butyn-1-ol with carbonyl cyanide.[13] Successful cyanoesterification would provide functionalized lactones such as **2a** in just two steps from commercially available 3-butynols. An intramolecular reaction provides control over regioselectivity issues encountered in intermolecular reactions, in which the nitrile might add to either alkyne terminus.

Table 1. Optimization of Intramolecular Cyanoesterification



entry	$Pd(PPh_3)_4$ (mol %)	solvent	t (^{o}C)	concn (M)	time	**6a:4a**[a]	**6a** (%)[b]
1	10	PhMe	110	0.1	24 h	–	0[c]
2	10	PhMe	115	0.03	48 h	1:1.5	17[c]
3	25	PhMe	115	0.03	24 h	1:1.5	16[c]
4	25	DMF	115	0.03	24 h	2.8:1	45
5	25	DMF	115	0.03	1.5 h	4:1	50
6	10	DMF	130	0.1	1.5 h	3.9:1	73
7	10	PhMe	130	0.1	1.5 h	1:1.3	21
8[d]	**10**	**DMF**	**200**	**0.1**	**5 min**	**16:1**	**80**[e]
9[d]	0	DMF	200	0.1	5 min	–	0

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] A significant amount of starting material was observed. [d] Reaction performed in microwave reactor. [e] Isolated yield. Carbonate **5a** (5%) was also isolated. **Bold** conditions (entry 8) indicate those used for exploring the reaction scope, Table 2.

We began with Nishihara's conditions,[10] which resulted only in unconsumed starting material (Table 1, entry 1). When the reaction was diluted to 0.03 M in toluene (entry 2), carbonate **4a** was formed as the major product, but a minor amount of another compound with a molecular weight corresponding to that of **2a** was also observed. Closer inspection of the NMR spectra indicated that the product was a structural isomer of **2a**, but with an endocyclic alkene (**6a**), likely resulting from isomerization of **2a**. Trials to increase the ratio of **6a:4a** by varying temperature, catalyst loading, and concentration failed (not shown). Recalling our previous successes with Lewis basic additives in somewhat similar cyanoamidation reactions,[6b,7] we added stoichiometric amounts of *N,N*-dimethylpropylene urea (DMPU) and *N*-methylpyrollidinone (NMP), thinking that the Lewis basic additives will coordinate to Pd to stabilize intermediate complexes. Although stoichiometric amounts of Lewis basic additives were not particularly fruitful (results not shown), a much higher ratio of **6a:4a** was observed when DMPU was used as a solvent. The subsequent removal of DMPU and isolation proved difficult, however (not shown). Our success with DMPU prompted us to employ a more convenient, lower boiling,

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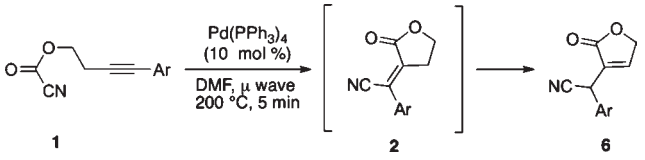
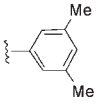
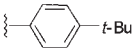
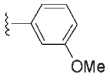
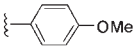
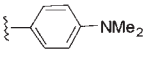
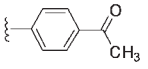
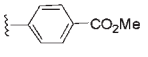
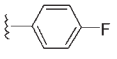
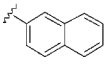
Lewis basic solvent, DMF, and a higher ratio of **6a:4a** was obtained (entry 4). As we monitored the reaction progress and altered the reaction temperatures, we observed that shorter reaction times (entry 5) and higher temperatures (entry 6) provided better yields of **6a**. In control experiment under similar conditions of higher temperature and lower reaction time, cyanoesterification in toluene provided a poor ratio of **6a:4a** (entry 7). Finally, when we switched to using a microwave reactor (5 min, 200 °C), an excellent ratio of **6a:4a** was observed (16:1, entry 8), with butenolide **6a** isolated in 80% yield. A control experiment subjecting **1a** to the same microwave irradiation conditions as those described in entry 8 but without any $Pd(PPh_3)_4$ catalyst resulted in no product formation (entry 9).

Table 2. Effects of Various Aryl Substituents



1 2 6

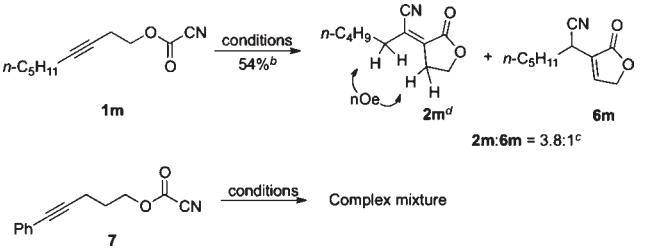
entry	ester 1	Ar	product	6 %[a]
1	**1a**	Ph	**6a**	80
2	**1b**		**6b**	96
3	**1c**		**6c**	73
4	**1d**		**6d**	53[b]
5	**1e**		**6e**	70
6	**1f**		**6f**	83
7	**1g**		**6g**	75
8	**1h**		**6h**	68
9	**1i**		**6i**	50[c]
10	**1j**		**6j**	54[d]
11	**1k**		**6k**	82
12	**1l**		**6l**	70

[a] Isolated yield after column chromatography. [b] Yield of **6d** based on the ^{1}H NMR spectrum of the product mixture. We could not separate butenolide **6d** from carbonate **4d**. [c] 22% alcohol **5i**. [d] 19% alcohol **5j**.

Using the microwave reactor conditions described in Table 1, entry 8, we explored the steric and stereoelectronic effects of various aryl substituents upon cyanoesterification (Table 2). We included the results from cyanoformate ester **1a** as a reference (entry 1). Cyanoesterification tolerates alkyl substitution at various positions of the ring (entries 2−5), with *p*-Me providing the highest yield of **6b** (96%, entry 2), while *o*-Me provided the lowest but still acceptable yield of **6d** (53%, entry 4). Electron-donating substituents like OMe and NMe_2 provided good yields of the corresponding butenolides (entries 6−8). Slightly lower yields of butenolides were observed when electron-withdrawing substituents [C(O)Me and CO_2Me] were incorporated at the *para* position (entries 9−10). With these substrates, minor amounts of the corresponding alcohols **5i** and **5j** were isolated. We note that the catalyst selectively activated the cyanoformate ester in the presence of another ester (entry 10).[14] Interestingly, cyanoesterification of 4-F-C_6H_4-substituted alkyne **1k** provided the butenolide **6k** in good yield (82%, entry 11). Other aromatic substituents like naphthalene provided butenolide **6l** in good yield (70%, entry 12).

Replacing the aryl substituent with an alkyl group, or extending the alkyne tether length drastically altered our product distribution (Scheme 2). When we subjected alkyl-substituted **1m** to our optimized cyanoesterification conditions, we observed the formation of lactone **2m**, with an exocyclic alkene, as the major product. The *Z*-geometry was assigned by NOE. The result indicates that when an alkyl group is present, the exocyclic double bond is less likely to undergo olefin isomerization compared to when an aryl group is present. Unfortunately, when we attempted to synthesize δ-lactones via the cyanoesterification with cyanoformate ester **7**, neither desired product was detected in the resulting complex mixture.

Scheme 2. Additional Cyanoesterification Substrates[a]



[a] Conditions: $Pd(PPh_3)_4$ (10 mol %), DMF, μ wave, 200 °C, 5 min. [b] Isolated yield after column chromatography: **2m** (42%) and **6m** (12%). [c] Ratio determined by ^{1}H NMR spectrum of the crude reaction mixture. [d] Alkene geometry assigned by NOE. Only the *Z* isomer was observed.

We propose the following mechanism based on these results and prior work on C−CN activation (Scheme 3).[6,7,10] Cyanoesterification likely begins with

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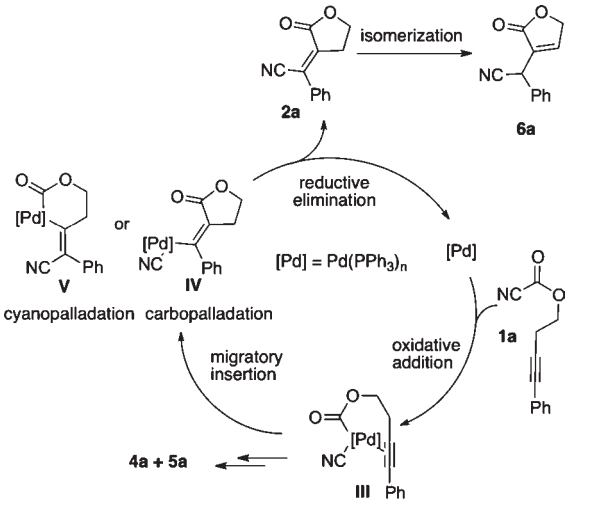
the oxidative addition of Pd(0) into the C−CN bond of the cyanoformate ester to form a Pd(II) complex **III** in which an alkyne π bond is coordinated to Pd. The DMF solvent likely coordinates to the Pd, stabilizing the resulting intermediate and decreasing competitive decarbonylation. Migratory insertion of the alkyne into the Pd−acyl bond in a 5-*exo*-dig, *syn* fashion provides the *Z* isomer of **IV**. Reductive elimination regenerates the Pd(0) catalyst while providing lactone **2a** with an exocyclic olefin. When an aryl group is present, the tetrasubstituted olefin readily isomerizes to the trisubstituted olefin of butenolide **6a**. Decarbonylation of **III** allows the subsequent formation of carbonate **4a** and alcohol **5a**, as detailed in Scheme 1. It is unclear to us why higher temperatures would favor cyanoesterification over decarbonylation pathways.

Alternatively, intermediate **III** might undergo cyanopalladation, rather than carbopalladation to provide intermediate **V** which upon reductive elimination would also result in lactone **2a**. Takemoto's mechanistic experiments in cyanoamidation (rather than cyanoesterification) suggest that cyanoamidation proceeds via carbopalladation rather than cyanopalladation.[5a] In analogy to Takemoto's work, cyanoesterification might also proceed via carbopalladation, though cyanopalladation cannot be ruled out.

The presence of electron-deficient (Table 2, entries 8, 9) and sterically congested substituents (entry 4) on the alkyne erodes the chemoselectivity of cyanoesterification and yields of butenolides **6**. The electron-withdrawing substituents lower the electron density on the alkyne, which could weaken Pd(II) coordination to the alkyne. Aryl groups possessing ortho substituents increase steric congestion, which might also weaken alkyne coordination. Poorer alkyne coordination might slow migratory insertion, thereby reducing the yield of butenolides **6**. Due to slowed migratory insertion, alternative decomposition pathways such as decarbonylation to provide **4** and **5** might compete. Moreover, extending the tether length may also slow coordination or migratory insertion, allowing alternative decomposition pathways to take place, with no cyanoesterification products observed. Based on these results, we propose that migratory insertion could be the product-determining step.

In conclusion, we discovered conditions for the C−CN activation and intramolecular cyanoesterification of alkynes in the presence of a relatively inexpensive and common palladium source, $Pd(PPh_3)_4$, to provide butenolides

Scheme 3. Plausible Reaction Mechanism for Cyanoesterification



in good to excellent yields. Formation of a carbonate byproduct can be minimized by employing high temperatures and short reaction times (microwave irradiation) in Lewis basic solvents. Sterically less encumbered, electron-rich alkynes underwent cyanoesterification with greater ease compared to sterically encumbered, electron-deficient alkynes. Our results led us to hypothesize that migratory insertion of the alkyne, rather than C−CN activation, is the product-determining step. Work on synthesizing lactones via the cyanoesterification of alkenes is underway.

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Supporting Information Available. Experimental procedures, ^{1}H and ^{13}C NMR spectra for new compounds, and tabulated characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.