Organic LETTERS

Letter

pubs.acs.org/OrgLett

Privilege Ynone Synthesis via Palladium-Catalyzed Alkynylation of "Super-Active Esters"

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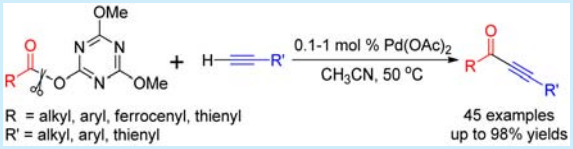
Supporting Information

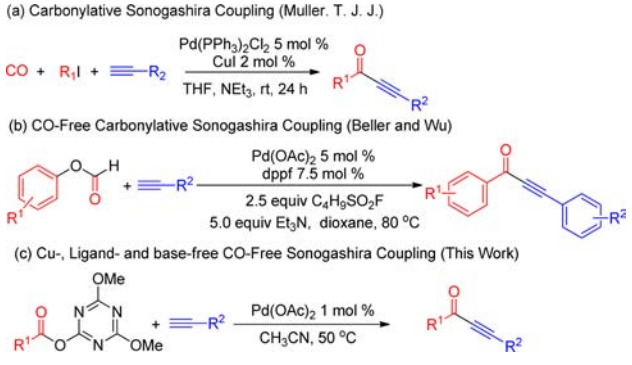
ABSTRACT: A neat palladium-catalyzed alkynylation reaction was developed with "super-active ester" as the carbonyl electrophile, which provides a clean and efficient synthetic protocol for a broad array of ynone compounds under CO-, Cu-, ligand-, and base-free conditions. The superior activity of triazine ester was rationalized by the strong electron-withdrawing ability and the unique affinity of triazine on palladium. A mechanistic experiment clearly demonstrated that the N−Pd coordination of triazine plays a crucial role for the highly efficient C−O activation.



Carbon−oxygen bonds are less active than carbon−halogen bonds, which need to be activated for organic transformation.[1] A range of C−O electrophiles such as pivalates,[2] acetates,[3] phosphonates,[4] carbamates,[5] carbonates,[6] phosphoramides,[7] phosphates,[8] tosylates,[9] mesylates,[10] sulfamates,[11] and heteroaryl ethers[12] have been introduced for application in metal-catalyzed cross-coupling reactions as coupling partners. Carboxylic acids can be converted to ester electrophiles using C−O bond-activating agents. The electron-withdrawing activators strongly polarize the C−O bond in these electrophiles, hence replacing carboxylic halides as more suitable alternatives in carbon−carbon and carbon−heteroatom bond formation reactions due to their higher diversity, abundance, and availability.[13] The coupling reactions of active esters provide a general and efficient strategy to synthesize symmetric and asymmetric ketones. Varying organometallic nucleophiles and electrophiles significantly diversify the structure of coupling products, by which numerous aryl, alkenyl, and alkyl ketones were successfully synthesized via the palladium-catalyzed cross-coupling of Csp^2 and Csp^3 carbons, respectively.[14]

α,β-Acetylenic carbonyl derivatives, especially ynones, are important structural motifs in natural products.[15] They are often employed as key intermediates, which appear in many biologically active molecules and play crucial roles toward the rapid construction of sophisticated synthetic targets.[16] The direct attachment of a carbonyl to an acetylene moiety offers numerous synthetic outlets for the various heterocyclic structures.[17] Palladium-catalyzed carbonylative Sonogashira coupling is a valuable route for the synthesis of 1,3-ynone compounds by avoiding air-sensitive lithium reagents (Scheme 1, a).[18] However, the high toxicity and odorless and flammable character of CO gas means that transformations using CO gas must be operated with special care, and often require elevated CO pressures, so that it has actually hindered the application of such reactions. While aryl formates are adopted as CO surrogates for carbonylative Sonogashira coupling, the implementation of new chemical

Scheme 1. Pd-Catalyzed Carbonylative Sonogashira Cross-Couplings



bond transformations significantly diversifies the synthetic protocol of organic ynones (Scheme 1, b).[19] The gold-catalyzed rearrangement of propargylic pivalates followed by oxidation with $PhI(OAc)_2$ provides a new efficient approach to ynones under air.[20] Huang and co-workers utilized the oxidative C−C bond cleavage of aldehydes to construct ynones.[21] Despite these elegant contributions, an efficient cross-coupling C−C formation under CO free conditions is still highly desirable for preparation of 1,3-ynones.

In fact, under the classic Sonogashira reaction conditions, the Pd and Cu bimetallic systems can catalyze the cross-coupling of acyl chloride and terminal alkynes.[22] However, the general stability of acid chlorides is limited, and they are often only accessible with a narrow scope of functional groups. Another disadvantage of the catalyst system is that the homocoupling byproducts and high catalyst loadings (5−10 mol %) remain problematic and hamper the utility of Pd/Cu-catalyzed systems

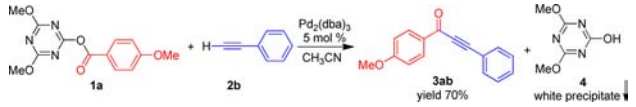
Received: May 19, 2015
Published: June 12, 2015

DOI: 10.1021/acs.orglett.5b01466
Org. Lett. 2015, 17, 3298−3301

in the wider scope. Therefore, clearly, improvement of the efficiency of the Cu-free catalyst system is still a significant challenge.[23] Exploration for electrophiles is a new effort to develop the cross-coupling reactions. Herein, we report that the 1,3,5-triazinyl heterocycle strongly activates the C−O bonds of carboxylic acid esters for CO-, Cu-, ligand-, and base-free synthesis of ynone compounds. Under very mild conditions, submolar % Pd catalyzed cross-coupling of triazine esters with terminal alkynes in high yields, which are then developed as a facile synthesis of diverse aryl and alkyl 1,3-ynones (Scheme 1, c).

The activity of the so-called "super-active ester"[24] of *p*-methoxybenzoic acid **1a** was first evaluated for the cross-coupling with phenylacetylene under standard Sonogashira conditions (Scheme 2).[22] The reaction of **1a** and **2b** catalyzed by $Pd_2(dba)_3$/

Scheme 2. Pd-Catalyzed Cross-Coupling of Triazine Ester with Phenylacetylene



CuI and PPh_3 (5 mol %) in toluene at 110 °C for 10 h afforded no product, but trace diphenylacetelyene as homocoupling product was detected. Interestingly, after removal of co-catalyst CuI and ligand PPh_3, a small amount of ynone was detected by GC−MS. In acetonitrile, to our surprise, a white precipitate was observed at the end of the reaction course. The column chromatographic separation on the reaction mixture produced a 70% yield of ynone **3ab**. Elemental and GC−MS analyses confirmed the precipitate **4** as 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT).[24]

The reaction conditions were systematically optimized and listed in Table 1. The solvents played a pivotal role for the Pd-catalyzed cross-coupling of **1a** and **2b**. Only in acetonitrile did the reaction occur smoothly (entry 1). Other two-electron donor solvents, such as THF, dioxane, and ethanol, failed to maintain the catalytic cycle of the cross-coupling reaction (entries 3−5). As for precatalyst, both Pd(0) and Pd(II) were active for promotion of the cross-coupling of **1a** and **2b** (entries 1 and 9).

Table 1. Optimization of Conditions for "Superactive Ester" 1a Coupled with Phenylacetylene 2b[a]

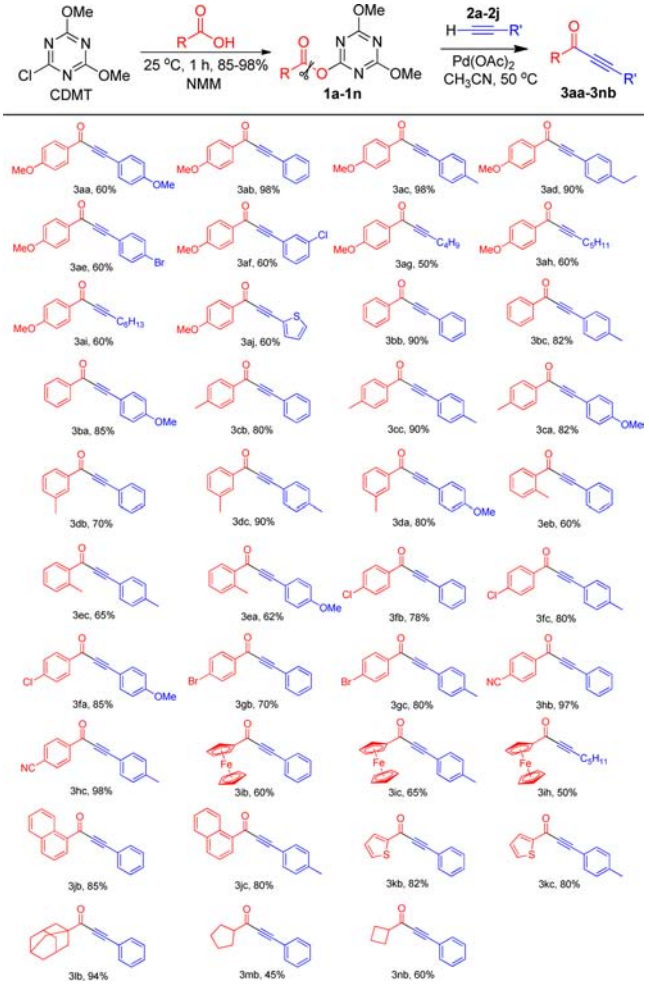
entry	catalyst	solvent	yield[b] (%)
1	$Pd_2(dba)_3$, 5 mol %	CH_3CN	70
2	$Pd_2(dba)_3$, 5 mol %	toluene	<5
3	$Pd_2(dba)_3$, 5 mol %	THF	<5
4	$Pd_2(dba)_3$, 5 mol %	dioxane	ND
5	$Pd_2(dba)_3$, 5 mol %	C_2H_5OH	<5
6	$PdCl_2$, 5 mol %	CH_3CN	<5
7	$Pd(PPh_3)_2Cl_2$, 5 mol %	CH_3CN	ND
8	$Pd(PPh_3)_4$, 5 mol %	CH_3CN	ND
9	$Pd(OAc)_2$, 5 mol %	CH_3CN	98
10	$Pd(OAc)_2$, 1 mol %	CH_3CN	98
11	$Pd(OAc)_2$, 0.5 mol %	CH_3CN	90
12	$Pd(OAc)_2$, 0.1 mol %	CH_3CN	55
13	Pd(OAc), PPh_3, 5 mol %	CH_3CN	ND
14	none	CH_3CN	ND

[a]Reaction conditions: a mixture of triazine esters (0.5 mmol), alkynyl reagent (0.75 mmol), and 3 mL of CH_3CN was stirred at 50 °C for 10 h. [b]Isolated yield.

Chloride and phosphine ligands, however, were unfavorable coligands. $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, and $PdCl_2$ could not catalyze the reaction (entries 8−10). Palladium acetate was found to be the most active precatalyst, which efficiently catalyzed the reaction with 98% isolated yield (entries 9 and 10). Even with submolar % catalyst loading, 0.5 mol % and 0.1 mol % of $Pd(OAc)_2$ gave 90% and 55% yields, respectively. The phosphine ligand, however, inhibited the catalytic activity of $Pd(OAc)_2$. In the control reaction without palladium catalyst, no cross-coupling product of ynone **3ab** was detected.

Triazine esters are stable white crystals that can be easily handled without any protection from oxygen, moisture, or light and could be prepared nearly quantitatively through the reaction of carboxylic acids with 2-chloro-4,6-dimethoxy-1,3,5-triazine in the presence of *N*-methylmorpholine.[25] The facile synthesis of ynone compounds was developed by the cross-coupling between various triazine esters and terminal alkynes. The scope and limitation of the synthetic protocol were explored using aromatic, alkyl, and cyclic and heterocyclic substrates (Scheme 3, **1a**−**n**). Triazine esters derived from aryl carboxylic acids are highly active for the cross-coupling reactions, in which aromatic substitents at the *para*-, *meta*-, or *ortho*-position are compatible with the Pd-

Scheme 3. Privileged Ynone Synthesis via Pd-Catalyzed Cross-Coupling of Triazine Ester with Terminal Alkynes[a,b]



[a]Reaction conditions: a mixture of triazine esters (0.5 mmol), $Pd(OAc)_2$ (1 mol %), alkynyl reagent (0.75 mmol), and 3 mL of CH_3CN was stirred at 50 °C for 10 h. [b]Isolated yield.

DOI: 10.1021/acs.orglett.5b01466
Org. Lett. 2015, 17, 3298−3301

catalyzed reactions. 4-Methoxybenzoic acid ester **1a** coupled to aromatic alkynes **2a**–**f** with 60–98% yields. Arylacetylenes bearing 4-alkyl groups gave over 90% yields (**3ab**, **3ac**, and **3ad**), while **3aa** with methoxy groups at the *para* position was isolated in 60% yield. Notably, both C–Cl (**3af**) and C–Br (**3ae**) were well tolerated, offering the potential for further orthogonal functionalization for ynone products.[26] The alphatic terminal alkynes are less active and gave the corresponding alkyl ynones (**3ag**, **3ah**, and **3ai**) with 50–60% yields.

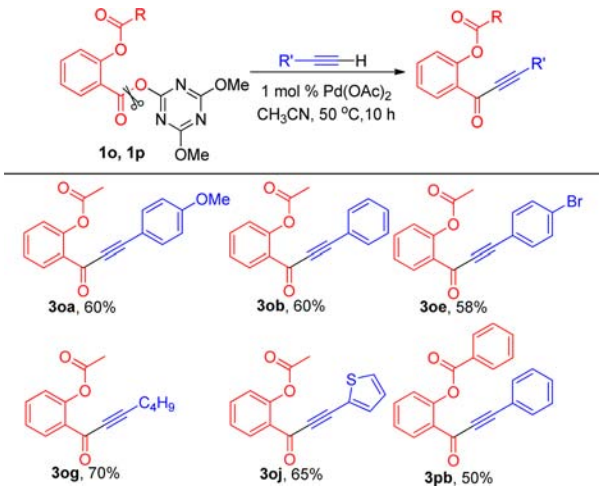
The scope of triazine esters was examined in detail under the optimized reaction conditions. To our delight, both electron-donating (**1a**–**e**) and electron-withdrawing (**1f**–**h**) groups at the aromatic triazine ester reacted with arylacetylenes **2a**–**c** in good to excellent yields. Steric factors rather than electronic factors affected the efficiency of the cross-coupling reactions. *Para*-substituted esters gave **3ca**–**3cc** and **3fa**–**3fc** with 80–90% yields. *o*-Methyl groups of **3ea**–**ec** affected the reaction in which 60–65% yields of ynones were isolated. An electron-withdrawing –CN group seemed to accelerate the alkynylation of triazine esters, and the corresponding ynones (**3hb**–**hc**) were isolated nearly quantitatively. Ferrocene carboxylic acid triazine ester (**3i**) successfully transformed to desirable products in moderate yields (**3ib**, **3ic**, and **3ih**). The triazine ester bearing a naphthalene group afforded the expected products in 80–85% yields (**3jb**, **3jc**). Steric bulky 1-adamantyl ester **3l**, to our surprise, easily coupled to phenylacetylene with 94% yield. Cyclopentane and cyclobutane groups were intact, and the corresponding cyclic ynones were obtained with 45% and 60% yields, respectively (**3mb**–**mb**). Finally, thiophene-yl heterocycles were efficiently introduced to ynone compounds, **3aj**, **3kb**, and **3kc** from the corresponding ester **1k** or alkyne **2j**.

The superior activity of triazine esters was further demonstrated in the reaction using acetylsalicylic acid ester **1o** and 2-(benzoyloxy) benzoic acid ester **1p**, in which two adjacent esters potentially can both convert to ynones (Scheme 4). It was found that terminal alkynes selectively couple with triazine esters. The corresponding ynones (**3oa**–**pb**) were isolated with 50–70% yields. In the reactions, no acetyl or benzoyl ynones were detected, indicating that triazine-activated C–O bonds are far more reactive than C–O bonds of conventional carboxylic esters. Furthermore, under the mild base-free conditions, the acetyl ester group in ynone is well tolerated, offering key starting material for the concise synthesis of flavonoid compounds.[27]

To our pleasure, the side product **4** can be filtered off from the coupling reaction and readily converted to trazine ester with high yields.[28] Therefore, the triazine activator can be recycled. To gain insight into the activation of C–O bonds, the single crystals of seven esters were grown via the diffusion of hexane into the ethyl acetate or CH_2Cl_2 solution of esters at 0 °C. In the molecular structures of these triazine esters, the C–O bond lengths range from 1.375 to 1.368 Å (see the Supporting Information), much longer than the 1.275 Å C–O bond length in benzoic acid, indicating the triazine ring strongly activates C–O bond. The further comparison of the C–O bond length revealed that triazine is more electron-withdrawing than other ester electrophiles such as 4-nitrophenyl ester (1.359 Å) and pyridine ester (1.350 Å). Interestingly, the diphenyl carboxylate (1.371 Å) and activated *N*-hydroxysuccinimide ester (1.388 Å) are not as active as their triazine analogues[29] and did not react with phenylacetylene in the presence of Pd catalyst, which led us to want to identify the nature of the C–O activation ability of the triazine moiety. In the pharmacy industry, the derivatives of triazine have been applied to removal of palladium contaminants.[30] Therefore, the unprecedented reactivity of triazine esters might result from the synergistic activation effect of the strong electron-withdrawing ability and the unique coordination chemistry of the 1,3,5-triazine ring.

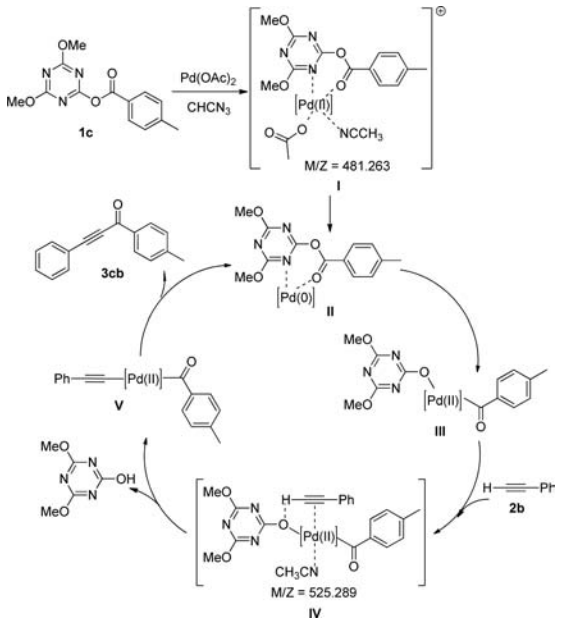
To elucidate the mechanism (Scheme 5), the cross-coupling reaction of 4-methylbenzoic triazine ester **1c** and phenylacetylene **2b** was investigated spectroscopically. In CD_3CN solution, as soon as phenylacetylene was added, the characteristic peak of the methoxy group on the triazine ring started to diverge. The resonances of the product appeared at the corresponding regions. After the reaction continued in an NMR tube at 50 °C for 4 h, the NMR spectrum of the reaction mixture clearly showed that most of the **1c** was consumed along with the

Scheme 4. Preparation of *o*-Alkynoylphenyl Carboxylate via Selective Cross-Coupling of Terminal Alkynes with 1o (1p)[a,b]



[a]Reaction conditions: a mixture of triazine esters (0.5 mmol), $Pd(OAc)_2$ (1 mol %), alkynyl reagent (0.75 mmol), and 3 mL of CH_3CN was stirred at 50 °C for 10 h. [b]Isolated yield.

Scheme 5. Proposed Reaction Mechanism



DOI: 10.1021/acs.orglett.5b01466
Org. Lett. 2015, 17, 3298–3301

formation of cross-coupling product **3cb** (Figures S1−2, Supporting Information).

ESI-MS analysis unveiled two palladium triazine species during the reaction course (Supporting Information, Figures S3−10). The adduct of palladium acetate and triazine ester was detected as cationic fragment **I** of m/z = 481.263, in which Pd might coordinate to the triazine ring.[30b,31] The cationic Pd species with m/z = 525.289 was assigned as the oxidative addition intermediate **IV**. Therefore, a catalytic cycle is proposed in Scheme 5. The triazine ester **1c** first chelates $Pd(OAc)_2$, and intermediate **I** forms via the N−Pd coordination on triazine ester. After being reduced by phenylacetylene, the palladium center oxidatively adds to adjacent C−O bond of **1c**, and **II** and **III** form sequentially. The reduced product was identified as Glaser diyne (m/z = 202.1) by GC−MS. Phenylacetylene enters the inner sphere of **IV** via coordination to Pd(II). Since the triazine activator is basic,[32] the deprotonation of the coordinated phenylacetylene is accelerated as the heterocycle leaves the coordination sphere of **IV**. Finally, the reductive elimination releases 1,3-ynone product **3bc**, and the catalytic active Pd(0) species recycles.

In summary, palladium-catalyzed alkynylation reactions using carboxylic triazine esters as electrophiles have been developed. The C−O activation of triazine is so efficient that it enables clean C−C couplings showing a wide range of functional tolerance and unprecedented selectivity. The corresponding 1,3-ynones were synthesized in excellent yields upon reaction with aryl and alkyl terminal alkynes, respectively. The development of this protocol with other C−O bond activations and detailed mechanistic studies are underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01466.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the 111 Project (B14041), Innovative Research Team in University of China (IRT_14R33), National Natural Science Foundation of China (21171112, 21271124, 21371112, 21446014), Fundamental Research Funds for the Central Universities (GK201501005, 201503029), Fundamental Doctoral Fund of Ministry of Education of China (20120202120005), and Shaanxi Innovative Team of Key Science and Technology (2013KCT-17).

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DOI: 10.1021/acs.orglett.5b01466
Org. Lett. 2015, 17, 3298−3301