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Silver and Palladium Cocatalyzed Carbonylative Activation of Benzotriazoles to Benzoxazinones under Neutral Conditions

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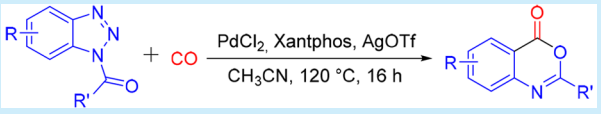
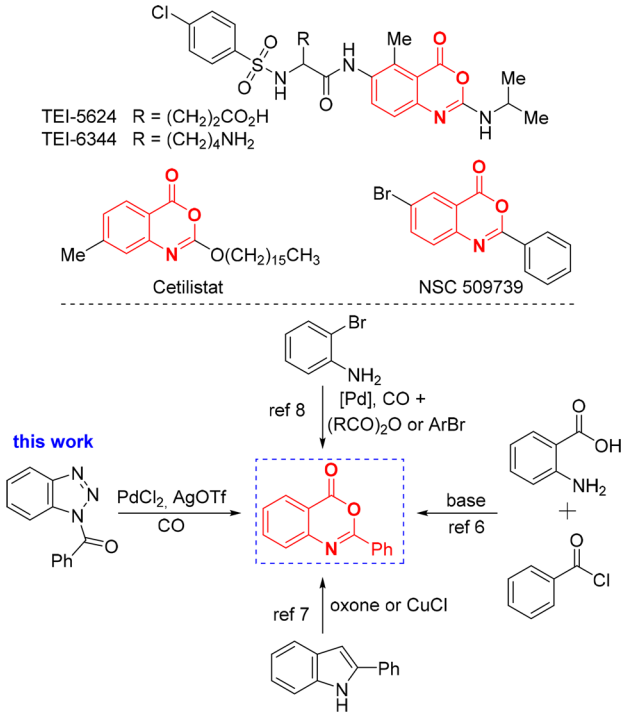
Supporting Information

ABSTRACT: A novel and efficient method for the carbonylative activation of benzotriazoles to benzoxazinones has been developed. By using a silver and palladium bimetallic catalyst system, a broad range of benzotriazoles were transformed into the corresponding benzoxazinones in moderate to good yields with excellent functional group tolerance. Notably, this procedure proceeds under neutral conditions.



Benzoxazinones are one of the most important heterocyclic compounds endowed with a broad spectrum of biological activities.[1] For example, Cetilistat is an inhibitor of pancreatic lipase, which can potentially be used for the treatment of obesity with or without diabetes (Scheme 1).[2] TEI-5624 and TEI6344 were found to be the inhibitors of human leukocyte elastase (HLE) and may exert potent therapeutic effects on pulmnoary emphysema, an adult respiratory distress syndrome.[3] In addition, benzoxazinones are also used as inhibitors of HSV-1 protease and chymotrypsin.[4] Furthermore, benzoxazinones also serve as crucial synthetic scaffolds in organic chemistry and medicinal chemistry for the synthesis of a biological active quinazolin-4(3*H*)-one derivative.[5] Despite their obvious importance, currently the most commonly applied methods to construct these heterocyclic compounds are based on anthranilic acids.[6] Alternative methodologies have been reported as well, such as oxidation of 2-arylindoles[7] and palladium-catalyzed carbonylation of *ortho*-haloanilines.[8] However, the reactions are usually carried out under basic or acidic conditions, which surely limit certain classes of functional groups.

Scheme 1. Selected Bioactive Benzoxazinones and Known Synthesis Procedures



On the other hand, 1,2,3-benzotriazoles are significant heterocyclic units and broadly used in medicinal chemistry,[9] biochemistry,[10] and material science.[11] One of their particular properties is that they can go through a ring-opening process to form the corresponding diazonium species.[12] This aforementioned reactive intermediate can undergo various transformations, including annulations[13] and cross-coupling reactions.[14] Due to our continuing interest in palladium-catalyzed carbonylative transformations,[15] we become interested in exploring the application of 1,2,3-benzotriazoles as substrates in carbonylative transformations. With such a procedure, readily available benzotriazoles can be further transformed; properties of the related materials and drugs can be modified. In addition, products such as benzoxazinone compounds can be effectively produced.

Additionally, bimetallic catalysis for new C−C and C−X (X = O, N, S, etc.) bond formation is a promising topic and increasing in importance in the synthetic toolbox.[16] New reactivity can be discovered with a bimetallic system which cannot be realized with any of the single catalysts. In this letter, we report a novel silver and palladium cocatalyzed carbonylative transformation of benzotriazoles to benzoxazinones. Notably, this procedure proceeds under neutral conditions.

Initially, the reaction was performed using **1a** as the model substrate to optimize the reaction conditions. The initial reaction trial was performed with $Pd(OAc)_2$ and Xantphos as

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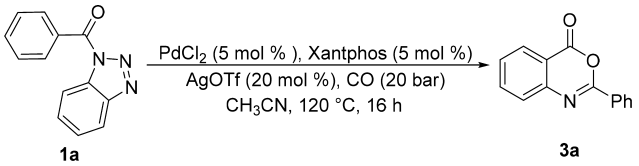
the catalytic system in MeCN under pressure of CO (20 bar) at 120 °C. To our delight, a 60% yield of the desired product was formed (Table 1, entry 1). The yield of the reaction decreased

Table 1. Optimization of the Reaction Conditions[a]



1a 3a

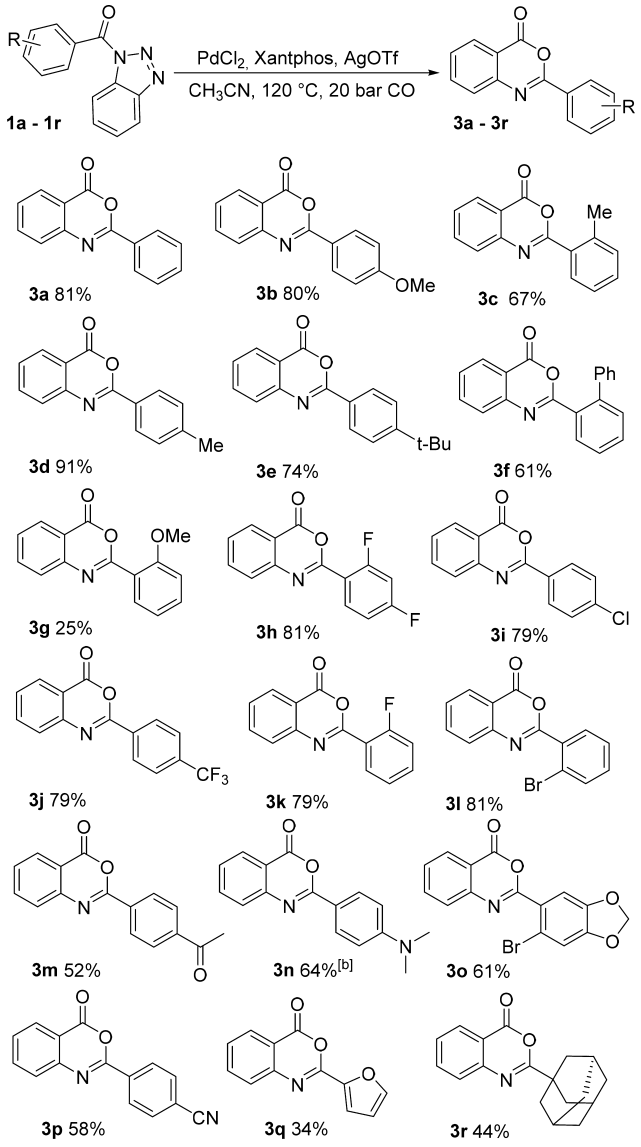
entry	variations from the standard conditions	yield (%)[b]
1	$Pd(OAc)_2$ instead of $PdCl_2$	60
2	$Pd(TFA)_2$ instead of $PdCl_2$	35
3	$Pd_2(dba)_3{\cdot}CHCl_3$ instead of $PdCl_2$	40
4	–	87, 81[c]
5	toluene instead of CH_3CN	79
6	1,4-dioxane instead of CH_3CN	19
7	$tBu_3P{\cdot}HBF_4$ (10 mol %) instead of Xantphos	75
8	$BuPAd_2$ (10 mol %) instead of Xantphos	73
9	DPPP (5 mol %) instead of Xantphos	80
10	$AgBF_4$ (20 mol %) instead of AgOTf	50
11	Ag_2CO_3 (10 mol %) instead of AgOTf	trace
12	AgF (20 mol %) instead of AgOTf	30
13	no ligand	63
14	no AgOTf	trace
15	CO 10 bar instead of 20 bar	50
16	100 °C instead of 120 °C	70
17	2% $PdCl_2$ instead of 5% $PdCl_2$	65

[a]Reaction scale: 0.2 mmol, solvent (2 mL). [b]GC yields were determined by using hexadecane as the internal standard. [c]Isolated yield. DPPP = 1,3-bis(diphenylphosphino)propane.

when using $Pd(TFA)_2$ as the palladium precursor (Table 1, entry 2). $Pd_2(dba)_3{\cdot}CHCl_3$ as the Pd(0) precursor has been tested as well; 40% of the target molecule was produced (Table 1, entry 3). Delightfully, 81% of 2-phenyl-4*H*-benzo[*d*][1,3]-oxazin-4-one can be isolated with $PdCl_2$ as the catalyst (Table 1, entry 4). The reaction efficiency slightly dropped with toluene as the reaction solvent, and only a 19% yield could be obtained if the reaction was performed in 1,4-dioxane (Table 1, entries 5 and 6). Then, though various other ligands were tested, the yield of the desired product still cannot be further improved (Table 1, entries 7–9). Afterward, we turned our attention to the effect of cocatalysts. Various silver salts were tested, but reaction efficiency could not be further improved (Table 1, entries 10–12). In the absence of ligand, the yield decreased to 63% (Table 1, entry 13). No reaction occurred in the absence of silver triflate (Table 1, entry 14). Additionally, the yield of the target product decreased with lower loading of the palladium catalyst, lower CO pressure, or lower reaction temperature (Table 1, entries 15–17). Finally, we found that the use of 5 mol % of $PdCl_2$, 5 mol % of Xantphos, and 20 mol % of AgOTf under CO pressure (20 bar) in MeCN at 120 °C gave the desired product **3a** in 81% isolated yield (Table 1, entry 4).

Having determined the best conditions, we then examined the scope of the reaction with a range of 1,2,3-triazoles. As shown in Scheme 2, the desired benzoxazinone products were formed in good yields with different electron-donating or -withdrawing groups in the *ortho* or *para* position of the substrates. Chloro and bromo substituted products can be

Scheme 2. Scope of Acyl 1,2,3-Benzotriazoles[a]



[a]**1a–1r** (0.2 mmol), $PdCl_2$ (5 mol %), Xantphos (5 mol %), AgOTf (20 mol %), CO (20 bar), dry CH_3CN (2 mL), 120 °C, 16 h, isolated yields. [b]CO (40 bar).

prepared from the corresponding substrates as well (Scheme 2, entries **3i**, **3l**, **3o**). Those substituents were ready for further transformations via cross-coupling reactions. Notably, substrate **1d** (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(*p*-tolyl)methanone can give the corresponding benzoxazinone product **3d** in 91% yield. Interestingly, 2-heterocyclic and 2-alkyl substituted benzoxazinones can also be produced from the corresponding 1,2,3-triazoles (Scheme 2, entries **3q**, **3r**). Furthermore, various 1,2,3-benzotriazoles with substitutions on the other aromatic rings were prepared and tested as well. As shown in Table 2, moderate to good yields of the desired products were achieved under the standard conditions. Since the two isomers of the 1,2,3-benzotriazoles (Table 2, entries 1 and 2) are impossible to separate, the products were obtained as a mixture of two isomers, and the product ratios of the two isomers are 2.2:1 and 3:1, respectively, determined by ^1H NMR. Halogen substituents on the aromatic ring were well tolerated in our reaction and gave the desired products in 68% and 63% yields (Table 2,

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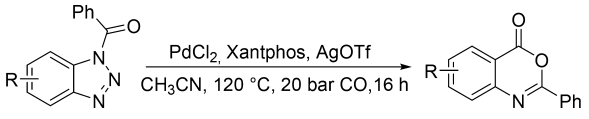
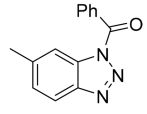
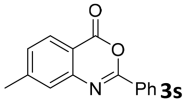
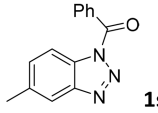
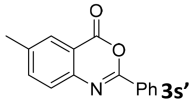
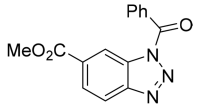
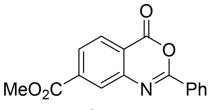
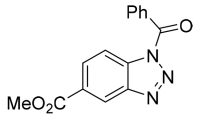
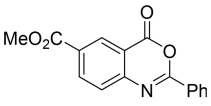
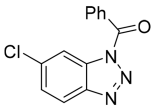
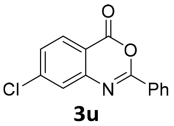
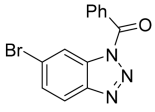
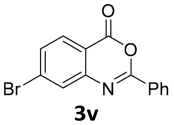
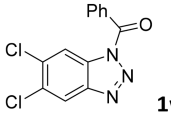
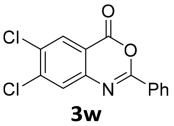
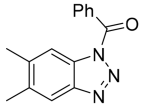
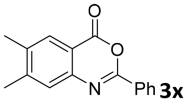
Table 2. Scope of Benzoyl 1,2,3-Benzotriazoles[a]



entry	substrate	product	yield (%)
1	 1s	 3s	70[b]
	 1s′	 3s′	
2	 1t	 3t	83[b]
	 1t′	 3t′	
3	 1u	 3u	68
4	 1v	 3v	63
5	 1w	 3w	66[c]
6	 1x	 3x	75

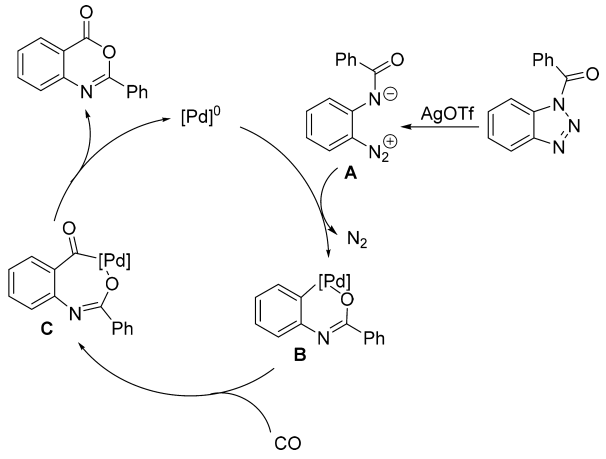
[a]Substrate (0.2 mmol), $PdCl_2$ (5 mol %), Xantphos (5 mol %), AgOTf (20 mol %), CO (20 bar), dry CH_3CN (2 mL), 120 °C, 16 h, isolated yields. [b]Yield of two isomers. [c]CO (40 bar).

entries 3−5). A good yield of two methyl substituted 1,2,3-benzotriazoles can be successfully transformed as well and gave the desired product in 75% yield (Table 2, entry 6).

Based on previous literature about the ring opening of 1,2,3-benzotriazoles,[12−14] a possible reaction mechanism is proposed (Scheme 3). First, arenediazonium intermediate **A** is generated from the starting material catalyzed by AgOTf, and then **A** would undergo oxidative addition with Pd(0) to produce the organopalladium complex **B**. After the coordination and insertion of CO, a seven-membered intermediate **C** will be formed, which then affords the final benzoxazinone products after reductive elimination while the active Pd(0) species is regenerated for the next catalytic cycle.

In summary, a novel and versatile protocol for carbonylative transformation of 1,2,3-benzotriazoles has been developed. With silver and palladium as the bimetallic catalyst system,

Scheme 3. Proposed Reaction Mechanism



various benzoxazinones were produced in moderate to good yields with excellent functional group tolerance. Notably, the reactions were performed under neutral conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03184.

General comments, general procedure, analytic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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