

# Palladium-catalyzed addition of 1,3-diones to ynamides: an entry to unprecedented alkoxy-substituted enamides

Lionel V. Graux,<sup>[a]</sup> Hervé Clavier,<sup>\*[a]</sup> and Gérard Buono<sup>[a]</sup>

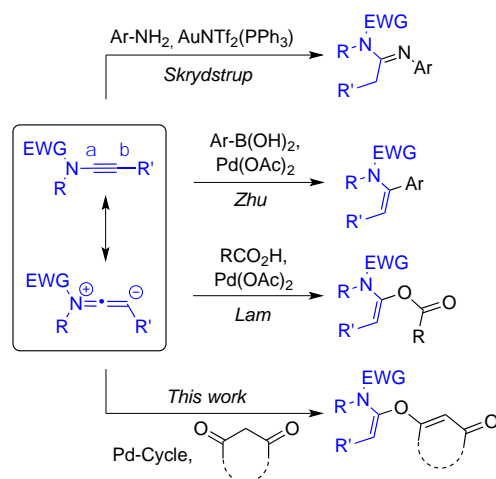
A new metal-catalyzed addition reaction of 1,3-diketones to ynamides providing an access to unprecedented alkoxy-substituted enamides is disclosed herein. A screening of catalytic systems showed that either a phosphapalladacycle or a cationic gold complex were efficient to promote rapidly and cleanly this reaction. The scope investigation revealed that variously substituted terminal ynamides and cyclic 1,3-diones were well tolerated. The use of internal ynamides led to the formation of both *E*- and *Z*-isomers with low to good selectivities. The mechanism proposal suggests that the phosphapalladacycle acts as a  $\pi$ -Lewis acid to activate the ynamide.

Alkynes and more particularly the subgroup of nitrogen-substituted alkynes, ynamides, are important and versatile building blocks used in a myriad of chemical transformations.<sup>[1]</sup> The electron-donating character of the nitrogen atom leads to a strong polarization of the triple bond, which alters perceptibly their reactivity compared to alkyl- or aryl-substituted alkynes. The keteniminium tautomeric form of ynamides shows clearly the regioselectivity of additions onto ynamides: nucleophiles

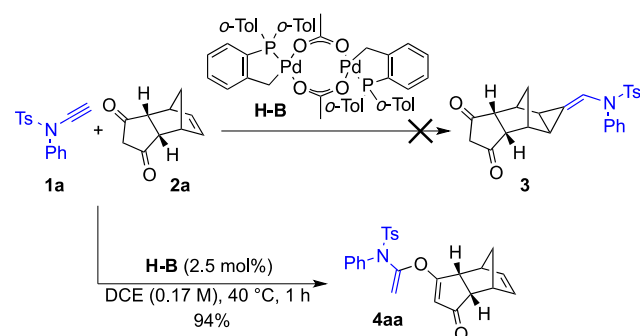
are added at the  $\alpha$ -position to the nitrogen atom and the  $\beta$ -position reacts with electrophiles (Scheme 1).<sup>[2,3]</sup> Since it gives a straightforward access to synthetically relevant functionalized enamides, additions of nitrogen-, carbon- or oxygen-containing nucleophiles at the position  $\alpha$  have been investigated using various catalytic systems.<sup>[4]</sup> For instance, Skrydstrup reported the gold-catalyzed addition of anilines to ynamides<sup>[5]</sup> using the cationic complex AuNTf<sub>2</sub>(PPh<sub>3</sub>) developed by Gagosz.<sup>[6]</sup> This catalyst was later used for ynamide dimerization giving rise to cyclopentadienes.<sup>[7]</sup> On the other hand, palladium(II) acetate was found to promote efficiently the addition of boronic acids, as disclosed by Zhu,<sup>[8]</sup> and the hydroacyloxylation of ynamides reported by Lam a couple of years ago.<sup>[9]</sup>

During the course of our researches on the [2+1] cycloaddition between alkynes and norbornene derivatives using palladium-based complexes prepared from secondary phosphine oxide preligands,<sup>[10]</sup> we noticed that the Herrmann-Beller phosphapalladacycle **H-B** promoted this transformation in the case of polarized carbon-carbon triple bonds such as ynamides (Scheme 2).<sup>[11,12]</sup> However, during the scope investigation, we observed that norbornene derivative **2a** containing a 1,3-cyclopentanedione moiety did not afford the expected [2+1] cycloadduct **3** but nearly quantitative yield of **4aa** resulting from the addition of the enol form of **2a** to ynamide **1a** (Scheme 2). Considering the fact that it gives an access to unprecedented alkoxy-substituted enamides, we decided to pursue the examination of this hitherto unknown reactivity.<sup>[13-15]</sup>

We started to investigate this original transformation by a thorough examination of the catalytic system using benchmark substrates: ynesulfonamide **1a** and dimedone **2b** (Table 1). Surprisingly, the  $\alpha$ -addition of 1,3-dione to ynamide occurs at room temperature without catalyst. However, after 4 days only 34% of **4ab** was isolated along with a large amount of degradation products which complicated the purification step



**Scheme 1.** Metal-catalyzed addition of *N*-, *C*- and *O*-nucleophiles to ynamides.

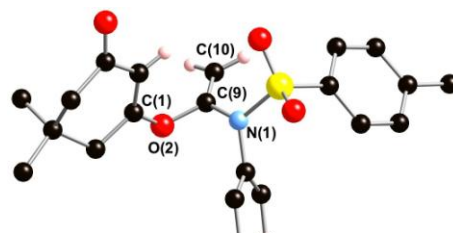


**Scheme 2.** Attempted Pd-catalyzed [2+1] cycloaddition of a 1,3-dione-containing norbornene with an ynamide.

[a] L. V. Graux, Dr. H. Clavier, Prof. Dr. G. Buono  
Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR  
7313, 13397, Marseille, France  
E-mail: herve.clavier@univ-amu.fr

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(entry 1). Of note, heating the reaction mixture led to the increase of the degradation rate. Herrman-Beller phosphapalladacycle **H-B** was found competent to catalyze rapidly and cleanly the addition of **2b** to **1a** (entry 2). The structure of **4ab** was unambiguously determined by X-ray crystallography (Figure 1).<sup>[16]</sup> The C(9)=C(10) bond distance of 1.305(3) Å is significantly short for C-C double bond, especially for enamides (typically bond lengths between 1.35 and 1.39 Å).<sup>[17]</sup> Such a bond length is generally observed for C=C in allenes. The bond angle O(2)-C(9)-N(1) of 110.3(2)° is smaller than expected (120°). Dihedral angles C(1)-O(2)-C(9)-C(10) and C(1)-O(2)-C(9)-N(1), respectively 109.1(3)° and 74.6(2)° indicate a relatively weak steric congestion around the carbon-carbon double bond. More importantly, adduct **4ab** was found quite stable in solution and could be easily purified by flash chromatography on silica gel. However, the newly formed C-O bond was found sensitive to acidic traces and its cleavage released the dimedone **2b** and *N*-phenyl tosylamide. Therefore, chloroform-*d*<sub>3</sub> was filtrated on basic alumina prior to use in order to slow down the hydrolysis process. Control experiences carried with PPh<sub>3</sub>, Pd(OAc)<sub>2</sub> and a mixture Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> (1:2) showed a low formation of adduct **4ab** in addition to noticeable amounts of degradation products (entries 3-5). Interestingly, gold-complex AuNTf<sub>2</sub>(PPh<sub>3</sub>) exhibited an analogous activity to the one observed with **H-B** (entry 6). In order to probe that the Lewis acid character of gold is responsible for the catalysis, the



**Figure 1.** Ball-and-stick representation of adduct **4ab** (most of the hydrogens have been omitted for clarity).

reaction was performed in the presence of a strong Brønsted acid, triflic acid (entry 7). No improvement in comparison to the non-catalyzed addition of dimedone to ynamide **1a** was noticed. Solvent screening revealed that, to the exception of DMF, various solvents were compatible with this palladium-mediated addition and **4ab** was isolated in good yields (entries 2, 8-13). In dioxane, the reaction proceeded with the formation of by-product **5ab** in 11% yield in addition to 65% of **4ab** (entry 11). With other solvents, only traces of **5ab** were detected by <sup>1</sup>H NMR from the crude reaction mixture.

Having established the optimal reaction conditions, we further investigated the reaction scope with a range of 1,3-diones or derivatives (Table 2). Cyclohexane-1,3-dione-based substrates **2b–2e** were found to be good nucleophiles and the corresponding alkoxy-substituted enamides **4ab–4ae** were isolated in satisfactory yields in short reaction times (entries 2–5). The dissymmetric dione **2d** gave rise to two isomers in ratio 4:1 in favour of **4ad** resulting from the attack of the more sterically demanding ketone (entry 4). 1,3-diketone **2f** was tested but the lack of reactivity - even at higher temperature - demonstrates that substitution in 2-position inhibits completely the addition (entry 5). Similarly to 6-membered 1,3-diones, 5-membered analogues were smoothly added to ynamide **1a** (entries 7-9). Despite a prolonged heating at 60 °C, 1,3-indandione **2j** did not react (entry 10). On the other hand, other aromatic 1,3-diones such as 1,3-phenalendione **2k** and 4-hydroxycoumarine **2l** led to the formation of the expected adduct in moderate yields, respectively 55 and 51% (entries 11 and 12). Finally, we were unable to carry out this transformation with acyclic 1,3-diones, for example **2m** (entry 13). More than the keto-enol equilibrium, we believe that the acidity of the 1,3-diones allows for the rationalization of the success of the addition. Indeed, *pK<sub>a</sub>* values for cyclic 1,3-diones, including 4-hydroxycoumarine **2l**, are around 5 (dimedone **2b**, *pK<sub>a</sub>* = 5.2), whereas acyclic analogues show higher values (**2m**, *pK<sub>a</sub>* = 9.2).<sup>[18]</sup> Similarly 1,3-indandione **2j** (*pK<sub>a</sub>* = 7.2) is significantly less acidic than other cyclic 1,3-diones which would explain the lack of reactivity observed for this substrate. In a general manner, all isolated compounds showed a good stability at solid state.

We then examined the transformation scope with respect to the ynamide partner (Table 3). In addition to the *N*-substituted phenylamide **1a**, analogues **1b–1e** afforded the corresponding adducts with good to excellent yields (entries 1–4). Other ynesulfonamides **1f** and **1g** were found to be good partners for the addition of dimedone **2b** (entries 5 and 6). Ynamides bearing different electron-withdrawing groups such

**Table 1.** Catalyst and solvent optimization.<sup>[a]</sup>

Entry	Catalyst <sup>[a]</sup>	Solvent	Time [h]	Yield [%]
1	none	DCM	96	34
2	<b>H-B</b>	DCM	3	84
3	PPh <sub>3</sub>	DCM	48	46
4	Pd(OAc) <sub>2</sub>	DCM	3	21
5	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub>	DCM	3	30
6	AuNTf <sub>2</sub> (PPh <sub>3</sub> )	DCM	3	82
7	TfOH	DCM	3	20
8	<b>H-B</b>	DCE	3	82
9	<b>H-B</b>	Toluene	3	80
10	<b>H-B</b>	THF	3	82
11	<b>H-B</b>	1,4-dioxane	3	65 <sup>[b]</sup>
12	<b>H-B</b>	MeCN	3	58
13	<b>H-B</b>	DMF	3	Traces

[a] Reaction conditions: **1a** (0.5 mmol), dimedone **2a** (0.5 mmol), 5 mol% of catalyst (2.5 mol% of dimeric **H-B**), Solvent (3 mL). [b] 11 mol% of **5ab** were also isolated. Tf = trifluoromethanesulfonyl (CF<sub>3</sub>SO<sub>2</sub>)

Entry	Substrate	Time [h]	Product	Yield [%]
1		3		82
2		3		84
3		3		85
4		2		79
				19
5		3		91
6 <sup>[b]</sup>		5		NR
7		2		73
8		2		72
9		5		69
10 <sup>[b]</sup>		5		NR
11		2		55
12		5		51
13 <sup>[b]</sup>		5		NR

[a] Reaction conditions: **1a** (0.5 mmol), 1,3-dione **2** (0.5 mmol), **H-B** (2.5 mol%), DCM(3 mL). [b] Reactions were also performed at 60 °C in DCE. NR = No Reaction.

as carbamate or amide were also found to be reactive in this transformation (entries 7 and 8). Only the vinylogous indole-containing ynamide **1j** gave the isolated product with a moderate yield (43%, entry 9).


Next, a series of internal benzylynamides **6** was studied and it appeared that a thermal activation at 80 °C was required

Entry	Ynamide	Time [h]	Product	Yield [%]
1		5		90
2		1		87
3		3		87
4		2		79
5		2		79
6		1		93
7		2		72
8		3		83
9		2		43

[a] Reaction conditions: ynamide **1** (0.5 mmol), dione **2b** (0.5 mmol), 2.5 mol% of **H-B cat**, DCM(3 mL). Ns = 4-nitrobenzenesulfonyl.

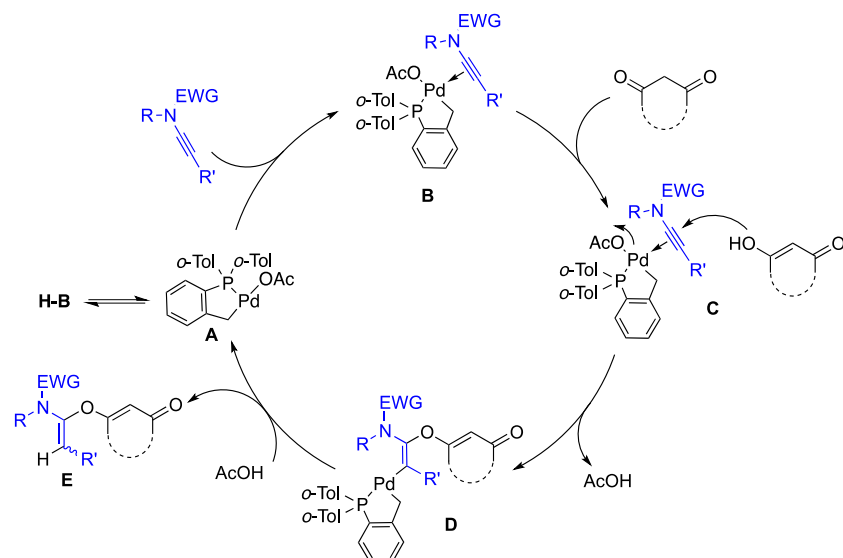
for the Pd-catalyzed addition to 1,3-diones (Table 4). With re-optimized reaction conditions, adducts **7b** bearing alkyl substituents were obtained with good yields (entries 1-3) and the phenyl-substituted product **7db** was isolated in a almost quantitative yield (entry 4). With the silylated ynamide **6e**, no product was detected in the crude mixture. We believe that the

**Table 4.** Investigation of reaction scope with internal ynamides.<sup>[a]</sup>

Entry	R'	Product	Yield [%]	E/Z <sup>[b]</sup>
1	Me, <b>6a</b>	<b>7ab</b>	66	2:1
2	<i>n</i> Bu, <b>6b</b>	<b>7bb</b>	61	5:1
3	 , <b>6c</b>	<b>7cb</b>	63	2.5:1
4	Ph, <b>6d</b>	<b>7db</b>	90	1:1
5	TIPS, <b>6e</b>	NR		

[a] Reaction conditions: ynamide **5** (0.5 mmol), dimedone **2b** (0.5 mmol), 2.5 mol% of **H-B cat**, DCE (3 mL), 80 °C, 5h. [b] Determined by <sup>1</sup>H NMR spectroscopy. TIPS = Tri-*iso*-propylsilyl.

lack of reactivity might be due to electronic reasons more than to the steric bulk of the TIPS group. Adducts **7ab-7db** were isolated as a mixture of *E* and *Z* isomers for which a ratio and the identification were determined by NMR spectroscopies, respectively <sup>1</sup>H and NOESY experiments.<sup>[19]</sup> No *E/Z* selectivity was noticed for phenyl-substituted ynamide **6d**



(entry 4), while a little selectivity has been observed with methyl- and **Scheme 3**. Mechanistic proposal.

cyclopropylsubstitutions (entries 1 and 3). Only the ynamide **7b** bearing *n*-butyl allowed to reach a good *E/Z* ratio.

A plausible mechanism to explain the catalytic role of the Herrmann-Beller catalyst **H-B** depicted in Scheme 3. **H-B** is in equilibrium with its monomeric form **A** which activates the ynamide C-C triple bond and promotes the attack of the 1,3-dione enol form.<sup>[20]</sup> The formation of intermediate **C** might be concomitant with an acetic acid release, unless the early departure of the acetate prompts the formation of the more nucleophilic enolate form. This will explain why only 1,3-diones with a *pK<sub>a</sub>* close to the one of acetic acid can be used in this transformation. Finally, acidolysis of **D** releases product **E** and catalytic active species **A**.

In summary, we reported an unprecedented palladium-catalyzed addition of 1,3-diones to ynamides giving rise to  $\alpha$ -alkoxy-substituted enamides which, to the best of our knowledge, hadnot been described so far.<sup>[21]</sup> This transformation was found to be compatible with acidic 1,3-diones (*pK<sub>a</sub>*  $\leq$  5) and most of the ynamides we have been tested. In a general manner, reactions proceeded smoothly at room temperature - for internal ynamides a heating at 80 °C is required - and gave high yields. Further investigations are underway in our laboratories to better apprehend the mechanism and improve both selectivities and yields of the addition with internal ynamide partners. The reactivity and synthetic applications of  $\alpha$ -alkoxy-substituted enamides arealso studied.

## Experimental Section

### General Procedure for the palladium-catalyzed addition of 1,3-diones to ynamides:

A 5 mL Schlenk flask, under nitrogen, was charged with Herrmann-Beller catalyst (**H-B**) (11.7 mg, 0.0125 mmol, 0.05 equiv. in palladium), and DCM (2 mL). Then, ynamide (0.5 mmol, 1 equiv.), 1,3-diketone derivatives (0.5 mmol, 1 equiv.) and DCM (1 mL) were added in turn. The reaction mixture was allowed to stir at 25°C for the indicated time (TLC monitoring). In the case of internal ynamides, reactions were performed in DCE at 80°C for 5h. Volatiles were removed under reduced pressure and the crude residue was purified by silica gel flash chromatography using petroleum ether and ethyl acetate (gradient 0 – 50%) as eluent leading the pure product.

## Acknowledgements

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**Keywords:** 1,3-dione • enamine • nucleophilic addition • palladium • ynamide

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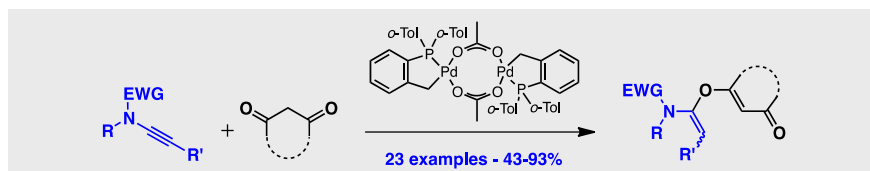
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## Entry for the Table of Contents (Please choose one layout)

Layout 2:

## COMMUNICATION



A new metal-catalyzed addition reaction of 1,3-diketones to ynamides providing an access to unprecedented alkoxy-substituted enamides is disclosed herein. After the optimization of the reaction conditions and the catalytic system, the scope investigation revealed a broad applicability to numerous ynamides and cyclic 1,3-diones.

*Lionel V. Graux, Hervé Clavier,\* Gérard Buono*

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