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Hervé Clavier,[a]* Aymeric Lepronier,[a] Nathalie Bengobesse-Mintsa,[a] David Gatineau,[a] Hélène Pellissier,[a] Laurent Giordano,[a] Alphonse Tenaglia,[a] and Gérard Buono[a]*

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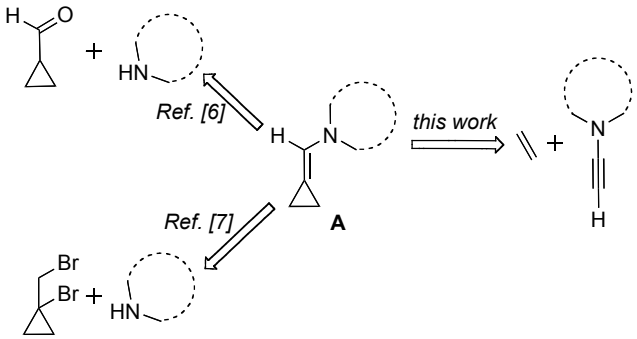
Abstract. An efficient palladium-catalyzed [2+1] cycloaddition between ynamides and norbornenes or norbornadienes is reported. Both phosphapalladacycles and palladium/secondary phosphine oxides catalytic systems were found competent at the transformation allowing the preparation of aminomethylenecyclopropanes. The reaction showed general applicability to various functionalized bicyclo[2.2.1]hept-2-enes and ynamides. A chiral phosphapalladacycle was tested to carry out this transformation in an enantioselective fashion.

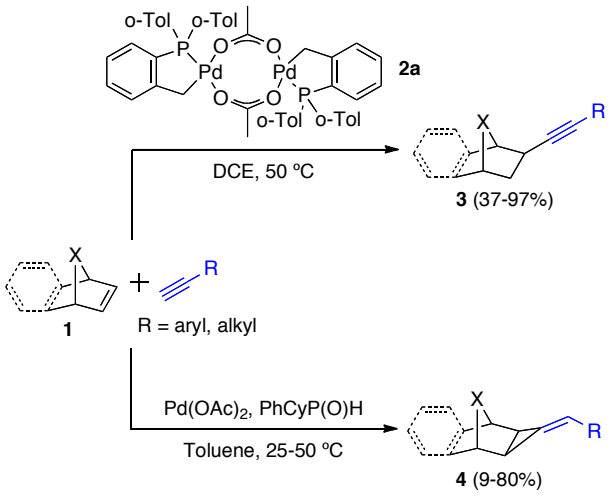
Keywords: Cycloaddition; Cyclopropane; Norbornene; Palladium; Phosphorus; Ynamide



Scheme 1. Main strategies for the preparation of aminomethylenecyclopropanes.

Methylenecyclopropanes (MCPs) are a unique class of carbocyclic compounds with strained three-membered ring and an *exo* methylene moiety.[1] In addition to be versatile synthons for a myriad of organic transformations,[2] they are found in natural products.[3] They have been also incorporated in biologically active substances such as nucleosides analogues established as powerful antiviral agents against a broad range of viruses.[4] In these drugs, the aminomethylenecyclopropane moiety **A** seems to play a crucial role. To date only few methods allow the preparation of such pattern.[5] As depicted in scheme 1, the aminomethylenecyclopropane synthesis has been achieved from the cyclopropanecarbaldehyde by aminal formation and subsequent rearrangement into **A** by heating.[6] For the synthesis of nucleosides analogues, Somekawa and Zemlicka independently reported the use of 1-bromo-1-(bromomethyl)cyclopropane for a *N*-alkylation, followed by an *in situ* β-elimination.[7,8] Herein, we report an alternative approach for the synthesis of aminomethylenecyclopropane **A** using a palladium-mediated [2+1] cycloaddition between an activated alkene and a partner ynamide.[9]

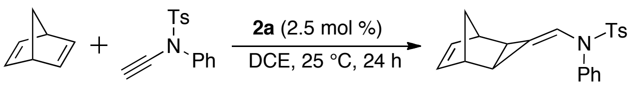
As a part of our research program dedicated to the transition-metal-promoted formations of carbocycles,[10] it was discovered that catalyst **2a** performed hydroalkynation of alkyl- and aryl-substituted alkynes to norbornadienes **1** to afford coupling products **3** (Scheme 2).[11] On the other hand, with the same reactants, the catalytic behavior of palladium(II) complexes prepared from secondary phosphine oxides (SPO)[12] was found different since MCP derivatives **4** were achieved.[13] These results prompted us to evaluate both palladium-based catalytic systems for the preparation of aminomethylenecyclopropane **A**.



Scheme 2. Palladium-mediated hydroalkynation *versus* [2+1] cycloaddition of norbornenes with alkynes.

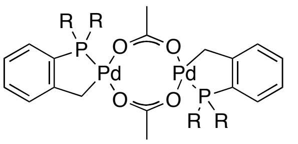
We started examining the benchmark substrates norbornadiene (nbd) **1a** and ynesulfonamide **5a** and found that the formation of aminomethylenecyclopropane **6a** could be achieved by using both catalytic systems (Table 1). Nonetheless, the combination of $Pd(OAc)_2$ (5 mol%) with SPOs was found less efficient and exclusively limited to the use of PhCyP(O)H as SPO (entries 4-6). The screening of several phosphapalladacycles **2** demonstrated that the use of **2c** as catalyst underwent the formation of by-product **7a** in 18% yield in addition to 48% of **6a**, while it was detected as traces by ^1H NMR from the crude reaction mixture using catalysts **2a** and **2b** (entries 1-3). The structure of compound **7a** was unambiguously determined by X-ray analysis (Figure 1). Its formation results from the valence isomerization process[13a,14] of **6a**, which seems favoured by electron-rich phosphapalladacycle **2c** triggering the splitting of the distal bond of the MCP subunit. Reaction time investigations showed that, at 25 °C, 24 h were required for consumption of ynamide **5a**; mass balance accounting for degradation (entries 11 and 12). However, a slight thermal activation to 40 and 60 °C led to a considerable decrease in reaction time (entries 13 and 14).

Table 1. Palladium-catalyzed [2+1] cycloaddition of norbornadiene **1a** with ynamide **5a**: Effect of Reaction Parameters.[a]



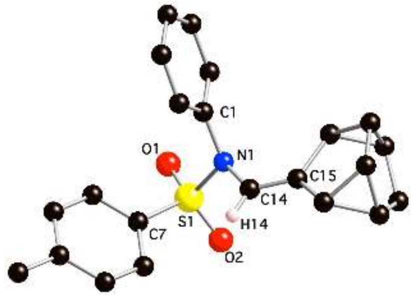
1a **5a** **6a**

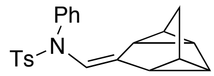
entry	change from "the standard conditions"	isolated yield (%)
1	**None**	**66**
2	Catalyst **2b** instead of **2a**	44
3	Catalyst **2c** instead of **2a**	48[b]
4	Catalyst $Pd(OAc)_2$/$[PhCyP(O)H]_2$ instead of **2a**	44
5	Catalyst $Pd(OAc)_2$/$[Ph\textit{t}BuP(O)H]_2$ instead of **2a**	-
6	Catalyst $Pd(OAc)_2$/$[PhMeP(O)H]_2$ instead of **2a**	-
7	Toluene instead of DCE	39
8	THF instead of DCE	66
9	Dioxane instead of DCE	39
10	DMF instead of DCE	36
11	8 h instead of 24 h	33
12	55 h instead of 24 h	50
13	**40 °C, 2 h instead of 25 °C, 24 h**	**62**
14	**60 °C, 1 h instead of 25 °C, 24 h**	**66**



2a, R = *o*-Tol
2b, R = Ph
2c, R = Cy

[a] *Reaction conditions*: ynamide **5a** (0.5 mmol), nbd **1a** (1 mmol), **2a** (2.5 mol% - 5 mol% [Pd]), DCE (3 mL, 0.17 M), 25 ºC.
[b] 18% of product **7a** were also isolated.



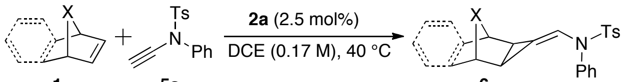


7a

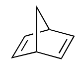
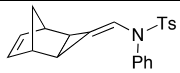
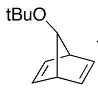
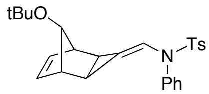
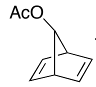
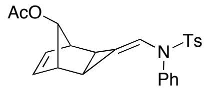
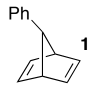
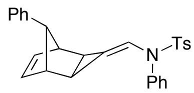
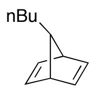
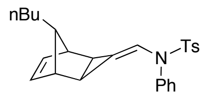
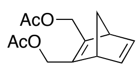
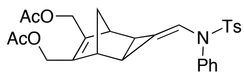
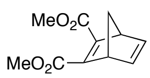
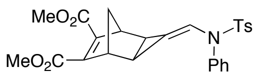
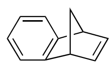
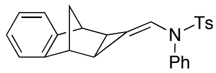
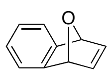
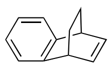
Figure 1. Ball-and-stick representation of by-product **7a** (most of the hydrogens have been omitted for clarity).

Having established the optimal reaction conditions, we further investigated the reaction scope with a range of bicyclo[2.2.1]hepta-2,5-diene derivatives (Table 2). 7- Oxygen substituted norbornadienes were tolerated but led to moderate yields or longer reaction times (entries 2 and 3) compared to electron-rich substituted equivalents (entries 4 and 5). Other bicyclic substrates were converted in the corresponding tricyclo[3.2.1.0^{2,4}]oct-6-enes **6**, except

Table 2. [2+1] cycloaddition with a variety of norbornadiene derivatives and ynamide **5a**[a]



1 **5a** **6**

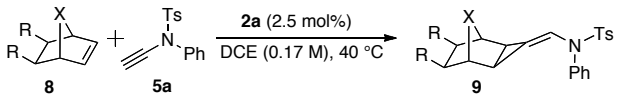
entry	substrate	time (h)	product	yield (%)
1	 **1a**	2	 **6a**	62
2	 **1b**	3	 **6b**	45
3	 **1c**	6	 **6c**	61
4	 **1d**	2	 **6d**	81
5	 **1e**	2	 **6e**	72
6	 **1f**	2		88
7		4		75
8	 **1h**	2	 **6h**	73
9	 **1i**	2	complex mixture	
10[b]	 **1j**	6		-

[a] *Reaction conditions*: ynamide **5a** (0.5 mmol), nbd **1** (1 mmol), **2a** (2.5 mol%), DCE (3 mL, 0.17 M), 40 ºC.
[b] Reaction carried out at 60 °C.

1,4-dihydro-1,4-epoxynaphthalene **1i** which gave rise to a complex mixture (entry 9). Despite extended heating at 60 °C, [2+1] cycloaddition on the less reactive 1,4-dihydro-1,4-ethano-naphthalene **1j** failed (entry 10).[15] In all the cases studied, reaction occurred on the less hindered double bond.

In the light of these results, we decided to examine the cycloaddition scope further by testing bicyclo[2.2.1]hept-2-ene derivatives **8** (Table 3). Although the reactivity was found lower, we were pleased to isolate the cycloadduct **9a** arising from the reaction of norbornene **8a** with a moderate yield (65%, entry 1). The treatment of substrates **8b** and **8c** with ynamide **5a** and phosphapalladacycle **2a** afforded the expected cycloadducts but with a low diastereoselectivity (entries 2 and 3). Whereas the diaza compound **8f** was well tolerated (entry 6), the reaction of maleic anhydride derivative **8d** and substituted oxanorbornene **8g** required heating to 60 °C to provide the corresponding products in low to moderate yields (entries 4 and 7). Under the same reaction conditions the electron-poor tetracyano compound **8e** was found inert (entry 5).

Table 3. [2+1] cycloaddition with a variety of norbornene derivatives **8** and ynamide **5a**[a]



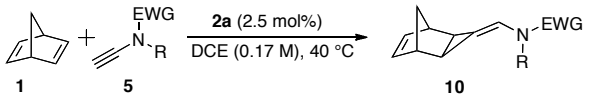
8 5a 9

entry	substrate	time (h)	product	yield (%)
1	**8a**	2	**9a**	65
2	**8b**	2	**9b**	71 (dr = 2:1)
3	**8c**	2	**9c**	77 (dr = 1.3:1)
4[b]	**8d**	5	**9d**	27
5[b]	**8e**	5		-
6	**8f**	4	**9f**	64
7[b]	**8g**	5	**9g**	26

[a] *Reaction conditions*: ynamide **5a** (0.5 mmol), norbornene **8** (0.6 mmol), **2a** (2.5 mol%), DCE (3 mL, 0.17 M), 40 ºC.
[b] Reaction carried out at 60 °C.

We then examined the transformation scope with respect to the ynamide partner (Table 4). In addition to the *N*-substituted phenyl ynamide **5a**, alkyl analogues **5b** and **5c** gave rise to the corresponding adducts with moderate yields (entries 1-2). On the other hand, allyl counterpart **5d** led to the formation of a complex mixture (entry 3). While ynesulfonamides were found to be relatively good partners for the [2+1] cycloaddition (entries 4 and 5), ynecarbamate, such as **5g,** gave the corresponding cycloadduct with a moderate yield (entry 6). The *para*-nosyl compound **10e**, isolated in good yield, was used to confirm the aminomethylenecyclopropane structure by single crystal X-ray determination (Figure 2). When the reaction was performed with the vinylogous indole-containing ynamide **5h**, the anticipated product was obtained, but as an inseparable mixture with an unidentified compound. Carrying out the reaction with the $Pd(OAc)_2$ / PhCyP(O)H system turned out to be cleaner since only **10h** was isolated in the satisfactory yield of 77% (entry 7).

Table 4. [2+1] cycloaddition with a variety of ynamides **5**[a]



1 5 10

entry	substrate	time (h)	product	yield (%)
1	**5b**	3	**10b**	55
2	**5c**	3	**10c**	45
3	**5d**	3	complex mixture	
4	**5e**	2	**10e**	74
5	**5f**	2	**10f**	45
6	**5g**	5	**10g**	26
7[b]	**5h**	1.5	**10h**	77
8	**5i**	5	**10i**	48

[a] *Reaction conditions*: ynamide **5** (0.5 mmol), norbornadiene **1** (1 mmol), **2a** (2.5 mol%), DCE (3 mL, 0.17 M), 40 ºC.
[b] reaction performed with 5 mol% of $Pd(OAc)_2$/$[PhCyP(O)H]_2$ instead of **2a**.
Ns = 4-nitrobenzenesulfonyl.

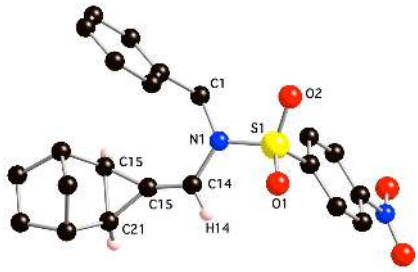
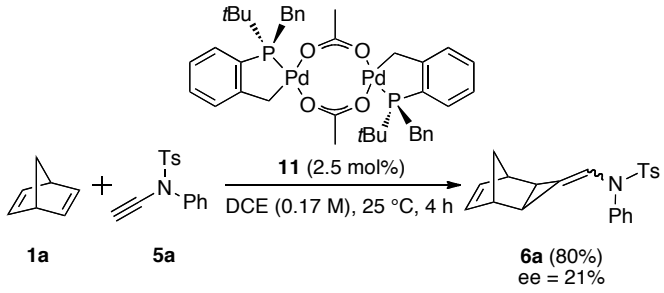


Figure 2. Ball-and-stick representation of the cycloadduct **10e** (hydrogen atoms have been omitted for clarity).

Due to the *E*/*Z* geometry of the carbon-carbon double bond in the methylenecyclopropane moiety, [2+1] cycloadducts showed a peculiar chirality called geometrical enantiomorphic isomerism (*cis-trans* enantiomerism or *Z-E* enantiomerism).[16,17] We previously demonstrated that the asymmetric [2+1] cycloaddition between alkyne and norbornene could be achieved using chiral secondary phosphine oxides as enantioselectivity inductors with enantiomeric excesses of up to 95% ee.[18] Since the synthesis of enantiopure phosphapalladacycle **11** has been recently reported,[19] we decided to test this catalyst in asymmetric [2+1] cycloaddition with ynamide **5a** (Scheme 3). Whereas the reaction proceeded smoothly at room temperature, 80% yield after 4 h, the chiral induction observed was modest but promising for further development considering that no optimization of catalyst design has been done.



Scheme 3. Asymmetric [2+1] cycloaddition using an optically active phosphapalladacycle.

In modern organic chemistry, there is always the need for new, efficient, and selective methodologies for the synthesis of complex molecules. Herein, we reported a new palladium-catalyzed intermolecular [2+1] cycloaddition of bicyclo[2.2.1]hept-2-ene derivatives with ynamides giving rise to aminomethylenecyclopropane **A**. We have shown that either phosphapalladacycles or the $Pd(OAc)_2$ / PhCyP(O)H combination are able to promote this transformation. Optimal catalytic conditions and key parameters have been identified. Thus, excellent yields have been reached, of up to 88%, for variously substituted ynamides and norbornenes. Preliminary results to perform this transformation in an enantioselective fashion are encouraging and further developments are underway in our laboratory as well as the study of mechanistic considerations.

Experimental Section

General procedure for the palladium-mediated [2+1] cycloaddition:

A Schlenk flask, under nitrogen, was charged with Herrmann-Beller catalyst (11.2 mg, 0.0125 mmol, 0.05 equiv in Pd.), and DCE (1 mL). Successively, were added norbornadiene derivative (1 mmol, 2 equiv.) or norbornene derivative (0.6 mmol, 1.2 equiv.), ynamide (0.5 mmol) and DCE (1 mL). The resulting mixture was stirred at the stipulated temperature for the indicated time. Volatiles were removed and the crude mixture was purified by column chromatography on silica gel using a Combiflash Companion (4 g SiO_2 45µm; PE/AcOEt 95:5 (5 min) – gradient).
The Supporting Information contains the experimental details, product characterization and NMR spectra. The CIF files of carbocycles **7a** and **10e** have also been deposited with the CCDC as, respectively, No. CCDC-870844 and CCDC-870845

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