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Palladium-Mediated [2+1] Cycloaddition of Norbornene Derivatives with Ynamides

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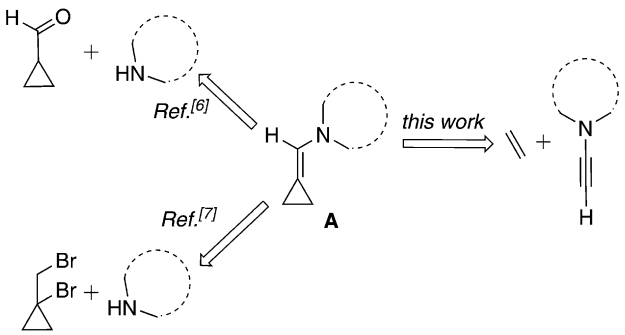
Abstract: An efficient palladium-catalyzed [2+1]cycloaddition between ynamides and norbornenes or norbornadienes is reported. Both phosphapalladacycles and palladium/secondary phosphine oxide catalytic systems were found to be competent for the transformation allowing the preparation of aminomethylenecyclopropanes. 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; cyclopropanes; norbornenes; palladium; phosphorus; ynamides

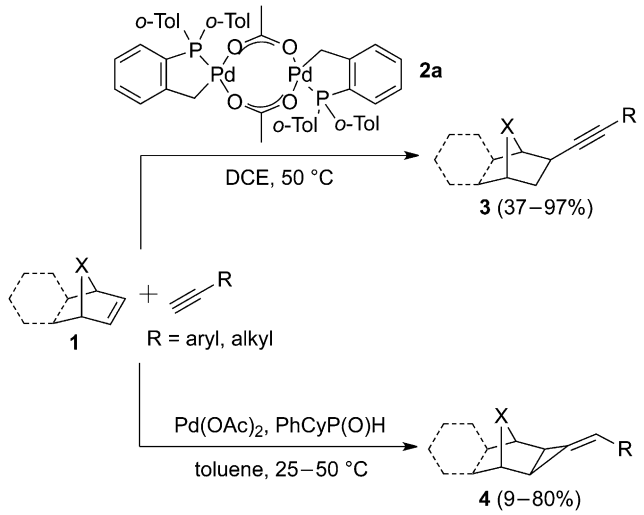


Scheme 1. Main strategies for the preparation of aminomethylenecyclopropanes.

Methylenecyclopropanes (MCPs) are a unique class of carbocyclic compounds with a strained three-membered ring and an *exo* methylene moiety.[1] In addition to being versatile synthons for a myriad of organic transformations,[2] they are found in natural products.[3] They have also been incorporated in biologically active substances such as nucleosides analogues that are 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 a pattern.[5] As depicted in Scheme 1, the synthesis of aminomethylenecyclopropanes has been achieved from the cyclopropanecarbaldehydes by aminal formation and subsequent rearrangement into **A** by heating.[6] For the synthesis of nucleoside analogues, Somekawa and Zemlicka independently reported the use of 1-bromo-1-(bromomethyl)cyclopropane for an *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 an ynamide partner.[9]

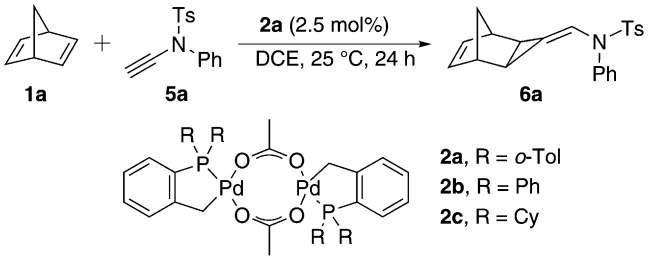
As a part of our research program dedicated to the transition metal-promoted formations of carbocycles,[10] it was discovered that catalyst **2a** promoted the hydroalkynation of alkyl- and aryl-substituted alkynes to norbornadienes **1** to afford coupling products **3** (Scheme 2).[11] On the other hand, with the same reactants, the catalytic behaviour of palladium(II) complexes prepared from secondary phosphine oxides (SPO)[12] was found to be 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**.

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 to be less efficient and exclusively limited to the use of PhCyP(O)H as SPO (entries 4–6). The screening of



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

Table 1. Palladium-catalyzed [2+1]cycloaddition of norbornadiene **1a** with ynamide **5a**: effect of reaction parameters.[a]



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 $Pd(OAc)_2$/$[PhtBuP(O)H]_2$ 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**

[a] *Reaction conditions*: ynamide **5a** (0.5 mmol), nbd **1a** (1 mmol), **2a** (2.5–5 mol% [Pd]), DCE (3 mL, 0.17 M), 25 °C.

[b] 18% of product **7a** were also isolated.

several phosphapalladacycles **2** demonstrated that the use of **2c** as catalyst proceeded with the formation of by-product **7a** in 18% yield in addition to 48% of **6a**,

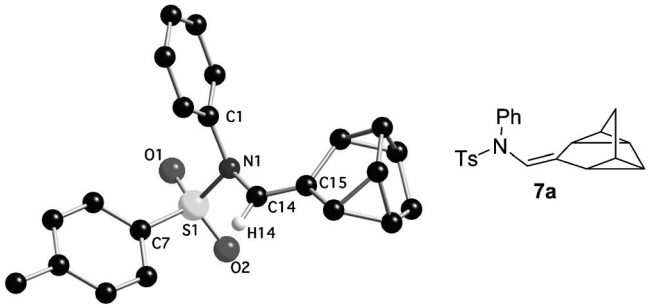


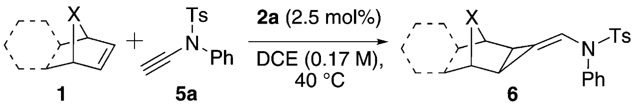
Figure 1. Ball-and-stick representation of by-product **7a** (most of the hydrogens have been omitted for clarity).

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 to be 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**; the 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).

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 for 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-ethanonaphthalene **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 scope of the cycloaddition further by testing bicyclo[2.2.1]hept-2-ene derivatives **8** (Table 3). Although the reactivity was found to be lower, we were pleased to isolate the cycloadduct **9a** arising from the reaction of norbornene **8a** in 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 cor-

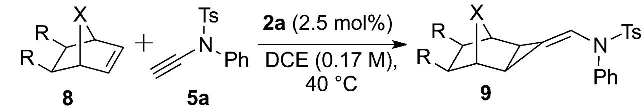
Table 2. [2+1] Cycloaddition with a variety of norbornadiene derivatives and ynamide **5a**.[a]



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 °C.
[b] Reaction carried out at 60 °C.

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



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 °C.
[b] Reaction carried out at 60 °C.

responding products in low to moderate yields (entries 4 and 7). Under the same reaction conditions the electron-poor tetracyano compound **8e** was found to be inert (entry 5).

We then examined the transformation scope with respect to the ynamide partner (Table 4). In addition to the *N*-substituted phenylynamide **5a**, the alkyl analogues **5b** and **5c** gave rise to the corresponding adducts with moderate yields (entries 1 and 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), an 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

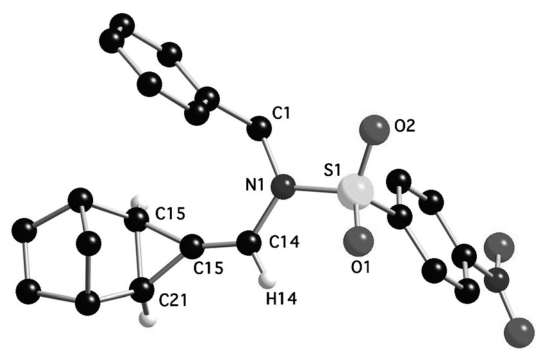
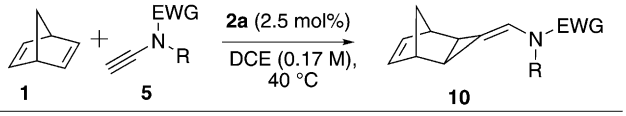
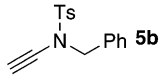
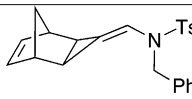
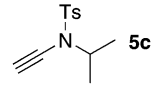
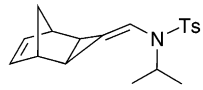
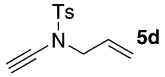
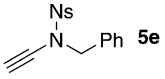
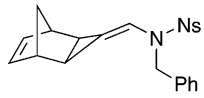
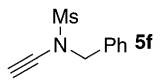
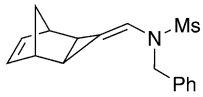
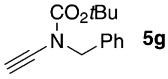
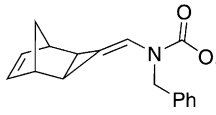
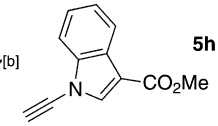
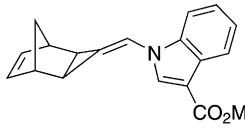
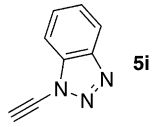
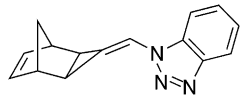


Figure 2. Ball-and-stick representation of the cycloadduct **10e** (hydrogen atoms have been omitted for clarity).

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



1 5 10

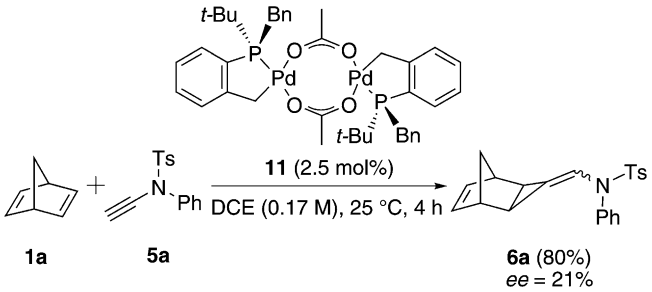
Entry	Substrate	Time [h]	Product	Yield [%]
1	 **5b**	3	 **10b**	55
2	 **5c**	3	 **10c**	45
3	 **5d**	3	complex mixture	
4	 **5e**	2	 **10e**	74
5	 **5f**	2	 **10f**	45
6	 **5g**	5	 **10g**	26
7[b]	 **5h**	1.5	 **10h**	77
8	 **5i**	5	 **10i**	48

[a] *Reaction conditions*: ynamide **5** (0.5 mmol), norbornadiene **1** (1 mmol), **2a** (2.5 mol%), DCE (3 mL, 0.17 M), 40 °C. Ns = 4-nitrobenzenesulfonyl.

[b] Reaction performed with 5 mol% of $Pd(OAc)_2$/$[PhCyP(O)H]_2$ instead of **2a**.

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).

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 had 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 an asymmetric [2+1] cycloaddition with ynamide **5a**



1a 5a **6a** (80%) *ee* = 21%

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

(Scheme 3). Whereas the reaction proceeded smoothly at room temperature, giving 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.

In modern organic chemistry, there is always the need for new, efficient, and selective methodologies for the synthesis of complex molecules. Herein, we have 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 also is 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 45 μm; 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 as CCDC 870844 and CCDC 870845. These data can be ob-

tained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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