Regio- and Diastereoselective Platinum-Catalyzed Tandem [2C+1C]/[3C+2C] Cycloadditions Sequence

Thierry Achard, Aymeric Lepronier, Yves Gimbert, Hervé Clavier,* Laurent Giordano,* Alphonse Tenaglia* and Gérard Buono*

In the context of sustainable chemistry, tandem reactions, so-called domino or cascade processes, have emerged as powerful strategies to assemble non-trivial carbon skeletons, in particular for the synthesis natural products.^[1] Interestingly, this implies generally C-C bond formations and atom-economy. Whereas tandem processes involving one cycloaddition step are quite widespread,^[2] those engaging two or more cycloaddition reactions are less common in the literature, especially with transition-metals.^[3,4]

Since few years, our group have been involved in the synthesis of secondary phosphine oxides (SPO) and their applications in coordination chemistry as preligand through P(III) form: phosphinous acids (PA).^[5,6] Thus, various complexes of palladium or platinum, such as those depicted in Figure 1, have been synthesized^[7] and used in several catalytic reactions.^[8] PA ligands were found to confer a particular activity to the metal and new catalytic transformations were developed. As an example, we reported platinum-mediated [2C+1C] cycloaddition between phenylethyne **1a** and norbornene derivatives (Scheme 1).^[9] During the scope examination, we observed that reaction carried out with alkyne **1b** in place of **1a** led to the formation of an unexpected tricyclic product **4b**.

This result prompted us to examine further this reaction in order to gain insight into the scope and the mechanism. Herein we report an unprecedented intermolecular tandem [2C+1C]/[3C+2C] cycloadditions of norbornadiene with alkynes.

Figure 1. PA-platinum complexes used in this work

Scheme 1. Chemoselectivity difference in platinum-mediated cycloaddition as a function of the alkyne

We started surveying an array of reaction parameters using norbornadiene and propargyl acetate **1c** as benchmark substrates (Table 1). We determined that well-defined platinum-based catalyst **Cat-1**, in presence of acetic acid in toluene at 55 °C after 20 h, promoted efficiently the formation of desired tricyclic compound **4c** (62 % yield, entry 1) along with 10 % of methylenecyclopropane (MCP) **2c**. Increasing the reaction time to 72 h allowed improvement of **4c** yield and disappearance of **2c** (entry 2). This suggests that **2c** is an intermediate for the formation of **4c**. Changing substituents of SPO pre-ligands or using the *in situ* generated

Table 1. Optimization of reaction parameters for platinum-mediated tandem [2+1]/[3C+2C] cycloadditions.^[a]

Entry	Change from "the standard conditions"	Isolated yield (%)	
		2c	4c
1	None	10	62
2	72 h instead of 20 h	-	71
3	Cat-2 instead of Cat-1	4	6
4	Cat-3 instead of Cat-1	8	10
5	Cat-4, AgOAc and Et ₃ N instead of Cat-1 ^[b]	-	30
6	40 °C instead of 55 °C	8	49
7	80 °C instead of 55 °C	-	55
8	THF instead of Toluene	7	4
9	DCE instead of Toluene	11	35
10	No AcOH	5	20

[a] Reaction conditions: Norbornadiene (0.5 mmol), **1c** (1 mmol), Catalyst (5 mol %), AcOH (1 mmol), Toluene (10 mL, 0.05 M), 55 °C, 20 h. [b] AgOAc (10 mol %), Et₃N (10 mol %).

[*] Dr. T. Achard, A. Lepronier, Dr. H. Clavier, Dr. L. Giordano, Dr. A. Tenaglia, Prof. Dr. G. Buono
Equipe Chirosciences - UMR CNRS 6263 – ISM2
Université Aix-Marseille III – Ecole Centrale de Marseille
Av. Escadrille Normandie Niemen, 13397 Marseille Cedex 20, France
Fax: (+33) (0)491 282 742
E-mail: herve.clavier@univ-cezanne.fr;
laurent.giordano@ec-marseille.fr; alphonse.tenaglia@univ-cezanne.fr; gerard.buono@ec-marseille.fr
Homepage: <http://cab.ism2.univ-cezanne.fr>

Dr. Y. Gimbert
Département de Chimie Moléculaire - UMR CNRS 5250 – ICMG FR-2607
Université Joseph Fourier de Grenoble
BP 53, 38041 Grenoble Cedex 9, France

[**] We are grateful to the CNRS and the ANR (program BLAN07-1_190839) for fundings. A.L. acknowledges the Ministère de la Recherche et de la Technologie for a Ph.D. grant. We thank Dr. Michel Giorgi for his kind assistance with X-ray analyses

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catalyst led to reduce dramatically yields of **4c** (entries 3-5). Carrying out experiments at 40 °C slowed down the reaction; whereas at 80 °C some degradation occurred (entries 6 and 7). Neither THF nor dichloroethane were found as competent as toluene. Furthermore, it was observed that acetic acid was a key parameter of the reaction. Of note, during the optimization step **4c** was isolated as a single regio- and stereoisomer, which was confirmed by 2D NMR spectroscopy experiments.

Then the scope of this catalytic transformation was examined with respect to the alkyne partner (Table 2). Aryl- or alkyl-substituted alkyne such as phenylethyne **1a** or 1-hexyne **1d**, led only to [2C+1C] adducts (entries 1 and 2). Dicyclopropanation adducts **3** have even been isolated: 52 % of **3a** and small amounts with **3d**.^[10] On the other hand, with ester-containing alkynes **1c**, **1e** and **1f** the tandem [2C+1C]/[3C+2C] cycloadditions took place almost exclusively to provide of tricyclic compounds **4** in fair to good yields (entries 4-6). Propargylic ethers **1b** and **1g-1j**, were found to be equally good candidates for the tandem process since up to 90 % of **4** was isolated (entries 3 and 7-10). Single crystal X-ray analysis of **4i**, unambiguous confirmed its structure as a single regio- and stereoisomer with a *trans* stereochemistry within the fused 5-membered ring (Figure 2). Alkyne **1k** bearing a carbonate group was found also competent for the tandem cycloadditions (entry 11). In the case of trimethylsilyl ether **1i**, the yield of the reaction dropped dramatically down to 21 %, due to some degradation occurring during the purification step (entry 12). Propargylic thioether **1m** was moderately tolerated giving adduct **2m** (26%) and trace amount of **4m** (entry 13). *The oxygen-atom in homopropargylic position appeared to be crucial in the tandem cycloaddition process.* Importantly, all cycloadducts **4** were isolated as single regio- and diastereomers.

Table 2. Scope investigation of tandem [2C+1C]/[3C+2C] cycloaddition sequence.^[a]

Entry	Alkyne	R =	Isolated yield (%)	
			2	4
1	1a	Ph	2a (17)	-
2	1d	<i>n</i> -Bu	2d (46)	-
3	1b	CH ₂ OBn	-	4b (65)
4	1c	CH ₂ OAc	2c (10)	4c (62)
5	1e	CH ₂ OBz	-	4e (44)
6	1f	CH ₂ OPiv	-	4f (44)
7	1g	CH ₂ O(2-Me-C ₆ H ₄)	-	4g (74)
8	1h	CH ₂ O(4-OMe-C ₆ H ₄)	-	4h (43)
9	1i	CH ₂ O(3-NO ₂ -C ₆ H ₄)	-	4i (50)
10	1j	CH ₂ O(2,4-(NO ₂) ₂ -C ₆ H ₃)	-	4j (90)
11	1k	CH ₂ OCO ₂ Bn	-	4k (52)
12	1l	CH ₂ OTMS	-	4l (21)
13	1m	CH ₂ S(2-Me-C ₆ H ₄)	2m (26)	Traces

[a] Reaction conditions: Norbornadiene (0.5 mmol), **1** (1 mmol), **Cat-1** (5 mol %), AcOH (1 mmol), Toluene (10 mL, 0.05 M), 55 °C, 20 h.

Since the MCP **2** was supposed to be the intermediate for the [3C+2C] cycloaddition, MCP **2c**^[11] and propargyl acetate **1c** in presence of **Cat-1** under usual reaction conditions led to tricycle **4c** as a single stereoisomer with a moderate yield (Scheme 2). Of note, mass balance accounted for unreacted MCP **2c**.

Figure 2. Ball-and-stick representation of tricyclic product **4i**

Scheme 2. Synthesis of tricyclic product **4c** with MCP **2c** as intermediate

Having established that MCP **2c**^[11] was the intermediate involved in the [3C+2C] cycloaddition, other alkyne partners in this transformation were examined (Scheme 3). In a first time, 1-hexyne **1d** has been picked because it did not contain any oxygen atom. We were pleased to isolate the desired product **5d** with a good yield. On the other hand, an unexpected by-product identified as compound **6d** was isolated in a significant yield (25 %). This unusual reactivity of alkylidenecyclopropane^[12] may be related to the palladium-mediated tandem [2C+1C] cycloaddition/ring expansion reported with tertiary propargylic acetates.^[8b] When we evaluated benzyldienecyclopropane **2a** for [3C+2C] cycloaddition with propargyl acetate, the MCP moiety was left unchanged. However, the tandem [2C+1C]/[3C+2C] cycloaddition process took place on the norbornene C-C double bond to form **7** as a 1:1 mixture of diastereomers. This attempt clearly showed that an allylic oxygen substituent plays a major role in the [3C+2C] cycloaddition.

Scheme 3. Cross experiments using MCPs as intermediates

[3C+2C] Examples that illustrate the scope of this new platinum-mediated cycloaddition are provided in Table 3. Among the various alkynes tested only phenylethyne **1a** led to a complex mixture of products (entry 1). Trimethylsilylethyne **1n** or trimethyl silyl ether **1i** were well tolerated, nevertheless some degradation of adducts **5l** and **5n** occurred upon purification over silica gel (entries 3 and 4). Therefore, unprotected propargyl alcohol **1o** was found

quite compatible providing **5o** in moderate yield and a small amount of by-product **6o** (entry 5). Propargyl aryl ether **1g** gave compound **5g** with a good isolated yield (entry 6). In spite of substantial amounts of by-products **6**, the platinum-based catalytic system was found tolerant to other heteroatom groups such as sulfonamide, phthalamide or sulfone (entries 7-9).

Table 3. Scope examination for [3C+2C] cycloaddition.^[a]

Entry	Alkyne	R =	Isolated yield (%)
			5 6
1	1a	Ph	Complex mixture of products
2	1d	<i>n</i> -Bu	5d (70) 6d (25)
3	1n	TMS	5n (61) ^[b] (< 5)
4	1l	CH ₂ OTMS	5l (67) ^[b] (< 5)
5	1o	CH ₂ OH	5o (39) 6o (7)
6	1g	CH ₂ O(2-Me-C ₆ H ₄)	5g (65) (< 5)
7	1p	CH ₂ NHTs	5p (38) 6p (10)
8	1q	CH ₂ Pht	5q (61) 6q (12)
9	1r	CH ₂ SO ₂ Ph	5r (63) 6r (26)

[a] Reaction conditions: Methylenecyclopropane **2c** (0.5 mmol), **1** (1 mmol), **Cat-1** (5 mol %), AcOH (1 mmol), Toluene (10 mL, 0.05 M), 55 °C, 20 h. [b] NMR conversion. Pht = Phthalamide

Of note, for all compounds **5** a single stereo- and regioisomer was observed by NMR spectroscopies of crude reaction mixtures. X-ray analysis of sulfone-containing adduct **5r** confirmed both atoms connectivity and stereochemistry (Figure 3).

Figure 3. Ball-and-stick representation of tricyclic product **5r**

Although the mechanism of this unusual [3C+2C] cycloaddition remains unclear at that time, we believe the cationic platinum species **A** coordinates the exocyclic C-C double bond on the *exo* face of MCP **2** triggering an oxidative coupling with the alkyne to form the platinumacyclopentene intermediate **C** (Scheme 4).^[13] Importantly, the regioselectivity accommodates steric interactions between substituents. At this stage, the oxygen atom could play a directing effect in assisting the cyclopropane fragmentation and therefore the 1,2 shift of the platinum (intermediate **D**, only one enantiomer depicted) giving rising to the platinumacyclohexene **E**.

Finally, a reductive elimination gives product **5** and regenerates active species **A**. This proposed mechanism takes into account the structural features of the cycloadducts and stereochemical issues.

Scheme 4. Postulated mechanism for [3C+2C] cycloaddition

Scheme 5. Proposed mechanism for the formation of by-products **6**

The formation of by-products **6** occurred only with allylic acetate **2c**. We assumed the formation of the platinum π -allyl species **F** through the release of the acetoxy group (Scheme 5). At this point, cyclopropane ring opening generates the symmetrical vinyl- π -allylplatinum species **G**, with the platinum center located on the *exo* face in order to minimize steric hindrance.^[14] A ligand exchange with the alkyne releases acetic acid and forms the dialkylplatinum species **H**. To end, a reductive elimination releases by-product **6** and restores active species **A**.

In summary, we have reported that secondary phosphine oxide-based platinum complexes catalyzed an unprecedented intermolecular [2C+1C]/[3C+2C] cycloadditions sequence of norbornadiene with several alkynes. The tandem [2C+1C]/[3C+2C] process was found to be restrained to alkyne bearing an oxygen substituent on the propargylic carbon, however in view of the pervasiveness of oxygen-containing functional groups in organic

molecules, reaction scope spanned various functionalities. We have also demonstrated that methylenecyclopropanes **2** are the intermediates for the [3C+2C] cycloaddition and we explored this transformation with various alkynes. To the best of our knowledge, most of the cycloadditions involving MCPs and alkynes are reported for intramolecular processes.^[15] The present work describes a rare example of such cycloadditions in an intermolecular fashion. The regio- and stereoselectivities suggest a specific mechanism and let us thinking that a promising enantioselective variant could be achieved using chiral SPO preligands.

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: Cycloaddition · Methylenecyclopropane · Platinum · Secondary Phosphine Oxide · Tandem reactions

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Layout 1:

Tandem Cycloadditions

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Regio- and diastereoselective Platinum-Catalyzed Tandem [2C+1C]/[3C+2C] Cycloadditions Sequence

Platinum-complexes bearing phosphinous acids (PA) were found efficient to promote a tandem intermolecular sequence of [2C+1C]/[3C+2C] cycloadditions giving access to novel tricyclic systems. These cascade reactions were found totally regio- and diastereoselective. The [3C+2C] cycloaddition has been further investigated and two different alkyne partners have been used.

Catch Phrase: A Tandem for Tricycles

Table 1. Optimization of reaction parameters for platinum-mediated tandem [2+1]/[3C+2C] cycloadditions.^[a]

Table 2. Scope investigation of tandem [2C+1C]/[3C+2C] cycloaddition sequence.^[a]

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7	80 °C instead of 55 °C	-	55
8	THF instead of toluene	7	4
9	DCE instead of toluene	11	35
10	No AcOH	5	20

[a] Reaction conditions: Norbornadiene (0.5 mmol), **1c** (1 mmol), Catalyst (5 mol %), AcOH (1 mmol), toluene (10 mL, 0.05 M), 55 °C, 20 h. [b] AgOAc (10 mol %), Et₃N (10 mol %).

Entry	Alkyne	R =	Isolated yield (%)	
			2	4
1	1a	Ph	2a (17)	-
2	1d	<i>n</i> -Bu	2d (46)	-
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7	1g	CH ₂ O(2-Me-C ₆ H ₄)	-	4g (74)
8	1h	CH ₂ O(4-OMe-C ₆ H ₄)	-	4h (43)
9	1i	CH ₂ O(3-NO ₂ -C ₆ H ₄)	-	4i (50)
10	1j	CH ₂ O(2,4-(NO ₂) ₂ -C ₆ H ₄)	-	4j (90)
11	1k	CH ₂ OCO ₂ Bn	-	4k (52)
12	1l	CH ₂ OTMS	-	4l (21)
13	1m	CH ₂ S(2-Me-C ₆ H ₄)	2m (26)	Traces

[a] Reaction conditions: Norbornadiene (0.5 mmol), **1** (1 mmol), **Cat-1** (5 mol %), AcOH (1 mmol), toluene (10 mL, 0.05 M), 55 °C, 20 h.

Table 3. Scope examination for [3C+2C] cycloaddition.^[a]

Entry	Alkyne	R =	Isolated yied (%)	
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4	1l	CH ₂ OTMS	5l (67) ^[b]	(< 5)
5	1o	CH ₂ OH	5o (39)	6o (7)
6	1g	CH ₂ O(2-Me-C ₆ H ₄)	5g (65)	(< 5)
7	1p	CH ₂ NHTs	5p (38)	6p (10)
8	1q	CH ₂ Pht	5q (61)	6q (12)
9	1r	CH ₂ SO ₂ Ph	5r (63)	6r (26)

[a] Reaction conditions: Methylenecyclopropane **2c** (0.5 mmol), **1** (1 mmol), **Cat-1** (5 mol %), AcOH (1 mmol), toluene (10 mL, 0.05 M), 55 °C, 20 h. [b] NMR conversion. Pht = Phtalimide.