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# 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.<sup>[1]</sup> Interestingly, this implies generally C-C bond formations and atom-economy. Whereas tandem processes involving one cycloaddition step are quite widespread,<sup>[2]</sup> those engaging two or more cycloaddition reactions are less common in the literature, especially with transition-metals.<sup>[3,4]</sup>

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).<sup>[5,6]</sup> Thus, various complexes of palladium or platinum, such as those depicted in Figure 1, have been synthesized<sup>[7]</sup> and used in several catalytic reactions.<sup>[8]</sup> 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).<sup>[9]</sup> 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.

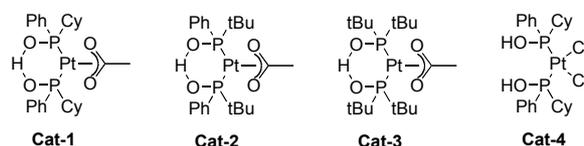
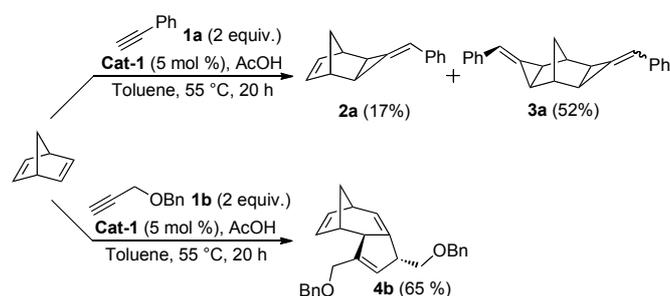


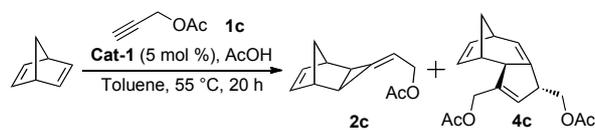
Figure 1. PA-platinum complexes used in this work



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.<sup>[a]</sup>



Entry	Change from "the standard conditions"	Isolated yield (%)	
		<b>2c</b>	<b>4c</b>
1	None	10	62
2	72 h instead of 20 h	-	71
3	<b>Cat-2</b> instead of <b>Cat-1</b>	4	6
4	<b>Cat-3</b> instead of <b>Cat-1</b>	8	10
5	<b>Cat-4</b> , AgOAc and Et <sub>3</sub> N instead of <b>Cat-1</b> <sup>[b]</sup>	-	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 %), Et<sub>3</sub>N (10 mol %).

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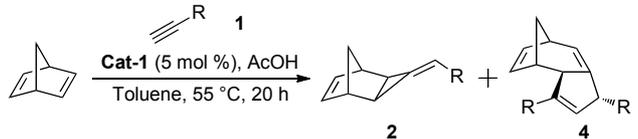
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catalyst led to reduce dramatically yields of **4c** (entries 3-5). Carrying out experiments at 40 °C slowed down the reaction; whereas at 80 °C some degradation occurred (entries 6 and 7). Neither THF nor dichloroethane were found as competent as 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**.<sup>[10]</sup> 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 **1l**, 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.

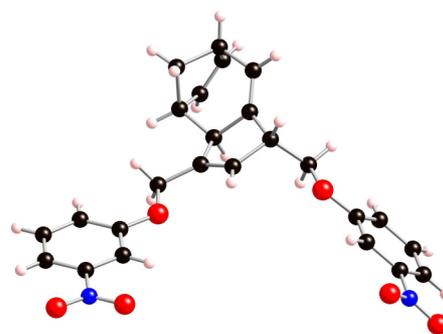
**Table 2.** Scope investigation of tandem [2C+1C]/[3C+2C] cycloaddition sequence.<sup>[a]</sup>



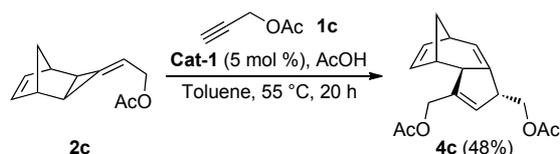
Entry	Alkyne	R =	Isolated yield (%)	
			<b>2</b>	<b>4</b>
1	<b>1a</b>	Ph	<b>2a</b> (17)	-
2	<b>1d</b>	<i>n</i> -Bu	<b>2d</b> (46)	-
3	<b>1b</b>	CH <sub>2</sub> OBn	-	<b>4b</b> (65)
4	<b>1c</b>	CH <sub>2</sub> OAc	<b>2c</b> (10)	<b>4c</b> (62)
5	<b>1e</b>	CH <sub>2</sub> OBz	-	<b>4e</b> (44)
6	<b>1f</b>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

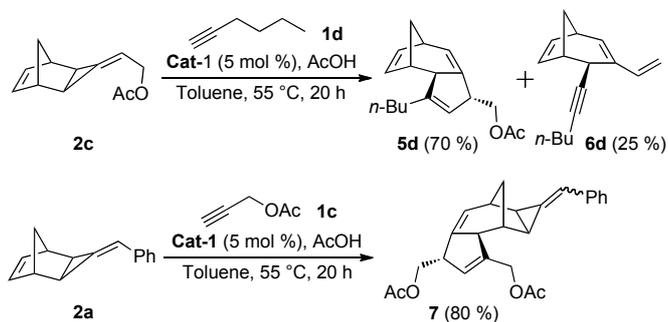


**Figure 2.** Ball-and-stick representation of tricyclic product **4i**



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

Having established that MCP **2c**<sup>[11]</sup> 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<sup>[12]</sup> may be related to the palladium-mediated tandem [2C+1C] cycloaddition/ring expansion reported with tertiary propargylic acetates.<sup>[8b]</sup> When we evaluated benzylidenecyclopropane **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.

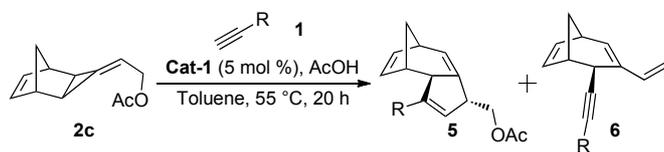


**Scheme 3.** Cross experiments using MCPs as intermediates

[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 trimethylsilyl ether **1l** 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).

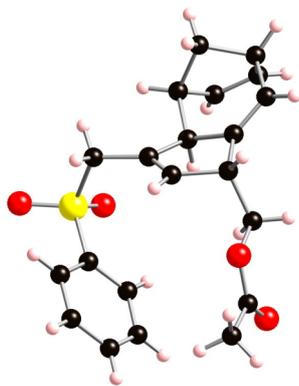
**Table 3.** Scope examination for [3C+2C] cycloaddition.<sup>[a]</sup>



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

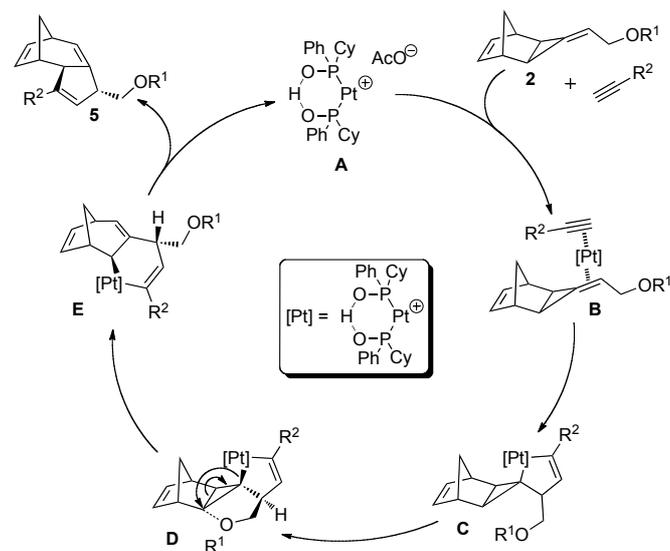
Of note, for all compounds **5** a single stereo- and regioisomer was observed by NMR spectroscopies of crude reaction mixtures. X-ray analysis of sulfone-containing adduct **5r** confirmed both atoms connectivity and stereochemistry (Figure 3).



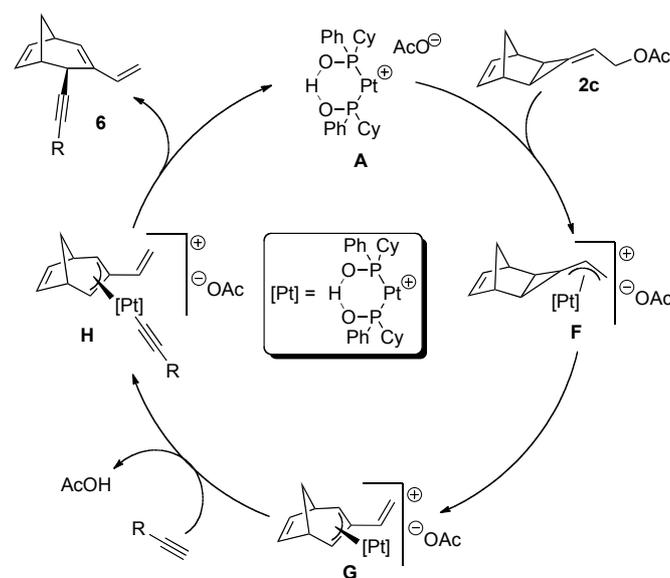
**Figure 3.** Ball-and-stick representation of tricyclic product **5r**

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).<sup>[13]</sup> 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  $\pi$ -allyl species **F** through the release of the acetoxy group (Scheme 5). At this point, cyclopropane ring opening generates the symmetrical vinyl- $\pi$ -allylplatinum species **G**, with the platinum center located on the *exo* face in order to minimize steric hindrance.<sup>[14]</sup> 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

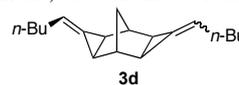
molecules, reaction scope spanned various functionalities. We have also demonstrated that methylenecyclopropanes **2** are the intermediates for the [3C+2C] cycloaddition and we explored this transformation with various alkynes. To the best of our knowledge, most of the cycloadditions involving MCPs and alkynes are reported for intramolecular processes.<sup>[15]</sup> 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.

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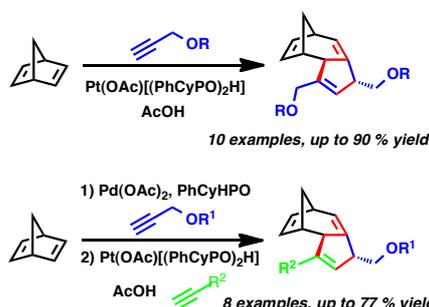
## Entry for the Table of Contents (Please choose one layout)

Layout 1:

### Tandem Cycloadditions

T. Achard, A. Lepronier, Y. Gimbert, H. Clavier,\* L. Giordano,\* A. Tenaglia,\* G. Buono\* \_\_\_\_\_ Page – Page

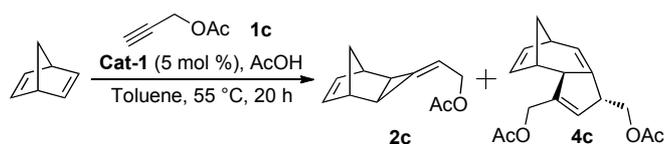
Regio- and diastereoselective Platinum-Catalyzed Tandem [2C+1C]/[3C+2C] Cycloadditions Sequence



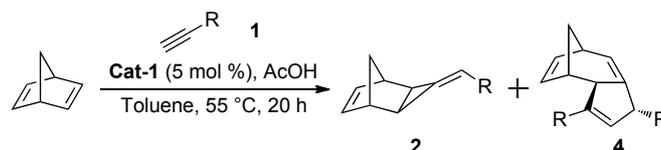
Platinum-complexes bearing phosphinous acids (PA) were found efficient to promote a tandem intermolecular sequence of [2C+1C]/[3C+2C] cycloadditions giving access to novel tricyclic systems. These cascade reactions were found totally regio- and diastereoselective. The [3C+2C] cycloaddition has been further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



**Table 2.** Scope investigation of tandem [2C+1C]/[3C+2C] cycloaddition sequence.<sup>[a]</sup>



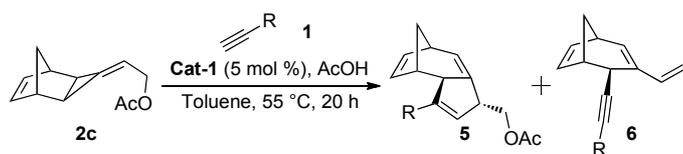
Entry	Change from "the standard conditions"	Isolated yied (%)	
		2c	4c
1	None	10	62
2	72 h instead of 20 h	-	71
3	<b>Cat-2</b> instead of <b>Cat-1</b>	4	6
4	<b>Cat-3</b> instead of <b>Cat-1</b>	8	10
5	<b>Cat-4</b> , AgOAc, Et <sub>3</sub> N instead of <b>Cat-1</b> <sup>[b]</sup>	-	30
6	40 °C instead 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 %), Et<sub>3</sub>N (10 mol %).

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



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

[a] Reaction conditions: Methylene cyclopropane **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.