

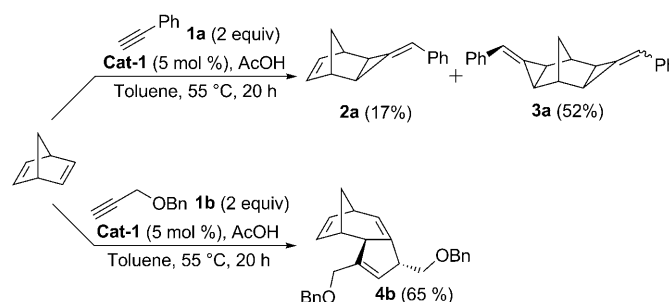
A Regio- and Diastereoselective Platinum-Catalyzed Tandem [2+1]/[3+2] Cycloaddition Sequence**

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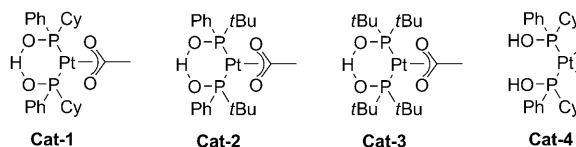
In the context of sustainable chemistry, tandem reactions, so-called domino or cascade processes, have emerged as powerful strategies to assemble nontrivial carbon skeletons, in particular for the synthesis of natural products.^[1] Interestingly, the implementation of this strategy implies general C–C bond formation and atom economy. Tandem processes involving one cycloaddition step are quite common,^[2] however, those engaging two or more cycloaddition reactions are rare, especially when transition metals are involved.^[3,4]

Over the last few years, our research group has been involved in the synthesis of secondary phosphine oxides (SPO) and their applications in coordination chemistry as a preligand in the P^{III} form, namely phosphinous acids (PA).^[5,6] Thus, various complexes of palladium or platinum, such as those depicted in Scheme 1, have been synthesized^[7] and used in several catalytic reactions.^[8] Phosphinous acid ligands were found to confer a particular activity to the metal and new catalytic transformations were developed. As an example, we

reported a platinum-mediated [2+1] cycloaddition between phenylethyne **1a** and norbornene derivatives (Scheme 2).^[9] During the examination of the reaction scope, we observed that reactions carried out with alkyne **1b** in place of **1a** led to the formation of an unexpected tricyclic product **4b**.



Scheme 2. Chemoselectivity difference in platinum-mediated cycloaddition as a function of the alkyne. Bn = benzyl.



Scheme 1. Phosphinous acid–platinum complexes used in this study. Cy = cyclohexyl.

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

We started with a survey of various reaction parameters using norbornadiene and propargyl acetate **1c** as benchmark substrates (Table 1). We determined that well-defined platinum-based catalyst **Cat-1**, in the presence of acetic acid in toluene at 55 °C after 20 hours, efficiently promoted formation of the desired tricyclic compound **4c** (62 % yield; Table 1, entry 1) along with 10 % of methylenecyclopropane (MCP) **2c**. Increasing the reaction time to 72 hours allowed improvement in the yield of **4c** and disappearance of **2c** (Table 1, entry 2). This result suggests that **2c** is an intermediate for the formation of **4c**. Changing the substituents on the SPO preligands or using the catalyst that was generated in situ led to dramatically lower yields of **4c** (Table 1, entries 3–5). Carrying out experiments at 40 °C slowed down the reaction, whereas at 80 °C some degradation occurred (Table 1, entries 6 and 7). Neither tetrahydrofuran (THF) nor 1,2-dichloroethane (DCE) solvents were as effective as toluene (Table 1, entries 8 and 9). Furthermore, it was observed that acetic acid was a key component of the reaction (Table 1, entry 10). Notably, during the optimization step **4c** was isolated as a single regio- and stereoisomer. This outcome was confirmed by 2D NMR spectroscopy experiments.

Next, the scope of this catalytic transformation was examined with respect to the alkyne partner (Table 2).

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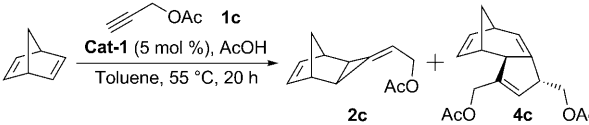
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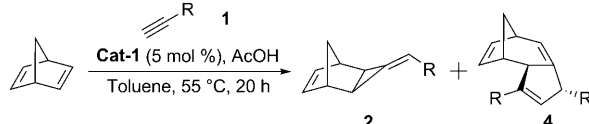
Table 1: Optimization of reaction parameters for the platinum-mediated tandem [2+1]/[3+2] cycloaddition sequence.^[a]



Entry	Change from the "standard reaction conditions"	Yield [%] ^[b]	
		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, Et ₃ N instead of Cat-1 ^[c]	—	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] Yield of isolated product. [c] AgOAc (10 mol %), Et₃N (10 mol %).

Table 2: Investigation of the scope for the tandem [2+1]/[3+2] cycloaddition sequence.^[a]



Entry	Alkyne	R	Yield [%] ^[b]	
			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-MeC ₆ H ₄)	—	4g , 74
8	1h	CH ₂ O(4-OMeC 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-MeC 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. [b] Yield of isolated product. Bz = benzoyl, Piv = pivaloyl, TMS = trimethylsilyl.

Aryl- or alkyl-substituted alkynes such as phenylethyne **1a** or 1-hexyne **1d**, led only to [2+1] adducts (Table 2, entries 1 and 2). Also, dicyclopropanation adducts **3** were isolated in 52 % yield for **3a** (Table 2, entry 1) and a small amount for **3d** (Table 2, entry 2).^[10] On the other hand, with ester-containing alkynes **1c**, **1e**, and **1f** the tandem [2+1]/[3+2] cycloaddition sequence took place almost exclusively to provide of tricyclic compounds **4** in fair to good yields (Table 2, entries 4–6). Propargylic ethers **1b** and **1g–1j**, were found to be equally good candidates for the tandem process and up to 90 % of **4**

was isolated (Table 2, entries 3 and 7–10). Single-crystal X-ray analysis of **4i** unambiguously confirmed its structure as a single regio- and stereoisomer with a *trans* configuration within the fused five-membered ring (Figure 1).^[11] Alkyne **1k** bearing a

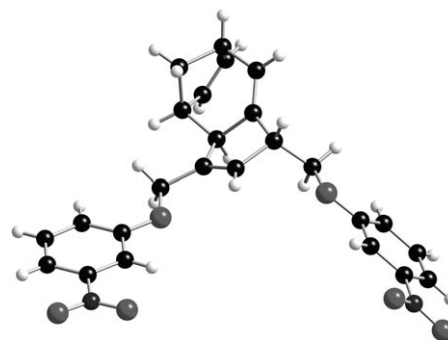
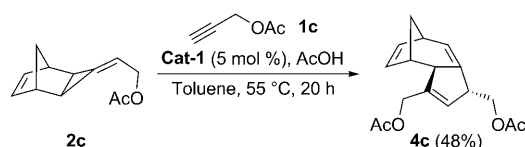


Figure 1. Ball-and-stick representation of tricyclic product **4i**.

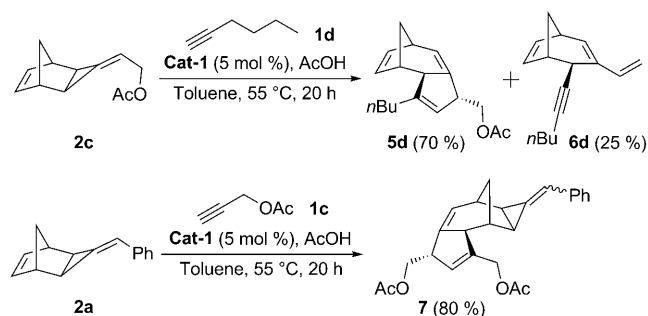
carbonate group was also effective for the tandem cycloaddition reactions (Table 2, entry 11). In the case of trimethylsilyl ether **1l**, the yield of the reaction dropped dramatically down to 21 %, owing to some degradation that occurred during the purification step (Table 2, entry 12). Propargylic thioether **1m** was moderately tolerated and gave adduct **2m** (26 %) and a trace amount of **4m** (Table 2, entry 13). Overall, the oxygen atom in homopropargylic position appears to be crucial in the tandem cycloaddition process. Importantly, all cycloadducts **4** were isolated as single regio- and diastereoisomers.

Because MCP **2** was supposed to be the intermediate for the [3+2] cycloaddition, treatment of MCP **2c**^[12] with propargyl acetate **1c** in the presence of Cat-1 under the usual reaction conditions led to tricycle **4c** as a single stereoisomer with a moderate yield (Scheme 3). Notably, the remaining mass balance accounted for the starting material MCP **2c**.



Scheme 3. Synthesis of tricyclic product **4c** with MCP **2c** as the intermediate.

Having established that MCP **2c**^[12] was the intermediate involved in the [3+2] cycloaddition, other alkyne partners for this transformation were examined (Scheme 4). First, 1-hexyne **1d** was chosen because it did not contain any oxygen atoms. Pleasingly, we isolated the desired product **5d** in good yield. On the other hand, an unexpected by-product identified as **6d** was isolated in a significant 25 % yield. This unusual reactivity of alkylidenecyclopropane^[13] may be related to the palladium-mediated tandem [2+1] cycloaddition/ring expansion reported with tertiary propargylic acetates.^[8b] When we evaluated benzyldienecyclopropane **2a** for [3+2] cycloaddition with propargyl acetate,



Scheme 4. Cross-over experiments using MCPs as intermediates.

the MCP moiety was left unchanged. However, the tandem [2+1]/[3+2] cycloaddition process took place on the norbornene C–C double bond to form **7** as a 1:1 mixture of diastereomers (Scheme 4). This finding clearly shows that an allylic oxygen substituent plays a major role in the [3+2] cycloaddition.

Examples of [3+2] cycloaddition reactions that illustrate the scope of this new platinum-mediated method are provided in Table 3. Among the various alkynes tested, only

Table 3: Examination of the scope for the [3+2] cycloaddition reaction.^[a]

Entry	Alkyne	R	5	Yield [%] ^[b]	6
1	1a	Ph	a complex mixture		
2	1d	<i>n</i> Bu	5d , 70		6d , 25
3	1n	TMS	5n , 61 ^[c]		< 5
4	1l	CH ₂ OTMS	5l , 67 ^[c]		< 5
5	1o	CH ₂ OH	5o , 39		6o , 7
6	1g	CH ₂ O(2-MeC 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] Yield of isolated product. [c] Conversion determined by ¹H NMR spectroscopy. Pht = phthalimide, Ts = 4-toluenesulfonyl.

phenylethyne **1a** led to a complex mixture of products (Table 3, entry 1). Trimethylsilylethyne **1n** and trimethyl silyl ether **1l** were well tolerated, nevertheless some degradation of adducts **5l** and **5n** occurred upon purification on silica gel (Table 3, entries 3 and 4). Therefore, unprotected propargyl alcohol **1o** was quite compatible and provided **5o** in moderate yield along with a small amount of by-product **6o** (Table 3, entry 5). Propargyl aryl ether **1g** gave **5g** in good yield (Table 3, entry 6). In spite of substantial amounts of by-products **6**, the platinum-based catalytic system was found to be tolerant of other heteroatom groups such as sulfonamide, phthalimide, or sulfone (Table 3, entries 7–9).

Notably, for all compounds **5** a single stereo- and regioisomer was observed by NMR analysis of the crude reaction mixtures. X-ray crystallographic analysis of sulfone-containing adduct **5r** confirmed both atoms connectivity and configuration (Figure 2).^[11]

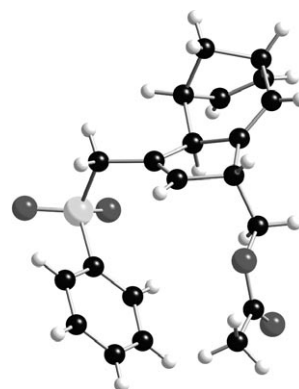
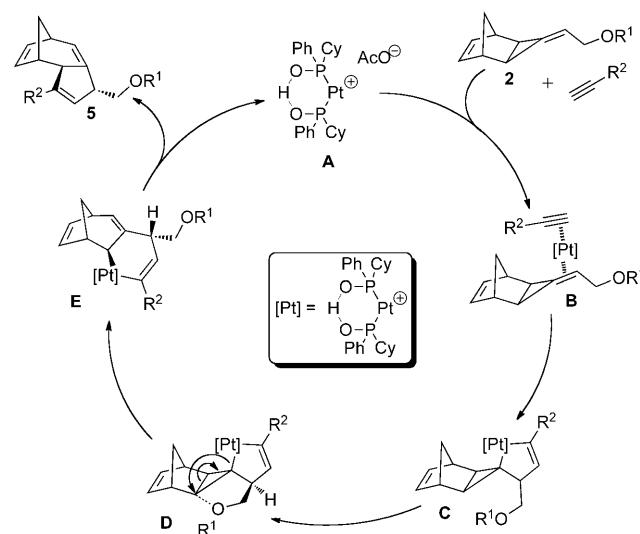


Figure 2. Ball-and-stick representation of tricyclic product **5r**.

Although the mechanism of this unusual [3+2] cycloaddition remains unclear at that time, we believe the cationic platinum species **A** coordinates to the exocyclic C–C double bond on the *exo* face of MCP **2**, thus triggering an oxidative coupling with the alkyne to form the platina-cyclopentene

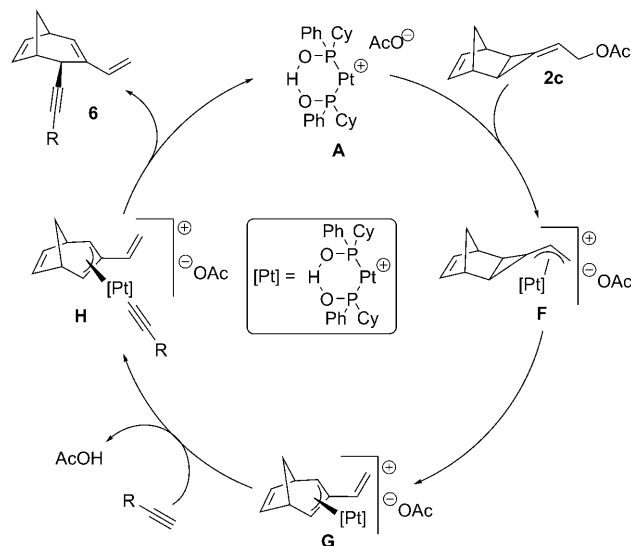


Scheme 5. Postulated mechanism for [3+2] cycloaddition.

intermediate **C** (Scheme 5).^[14] Importantly, the regioselectivity accommodates steric interactions between substituents. At this stage, the oxygen atom could have a directing influence by assisting the cyclopropane fragmentation and therefore the 1,2 shift of the platinum moiety (intermediate **D**, only one enantiomer depicted), therefore giving rise to the platina-cyclohexene **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 considerations.

The formation of by-products **6** occurred only with allylic acetate **2c**. We assume the formation of the platinum π -allyl species **F** through the release of the acetoxy group (Scheme 6). At this point, cyclopropane ring opening gen-



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

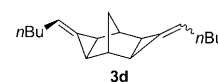
erates the symmetrical vinyl π -allylplatinum species **G**, with the platinum center located on the *exo* face to minimize steric hindrance.^[15] A ligand exchange with the alkyne unit releases acetic acid and forms the dialkylplatinum species **H**. Finally, a reductive elimination releases by-product **6** and restores active species **A**.

In summary, we have shown that secondary phosphine-oxide-based platinum complexes can catalyze an unprecedented intermolecular [2+1]/[3+2] cycloaddition sequence of norbornadiene with several alkynes. The tandem [2+1]/[3+2] process was found to be limited to alkynes bearing an oxygen substituent on the propargylic carbon atom, however in view of the pervasiveness of oxygen-containing functional groups in organic molecules, the reaction scope spanned various functionalities. We have also demonstrated that methylene-cyclopropanes **2** are the intermediates for the [3+2] cycloaddition and we explored this transformation with various alkynes. To the best of our knowledge, most of the cycloaddition reactions involving MCPs and alkynes have been reported for intramolecular processes.^[16] The present work describes a rare example of such cycloadditions in an intermolecular fashion. The regio- and stereoselective outcomes suggest a specific mechanism and imply to us that a promising enantioselective variant could be achieved using chiral SPO preligands.

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