Tandem Reactions

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

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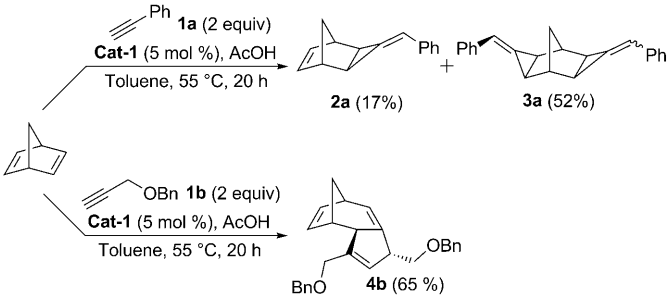
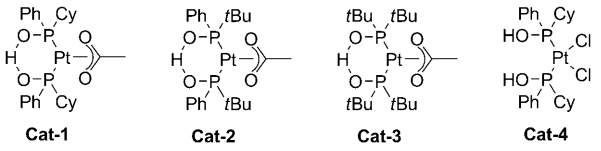
In the context of sustainable chemistry, tandem reactions, so-called domino or cascade processes, have emerged as powerful strategies to assemble nontrivial carbon skeletons, in particular for the synthesis of natural products.[1] Interestingly, the implementation of this strategy implies general C–C bond formation and atom economy. Tandem processes involving one cycloaddition step are quite common,[2] however, those engaging two of 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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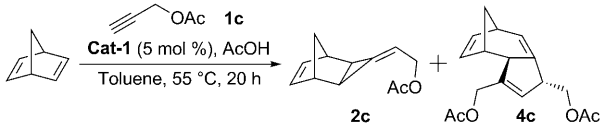
Table 1: Optimization of reaction parameters for the platinum-mediated tandem [2+1]/[3+2] cycloaddition sequence.[a]



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_3N 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%), Et_3N (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**	*n*Bu	**2d**, 46	–
3	**1b**	CH_2OBn	–	**4b**, 65
4	**1c**	CH_2OAc	**2c**, 10	**4c**, 62
5	**1e**	CH_2OBz	–	**4e**, 44
6	**1f**	CH_2OPiv	–	**4f**, 44
7	**1g**	$CH_2O(2\text{-}MeC_6H_4)$	–	**4g**, 74
8	**1h**	$CH_2O(4\text{-}OMeC_6H_4)$	–	**4h**, 43
9	**1i**	$CH_2O(3\text{-}NO_2C_6H_4)$	–	**4i**, 50
10	**1j**	$CH_2O(2,4\text{-}(NO_2)_2C_6H_4)$	–	**4j**, 90
11	**1k**	CH_2OCO_2Bn	–	**4k**, 52
12	**1l**	CH_2OTMS	–	**4l**, 21
13	**1m**	$CH_2S(2\text{-}MeC_6H_4)$	**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** unambiguous 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 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 diastereomers.

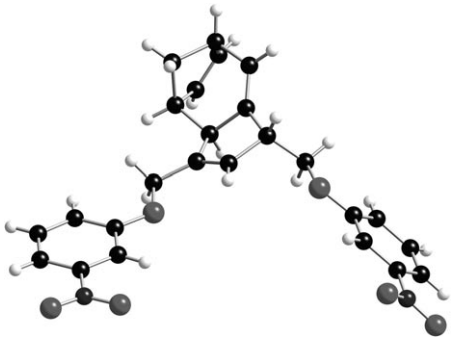
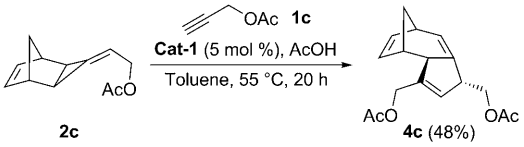


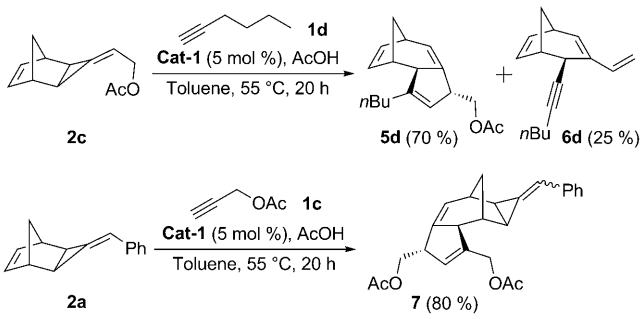
Figure 1. Ball-and-stick representation of tricyclic product **4i**.

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 byproduct 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 benzylidenecyclopropane **2a** for [3+2] cycloaddition with propargyl acetate,

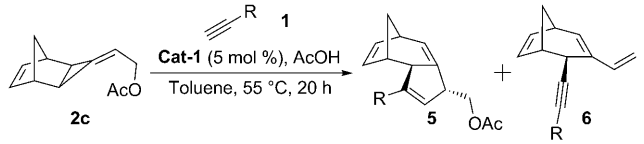


Scheme 4. Cross-over experiments using MCPs as intermediates.

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	Yield [%][b]	
			5	**6**
1	**1a**	Ph	a complex mixture	
2	**1d**	*n*Bu	**5d**, 70	**6d**, 25
3	**1n**	TMS	**5n**, 61[c]	< 5
4	**1l**	CH_2OTMS	**5l**, 67[c]	< 5
5	**1o**	CH_2OH	**5o**, 39	**6o**, 7
6	**1g**	$CH_2O(2\text{-}MeC_6H_4)$	**5g**, 65	< 5
7	**1p**	CH_2NHTs	**5p**, 38	**6p**, 10
8	**1q**	CH_2Pht	**5q**, 61	**6q**, 12
9	**1r**	CH_2SO_2Ph	**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 ^{1}H 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, phtalamide, 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]

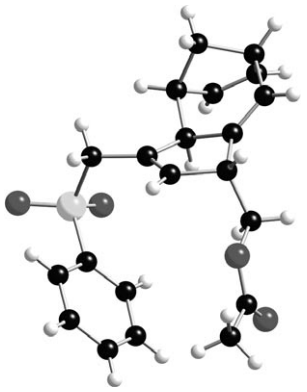
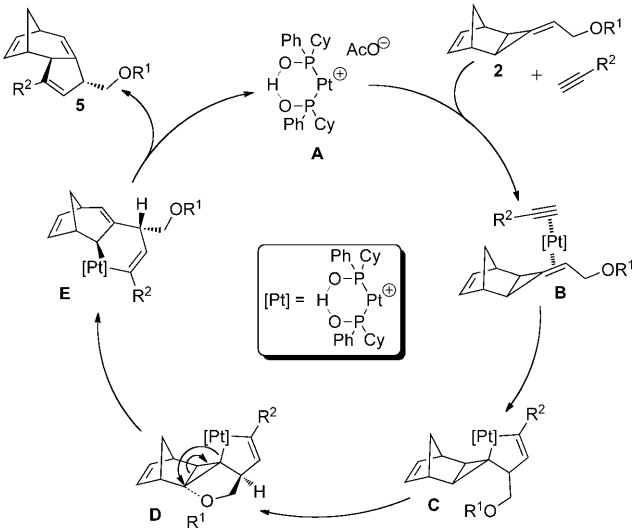


Figure 2. Ball-and-stick representation of tricyclic product **5r**.

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 platinacyclopentene

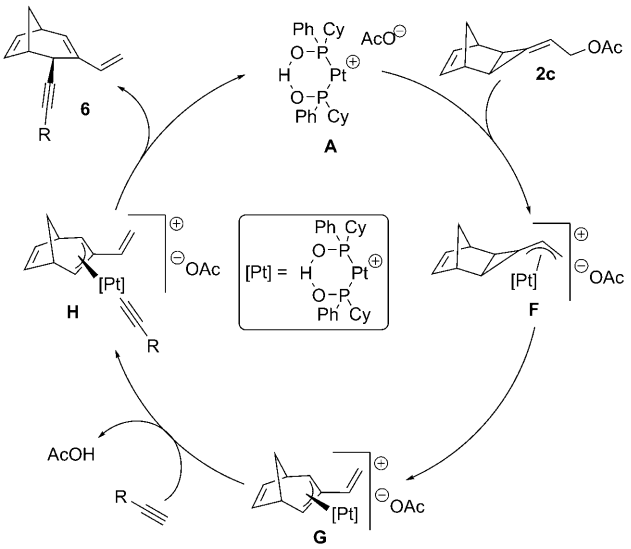


Scheme 5. Postulated mechanism for [3+2] cycloaddition.

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 rising to the platinacyclohexene **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 methylenecyclopropanes **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 a 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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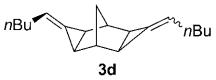
[10] Dicyclopropanation adduct **3d** was only detected by ^{1}H NMR analysis of the crude reaction mixture, but could not be isolated.



3d

[11] CCDC 803469 (**4i**), 803470 (**5r**), and 659994 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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