Domino Sequence

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$PtCl_4$-Catalyzed Domino Synthesis of Fused Bicyclic Acetals**

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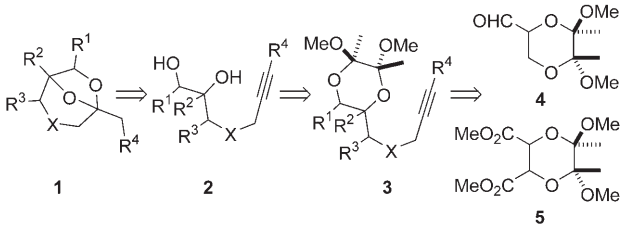
The search for new avenues to molecular complexity from relatively simple substrates has been one of the major objectives of organic chemists for the last decade.[1] In this regard, domino reactions have been established as a powerful tool to accomplish this goal, since it offers highly efficient transformations by allowing the build up of complex structures in fewer steps and increased overall yields.[2] Following this concept, transition-metal-catalyzed cycloisomerization reactions of ω-alkynols have been applied to the synthesis of oxygen-containing heterocycles.[3,4] The intramolecular nature of these transformations means that the regio- and stereoselectivities are often excellent, thus permitting the synthesis of a single compound after several bond-forming reactions. We therefore reasoned that the development of new approaches to the synthesis of structurally diverse scaffolds would likely benefit from metal-catalyzed cycloisomerization reactions.

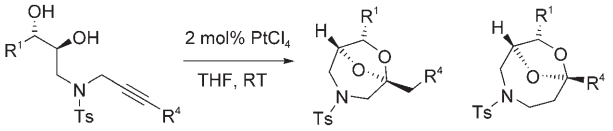
Recently, our research group has employed butane 1,2-diacetal (BDA) protected diols as a source of chiral information in the synthesis of fused bicyclic acetals, some of which have shown interesting cytotoxic properties.[5] Inspired by these results, we decided to seek new approaches directed towards the synthesis of heteroatom-containing fused bicyclic acetals of general structure **1** (Scheme 1). We envisioned that a Lewis acid catalyzed domino cycloisomerization-hydroalkoxylation reaction of a 6-heptyne-1,2-diol derivative **2** could be applied to the synthesis of bicyclic acetals **1**.[6] By taking advantage of the BDA-selective protection of the 1,2-diol, the homochiral protected diol **3** could be prepared in a few steps from the corresponding BDA-protected glyceraldehyde **4** or tartrate **5**.[7] The high stereoselectivity in many of the transformations performed using BDA derivatives, and the fact that both enantiomers are available and easily prepared on a multigram scale, make these substrates attractive building blocks for the synthesis of small molecules.



Scheme 1. Retrosynthetic analysis.

Using alkyne diol **2a** (Table 1, entry 1) as the starting material, a series of experiments with different catalysts under a number of reaction conditions was carried out. After this optimization process we found that the use of 2 mol% $PtCl_4$ in THF as the solvent afforded the desired bicyclic acetal **1a** in 93% yield as a single diastereoisomer after 2 h at room temperature. Similarly, diol **2b** was converted in 80% yield into the enantiopure bicyclic γ-amino ester **1b** (Table 1, entry 2).

Table 1: Domino cycloisomerization-hydroalkoxylation reaction of alkyne-diol derivatives **2** (R^2, R^3 = H; X = NTs).



Entry	Diol	R^1	R^4	Product	Yield[a]
1	**2a**	H	H	**1a**[b]	93
2	**2b**	CO_2Me	H	**1b**	80
3	**2c**	H	Ph	**6c**[b]	77
4	**2d**	H	2-BrC_6H_4	**6d**[b]	82
5	**2e**	H	3-ClC_6H_4	**6e**	75
6	**2f**	H	3-$MeOC_6H_4$	**6f**	81
7	**2g**	H	4-FC_6H_4	**6g**[b]	89
8	**2h**	H	4-$MeOC_6H_4$	**6h**[b]	83
9	**2i**	H	4-MeC_6H_4	**6i**[b]	86
10	**2j**	H	4-$CF_3C_6H_4$	**1j**[b] + **6j**[b]	75[c]
11	**2k**	H	4-$NO_2C_6H_4$	**1k**[b] + **6k**	83[d]

[a] Yield of isolated product based on alkyne-diol **2**. [b] Structure unambiguously established by X-ray crystallography. [c] 1:2.5 mixture of **1j**/**6j**. [d] 6:1 mixture of **1k**/**6k**. Ts = toluene-4-sulfonyl.

By applying the same reaction conditions we further explored the scope of this platinum-catalyzed double intramolecular hydroalkoxylation reaction with substrates **2c–k** that bear an aryl-substituted triple bond. In general, we observed that internal triple bonds are less reactive in these hydroalkoxylation reactions than terminal ones. Consequently, a longer reaction time (16 h) was required until thin-layer chromatography showed complete consumption of

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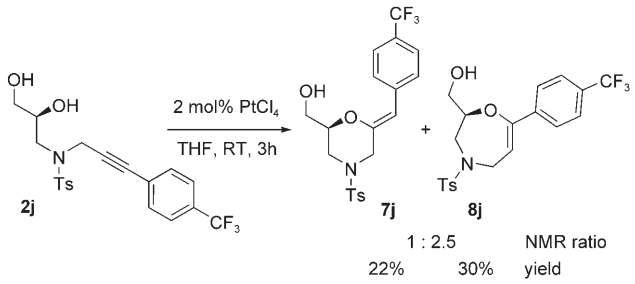
the starting material and formation of a new product. To our surprise, the major isolated product in most cases was the [4.2.1]bicyclic acetal **6**, which arises from an initial 7-*endo* cyclization, instead of the [3.2.1]bicyclic acetals **1**, formed by an initial 6-*exo* cyclization.[8] While the competition between 6-*endo* and 5-*exo* cycloisomerization reactions has been extensively studied,[4e,9] to the best of our knowledge, only one example of a 7-*endo* cyclization of an alkyne diol bearing a dialkyl-substituted triple bond has been reported.[4d,10] The structures of **6c**, **6d**, **6g**–**6j** were confirmed by single-crystal X-ray diffraction analysis.[11] The reaction proceeded in good yield for substrates without a strong electron-withdrawing substituent on the aromatic ring (**2c**–**i**), and gave the homochiral bicyclic acetals **6c**–**i** resulting from a 7-*endo* cycloisomerization reaction with high selectivity (Table 1, entries 3–9). However, the presence of an electron-withdrawing substituent in the *para* position of the aromatic ring diminishes the reactivity and changes the regioselectivity of the cycloisomerization reaction. Thus, in the case of *p*-CF_3 (**2j**) we observed a 1:2.5 ratio of the 6-*exo* product **1j** to the 7-*endo* product **6j** (Table 1, entry 10), which could be separated by column chromatography and their structures were confirmed by X-ray analysis. When the crude reaction mixture was analyzed by NMR spectroscopy after three hours, the enol ethers **7j** and **8j** were detected exclusively (Scheme 2). The ratio between the 6-*exo*-*dig* enol ether **7j** and the 7-*endo*-*dig* enol ether **8j** was the same as for the final products (1:2.5),



Scheme 2. The 6-*exo*-*dig* versus the 7-*endo*-*dig* cyclization reaction of diol **2j**.

which supports the hypothesis that these enol ethers are indeed intermediates in the formation of the fused bicyclic acetals. Both enol ethers could be isolated after column chromatography.[12] The strongly electron-withdrawing nature of the *p*-NO_2 group in **2k** resulted in the reaction proceeding much more slowly and, notably, the major isolated product was the fused bicyclic acetal **1k** arising from a 6-*exo* cyclization. However, the formation of several unidentified side products was observed in this reaction.

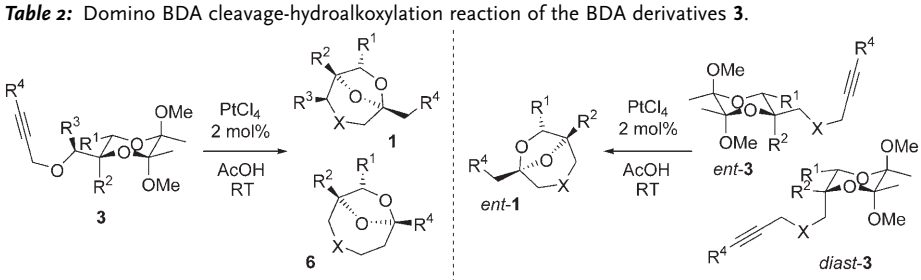
Encouraged by these results we decided to explore whether the platinum catalyst could directly convert the BDA-protected substrate **3** into the desired bicyclic acetal product by a domino deprotection-hydroalkoxylation sequence. Since acetal protecting groups can generally be removed by acid treatment, we reasoned that the Lewis acid catalyst should be capable of cleaving the BDA group and generating the diol **2** in situ,[13] which then should undergo a double intramolecular hydroalkoxylation reaction of the triple bond. Indeed, we found after some experimentation that 2 mol % $PtCl_4$ in acetic acid led to complete conversion of the starting material into the bicyclic acetal. Although other Lewis acids were able to cleave the BDA group and form the diol **2** as well, only $PtCl_4$ and $AuCl_3$ could catalyze the subsequent hydroalkoxylation reaction. Other solvent systems were not as effective for the domino sequence. In particular, the addition of excess water (5 % v/v) leads to complete deactivation of the catalyst and no conversion of the starting material was detected. Addition of trifluoroacetic acid to the reaction mixture resulted in faster conversion; however, we observed the formation of numerous decomposition products. Acetic acid alone did not give any conversion of the starting material, clearly demonstrating that the platinum catalyst is necessary for both steps of the domino reaction.

The cycloisomerization step of the domino reaction proceeded with the same regioselectivity as already observed, that is, terminal alkynes lead to [3.2.1]bicyclic acetals **1** by a 6-*exo* pathway, whereas aryl-substituted alkynes give rise to [4.2.1]bicycles **6** through a 7-*endo* cyclization (Table 2, entries 1–8). The yields of the isolated products for the domino process were generally good and comparable to the cycloisomerizations of the corresponding alkyne diols. The versatility of the BDA-protected building blocks allowed us to easily access a number of propargylic ethers **3** (X = O) with substituents at different positions (Table 2, entries 9–17). These substrates also underwent the domino deprotection-cyclization sequence in good yield.

A plausible mechanism for the cycloisomerization-hydroalkoxylation reaction is depicted in Scheme 3. Coordination of the platinum catalyst to the alkyne **2** provides the π-complex **9** in which the triple bond is activated towards an intramolecular nucleophilic attack by one of the hydroxy groups.[14] This step proceeds in such a way that the metal migrates to the sterically less encumbered position, and nucleophilic attack occurs at the end of the triple bond where the developing positive charge is best stabilized.[3b] Thus, terminal alkynes cyclize by the 6-*exo* pathway, whereas the cyclization of arylalkynes proceeds almost exclusively by the 7-*endo* pathway. Subsequent proton transfer leads to the enol ether **7** or **8**, respectively. In one case we were able to observe the initial formation of both enol ethers, which strongly supports their role as intermediates in the reaction.[15] Finally, the corresponding fused bicyclic acetals **1** or **6** are formed by a proton or Lewis acid catalyzed intramolecular hydroalkoxylation. In the cases where BDA-protected diols **3** are employed, the described sequence is preceded by a Lewis acid catalyzed deprotection of the substrate.

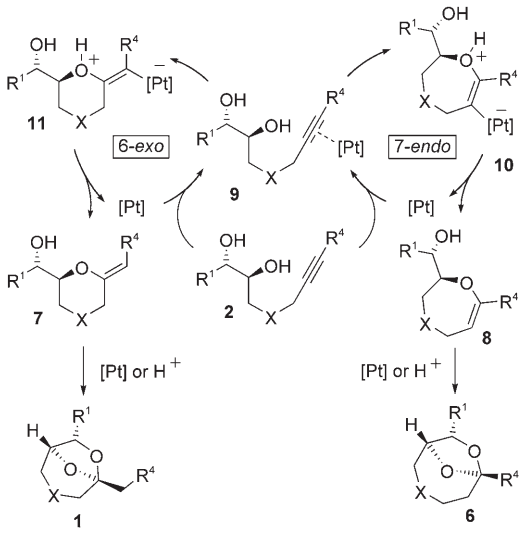
In the present study we have described for the first time the synthesis of [4.2.1]- and [3.2.1]-fused bicyclic acetals by an intramolecular double alkoxylation of alkyne diols. The course of the reaction depends on the substitution of the triple bond. Terminal alkynes give the [3.2.1]bicyclic product by a 6-*exo* pathway, whereas arylalkynes undergo a 7-*endo* cyclization to the [4.2.1]bicycles.

Table 2: Domino BDA cleavage-hydroalkoxylation reaction of the BDA derivatives **3**.



Entry	BDA	R^1	R^2	R^3	R^4	X	Product	Yield[a]
1	**3a**	H	H	H	H	NTs	**1a**	92
2	*diast*-**3a**	H	H	H	H	NTs	*ent*-**1a**	88
3	**3c**	H	H	H	Ph	NTs	**6c**	75
4	**3d**	H	H	H	2-BrC_6H_4	NTs	**6d**	77
5	**3e**	H	H	H	3-ClC_6H_4	NTs	**6e**	65
6	**3g**	H	H	H	4-FC_6H_4	NTs	**6g**	78
7	**3i**	H	H	H	4-MeC_6H_4	NTs	**6i**	72
8	**3j**	H	H	H	4-$CF_3C_6H_4$	NTs	**1j**+**6j**	63[b]
9	**3l**	CH_2OBn	H	H	H	O	**1l**	84
10	**3m**	CH_2OTs	H	H	H	O	**1m**	85
11	**3n**	CH_2OCH_2-4-BrC_6H_4	H	H	H	O	**1n**	80
12	*ent*-**3o**	$(CH_2)_2CHCH_2$	H	H	H	O	*ent*-**1o**	74
13	*diast*-**3p**	H	$C_{11}H_{23}$	H	H	O	*ent*-**1p**	79
14	**3q**	H	Pr	H	H	O	**1q**	75
15	**3r**	H	H	Bn	H	O	**1r**[c]	72
16	**3s**	CH_2OCH_2-4-BrC_6H_4	H	H	Ph	O	**6s**	57

[a] Yield of isolated product based on BDA-derivative **3**. [b] 1:2.5 mixture of **1j**/**6j**. [c] Structure established by X-ray crystallography. Bn = benzyl.



Scheme 3. Proposed mechanism for the domino cycloisomerization-hydroalkoxylation reaction.

The overall process allows for the straightforward synthesis of structurally complex acetals from simple starting materials. By using well-established BDA methodology, substrates with a variety of substitution patterns are easily accessible. Conveniently, not only the free diols but also the BDA-protected ones could be employed, thereby obviating the need for a separate deprotection step. Ongoing work in our research group is directed towards further exploring the substrate scope of the reaction, in particular with bisalkyl-substituted alkyne substrates, and exploiting this new synthetic strategy to obtain a number of structurally diverse compounds for subsequent biological evaluation.

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