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Gold- or Platinum-Catalyzed Cascade Processes of Alkynol Derivatives Involving Hydroalkoxylation Reactions Followed by Prins-Type Cyclizations

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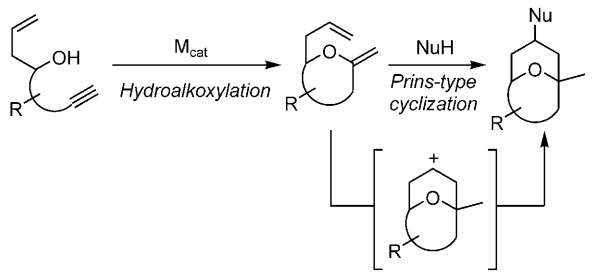
Abstract: An efficient method for the synthesis of [3.3.1]bicyclic compounds from easily available alkynol derivatives has been developed. The reaction is based on a gold- or platinum-catalyzed tandem process that involves an intramolecular hydroalkoxylation of a triple bond followed by a Prins-type cyclization. The reaction has been carried out with differently substituted alkynol derivatives and oxygen-, nitrogen-, and carbon-centered nucleophiles. The incorporation of halogen atoms as nucleophiles and elimination reactions has also been studied. Enantiomerically pure [3.3.1]bicyclic systems were easily synthesized from the chiral pool.

Keywords: bicyclic systems · cascade reactions · catalytic synthesis · cyclization · gold · platinum

Introduction

The increasing demand for molecules with unprecedented diversity requires the development of new methods for the efficient and stereocontrolled construction of architecturally complex structures from simple starting materials. To this end, tandem reactions (domino or cascade reactions) have emerged as very attractive tools as they allow several bond-forming and/or -cleaving events to occur in one synthetic operation, thus minimizing the costs and waste associated with one-reaction/one-vessel approaches.[1] Also, considerable focus has been directed towards organotransition-metal-catalyzed processes for the construction of complex cyclic structures owing to the ability of metallic species to promote reactions which would require many steps by traditional procedures.[2] In this context, gold and platinum salts or complexes have become very promising catalysts in organic chemistry due to their high activity and the mild reaction conditions required to perform nonconventional transformations.[3] One of the most interesting features of these catalysts is their ability to activate alkynes and promote the addition of nucleophiles. When the nucleophile is contained in the structure of the starting alkyne, interesting carbo- and heterocyclic compounds may be obtained through intramolecular additions to the triple bond. In this sense, various internal nucleophiles, such as alkenyl-,[4] aryl-,[5] 1,3-dicarbonyl-,[6] oxygen-,[7] and nitrogen-containing functions,[8] have been used.

Following our interest in the development of new tandem reactions promoted by a single catalyst[9] (concurrent tandem catalysis),[10] we envisaged a strategy that employs readily available alkynol derivatives for the construction of interesting bicyclic compounds (Scheme 1).[11] The sequence would involve an initial *exo* addition of the hydroxy group to the triple bond to give an enol ether. If this enol ether contains an allyl moiety at an appropriate position and in the presence of a suitable nucleophile, it could participate in



Scheme 1. The concept of the tandem catalytic hydroalkoxylation/Prins-type cyclization reaction for the synthesis of bicyclic ethers. M = metal, Nu = nucleophile.

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a subsequent Prins-type cyclization[12] to finally give bicyclic ethers in an apparently very simple way. By varying both the structure of the alkynol derivative and the nucleophile, the sequence would provide an excellent method for the synthesis of structurally diverse collections of small molecules. Detailed studies on this process are reported herein.

Results and Discussion

Initial experiments and selection of appropriate catalysts: Initial attempts to promote the tandem sequence discussed above were performed by using the model diallyl-substituted alkynol **1a** as the starting material and methanol as both the solvent and nucleophile. First, we focused on finding the appropriate catalyst, and so we treated alkynol **1a** with several metallic complexes. The most significant results are summarized in Table 1.

Table 1. Cycloisomerization reactions of the alkynol **1a**: optimization of the catalyst.

1a **2a**

Entry	ML_n	x [mol%]	Conditions[a]	[h]	Yield [%][b]
1	AgOTf	5	65°C	15	>95
2	$Cu(OTf)_2$	5	65°C	168	>95
3	$AuCl_3$	2	RT	1	>95 (94)
4	$AuCl_3$	1	RT	6	>95
5	$AuCl_3$	0.5	RT	30	>95
6	AuCl	2	65°C	12[c]	56 (55)
7	$[AuCl(PPh_3)_3]$	2	65°C	24[d]	0
8	$[AuCl(PPh_3)_3]/AgSbF_6$	2	65°C	7	>95 (95)
9	$[AuCl(tht)]/AgSbF_6$[e]	1	65°C	6	>95
10	$[PtCl_2(cod)]$	2	RT	24[d]	0
11	$[PtCl_2(cod)]$	2	65°C	12	>95 (95)
12	$PtCl_4$	2	RT	3[e]	68 (66)
13	$PtCl_4$	2	65°C	0.5	>95 (96)
14	$PtCl_4$	0.5	65°C	2	>95
15	$PtCl_4$	0.1	65°C	18	>95 (95)
16	$PdCl_2$	2	65°C	18	>95
17	$[PdCl_2(PPh_3)_2]$	2	65°C	24[d]	0

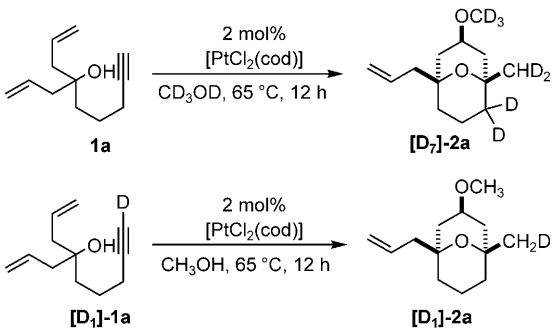
[a] Unless otherwise stated, the time shown is that required to reach >99% conversion. [b] The yield of product **2a** as determined by GC; the yield of the isolated spectroscopically pure product **2a** is given in parentheses. [c] A conversion of 56% was determined by GC; 42% yield of **1a** recovered after column chromatography. [d] No conversion as determined by GC. [e] A conversion of 70% was determined by GC. L = ligand, OTf = trifluoromethanesulfonate.

Silver(I) and copper(II) triflate salts were proven to be effective catalysts for the tandem process (Table 1, entries 1 and 2). However, to obtain complete conversion of the starting materials, high catalyst loading and long reaction times were required. More effective were the gold catalysts. In fact, by using the gold(III) compound $AuCl_3$, the reaction could be performed at room temperature (Table 1, entries 3–5). Moreover, the catalyst loading could be decreased to 1 mol% (complete conversion required 6 h; Table 1, entry 4) or even to 0.5 mol% (complete conversion required 30 h; Table 1, entry 5); also, gold(I) compounds catalyzed the reaction. However, some comments on the use of these catalysts should be made: When 2 mol% of AuCl was used, **2a** was formed, although the conversion was only 56% after 12 hours at 65°C (55% yield of isolated **2a**; Table 1, entry 6). We did not observe any transformation by using $[AuCl(PPh_3)_3]$ (Table 1, entry 7). However, by mixing 2 mol% of $[AuCl(PPh_3)_3]$ and 2 mol% of $AgSbF_6$ to generate the cationic gold(I) complex, we observed the exclusive formation of product **2a** after 7 hours at 65°C (Table 1, entry 8). Similar results were found by using the cationic gold(I) complex generated from [AuCl(tht)] (tht = tetrahydrothiophene). In this case, the catalyst loading could be decreased to 1 mol% (Table 1, entry 9).

Next, we turned our attention to platinum complexes. The reaction with the platinum(II) complex $[Pt(cod)Cl_2]$ (cod = 4-cycloocta-1,5-diene) did not proceed at room temperature (Table 1, entry 10). However, on warming to 65°C for 12 hours it was possible to isolate the final product **2a** in 95% yield (catalyst loading was 2 mol%; Table 1, entry 11). Regarding the platinum(IV) complexes, we tried the reaction with $PtCl_4$ and found that this was an excellent catalyst to perform the transformation of **1a** into **2a** (Table 1, entries 12–15). The reaction proceeded slowly at room temperature with 2 mol% of $PtCl_4$, and **2a** was isolated in only 66% yield after 3 hours (68% conversion; Table 1, entry 12). However, the reaction was complete after 30 minutes at 65°C using 2 mol% of $PtCl_4$, and **2a** was isolated in 96% yield (Table 1, entry 13). The amount of catalyst could be decreased to 0.5 mol% (complete conversion required 2 h; Table 1, entry 14). By using only 0.1 mol% of $PtCl_4$, the reaction took 18 hours to go to completion (Table 1, entry 15). Under these conditions, product **2a** was isolated in 95% yield as a single diasteresoisomer.

Finally, the process was attempted with palladium(II) complexes as catalysts. The reaction worked well with 2 mol% of $PdCl_2$, although it was slower (complete conversion required 18 h at 65°C) than those reactions performed with platinum or gold catalysts (Table 1, entry 16). We did not observe any transformation by using $[PdCl_2(PPh_3)_2]$ as the catalyst (Table 1, entry 17). From this extensive study, it can be concluded that silver(I), copper(II), gold(III), gold(I), platinum(II), platinum(IV), and palladium(II) compounds could be appropriate catalysts for our tandem process. However, in general, we decided to use $AuCl_3$, $[PtCl_2(cod)]$, or $PtCl_4$ as catalysts in successive experiments due to their higher activity and/or ease of handling (in some cases, cationic gold(I) complexes were also considered).

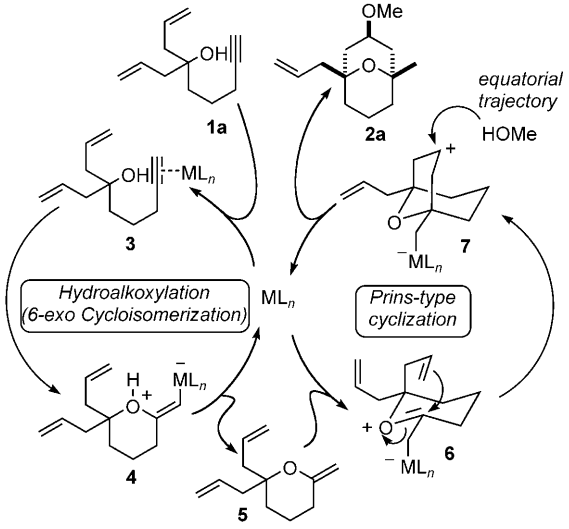
Mechanism of the reaction: To gain insight into the mechanism of the reaction we performed labeling studies with deuterated starting materials or solvents (Scheme 2). The reaction of **1a** in CD_3OD in the presence of 2 mol% of $[PtCl_2$-



Scheme 2. Labeling experiments for the catalytic transformation of **1a** and [D_1]-**1a**.

(cod)] at 65 °C for 12 hours cleanly afforded the heptadeuterated compound [D_7]-**2a** in 93% yield. Moreover, reaction of the deuterated alkyne [D_1]-**1a** in CH_3OH under the same conditions led to the formation of product [D_1]-**2a** in 92% yield.

All these experiments support a mechanism for the formation of **2a** based on a tandem sequence that involves an intramolecular hydroalkoxylation reaction in the first place followed by a Prins-type cyclization process (Scheme 3). The



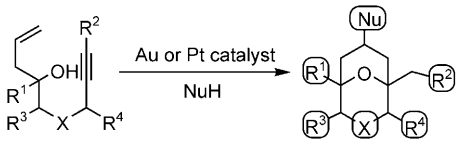
Scheme 3. Proposed mechanism for the formation of eight-membered carbocycle **2a** from alkynol **1a**.

reaction is initiated by coordination of the platinum or gold complex to the triple bond of the starting alkynol **1** to form intermediate **3** according to the Dewar–Chatt–Duncanson model.[13] Intramolecular addition of the hydroxy group to the internal carbon atom of the triple bond generates **4**. Protodemetallation of the latter affords the *exo*-cyclic enol ether **5** and regenerates the catalytic species. At this point, the second part of the tandem sequence, the Prins-type cyclization, is initiated. Thus, after an initial coordination of the catalyst to the double bond of the enol ether, the oxonium intermediate **6** is formed. The subsequent cyclization step is believed to proceed through a chair-like transition state in which the axial allyl moiety reacts to form the oxocarbenium ion **7**. Further nucleophilic trapping from an equatorial trajectory by a molecule of methanol accounts for the formation of **2a** and the regeneration of the catalytic species after a final proto-demetallation step.[14]

This rationalization is consistent with the configuration of the stereogenic centers observed in **2a**. Additional support for this mechanistic proposal can be found in the previously commented upon labeling experiments. Formation of deuterated compounds [D_1]-**2a** and [D_7]-**2a** clearly support a Lewis acid-type activation of the starting alkyne, thus ruling out any possible mechanism initiated by an insertion of the metallic species into the terminal C–H (or C–D) bond of the triple bond. Also, formation of the deuterated compound [D_7]-**2a** is in good agreement with the participation of an oxocarbenium ion **6** as an intermediate. Thus, the acidic hydrogen atoms in the α position to the oxocarbenium group are deuterated by CD_3OD prior to the cyclization step.

An intriguing question related to the mechanism of this process is the identity of the catalytic species responsible for the two catalytic cycles proposed in Scheme 3. In principle, both Lewis and Brønsted acids could catalyze the hydroalkoxylation and the Prins-type cyclization reactions. It should be taken into account that traces of Brønsted acids could be formed in the reaction media from the platinum or gold complexes and these protic acids could be responsible for both or at least one of the catalytic cycles proposed in Scheme 3.[15] So, to shed light on this issue, alkynol **1a** was subjected to a range of reaction conditions with methanol as the solvent. No reaction was observed in the absence of platinum or gold complexes or by treatment of **1a** with Brønsted acids such as *para*-toluenesulfonic acid (*p*-TsOH) and tetrafluoroboric acid, thus demonstrating the necessity of the metallic complex at least for the hydroalkoxylation reaction. Also, to eliminate the possibility of competing Brønsted acid catalysis in the second catalytic cycle (i.e., the Prins-type reaction), we performed control experiments using a nonpoisoning base. Thus, when **1a** was treated with 5 mol% of $PtCl_4$ in a solution containing 2.5 mol% of the strong phosphorine base 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) in methanol, we observed the formation of the expected product **2a** after 1 h at room temperature. These results suggest that residual Brønsted acids are not responsible because these would be quenched by BEMP (at 2.5 mol%). So we believe that the gold or platinum catalytic species are involved in both the catalytic cycles proposed in Scheme 3.[16]

Generalization of the reaction—variation of the alkynol and the alcohol used as the nucleophile: Once we had found the appropriate catalysts and conditions to perform the reaction, we focus on the scope of this process. It is important to note that, in principle, this reaction offers the possibility of accessing interesting bicyclic compounds with many points of diversity in a very simple way (Scheme 4). Moreover, as the

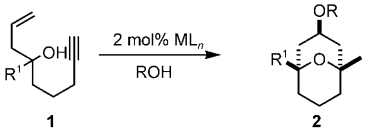


Scheme 4. From simple alkynols to bicyclic compounds. Potential diversity points are highlighted.

reaction occurs with total regio- and diastereoselectivity, it would be possible to synthesize enantiomerically pure products.

We began our study on the generality of the reaction by using simple variations in the structure of the starting alkynol derivative and the alcohol used as the nucleophile. Different substituents at the carbon atom bearing the hydroxy group were tolerated (Table 2). Additionally, a number of

Table 2. Reaction of the alkynol derivatives **1a–f** in the presence of different alcohols.[a]



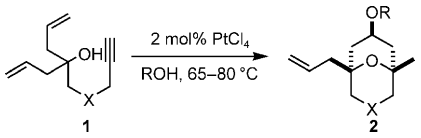
Alkynol	R^1	ML_n	Product	R	Yield [%][b]
1a	allyl	$[Pt(cod)Cl_2]$	**2b**	Et	92
1a	allyl	$AuCl_3$	**2c**	Pr	94
1a	allyl	$[AuCl(tht)]/AgSbF_6$[c]	**2d**	Bn	80
1b	Me	$[PtCl_2(cod)]$	**2e**	Me	94
1b	Me	$AuCl_3$	**2f**	Et	96
1c	Bu	$[PtCl_2(cod)]$	**2g**	Me	92
1d	*i*Pr	$[PtCl_2(cod)]$	**2h**	Me	92
1d	*i*Pr	$AuCl_3$	**2i**	Et	88
1e	*t*Bu	$[PtCl_2(cod)]$	**2j**	Me	90
1e	*t*Bu	$AuCl_3$	**2k**	Et	91
1f	H	$PtCl_4$	**2l**	Me	88

[a] The reactions were performed at room temperature when $AuCl_3$ was used as the catalyst, whereas the reactions were performed at 65–80 °C with all the other catalysts. [b] The yield of the isolated spectroscopically pure product **2**.

alcohols proved to be effective nucleophiles. All the catalysts, that is, those based on platinum(II), platinum(IV), gold(III), and cationic gold(I), gave the corresponding bicyclic compounds **2** in essentially the same yield. It is also important to note that in all cases only one diastereoisomer of the final product was formed.

To increase the molecular diversity, a number of experiments were attempted by using alkynol derivatives **1**, which contain a heteroatom in the chain that connects the hydroxy functionality and the triple bond, as starting materials (Table 3). We studied the effect of the presence of both oxygen and nitrogen atoms. The reaction led to the expected bicyclic compounds **2** in high yield and as single diastereoisomers (Table 3). The structure of compound **2r** was verified by X-ray crystallographic analysis.[17] Although results summarized in Table 3 correspond to those reactions performed by using $PtCl_4$ as the catalyst, it should be noted

Table 3. Cycloisomerization reactions of heteroatom-containing alkynol derivatives **1g–j** in the presence of different alcohols.



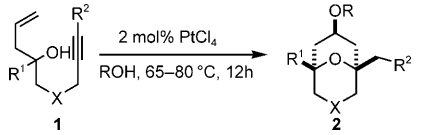
Alkynol	X	Product	R	Yield [%][a]
1g	O	**2m**	*i*Pr	93
1g	O	**2n**	Me	95
1g	O	**2o**	Pr	91[b]
1h	PhN	**2p**	Me	89
1i	4-MeOC_6H_4N	**2q**	Me	90
1j	TsN	**2r**	Me	93

[a] The yield of the isolated spectroscopically pure product **2**. [b] Reaction carried out with $AuCl_3$ (2 mol %) as the catalyst at room temperature. Ts = *para*-toluenesulfonyl.

that similar results were observed by using the corresponding platinum(II), gold(III), and gold(I) complexes.

Another interesting point for appendage variation is the triple bond of the starting alkynol derivative. In all the examples shown so far, we have used alkynol derivatives with a terminal triple bond as the starting materials. However, the reaction also worked with internal triple bonds (Table 4), and both aryl and alkyl groups at the triple bond

Table 4. Cycloisomerization reactions of the alkynol derivatives **1k–o** containing an internal triple bond in the presence of different alcohols.

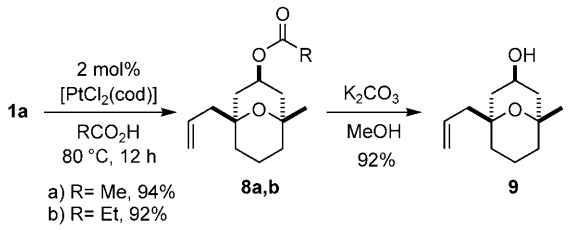


Alkynol	R^1	R^2	X	Product	R	Yield [%][a]
1k	Et	Ph	CH_2	**2s**	Me	81
1l	allyl	Me	O	**2t**	Me	89
1m	allyl	Et	O	**2u**	Me	91
1n	allyl	Pr	O	**2v**	Me	89
1n	allyl	Pr	O	**2w**	Et	93
1o	allyl	Ph	O	**2x**	Me	87

[a] The yield of isolated spectroscopically pure product **2**.

were appropriate substituents. We observed that for this type of substrate the most suitable catalyst was $PtCl_4$. So, in general, these reactions were performed by warming a solution of alkynol **1** in the corresponding alcohol at 65–80 °C (depending on the alcohol used as nucleophile) for 12 hours and utilizing 2 mol % of $PtCl_4$ as the catalyst.

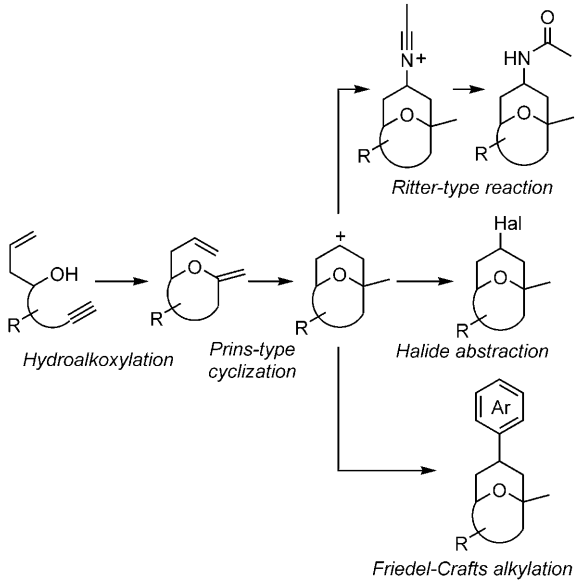
Other oxygen-centered nucleophiles: At this point, we turned our attention to the nucleophile and, in particular, to the use of other oxygenated nucleophiles than alcohols. Thus, we investigated the reaction with carboxylic acids as the nucleophiles. These reactions were performed by mixing alkynol **1a** with 2 mol % of $[PtCl_2(cod)]$ in the corresponding carboxylic acid as the solvent at 80 °C for 12 hours (Scheme 5). Under these conditions, the ester derivatives



Scheme 5. Carboxylic acids as nucleophiles: the catalytic synthesis of ester derivatives **8a**,**b** and further transformation into alcohol **9**.

8a,**b** were isolated in high yield and as single diastereoisomers. Furthermore, treatment of the propionic acid derivative **8b** with potassium carbonate in methanol led to the formation of the hydroxy-substituted eight-membered carbocycle **9**. This result is interesting because **9** is formally obtained from a reaction in which H_2O is used as the nucleophile. It should be noted that we could not achieve the direct reaction of alkynols **1** and water as the nucleophile under any of the reaction conditions attempted. So, the alternative sequence shown in Scheme 5 seems an appropriate strategy to obtain hydroxy-substituted derivatives such as **9**.

Nitrogen-centered, carbon-centered, and halogen nucleophiles: Having succeeded in the introduction of oxygen-centered nucleophiles and bearing in mind that the tandem hydroalkoxylation/Prins-type cyclization would formally provide a carbocationic intermediate, we thought that this carbocation could be trapped by other types of nucleophiles (Scheme 6). For example, for the introduction of nitrogen-centered nucleophiles we considered the possibility of a Ritter-type reaction.[18] We also believed that halogenated compounds could be obtained as a result of halide abstraction from a halocarbon atom by the intermediate cation.[19]

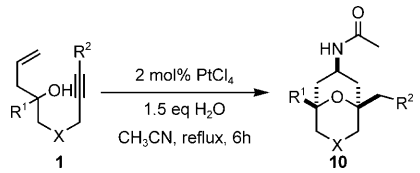


Scheme 6. Proposed reactions for the incorporation of nitrogen-, halogen-, and carbon-centered nucleophiles.

And finally, a Friedel–Crafts alkylation could be considered for the introduction of carbon-centered nucleophiles (Scheme 6).[20]

So, we heated a solution of alkynols **1** in acetonitrile and 1.5 equivalents of H_2O in the presence of 2 mol% of $PtCl_4$ to reflux for 6 h to introduce the nitrogen-centered nucleophiles. Under these conditions, amide derivatives **10** were isolated in very high yield and as single diastereoisomers (Table 5). Crystals of **10a** were obtained from a pentane/dichloromethane mixture that were suitable for X-ray analysis, thus confirming the proposed structure.[17] We also observed that these reactions may also be carried out with 2 mol% of $AuCl_3$ as the catalyst.

Table 5. Catalytic synthesis of amide derivatives **10** using nitrogen-centered nucleophiles.



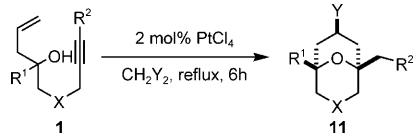
Alkynol	R^1	R^2	X	Product	Yield [%][a]
1a	allyl	H	CH_2	**10a**	86
1c	Bu	H	CH_2	**10b**	84
1g	allyl	H	O	**10c**	89
1k	Et	Ph	CH_2	**10d**	87

[a] The isolated yield of the isolated spectroscopically pure product **10**.

Next, we studied the possibility of introducing a halogen atom into the molecule. The use of CH_2Cl_2 and CH_2Br_2 as both the solvents and halogen sources resulted in the efficient incorporation of chlorine and bromine atoms into the reaction products. These reactions were performed with 2 mol% of $PtCl_4$ as the catalyst to provide compounds **11** in high yield as single diastereoisomers (Table 6).

Interestingly, when the reaction discussed above was carried out with 2 mol% of [AuCl(PPh_3)]/AgOTf as the catalyst in dichloromethane as the solvent, we did not observe

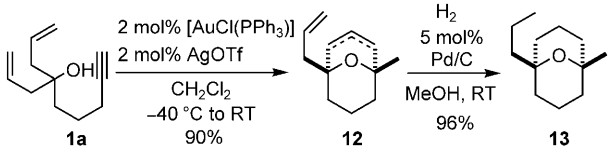
Table 6. Catalytic synthesis of halogenated derivatives **11**.



Alkynol	R^1	R^2	X	Y	Product	Yield [%][a]
1a	allyl	H	CH_2	Cl	**11a**	92
1a	allyl	H	CH_2	Br	**11b**	76[b]
1b	Me	H	CH_2	Cl	**11c**	90
1g	allyl	H	O	Cl	**11d**	78
1k	Et	Ph	CH_2	Cl	**11e**	83
1p	Et	H	CH_2	Cl	**11f**	85

[a] The yield of the isolated spectroscopically pure product **11**. [b] Trace amounts of the corresponding chlorinated compound **11a** were detected in the crude product.

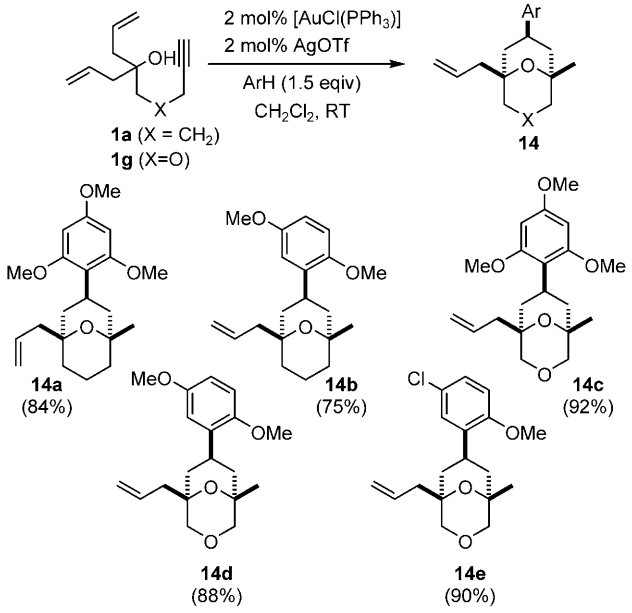
the incorporation of a chlorine atom into the final product; instead, the elimination product **12** was isolated as a mixture of two regioisomers (Scheme 7). Further catalytic hydrogenation of this mixture afforded **13** as a single isomer in 96%



Scheme 7. Catalytic synthesis of diene derivatives **12** and further transformation into bicyclic ether **13**.

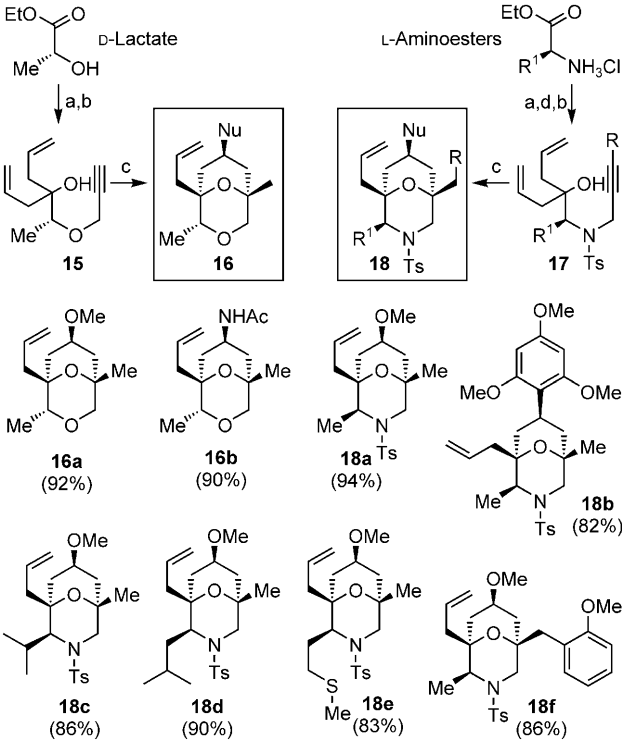
yield. Formally, this simple two-step sequence could be seen as a tandem hydroalkoxylation/Prins-type cyclization reaction in which a hydride ion acted as the nucleophile.

From the point of view of organic synthesis, a major challenge is the creation of new carbon–carbon bonds. So the possibility of employing carbon-centered nucleophiles in our reaction was an attractive goal. To this end, as previously noted, we considered the tandem hydroalkoxylation/Prins-type cyclization/Friedel–Crafts alkylation shown in Scheme 6. These reactions were performed by treating alkynol **1a**,**g** with 2 mol% of [AuCl(PPh$_3$)]/AgOTf in the presence of the corresponding aromatic compound (1.5 equivalents) and with dichloromethane as the solvent (Scheme 8). As shown, electron-rich aromatic compounds were appropriate reagents to effect this reaction. Thus, compounds **14** were isolated in high yield as single diastereoisomers.



Scheme 8. Carbon-centered nucleophiles: the catalytic synthesis of bicyclic compounds **14**.

Synthesis of enantiomerically pure products: α-Hydroxy acids and α-amino acids are useful building blocks in organic synthesis and are common core structures for a number of synthetically challenging and medicinally important agents. In this context, we thought that our tandem catalytic reaction could be applied to alkynols derived from lactic acid and natural α-amino acids to obtain enantiomerically pure compounds with potential utilities in pharmacological areas. We then synthesized alkynol derivatives **15** and **17** from (−)-ethyl D-lactate and several L-amino esters, respectively, by using conventional organic transformations (Scheme 9).



Scheme 9. Enantiopure bicyclo[3.3.1]nonanes derived from D-lactate and L-amino esters. Reagents and conditions: a) NaH, RC≡CCH$_2$Br; b) H$_2$C=CHCH$_2$MgBr; c) PtCl$_4$ (2 mol%) in MeOH, CH$_3$CN/H$_2$O, or 1,3,5-trimethoxybenzene/CH$_2$Cl$_2$; d) TsCl, Et$_3$N. See the Supporting Information for details. The yields in parenthesis refer to the last step (c). Ts = *para*-toluenesulfonyl.

Further treatment of these alkynol derivatives with 2 mol% of PtCl$_4$ in the presence of an appropriate nucleophile under the optimized reaction conditions previously described led to the formation of **16** or **18** in high yield and as single diastereoisomers and enantiomers. The structures of **16b** and **18b**,**d** were verified by X-ray crystallographic analysis.[17]

Interestingly, we observed the opposite chiral induction when starting from alkynol **15**, derived from D-lactate, or from alkynol **17**, derived from L-amino acids. To justify this fact, we need focus on the mechanism of the reaction and, in particular, on the structure of the corresponding intermediate **6** (Scheme 3 and Figure 1). Thus, for D-lactate-derived product **16** the reaction should proceed through inter-

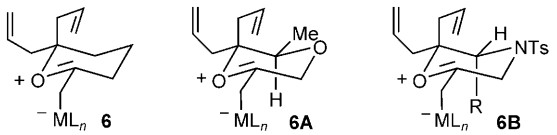


Figure 1. Proposed intermediates **6** that justify the stereochemistry observed in **16**–**18**.

mediate **6A** (Figure 1). As shown, the methyl group is placed in a pseudoequatorial position in this structure. However, to explain the formation of **18**, derived from L-amino acids, the reactions should proceed through intermediate **6B** in which the R group is placed in a pseudoaxial position (Figure 1).[21]

Conclusions

We have developed a new, highly efficient method for the synthesis of complex bicyclic compounds from easily available alkynol derivatives. The reaction is based on a tandem process that involves an intramolecular hydroalkoxylation of a triple bond followed by a Prins-type cyclization. Although several metallic complexes catalyzed this transformation, those complexes derived from gold and platinum were the most efficient. Simple variations on the structure of the starting alkynol derivative or in the nature of the nucleophile used allowed the synthesis of more than fifty new compounds, including products in their enantiomerically pure form. The [3.3.1]bicyclic systems obtained through this strategy are natural-like structural motifs that might be of value in the discovery of biologically active molecular agents. In this context, the process described herein is well-suited for drug-discovery programs, and the enantiomerically pure products that are easily obtained from α-amino acids and lactic acid are remarkable products.

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