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Tandem Intramolecular Hydroalkoxylation–Hydroarylation Reactions: Synthesis of Enantiopure Benzofused Cyclic Ethers from the Chiral Pool

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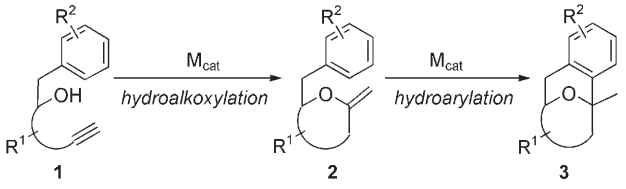
Nowadays, one of the main challenges that organic chemists face is the production of architecturally complex molecules in facile, efficient, and economical ways.[1] In this context, concurrent tandem catalysis provides a means to improve chemical transformations and thus synthetic efficiency.[2] Accordingly, our research group has recently developed some new tandem catalytic reactions for the synthesis of attractive skeletal cores from simple starting materials.[3,4] Having in mind the superb ability of gold and platinum catalysts to accomplish otherwise difficult hydroalkoxylation[5] and hydroarylation[6] reactions of unsaturated substrates,[7] we were drawn to the possibility of combining these two different reactions in a single synthetic operation.[8] We envisaged that starting from benzyl-substituted alkynol derivatives **1**, an initial intramolecular hydroalkoxylation reaction would provide the enol ethers **2**. This substrate would be disposed to undergo a catalytic intramolecular hydroarylation reaction to give interesting benzo-fused ethers (Scheme 1).

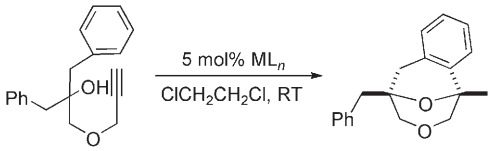


Scheme 1. Concept of the tandem catalytic hydroalkoxylation–hydroarylation reaction for the synthesis of benzofused bicyclic ethers.

Our final objective was to find the appropriate conditions to perform both steps in a one-pot approach by using a single catalyst. Also appealing was the possibility of applying this reaction for the modification of some natural products to generate enantiomerically pure compounds with potential biological activity. Herein, we report our findings in this field.

To check the feasibility of the proposed tandem catalytic reaction, the initial proof-of-concept studies were performed by using the model dibenzyl-substituted alkynol **1a** as starting material. Thus, we treated compound **1a** with 5 mol% of several gold, platinum, and silver complexes in 1,2-dichloroethane as solvent at room temperature (Table 1). When [Ph_3PAuCl] was used as catalyst, the reaction did not proceed, and the starting compound **1a** was quantitatively recovered after 24 h (Table 1, entry 1). However, we found that the desired ether **3a** was produced in 96% yield as a single diastereoisomer when the reaction was performed with the cationic gold(I) catalyst generated in situ from

Table 1. Cycloisomerization reactions of the alkynol **1a** with several gold, platinum and silver catalysts.



Entry	Catalyst (ML_n)	t [h]	Yield [%][a]
1	[Ph_3PAuCl]	24	0
2	[Ph_3PAuCl]/AgOTf	1	96
3	AgOTf	24	<10[b]
4	$AuCl_3$	6	50[c]
5	[(cod)$PtCl_2$]	24	0
6	[(cod)$PtCl_2$]/AgOTf	1	94
7	$PtCl_4$	1	92

[a] Yield of isolated product based on the starting alkynol **1a**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture; the starting alkynol **1a** was the major product (ca. 90%). [c] 42% of the starting alkynol **1a** was recovered.

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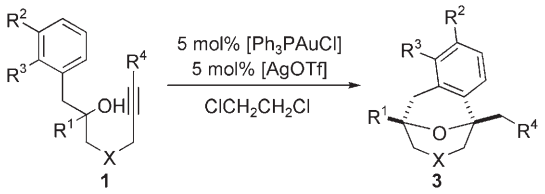
[Ph_3PAuCl] and AgOTf (Table 1, entry 2). To ensure that the silver complex was not responsible for the catalytic process, we carried out an experiment with 5 mol% AgOTf (Table 1, entry 3). However, under these conditions, compound **3a** was generated in less than 10% yield after 24 h at room temperature. Next, we tried the reaction with the higher valent gold complex [$AuCl_3$] (Table 1, entry 4). This complex turned out to be less active than the cationic gold(I) complex mentioned above; the product **3a** was isolated in 50% yield after 6 h.

The use of [(cod)$PtCl_2$] (cod = 1,5-cyclooctadiene) was completely ineffective and the starting material was recovered after 24 h at room temperature (Table 1, entry 5). However, the use of the cationic platinum(II) complex formed in situ by mixing [(cod)$PtCl_2$] and AgOTf gave excellent results, allowing the complete transformation of alkynol **1a** into bicyclic compound **3a** (94% yield) after only 1 h (Table 1, entry 6). Finally, the platinum(IV) complex $PtCl_4$ also catalyzed this process to give **3a** in 92% yield after 1 h (Table 1, entry 7).

All these experiments allowed us to determine that both cationic Pt^{II} and Au^{I}, and also Pt^{IV} complexes were appropriate catalysts to perform the synthesis of benzofused bicyclo[3.3.1]nonanes such as **3a**. With proof-of-concept established, the scope of this catalytic process was evaluated by changing the nature of the substituents of the starting alkynol derivative **1** at several points. The results are summarized in Table 2.

Table 2. Benzofused bicyclo[3.3.1]nonanes **3** by tandem hydroalkoxylation–hydroarylation reactions of the alkynol derivatives **1**.[a]



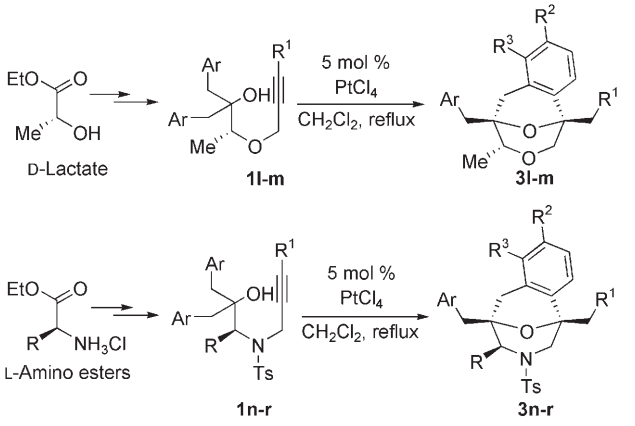
Entry	**1**	R^1	R^2	R^3	R^4	X	**3**	Yield [%][b]
1	**1a**	Bn	H	H	H	O	**3a**	96
2	**1b**	3-MeOBn	OMe	H	H	O	**3b**	96
3	**1c**	Bn	H	H	Ph	O	**3c**	92
4	**1d**	Bn	H	H	H	CH_2	**3d**	95
5	**1e**	Bn	H	H	Ph	CH_2	**3e**	92
6	**1f**	3-MeOBn	OMe	H	H	CH_2	**3f**	88
7	**1g**	3-MeBn	Me	H	H	CH_2	**3g**	90
8	**1h**	H	OMe	H	H	CH_2	**3h**	70
9	**1i**	Et	Me	H	H	CH_2	**3i**	82
10	**1j**	1-NaphCH_2[c]	-$(CH)_4$-		H	CH_2	**3j**	88
11	**1k**	Bn	H	H	H	NTs	**3k**	90

[a] Reactions stirred at room temperature till consumption of the starting material (1–8 h). [b] Yield of isolated product based on starting alkynol **1**. [c] 1-NaphCH_2 = 1-naphthylmethyl.

Interestingly, for example, the chain connecting the hydroxyl group and the alkyne of starting compound **1** may contain not only an oxygen atom (Table 2, entries 1–3), but also a CH_2 group (Table 2, entries 4–10) or a nitrogen atom (Table 2, entry 11). Thus, different eight-membered carbocycles and oxygen- and nitrogen-containing heterocycles **3** are readily obtained in high yield and as single diastereoisomers. The reaction can also be performed with alkynols **1c** and **1e** containing internal triple bonds (Table 2, entries 3 and 5). The R^1 group attached to the carbon atom containing the hydroxy group could also be varied (Table 2). Structural assignments of compounds **3** were based on a series of NMR studies. Finally, it should be noted that although the products shown in Table 2 were obtained by reactions performed with [Ph_3PAuCl]/AgOTf as catalyst, essentially the same results were observed by using [(cod)$PtCl_2$]/AgOTf or $PtCl_4$ as catalysts.

The importance of natural products as lead structures for the generation of small-molecule libraries has been emphasized in recent years.[9] In this context, we thought that α-hydroxy- and α-amino acids were ideal templates for the synthesis of potentially bioactive compounds by applying the tandem catalytic reaction described above. Thus, by conventional organic chemistry reactions, D-lactate and several L-amino esters were easily transformed into the chiral alkynol derivatives **1l–r** (Table 3). Further treatment of these compounds with 5 mol% $PtCl_4$ in dichloroethane at reflux readily afforded the α-hydroxy acid derivatives **3l**,**m** or the α-amino acid derived products **3n–r** in very high yield as single diastereomers and enantiomers. As shown, this protocol allows the synthesis of enantiomerically pure bicyclo[3.3.1]nonanes with a high degree of diversity from readily available α-hydroxy acids or α-amino acids. Structural as-

Table 3. Enantiopure benzofused bicyclo[3.3.1]nonanes.

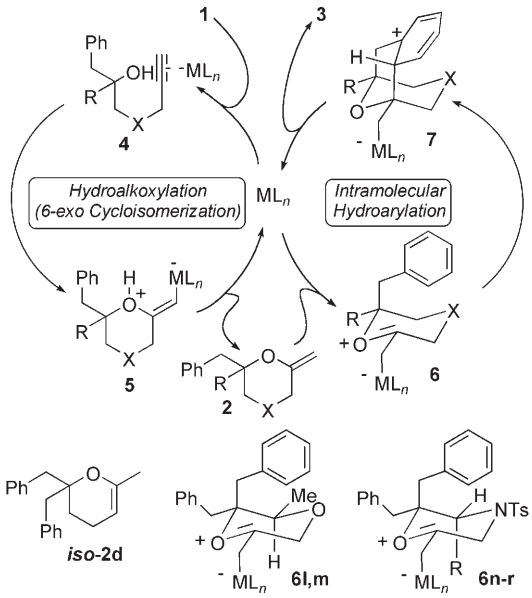


Entry	**1**	Ar	R^1	R	**3**	R^2	R^3	Yield [%][a]
1	**1l**	Ph	H	–	**3l**	H	H	95
2	**1m**	3-MeOC_6H_4	Ph	–	**3m**	OMe	H	95
3	**1n**	Ph	H	Me	**3n**	H	H	93
4	**1o**	Ph	Ph	Me	**3o**	H	H	88
5	**1p**	3-MeOC_6H_4	H	Bn	**3p**	OMe	H	95
6	**1q**	Ph	H	*i*Bu	**3q**	H	H	66
7	**1r**	1-Naph[b]	H	*i*Bu	**3r**	-$(CH)_4$-		93

[a] Yield based on starting alkynol **1**. [b] 1-Naph = 1-naphthyl.

signments of these new compounds were based on a series of NMR studies. Additionally, the structures of compounds **3n**, **3o**, and **3q** were confirmed by single-crystal X-ray structure analysis.[10] Surprisingly, we observed the opposite chiral induction when starting from alkynols **1l**,**m**, derived from D-lactate, or from alkynols **1n**–**r**, derived from L-amino acids.

A tentative mechanism for the formation of compounds **3**, based on a tandem sequence involving a 6-*exo*-cycloisomerization reaction followed by an intramolecular hydroarylation process, is presented in Scheme 2. Thus, the reaction is



Scheme 2. Proposed mechanism for the formation of benzofused bicyclo-[3.3.1]nonanes **3** from alkynols **1**.

initiated by coordination of the metallic complex to the triple bond of the starting alkynol **1** to form intermediate **4**. Intramolecular addition of the hydroxy group to the internal carbon of the triple bond generates **5**. Protodemetalation of the latter affords the enol ether **2** and releases the catalytic species. Once enol ether **2** is formed, it enters the second catalytic cycle. Thus, after an initial coordination of the catalyst to the double bond of the enol ether **2**, the oxonium intermediate **6** is formed. Further nucleophilic attack of the phenyl group affords the intermediate **7**. Interestingly, the stereochemistry of all new stereocenters is fixed by the axial position of the benzyl group required for the cyclization step. Finally, from **7**, a rearomatization and a protodemetalation step lead to the final product **3**, regenerating the catalytic species.

The role of enol ethers **2** as intermediates of the reaction was supported by the isolation of enol ether ***iso*-2d** (see Scheme 2) when an experiment was performed with alkynol **1d** in dichloromethane at −20 °C and using 5 mol % $PtCl_4$ as catalyst. To corroborate the formation of **3d** from ***iso*-2d** we treated the latter with 5 mol % $PtCl_4$ in dichloromethane at room temperature. After 1 h, complete conversion to **3d** was observed.

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 2. In principle, both Lewis and Brønsted acids could catalyze the hydroalkoxylation and hydroarylation reactions. Traces of Brønsted acids could be present in the reaction media coming from the platinum or gold complexes (or the solvent), and these protic acids could be the responsible for both or at least one of the catalytic cycles proposed in Scheme 2.[11] To shed light on this issue, the alkynol **1d** was subjected to a range of reaction conditions. No reaction was observed in the absence of platinum or gold complexes or by treatment of **1d** with Brønsted acids, which demonstrates the necessity of the platinum or gold complexes at least for the hydroalkoxylation reaction. To eliminate the possibility of competing Brønsted acid catalysis in the second catalytic cycle (the hydroarylation reaction), we performed some control experiments by using a non-poisoning base. Thus, when compound **1d** was allowed to react with 5 mol % $PtCl_4$ in a dichloromethane solution containing 2.5 mol % of the strong phosphorine base BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine), we observed the formation of the expected product **3d** after 1 h at room temperature. Additionally, we performed an experiment in which we treated **1d** with 5 mol % $PtCl_4$ in dichloromethane at −20 °C and once we observed the complete conversion (by GC-MS) to the intermediate ***iso*-2d**, we added 2.5 mol % BEMP. The solution was warmed to room temperature, and after 1 h complete conversion to the final product **3d** was observed. All these results suggest that residual Brønsted acids are not responsible, because these would be quenched by BEMP (at 2.5 mol %). Accordingly, we believe that the gold or platinum catalytic species are involved in both catalytic cycles proposed in Scheme 2.[12]

To verify the stereochemistry observed in the products derived from D-lactate and L-amino acids (see Table 2), we focused on the structure of the corresponding intermediate **6**. Thus, for D-lactate derived products **3l**,**m** we suppose that the reactions proceed via the intermediates **6l**,**m** (Scheme 2). As shown, in this structure the methyl group is placed in a pseudo-equatorial position. However, to explain the formation of compounds **3n**–**r**, derived from L-amino acids we suppose that the reactions proceed via intermediates **6n**–**r**, in which the R group is placed in a pseudo-axial position.[13]

In summary, we have developed a highly efficient and general method for the diastereoselective synthesis of benzo-fused eight-membered carbo- and heterocycles. The method is based on a new tandem gold- or platinum-catalyzed hydroalkoxylation–hydroarylation reaction. The tandem sequence described allows the straightforward and efficient synthesis of complex final products. The number of points of diversity present in the reaction products, together with the simplicity of the starting materials, makes this tandem reaction a powerful method for both library genera-

tion and target synthesis. The simple transformation of α-hydroxy and α-amino acid derivatives into enantiomerically pure benzofused cyclic ethers reported in this work is a clear example of the possibilities that this new reaction offers for the synthesis of potentially pharmacological active compounds.

Experimental Section

Experimental details and NMR spectroscopic and mass spectrometric data for the experiments reported in Tables 1–3 are given in the Supporting Information.

Acknowledgements

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Keywords: cyclization · domino reactions · gold · homogeneous catalysis · platinum

[1] a) Cambridge University Press, Cambridge, **2001**, p. 168; b) L. F. Tietze, F. Hautner in *Stimulating Concepts in Chemistry* (Eds.: F. Vögtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, p. 38; c) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; d) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2] a) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; see also, b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; c) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reaction in Organic Synthesis* Wiley-VCH, Weinheim, **2006**, p. 672; d) H. Pellisier, *Tetrahedron* **2006**, *62*, 1919–1965, 2143–2173; e) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; f) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; g) T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, **1992**, p. 502.

[3] a) J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2006**, *118*, 2145–2147; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091–2093; b) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, T. Sordo, P. Campomanes, *Chem. Eur. J.* **2005**, *11*, 5735–5741; c) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2005**, *117*, 128–130; *Angew. Chem. Int. Ed.* **2005**, *44*, 126–128.

[4] For some theoretical studies, see: T. Sordo, P. Campomanes, A. Diéguez, F. Rodríguez, F. J. Fañanás, *J. Am. Chem. Soc.* **2005**, *127*, 944–952. See also reference [3b].

[5] For selected examples about the hydroalkoxylation of alkynes, see: a) A. Diéguez-Vázquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley, *Angew. Chem.* **2008**, *120*, 216–219; *Angew. Chem. Int. Ed.* **2008**, *47*, 209–212; b) B. Liu, J. K. De Brabander, *Org. Lett.* **2006**, *8*, 4907–4910; c) V. Belting, N. Krause, *Org. Lett.* **2006**, *8*, 4489–4492; d) S. Antoniotti, E. Genin, V. Michelet, J.-P Genêt, *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977; e) E. Genin, S. Antoniotti, V. Michelet, J.-P Genêt, *Angew. Chem.* **2005**, *117*, 5029–5033; *Angew. Chem. Int. Ed.* **2005**, *44*, 4949–4953; f) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409–5412; g) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

[6] For a review, see: a) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167–182. For some recent selected examples, see: b) A. S. K. Hashmi, M. C. Blanco, *Eur. J. Org. Chem.* **2006**, 4340–4342; c) C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155–3164; d) Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049–5054; e) D. Karshtedt, A. T. Bell, T. D. Tilley, *Organometallics* **2004**, *23*, 4169–4171.

[7] For some recent reviews on gold and platinum catalysis, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 4118–4136; *Angew. Chem. Int. Ed.* **2007**, *46*, 4042–4059; c) D. J. Gorin, D. Toste, *Nature* **2007**, *446*, 395–403; d) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; f) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; g) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; h) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387–391; i) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65.

[8] S. Bhuvaneswari, M. Jeganmohan, C. Cheng, *Chem. Eur. J.* **2007**, *13*, 8285–8293.

[9] a) S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol.* **2005**, *9*, 248–258; b) J. Y. Ortholand, A. Ganesan, *Curr. Opin. Chem. Biol.* **2004**, *8*, 271–280; c) A. M. Boldi, *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286.

[10] CCDC-678706, -678707, and -678708 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.

[11] The possibility of Brønsted acid catalysis in reactions where Lewis acids are used has been suggested by other authors. See: a) G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247–1252; b) M. Georgy, V. Boucard, J.-C. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181; c) M. Yasuda, T. Somyo, A. Baba, *Angew. Chem.* **2006**, *118*, 807–810; *Angew. Chem. Int. Ed.* **2006**, *45*, 793–796; d) R. Sanz, A. Martínez, D. Miguel, J. M. Alvarez-Gutiérrez, F. Rodríguez, *Adv. Synth. Catal.* **2006**, *348*, 1841–1845.

[12] The role of the gold and platinum species seems obvious, and a Brønsted acid catalysis seems very unlikely. However, for the second proposed cyclization, the possibility of Lewis acid-assisted Brønsted acid catalysis, resulting from the gold or platinum catalysts in the presence of adventitious water or another proton donor such as the starting alcohol **1**, cannot be totally ruled out. For selected examples about this kind of catalysis, see: a) T. Yang, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071; b) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 3647–3655.

[13] This proposal is supported by DFT calculations performed on compounds analogous to **6l**,**m** and **6n**–**r**. These studies show that the conformers depicted in Scheme 2 are more stable than those with the methyl group (or R group) at a pseudo-axial (pseudo-equatorial) position.

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