Gold Catalysis

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Gold(I)-Catalyzed Tandem Reactions Initiated by 1,2-Indole Migrations**

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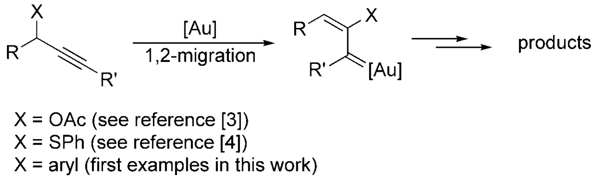
Dedicated to Professor Rafael Pedrosa on the occasion of his 60th birthday

Recent years have witnessed tremendous growth in the number of gold-catalyzed transformations.[1] Most of these new processes are based on the ability of gold complexes to activate alkynes. Particularly interesting is the chemistry of propargylic esters because of their propensity to undergo 1,2- and 1,3-acyl migration reactions.[2] Notably, the 1,2-acyl migration reaction leads to the formation of a Au–carbene complex, which can be poised for subsequent reactions to ultimately afford a range of diverse products (Scheme 1).[3]



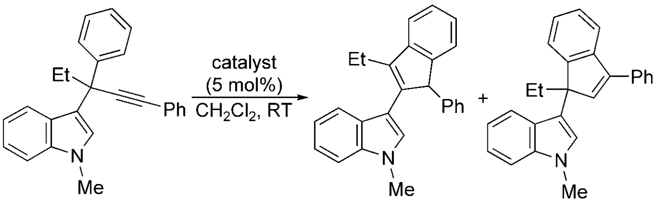
Scheme 1. Gold-promoted 1,2-migration reactions.

Very recently, propargylic sulfides have been shown to participated in related 1,2-sulfur migration reactions (Scheme 1).[4] In this context, highly interesting processes would be the 1,2-migration of propargylic alkyl or aryl groups, as they would imply the rupture and formation of carbon–carbon bonds (Scheme 1).[5] However, as far as we know, these reactions have not been reported and herein we present the first examples. In particular, we describe new gold-catalyzed tandem reactions of propargylic indoles which are initiated by an unprecedented 1,2-indole migration.

Our research group has been involved in the development of new catalytic methods for the direct substitution of the hydroxy group in alcohols by nucleophiles.[6] In this context, we have reported the C3-selective propargylation of indoles with alcohols catalyzed by Brønsted acids.[7] Mindful of the importance of indoles in organic and medicinal chemistry,[8] we thought that these C3-propargylated indoles could be interesting precursors for elaborated indole derivatives, and which could be obtained through gold-catalyzed processes.[9]

Initially, we used indole **1a** as a model substrate (Table 1). Thus, **1a** was treated with a catalytic amount of several gold and platinum complexes in dichloromethane at room temperature. No reaction was observed with [AuCl(Ph$_3$P)], AuCl$_3$, [PtCl$_2$(cod)], or the cationic platinum complex which was generated in situ by mixing [PtCl$_2$(cod)] and AgSbF$_6$ (Table 1, entries 1–4; cod = cycloocta-1,5-diene). Gratifyingly, complete conversion of **1a** into the 2-indenylindole derivative **2a** was observed by using (as catalysts) the cationic gold(I) complex which was generated in situ from [AuCl(Ph$_3$P)] and AgSbF$_6$, or the bis(trifluoromethanesulfonyl)imidate derivatives [AuNTf$_2$(Ph$_3$P)] and [AuNTf$_2$(SPhos)] (Table 1, entries 5–7; SPhos = 2-dicyclohexylphosphino-2′,6′-dimeth-

Table 1: Effect of the catalyst on the reactivity of **1a**.



1a **2a** **3a**

Entry	Catalyst	*t* [h]	**2a**/**3a**[a]	Yield [%][b]
1	[AuCl(Ph$_3$P)]	24	–	0[c]
2	AuCl$_3$	24	–	0[c]
3	[PtCl$_2$(cod)]	24	–	0[c]
4	[PtCl$_2$(cod)]/AgSbF$_6$	24	–	0[c]
5	[AuCl(Ph$_3$P)]/AgSbF$_6$	2	12:1	74
6	[AuNTf$_2$(Ph$_3$P)]	1	12:1	79
7	[AuNTf$_2$(SPhos)]	2	10:1	76
8	[AuCl(IMe)]/AgSbF$_6$	2	3:1	55[d]

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **2a** based on indole **1a**. [c] Indole **1a** was recovered. [d] **3a** was isolated in 18% yield.

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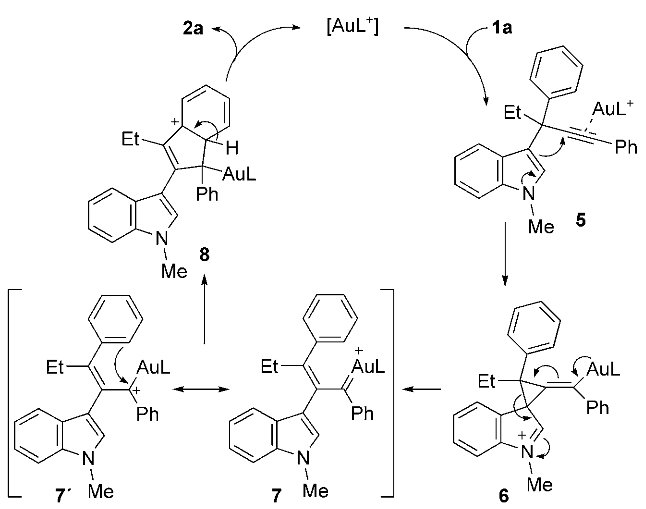
oxybiphenyl).[10] In these reactions we also observed the formation of trace quantities of isomeric 1-indenylindole derivative **3a**. The amount of **3a** generated increased by using the cationic gold(I) complex derived from [AuCl(IMe)] with an N-heterocyclic carbene ligand (Table 1, entry 8; IMe = 1,3,4,5-tetramethylimidazol-2-ylidene).[11]

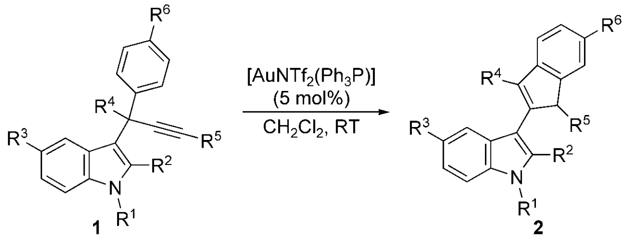
Taking into consideration investigations by Nolan and co-workers on the reactivity of propargylic esters,[12] the formation of the minor indene derivative **3a** might be expected. This compound is generated by a simple intramolecular hydroarylation of the triple bond, which is favored by an initial coordination of the gold complex to the alkyne. However, the reaction leading to the 2-indenylindole derivative **2a** is much more interesting. The structure of this compound indicates that a 1,2-indole migration has occurred at some point in the catalytic process. A tentative mechanism for the formation of **2a** is proposed in Scheme 2. Thus, an initial coordination of the gold complex to the triple bond of **1a** generates the intermediate **5**. Intramolecular attack of the indole on the activated alkyne gives the vinyl–gold complex **6**, which becomes the gold carbene complex **7** through a 1,2-migration of the indole. Carbene complex **7** can also be represented as the resonance form **7′**. Further intramolecular nucleophilic attack of the phenyl group on the carbene carbon center leads to the formation of intermediate **8**. Finally, a rearomatization step and subsequent protodemetalation affords the final product **2a** and regenerates the catalytic gold species. Formation of **2a** from carbene intermediate **7** can also be explained through a simple C–H insertion reaction.[13] Alternatively, the intramolecular nucleophilic attack of the phenyl group on the vinyl–gold intermediate **6** to give **8** could also be considered.[3b]



Scheme 2. Proposed mechanism for the formation of **2a** from **1a**. Tandem 1,2-indole migration/C–H insertion reactions. L = ligand.

Whichever mechanism is invoked, this new reaction may be considered a tandem sequence involving a 1,2-indole migration followed by a formal intramolecular C–H insertion reaction. To evaluate the scope of the process we performed a set of experiments using the C3-propargylated indole derivatives **1** as starting materials (Table 2). The results shown in Table 2 correspond, in general, to reactions performed with [$AuNTf_2(Ph_3P)$] as the catalyst. This catalyst was chosen for its availability and for ease of handling. However, similar results were obtained by using the more sophisticated [$AuNTf_2$(SPhos)] catalyst or the cationic complex which was generated in situ from [$AuCl(Ph_3P)$] and $AgSbF_6$. Table 2 outlines the allowed substituents of alkyne **1** at both the propargylic position (R^4) and at the terminal position (R^5). Regarding the indole moiety, not only *N*-methylindole derivatives but also N-unsubstituted indole derivatives (including those with electron-withdrawing substituents) as well as 2-methylindole derivatives were appropriate substrates for this reaction (Table 2, entries 1–13). In general, high yields of the corresponding 2-indenylindole derivative **2** were obtained, and only trace amounts of the corresponding isomeric derivatives analogous to **3a** were detected in the crude samples for some of the reactions. Structural assignments of all new compounds were based on a series of NMR studies. Additionally, the structures of **2c** and **2e** were confirmed by single-crystal X-ray diffraction analysis.[14]

Table 2: Preparation of 3-(1*H*-inden-2-yl)-1*H*-indoles **2** by tandem 1,2-indole migration/C–H insertion reactions of C3-propargylated indole derivatives **1**.[a]

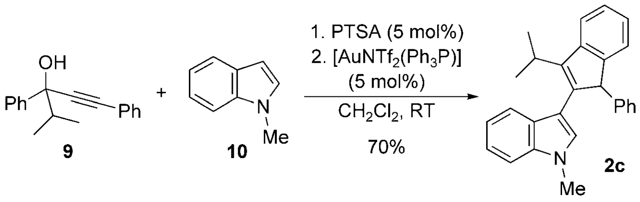


Entry	**1**	R^1	R^2	R^3	R^4	R^5	R^6	**2**	Yield [%][b]
1	**1a**	Me	H	H	Et	Ph	H	**2a**	79
2	**1b**	Me	H	H	*n*Pr	Ph	H	**2b**	75
3	**1c**	Me	H	H	*i*Pr	Ph	H	**2c**	76
4	**1d**	Me	H	H	*i*Pr	*n*Bu	H	**2d**	73
5	**1e**	Me	H	H	Me	*n*Bu	Cl	**2e**	79[c]
6	**1f**	H	H	H	Me	Ph	H	**2f**	50
7	**1g**	H	H	H	*n*Pr	Ph	H	**2g**	60
8	**1h**	H	H	H	Me	*n*Bu	H	**2h**	66
9	**1i**	H	H	CO_2Me	Et	*n*Bu	H	**2i**	70
10	**1j**	H	H	Br	Me	*n*Bu	H	**2j**	69
11	**1k**	H	Me	H	Me	Ph	H	**2k**	68
12	**1l**	Me	Me	H	Me	Ph	H	**2l**	68[c]
13	**1m**	Me	Ph	H	Me	Ph	H	**2m**	73

[a] Reaction mixtures stirred at room temperature until the starting material was consumed (as evident by GC-MS analysis; 0.5–7 h). [b] Yield of isolated product based on indole **1**. [c] Reaction performed with [$AuCl(Ph_3P)$]/$AgSbF_6$ as the catalyst.

Mindful that the starting indole-containing alkyne derivatives **1** were synthesized from the corresponding propargylic alcohols by our reported Brønsted acid catalyzed procedure,[7] we wondered if access to indene derivatives **2** from readily available propargylic alcohols, by using a concurrent tandem catalysis protocol, was possible.[15]

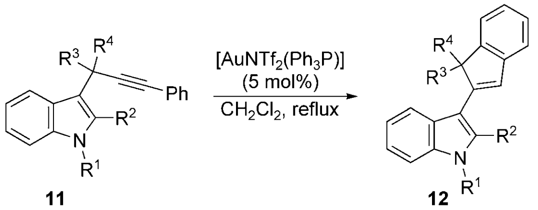
Thus, as shown in Scheme 3, the consecutive reaction of propargylic alcohol **9** and *N*-methylindole (**10**) with PTSA (5 mol%) and [AuNTf$_2$(Ph$_3$P)] (5 mol%) led to the formation of 1-methyl-3-(3-isopropyl-1-phenyl-1*H*-inden-2-yl)-1*H*-indole (**2c**) in 70% yield. Notably, this one-pot process does not require any solvent change or removal of PTSA prior to the addition of the gold catalyst. By following this strategy the isolation of the indole-containing alkynes **1** is avoided, and the reaction can be performed from readily available propargylic alcohols and indoles in a straightforward synthetic protocol.



Scheme 3. One-pot synthesis of **2c** from propargylic alcohol **9** and *N*-methylindole (**10**).

To further study the new 1,2-indole migration reaction, and in particular the reactivity of gold carbene intermediates analogous to **7** (Scheme 2), we performed a set of experiments with indole-containing alkynes **11** (Table 3). These starting materials differ from alkynes **1** in that they do not bear an aryl substituent at the propargylic position, and so the subsequent formal C–H insertion reaction is not possible. When alkynes **11** were treated with 5 mol% of [AuNTf$_2$(Ph$_3$P)] in methylene chloride at reflux, the new 2-indenylindole derivatives **12** were obtained exclusively in high yields (Table 3, entries 1–6). Surprisingly, in these reactions the phenyl group that participates in the formation of the indene skeleton is that at the terminal position of the triple bond. In contrast, as shown in Scheme 2, the formation of 2-indenylindole derivatives **2** supposes the reaction of the aryl group at the propargylic position. Structural assignments of the new compounds **12** were based on a series of NMR studies. Additionally, the structures of **12a** and **12b** were confirmed by single-crystal X-ray diffraction analysis.[14]

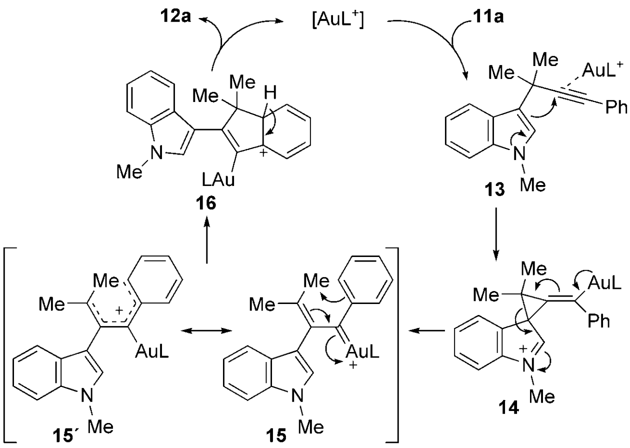
Table 3: Preparation of 3-(2-indenyl)indoles **12** by gold-catalyzed reactions of propargylated indole derivatives **11**.[a]



Entry	11	R^1	R^2	R^3	R^4	12	Yield [%][b]
1	**11a**	Me	H	Me	Me	**12a**	82
2	**11b**	Me	H	Et	Et	**12b**	55
3	**11c**	Me	H	Me	*c*-C$_3$H$_5$	**12c**	87
4	**11d**	Me	Me	Me	Me	**12d**	72
5	**11e**	H	H	Me	*c*-C$_3$H$_5$	**12e**	75
6	**11f**	H	Me	Me	*c*-C$_3$H$_5$	**12f**	80

[a] Reaction mixtures stirred at reflux until the starting material was consumed (as evident by GC-MS analysis; 1–24 h). [b] Yield of isolated product was based on indole **11**.

Shown in Scheme 4 is a tentative mechanism for the formation of 2-indenylindole derivatives **12**. The initial steps are analogous to those previously proposed in Scheme 2. Thus we suppose the formation of the gold carbene complex **15** by a gold-mediated 1,2-indole migration and through intermediates **13** and **14**. The cationic pentadienyl resonance form **15′** contributes to the gold carbene complex **15**. This intermediate may evolve through a Nazarov-type cyclization to give **16** and, ultimately, after a rearomatization and protodemetalation, the isolated product **12**. To the best of our knowledge, tandem sequences involving 1,2-migration reactions followed by Nazarov-type cyclizations have not been described previously. [16]



Scheme 4. Proposed mechanism for the formation of **12** from **11**. Tandem 1,2-indole migration/Nazarov cyclization reactions.

In summary, we have discovered that C3-propargylated indoles react under gold-catalyzed conditions through unprecedented 1,2-indole migrations. These are the first examples where the migrating group at the propargylic position is not an heteroatom-centered moiety, and so these are the first examples where the 1,2-migration reaction supposes the rupture and formation of carbon–carbon bonds. Thus, new tandem processes involving 1,2-indole migration/C–H insertion reactions and 1,2-indole migration/Nazarov cyclization reactions have been described. Different indene-containing indole scaffolds have been easily prepared by these protocols. These new compounds contain two medicinally relevant substructures, the indole unit and the indene unit,[8,17] therefore the strategy described here could be applied to the synthesis of compounds that could be potentially bioactive. The possibility of performing the reactions following a concurrent tandem catalysis protocol starting from readily available propargylic alcohols and indoles should also be noted. Further studies to extend the scope of the 1,2-indole migration reaction and the development of other indole migration processes are in progress.

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[1] For recent reviews on gold catalysis, see: a) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181; b) J. Muzart, *Tetrahedron* **2008**, *64*, 5815–5849; c) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; d) D. J. Gorin, D. Toste, *Nature* **2007**, *446*, 395–403; e) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; f) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; g) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; h) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; i) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; j) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555–4563; k) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387–391; l) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65.

[2] For excellent accounts see the following and references therein: a) A. Correa, N. Marion, L. Fensterbank, M. Malacria, S. P. Nolan, L. Cavallo, *Angew. Chem.* **2008**, *120*, 730–733; *Angew. Chem. Int. Ed.* **2008**, *47*, 718–721; b) N. Marion, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 2806–2809; *Angew. Chem. Int. Ed.* **2007**, *46*, 2750–2752; c) J. Marco-Contelles, E. Soriano, *Chem. Eur. J.* **2007**, *13*, 1350–1357.

[3] For some leading works involving 1,2-acyl migrations promoted by gold complexes, see: a) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655; b) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803; c) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003; d) C. H. M. Amijs, V. López-Carrillo, A. M. Echavarren, *Org. Lett.* **2007**, *9*, 4021–4024; e) D. J. Gorin, I. D. G. Watson, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737; f) G. Li, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 3740–3741.

[4] L. Peng, X. Zhang, S. Zhang, J. Wang, *J. Org. Chem.* **2007**, *72*, 1192–1197.

[5] For a gold-catalyzed 1,2-alkyl and -aryl migration in allenyl ketones, see: A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287–5289; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195–5197.

[6] a) R. Sanz, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2006**, 1383–1386; b) R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Adv. Synth. Catal.* **2006**, *348*, 1841–1845; c) R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Org. Lett.* **2007**, *9*, 727–730; d) R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Org. Lett.* **2007**, *9*, 2027–2030; e) R. Sanz, A. Martínez, V. Guilarte, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2007**, 4642–4645; f) R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Synthesis* **2007**, 3252–3256.

[7] R. Sanz, D. Miguel, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Synlett* **2008**, 975–978.

[8] R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1996**.

[9] For interesting examples of gold-catalyzed reactions involving indoles, see: a) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; b) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123–1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; c) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358–1373; d) S. Bhuvaneswari, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2007**, *13*, 8285–8293; e) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814–1815.

[10] For bis(trifluoromethanesulfonyl)imidate-based gold catalysts, see: N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136; for biphenylphosphine-based gold catalysts, see: C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

[11] P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411–2418.

[12] N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729–3732; *Angew. Chem. Int. Ed.* **2006**, *45*, 3647–3650.

[13] a) K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505–8513; b) B. A. Bhanu Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469.

[14] CCDC 689754 (**2c**), 689755 (**2e**), 689756 (**12a**), and 689757 (**12b**) 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.

[15] For excellent accounts on concurrent tandem catalysis, see: a) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; b) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477–1489.

[16] For gold-catalyzed tandem reactions involving an initial [3,3] rearrangement followed by a Nazarov-type cyclization, see: a) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443; b) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2007**, *9*, 2207–2209; c) F.-Q. Shi, X. Li, Y. Xia, L. Zhang, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 15503–15512; for a platinum-catalyzed tandem reaction involving an initial 6-*exo*-dig cyclization reaction followed by a Nazarov-type cyclization, see: d) S. M. A. Sohel, S.-H. Lin, R.-S. Liu, *Synlett* **2008**, 745–750.

[17] a) I.-M. Karaguni, K.-H. Glüsenkamp, A. Langerak, C. Geisen, V. Ullrich, G. Winde, T. Möröy, O. Müller, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 709–713; b) A. Kort, J. Legros, C. Bolm, *Synlett* **2004**, 2397–2399.