Heterocycles

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Consecutive C–H Functionalization Reactions of Arenes: Synthesis of Carbo- and Heteropolycyclic Skeletons**

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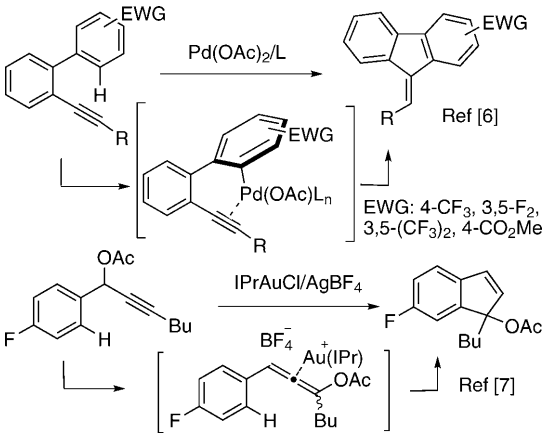
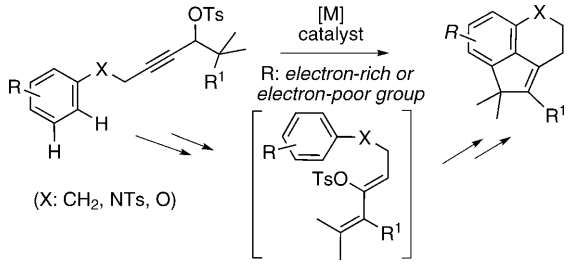
The use of domino reactions allows a rapid elaboration of molecular complexity from simple precursors.[1] Benzofused rings are often assembled by using intramolecular Friedel–Crafts processes,[2] and advances in alkyne hydroarylation reactions have contributed to expand the field.[3] As for the mechanism, these carbocyclizations are typically assumed to be electrophilic aromatic substitution reactions and require electron-rich arenes to occur.[4,5] The involvement of electron-poor arenes in hydroarylation reactions of alkynes has little precedent,[6–10] and it involves other mechanistic pathways (Scheme 1). Thus, Chernyak and Gevorgyan prepared fluorenes by palladium-catalyzed *5-exo-dig* hydroarylation of



Scheme 1. Arene–alkyne cyclizations of electron-poor arene units. EWG = electron-withdrawing group.

ortho-alkynyl biaryls through *o*-palladation, insertion, and protiodemetalation steps.[6] Nolan and co-workers reported a gold(I)-catalyzed synthesis of indenes from aryl propargyl acetates that takes place through isomerization and subsequent allene arylation.[7,8]

Herein, we report a catalytic polycyclization reaction of tethered ω-aryl propargyl esters that is compatible with arenes substituted by electron-withdrawing groups (Scheme 2).[11] Its utility to access carbo- and heterocyclic scaffolds is also documented.[12]



Scheme 2. New domino reaction of ω-aryl alkyne derivatives. Ts = 4-toluenesulfonyl

Initially, we investigated the reactivity of propargylic esters towards gold catalysts.[13] Our research group has recently reported the catalytic assembly of cyclopent-2-enimines by [4+1] cyclization of propargyl tosylates and *N*-tosyl imines.[14] The reaction comprises an isomerization to a 2-tosyloxi-1,3-diene through two selective 1,2-migrations.[15] On this basis, we reasoned that it might be possible to catalytically generate a class of dienes that could subsequently give rise to new arylation strategies. Readily available aryl propargyl ethers, *N*-tosyl-amines, or even 4-phenyl-1-butyne were elaborated into precursors by the reaction with aldehydes and subsequent esterification. Based on our past experience, pivalaldehyde was chosen and added to *N*-propargyl-*N*-tosylaniline to eventually afford appropriate model compounds upon esterification.[16] These esters were reactive towards different metal precatalysts like Lewis and Brønsted acids. Pivaloate and acetate derivatives failed to give cyclization: either the starting material or the Meyer–Schuster rearranged enone were isolated.[17] Nevertheless, the bis(tosylate) **1a** gave **2a**, which contains a cyclopenta[*de*]quinoline core and arises from a double C–H functionalization of the arene and a selective 1,2-alkyl-migration (Scheme 3).

Initial trials showed that heating the reaction mixture at about 60 °C was required for the cyclization to occur and that 1,2-dichloroethane (DCE) was an appropriate solvent. Several catalytic systems were assayed in this polar, low coordinating solvent—the use of toluene or acetonitrile severely slowed down or inhibit the process depending on the catalytic system—and the results are outlined in Table 1.

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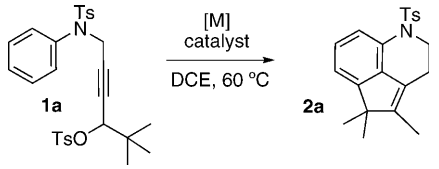
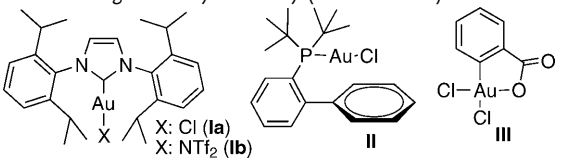


Scheme 3. Carbocyclization of **1a** into **2a** (see Table 1 for the reaction conditions).

For the catalytic system, satisfactory results were obtained when using gold(I) from IPrAuCl/$AgBF_4$[18] or $Sc(OTf)_3$[19] (Table 1, entries 3 and 7), while Pt^{II}, Au^{III}, and several Brønsted acids were ineffective (Table 1, entries 9, 6, and 10–15, respectively).

Table 1: Screening for catalytic activity (see Scheme 3).[a]



Entry	Catalyst (5 mol%)	*t* [h]	Yield of **2a** [%][b]
1	$[Au(PPh_3)]NTf_2$	24	–
2	$[Au(PPh_3)]Cl/AgBF_4$	22	28
3	**Ia**/$AgBF_4$	24	64
4	**Ib**	24	–
5	**II**/$AgBF_4$	24	21
6	**III**	24	–
7	$Sc(OTf)_3$	21	67
8	$Ga(OTf)_3$[c]	24	20
9	$PtCl_2$[c]	14	–
10	HOTs[d]	27	–
11	HOTf[e]	20	–
12	HOTf[f]	24	–
13	HOTf[g]	24	–
14	$HNTf_2$[f]	24	–
15	none	24	–

[a] **1a** (0.2 mmol) was dissolved in anhydrous DCE (2 mL) under an argon atmosphere, the catalyst was added, and the mixture heated at 60°C. [b] Yield of isolated product after purification by column chromatography. [c] 7.5 mol% of catalyst was added. [d] 5 and 10 mol% of catalyst were tested. [e] 5 mol% of catalyst was added resulting in the decomposition of **1a**. [f] 1 mol% of catalyst was added resulting in the recovery of most of **1a**. [g] 2 mol% of catalyst was added resulting in the partial recovery (77%) of **1a**. Tf = trifluoromethanesulfonyl.

The former two catalysts were further tested with **1b**, which is an oxygen-tethered compound. Although the scandium-catalyzed cyclization took place and furnished the related dihydrocyclopenta[*de*]-2*H*-chromene derivative **2b** (Table 2, entry 1), a complex mixture was obtained for gold catalysis and no evidence for the presence of **2b** was observed. For carbon-based **1c**, the outcomes were similar for the two catalytic systems in terms of both yield and reaction time, which was much shorter than for the related heteroatom-containing precursors (Table 2, entry 2). Thus, $Sc(OTf)_3$ was used to test the scope of the process with respect to the nature of the migrating group (R^1 in Scheme 2, see Table 2) and the arene (R in Scheme 2, see Table 3). The

Table 2: $Sc(OTf)_3$-catalyzed reaction of ω-aryl propargyl tosylates **1**.[a]

Entry	Alkyne	Product	*t* [min]	Yield [%][b]
1	**1b**, X = O	**2b**, X = O	40	60
2	**1c**, X = CH_2	**2c**, X = CH_2	30	66[c]
3	**1d**, X = NTs	**2d**, X = NTs	40	61
4	**1e**, X = CH_2	**2e**, X = CH_2	5	80
5	**1f**	**2f**	180	92[d]
6	**1g**	**3g**	60	54[e]

[a] 0.1 M in DCE, at 60°C, $Sc(OTf)_3$ (5 mol%). [b] Yield of isolated product after purification by column chromatography. [c] The alternative gold(I)-catalyzed reaction gave **2c** in 60% yield after isolation (IPrAuCl/$AgBF_4$ (5 mol%), 30 min, 60°C, DCE). [d] Reaction carried out at room temperature. [e] In C_6H_5Cl at 120°C.

reaction took place selectively with migration of either a methyl group, a primary alkyl chain with concomitant ring-expansion, a phenyl ring, or hydrogen. For the latter case, the subsequent cyclization was not observed and the conjugate diene **3g** was isolated (Table 2, entry 6).[20] This cyclization gives access to partially saturated skeletons as either heterocycles (quinoline derivatives **2a**, **2d**, **2f**, and **3g**; Table 2, entries 3, 5, and 6), chromene **2b** (Table 2, entry 1), or pure carbocycles (acenaphthylene **2c** or fluoranthene **2e**; Table 2, entries 2 and 4). Next, the influence of the arene substituent was tested (Table 3). This C–H functionalization works for an array of arenes featuring different substitution patterns. Remarkably, strong electron-withdrawing groups are nicely tolerated (see **2k** and **2m**; Table 3, entries 4 and 6). In fact, these results help to expand the scope of the metal-catalyzed arene–alkyne cyclization process.

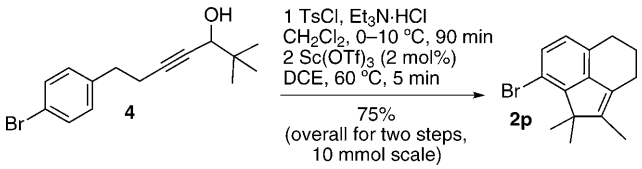
Also, **2p** was prepared in 75% yield on a 10 mmol scale from the parent alcohol. Compound **2p** was tosylated and then taken to the cyclization step without further purification, thereby showing the convenience of this transformation. The catalyst load was reduced to 2 mol% and an efficient cyclization was still obtained (Scheme 4).

A tentative mechanistic proposal to account for the observed results is outlined in Scheme 5. Activation of the alkyne upon coordination to the electrophilic metal[19,21] launches a tosylate migration with a concomitant 1,2-shift of

Table 3: Cyclization of **1** to **2**: arene substitution tolerance.[a]

Entry	Alkyne	Product	*t* [h]	Yield [%][b]
1	**1h**, R = F	**2h**, R = F	40	62[c]
2	**1i**, R = I	**2i**, R = I	32	54[d]
3	**1j**, R = Me	**2j**, R = Me	22	68[e]
4	**1k**, R = CN	**2k**, R = CN	24	60
5	**1l**, R = Ph	**2l**, R = Ph	5	77
6	**1m**, R = NO_2	**2m**, R = NO_2[f]	35	56[g]
7	**1n**, R = Ph	**2n**, R = Ph	24	70
8	**1o**, R = Br	**2o**, R = Br	5	91
9	**1p**	**2p**	0.1	87
10	**1q**	**2q**	21	36

[a] 0.1 M in DCE, at 60 °C, $Sc(OTf)_3$ (5 mol%). [b] Yield of isolated product after purification by column chromatography. [c] Alternatively, $IPrAuCl/AgBF_4$ (5 mol%), at 80 °C in DCE for 44 h gives **2h** (27% yield). [d] Gold(I)-catalyzed reaction ($IPrAuCl/AgBF_4$ (5 mol%), at 60 °C in DCE). [e] **2j** was isolated in 70% yield from the gold(I) process. [f] Structure of **2m** was confirmed by X-ray analysis.[28] [g] **1m** (21%) and *p*-$NO_2C_6H_4OH$ (14%) recovered.



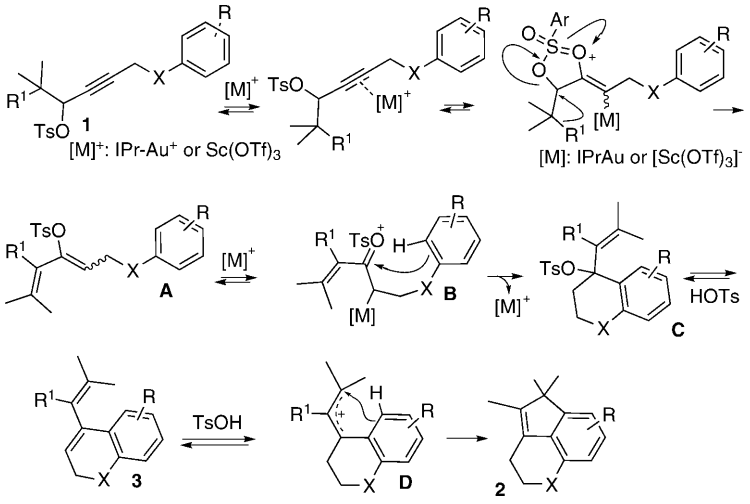
Scheme 4. C–H functionalization of ω-aryl-substituted propargylic alcohol derivatives: tosylation and double arylation reactions.

R^1 that is followed by loss of a proton and a subsequent protiodemetalation to furnish the diene **A**.[14,22] Next, electrophilic activation of the conjugated diene[23] yields a stabilized carbocation **B** that enters the first electrophilic aromatic substitution event. The resulting cycloisomerization process would render the conversion of **1** into **C**, which could then further evolve under the reaction conditions. As a function of the nature of the R^1 and R substituents, **C** would either simply suffer TsOH loss to afford **3**[24] or keep advancing through a cationic intermediate **D** to afford **2**. The following facts provide support for some aspects of this mechanistic proposal.

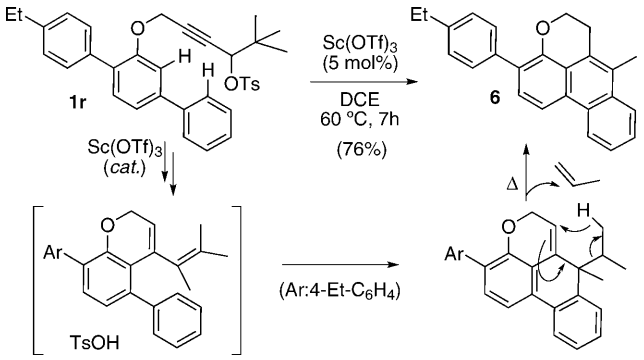
Thus, a minor amount of **3h** was isolated from the reaction of **1h** with the catalytic system based on gold. The evolution of this intermediate was studied under different reaction conditions. So, addition of catalytic amounts of $Sc(OTf)_3$ or $IPrAuCl/AgBF_4$ to **3h** led to the formation of only trace amounts of **2h**. However, when pure **3h** was exposed to TsOH (1 equiv) in DCE at 60 °C for 15 hours, a clean, fast, and efficient conversion into **2h** took place. As the formation of **3** gives rise to a stoichiometric amount of TsOH, the second cyclization event could reasonably be promoted by the Brønsted acid formed as the reaction progresses.[25] A central role for the tosylate group in the evolution of **A** to **C** is supported by the absence of **2** from (5,6-dimethyl-hepta-3,5-dienyl)benzene **5**[26] upon exposure to $Sc(OTf)_3$.[27]

Moreover, reactions of [D_1]-**1p** (deuterated at the propargylic position), [D_1]-**1n** (deuterated at the active *ortho*-position), or [D_2]-**1n** (deuterium at both the active *ortho* and propargylic positions) revealed exclusive incorporation of deuterium at C8-position for the carbocycle **2p** and the C3-position for the heterocycle **2n**. In both cases, the label resides only at the methylene unit built from the sp carbon atom in the parent alkyne **1**. Finally, a cross-over experiment between [D_2]-**1n** and **1c** again shows the formation of deuterated **2c**, with incorporation of deuterium only at the new methylene carbon unit arising from the starting alkyne carbon atom.[16]

The scope of this cyclization was expanded to accomplish the functionalization of two linked arene units. So, when **1r** was subjected to the $Sc(OTf)_3$-catalyzed cyclization then compound **6**, which has the structure of a 5,6-dihydronaphtho[3,2,1-*de*]chromene, was isolated in 76% yield (Scheme 6). Also, the formation of **6** implies major differences at the final steps. After the Lewis acid catalyzed



Scheme 5. Proposed working-model for the evolution of **1** into **2**.



Scheme 6. Mechanistic interpretation for the formation of **6**.

isomerization and the initial cyclization has occurred, the resulting diene could cyclize through C–H functionalization of the second arene nucleus: a process that could be likely catalyzed by the liberated Brønsted acid. Eventually, a retro-ene reaction would aromatize the ring at the time that the noticed C–C bond breaking occurs to liberate propene.

Overall, the reactions reported here open up new perspectives for advancing the topic of hydroarylation of unsaturated systems. These intramolecular domino reactions of propargyl tosylates and arenes with catalytic $Sc(OTf)_3$ provide smooth access to a variety of carbo- and hetero-polycyclic frameworks. The process is tolerant of strong electron-withdrawing groups on the arene unit. Also, a comparison of the scandium- and gold-catalyzed reactions gives interesting insights for the challenges related to the activation of unsaturated systems.

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[1] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115 – 136; b) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[2] Review: M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527 – 3544.

[3] Review: a) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167 – 182; recent intramolecular reaction: b) C. Dal Zotto, J. Wehbe, D. Virieux, J. M. Campagne, *Synlett* **2008**, 2033 – 2035; recent intermolecular reaction: c) J. Oyamada, T. Kitamura, *Chem. Commun.* **2008**, 4992 – 4994.

[4] a) J. A. Tunge, L. N. Foresee, *Organometallics* **2005**, *24*, 6440 – 6444; b) E. Soriano, J. Marco-Contelles, *Organometallics* **2006**, *25*, 4542 – 4553.

[5] For metal–cyclopropylcarbene intermediates in gold- and platinum-catalyzed *6-endo-dig* cyclization reactions, see: a) C. Nevado, A. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155 – 3164; b) C. Ferrer, C. H. M. Amijs, A. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358 – 1373.

[6] N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 5636 – 5637.

[7] 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.

[8] Platinum-catalyzed indene synthesis through metallocarbenoids: a) B. A. Bhanu Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* **2005**, *127*, 12468 – 12469; b) Y. Nakanishi, K. Miki, K. Ohe, *Tetrahedron* **2007**, *63*, 12138 – 12148; Ruthenium-catalyzed process: c) K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505 – 8513.

[9] L. Cui, G. Zhang, Y. Peng, L. Zhang, *Org. Lett.* **2009**, *11*, 1225 – 1228.

[10] A. Saito, S. Oda, H. Fukaya, Y. Hanzawa, *J. Org. Chem.* **2009**, *74*, 1517 – 1524.

[11] Metal-catalyzed intramolecular cyclizations of aryl-substituted propargylic alcohols via an allenyl cation: a) T. Ishikawa, S. Manabe, T. Aikawa, T. Kudo, S. Saito, *Org. Lett.* **2004**, *6*, 2631 – 2634; b) W. Huang, Q. Shen, J. Wang, X. Zhou, *J. Org. Chem.* **2008**, *73*, 1586 – 1589; c) W. Huang, P. Zheng, Z. Zhang, R. Liu, Z. Chen, X. Zhou, *J. Org. Chem.* **2008**, *73*, 6845 – 6848; d) W. Huang, L. Hong, P. Zheng, R. Liu, X. Zhou, *Tetrahedron* **2009**, *65*, 3603 – 3610.

[12] For reviews on metal-catalyzed reactions for carbo- and heterocyclic synthesis, see: a) G. Balme, D. Bouyssi, T. Lomberget, N. Monteiro, *Synthesis* **2003**, 2115 – 2134; b) S. F. Kirsch, *Synthesis* **2008**, 3183 – 3204; c) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395 – 3442.

[13] Review: a) N. Marion, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 2806 – 2809; *Angew. Chem. Int. Ed.* **2007**, *46*, 2750 – 2752; selected recent work: b) A. S. Dudnik, T. Schwier, V. Gevorgyan, *Org. Lett.* **2008**, *10*, 1465 – 1468; c) P. W. Davies, S. J.-C. Albrecht, *Chem. Commun.* **2008**, 238 – 240; d) M. Uemura, I. D. G. Watson, M. Katsukawa, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 3464 – 3465; e) P. Mauleón, J. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 4513 – 4520; f) Y. Peng, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 5062 – 5063.

[14] S. Suárez-Pantiga, E. Rubio, C. Álvarez-Rúa, J. M. González, *Org. Lett.* **2009**, *11*, 13 – 16.

[15] Review: B. Crone, S. F. Kirsch, *Chem. Eur. J.* **2008**, *14*, 3514 – 3522.

[16] For experimental details and characterization data for compounds **1**–**6**, as well as labeling experiments, see the Supporting Information.

[17] R. S. Ramón, N. Marion, S. P. Nolan, *Tetrahedron* **2009**, *65*, 1767 – 1773.

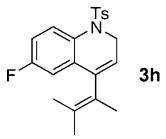
[18] a) P. de Fremont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411 – 2418; b) N. Marion, R. S. Ramón, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448 – 449.

[19] For reviews on the use of $Sc(OTf)_3$ in organic synthesis, see: a) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15 – 27; b) S. Kobayashi in *Lewis Acids in Organic Synthesis*, *Vol. 2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**, pp. 883 – 910; seminal work on $Sc(OTf)_3$-catalyzed alkyne hydroarylation: c) T. Tsuchimoto, T. Maeda, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2000**, 1573 – 1574; d) C. E. Song, D. Jung, S. Y. Choung, E. J. Roh, S.-g. Li, *Angew. Chem.* **2004**, *116*, 6309 – 6311; *Angew. Chem. Int. Ed.* **2004**, *43*, 6183 – 6185; e) M. Y. Yoon, J. H. Kim, D. S. Choi, U. S. Shin, J. Y. Lee, C. E. Song, *Adv. Synth. Catal.* **2007**, *349*, 1725 – 1737.

[20] Under these reaction conditions the reaction did not go to completion. Products **1g** (9%) and *N*-tosylaniline (12%) were isolated by column chromatography. Longer reaction times caused decomposition. The use of microwave radiation did not result in any major improvement.

[21] For a review on carbophilic activation by π-acids, see: A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478 – 3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449.

[22] The [4+1] cyclization described in reference [14] can be accessed using a catalytic amount of $Sc(OTf)_3$, although giving a lower yield than for gold-catalysis and is also accompanied by other side products. See the Supporting Information.
[23] $Sc(OTf)_3$-induced Friedel–Crafts cyclization of 1,3-bis-exocyclic dienes leading to 4a-methyltetrahydrofluorenes: T. Lomberget, E. Bentz, D. Bouyssi, G. Balme, *Org. Lett.* **2003**, *5*, 2055 – 2057.
[24] See for instance the conversion of **1g** into **3g**. Also, minor amounts of **3h** were isolated from the gold-catalyzed reaction of **1h**.



3h

[25] The inhibition of the conversion of **1a** into **2a** upon exposure to catalytic amounts of $Sc(OTf)_3$ in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) supports this hypothesis. In this case, upon heating for 24 h in DCE, the reaction gives the corresponding diene **3a** (25%), which arises from a single cyclization rather the double cyclization product **2a**. For the use of TTBP in metal-catalyzed reactions, see: T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868 – 9878.
[26] **5** was prepared by a cross-coupling reaction, see the Supporting Information.
[27] After heating at 60 °C for 40 min only compound **5** was present in the reaction mixture. By extending the reaction time to 1 h it allowed the identification of significant amounts of unchanged **5**, although some decomposition was evident by TLC. This trend was still noticed when heating lasted foe 3 or 7 h. After 24 h, only trace amounts of **5** were present, and a complex mixture was formed without any evidence for the formation of a type-**2** product.
[28] CCDC 734150 (**2m**) contains 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.

