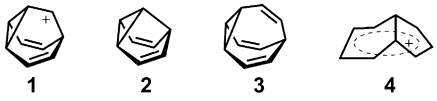
Fluxional Intermediates

DOI: 10.1002/ange.201207682

Gold for the Generation and Control of Fluxional Barbaralyl Cations**

*Paul R. McGonigal, Claudia de León, Yahui Wang, Anna Homs, César R. Solorio-Alvarado, and Antonio M. Echavarren**

Fluxional molecules which rapidly pass back and forth between a large number of constitutional isomers through low-energy rearrangements have fascinated chemists[1] owing to their role in the study of fundamental theoretical concepts[2] and their potential to adapt their chemical structures in response to their environment[3] or to act as prototypical molecular transport systems.[4] They represent a facet of systems chemistry[5] that is relatively unexplored, in which a dynamic structural library can be contained within a single molecule. The 9-barbaralyl[6] cation (**1**) is a hugely fluxional

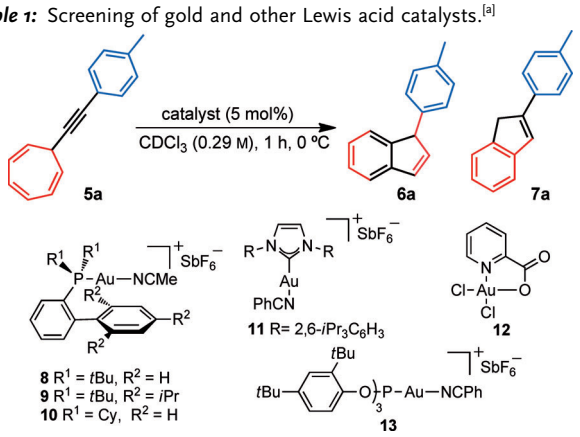


$C_9H_9^+$ hydrocarbon that exists as a mixture of 181 400 degenerate forms[7] which interconvert rapidly at temperatures as low as −135 °C[8]—each carbon atom may exchange with every other carbon atom in the structure through a series of pericyclic reactions. Unlike the neutral homologues semibullvalene (**2**; two degenerate tautomers)[2a,9a] and bullvalene (**3**; 1209 600 degenerate tautomers),[1–3] which are stable compounds under ambient conditions, **1** is highly reactive and undergoes irreversible rearrangement to 1,4-bishomotropylium cation (**4**)[9] above −125 °C.[8] Functionalized barbaralanes may be suitable candidates for switchable, fluxional molecules. However, the difficulty in handling these compounds coupled with the low-yielding, multistep syntheses[10] and harsh reaction conditions (typically featuring strongly or super acidic media) employed in the generation of **1** and its derivatives[10–12] have so far limited the extent to which the chemistry of this fascinating dynamic carbon skeleton has been explored.

Gold complexes are potent activators of π bonds towards nucleophilic attack by nucleophiles[13] and in the cyclization of 1,*n*-enynes,[13f,14] in which gold exerts exquisite control over the competitive reaction pathways by the stabilization of intermediates with carbenic character.[15–17] As part of a study of the gold-catalyzed activation of cycloheptatrienes,[18] we examined the reactivity of their alkynyl derivatives. Herein we report the generation of fluxional barbaralyl intermediates from 7-alkynyl cycloheptatrienes **5** under very mild conditions. The gold-stabilized barbaralyl intermediates evolve to furnish 1- or 2-substituted indenes, depending on the catalyst. The formation of 1-substituted indenes involves a remarkable transformation in which the alkyne carbon atoms end up at the bridge of the indene.

We first investigated the reaction of **5a** in the presence of gold salts and other known π Lewis acids as catalysts (Table 1). The treatment of **5a** with a variety of gold complexes led to rapid isomerization to indene products **6a** and **7a** (Table 1, entries 1–9). Other common π acids were not

Table 1: Screening of gold and other Lewis acid catalysts.[a]



Entry	Catalyst	Conversion [%][b]	**6a**/**7a**[b]
1	$[Ph_3PAuNCMe]SbF_6$	>99	48:52
2	**8**	>99	84:16
3	**9**	>99	80:20
4	**10**	>99	62:38
5	**11**	>99	84:16
6	$AuCl_3$	>99	87:13
7	AuCl	50	96:4
8	**12**	**>99**	**>99:1**
9	**13**	**>99**	**0:100**
10	$PtCl_2$	0	–
11	$GaCl_3$	0	–
12	AgOTf	0	–

[a] For full details, see the Supporting Information. [b] Conversion and the product ratio were determined by ^{1}H NMR spectroscopy. Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

[*] Dr. P. R. McGonigal, C. de León, Y. Wang, A. Homs, C. R. Solorio-Alvarado, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: aechavarren@iciq.es
Prof. A. M. Echavarren
Departament de Química Analítica i Química Orgànica
Universitat Rovira i Virgili
C/Marcel·li Domingo s/n, 43007 Tarragona (Spain)

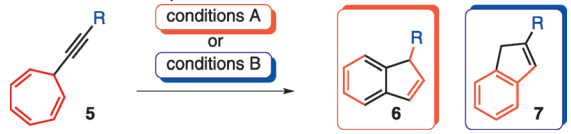
[**] We thank the MICINN (CTQ2010-16088/BQU and FPI fellowship to A.H.), the AGAUR (2009 SGR 47), AtMol (Contract No. ICT-270028), and the ICIQ Foundation for financial support. We also thank the ICIQ X-ray diffraction unit for the solid-state structures of **16**/**16′**, **17**, **18**, and **7v**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207682.

catalytically active (Table 1, entries 10–12). The ratio of regioisomers **6a**/**7a** was sensitive to the gold source employed. Gold trichloride and cationic phosphine–gold(I) and N-heterocyclic carbene–gold(I) complexes generated mixtures (Table 1, entries 1–6). However, AuCl and complex **12** exhibited excellent bias towards regioisomer **6a** (Table 1, entries 7 and 8). Remarkably, use of the highly electrophilic phosphite–gold(I) complex **13**[16b] led exclusively to 2-(*p*-tolyl)-1*H*-indene (**7a**; Table 1, entry 9).[19]

The catalyst-controlled regioselectivity observed in the cycloisomerization of **5a** was retained for the majority of substrates, although in two instances mixtures were obtained (Table 2, entries 4 (under conditions B) and 16 (under conditions A)). In general, reactions were complete within 1 h at 0 °C, and the picolinate catalyst **12** afforded 1-substituted indenyl products in good yields (55–88%), whereas catalyst **13** produced the 2-substituted indenyl isomers in lower yields (23–76%), probably as a result of partial decomposition in the presence of the more reactive phosphite complex. Substrates bearing aryl groups with substituents in the 2-, 3-, or 4-positions performed similarly (Table 2, entries 1–12), and electron-donating or electron-withdrawing substituents were tolerated (Table 2, entries 5 and 6). Fused aromatic and heteroaromatic alkynyl derivatives were also suitable substrates (Table 2, entries 13 and 14), although slightly more forcing conditions were necessary with the thienyl enyne **5n** when catalyst **12** was used. The ferrocenyl alkyne **5o** underwent cycloisomerization under conditions B, albeit in low yield (Table 2, entry 15), and the benzyl substrate **5p** underwent successful isomerization to indene products (Table 2, entry 16). The homobenzyl derivative **5q** and terminal alkyne **5r** were both unreactive under conditions A, but could be converted into indenes in moderate yield with catalyst **13** (Table 2, entries 17 and 18).

Table 2: Substrate scope.[a]

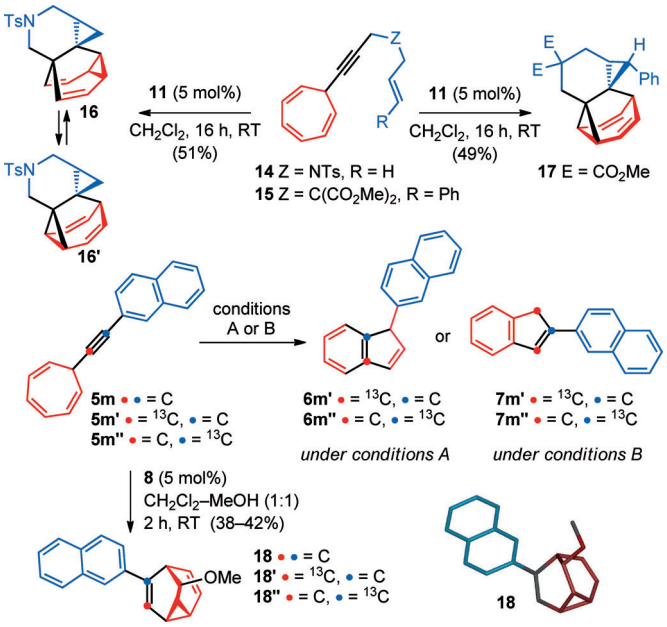


Entry	Substrate	Yield [%][b] (product) conditions A[c]	conditions B[d]
1	**5a**, R = *p*-Tol	86 (**6a**)	60 (**7a**)
2	**5b**, R = Ph	64 (**6b**)	51 (**7b**)
3	**5c**, R = *m*-Tol	55 (**6c**)	50 (**7c**)
4	**5d**, R = *o*-Tol	76 (**6d**)	48 (1:1.8 **6d**/**7d**[e])
5	**5e**, R = *p*-MeOC$_6$H$_4$	69 (**6e**)	30 (**7e**)
6[f]	**5f**, R = *p*-FC$_6$H$_4$	63 (**6f**)	60 (**7f**)
7	**5g**, R = *p*-ClC$_6$H$_4$	80 (**6g**)	59 (**7g**)
8	**5h**, R = *p*-BrC$_6$H$_4$	82 (**6h**)	57 (**7h**)
9	**5i**, R = *o*-PhC$_6$H$_4$	77 (**6i**)	76 (**7i**)[g]
10	**5j**, R = *o*-ClC$_6$H$_4$	88 (**6j**)	35 (**7j**)
11	**5k**, R = *o*-BrC$_6$H$_4$	85 (**6k**)	38 (**7k**)
12	**5l**, R = 2,4-F$_2$C$_6$H$_4$	60 (**6l**)	40 (**7l**)
13	**5m**, R = 2-naphthyl	75 (**6m**)	51 (**7m**)
14[f]	**5n**, R = 3-thienyl	66 (**6n**)	41 (**7n**)
15	**5o**, R = ferrocenyl	–	23 (**7o**)
16	**5p**, R = Bn	76 (1:2 **6p**/**7p**[e])	57 (**7p**)
17	**5q**, R = CH$_2$Bn	–	31 (**7q**)
18	**5r**, R = H	–	54 (**7r**)[g]
19[h]	**5j**	41 (**6j**), 5 (**7j**)	
20[h]	**5k**	47 (**6k**), 6 (**7k**)	
21[h]	**5l**	29 (**6l**), 2 (**7l**)	

[a] For full details, see the Supporting Information. [b] Yield of the isolated product. [c] Conditions A: **12** (1 mol%), CH_2Cl_2 (0.3 M), 0 °C, 1 h. [d] Conditions B: **13** (5 mol%), PhMe (0.3 M), 0 °C, 1 h. [e] Isolated as a mixture. [f] **12** (5 mol%), 23 °C, 2 h. [g] The yield was determined by ^{1}H NMR spectroscopy. [h] The substrate was generated in situ from the terminal-alkyne precursor (3 equiv) and 7-methoxycyclohepta-1,3,5-triene (1 equiv); reaction conditions: **8** (1 mol%), CH_2Cl_2 (0.3 M), 23 °C, 24 h. Bn = benzyl.

We also discovered a method that allowed this reaction to be conducted in a single step (Table 2, entries 19–21). Catalyst **8** (1 mol%) mediated the nucleophilic substitution reaction of 7-methoxycyclohepta-1,3,5-triene with terminal alkynes to form **5** in situ (presumably via a gold acetylide), which subsequently underwent cycloisomerization to indenes **6** and **7**. The overall reaction was slower than the cycloisomerization of premade **5**, and the yields were modest; however, it is straightforward method by which to access the cycloisomerization pathway.

We hypothesized that the intermediacy of barbaralyl species,[20] generated by an initial 1,6-enyne cyclization,[13f,14] could be responsible for the observed reactivity and hoped to gain insight into the process by trapping intermediates with tethered olefins (Scheme 1).[21] Substrates **14** and **15**, which feature pendant olefins, underwent cycloisomerization with the cationic gold catalyst **11** to form barbaralanes **16**/**16′** and **17**, respectively. The tautomeric barbaralanes **16** and **16′** interconvert rapidly on the NMR timescale at room temperature in $CDCl_3$ through a strain-assisted Cope rearrange-



Scheme 1. Trapping and labeling experiments for the elucidation of the intermediate species in the gold-catalyzed cycloisomerization of 7-alkynyl cyclohepta-1,3,5-trienes and stick representation of the solid-state structure of **18**. Ts = *p*-toluenesulfonyl.

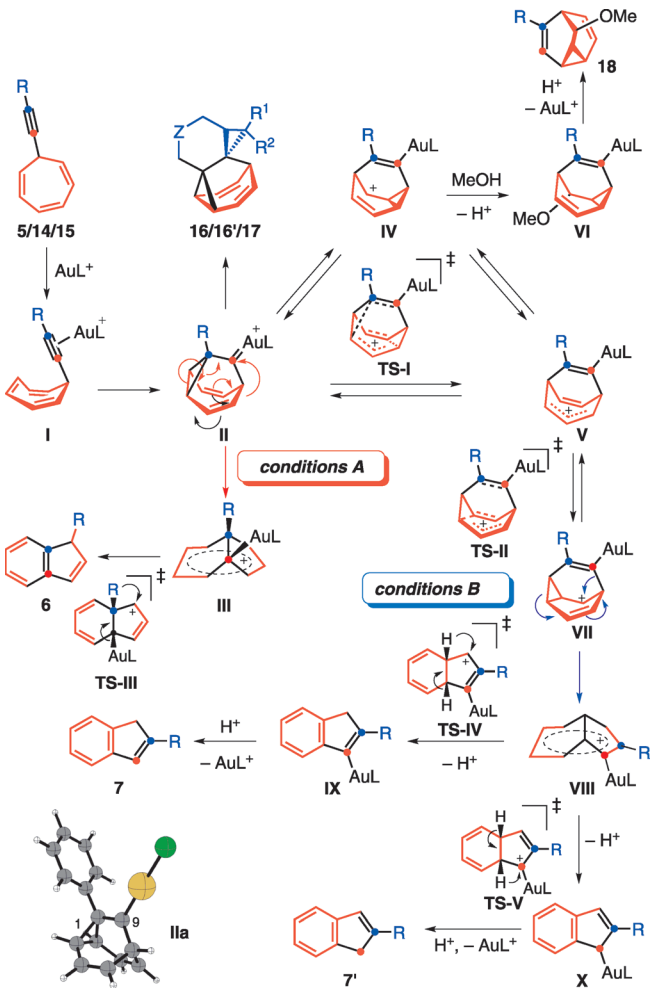
ment[22] and were detected as a 1:1 mixture in the crystal state,[23,24] whereas **17** was observed as a single tautomer.[24]

Additional evidence for the involvement of barbaralyl gold intermediates was obtained from the cyclization of **5m** in $MeOH/CH_2Cl_2$ (1:1) to form the barbaralane methyl ether **18** in 40% yield, along with minor amounts of indenes **6m** and **7m** (Scheme 1). The structure of **18**, a product of alkoxycyclization,[14] was confirmed by crystallographic analysis.[24]

To determine whether the short-lived, cationic barbaralyl species evolve through a short series of steps or whether they undergo numerous rearrangements, we prepared two alkynyl cycloheptatrienes containing a ^{13}C label as part of the alkyne either at the position adjacent to the cycloheptatriene moiety (red dot, **5m′**) or attached to the naphthyl ring system (blue dot, **5m″**). If the barbaralyl intermediate could undergo manifold pericyclic rearrangements, the ^{13}C label would be expected to be dispersed throughout the barbaralane skeleton.

Cycloisomerization of **5m′** and **5m″** under conditions A afforded the single isotopomers **6m′** and **6m″**, respectively, with the ^{13}C label at the bridging positions of the indene core and thus separated from the naphthalene unit by an extra bond relative to its position in the starting alkynyl cycloheptatriene (Scheme 1). The transformation of **5m′** under the catalysis of phosphite complex **13** (conditions B) led to product **7m′** as a mixture of two isotopomers with the ^{13}C label located in either the 1- or the 3-position of the indene. The methoxycyclization of **5m′** or **5m″** generated **18′** or **18″**, in which the ^{13}C label had been transferred with complete fidelity to a single position.

These results are indicative of a mechanism that proceeds through a small number of steps. Experimental and theoretical studies have established that the $C_9H_9^+$ barbaralyl cation (**1**) fluctuates between degenerate isomers through a unique network of reaction paths involving 30240 degenerate divinylcyclopropylcarbinyl cation–divinylcyclopropylcarbinyl cation rearrangements (dvcpc–dvcpc; one cyclopropyl bond is broken as another forms) and 90720 rearrangements which pass through a bicyclo[3.2.2]nona-3,6,8-trien-2-yl transition state.[7] Although the number of energetically accessible nondegenerate isomers, and hence the number of possible rearrangements, is reduced in substituted systems,[12c] such as ours, the key mechanistic features remain the same. The most concise mechanistic rationale that accounts for our experimental observations was formulated on the basis of these known steps (Scheme 2). We propose that coordination of the catalyst to the alkyne initiates the cyclization to afford the barbaralyl–gold complex **II**,[25] pictured by invoking the gold–carbene resonance form.[15,16a] Intermediate **II** can be transformed irreversibly into the homoaromatic bicyclo[4.3.0]nonatrienyl cation **III**[9b] (red arrow), which can undergo deauration with a concomitant 1,2-shift via **TS-III** to establish aromaticity through the formation of the 1-substituted indene **6**. As a consequence of the 1,2-shift, the R group is separated from the carbon atoms that originated from the alkyne of **5** (red and blue dots), as detected in products **6m′** and **6m″** (Scheme 1). Alternatively, a reversible dvcpc–dvcpc rearrangement of **II** (black arrows) via transition state **TS-I** generates the isomeric barbaralyl–gold complex **IV**,



Scheme 2. Mechanistic rationale for the formation and evolution of barbaralyl gold cations.

a precursor to the methoxycyclization product **18**. By analogy with the reversible isomerization process in $C_9H_9^+$ (**1**),[7] the barbaralyl–gold complex **VII** can be accessed by the evolution of **TS-I** via **V** and **TS-II**. The homoaromatic bicyclo[4.3.0]nonatrienyl cation **VIII** is then formed irreversibly (blue arrow) and can undergo aromatization through two pathways to generate either **IX** or **X**. Protodeauration of either intermediate liberates the same 2-substituted indene product **7**. The preceding steps are only distinguishable in the case of the ^{13}C-labeled indene **7m′**, which was isolated in a near 1:1 mixture of isotopomers.

Gold-stabilized barbaralyl cations generated in this reaction can fluctuate between a minimum of three structures: **II**, **IV**, and **VII**. In the case of reactions performed with catalyst **8**, experimental evidence shows that all three of these intermediates are accessed, as indenes **6** and **7** and barbaralane **18** have all been isolated. It is therefore remarkable that the picolinate complex **12** and phosphite complex **13** are able to exercise such a high level of control over the pathway that is followed. It is possible that other low-energy, transient barbaralyl intermediates are present during the course of these reactions but have escaped detection, as they are not

direct precursors to any of the compounds isolated in this study.

The sheer number of conceivable permutations in the isomerization of barbaralyl cations makes it impractical to perform calculations to determine the relative energies of all possible isomers;[7,8,11a,12b] however, DFT modeling of our proposed intermediates with the M06 functional showed in all cases[25] that the minimum structures correspond to 1-aryl 9-barbaralyl gold species, such as **IIa**: intermediate structures between gold-stabilized barbaralyl cations and barbaralyl gold carbenes. The C1–C9 bond lengths of 1.38–1.41 Å in these structures are between those of single and double carbon–carbon bonds (Scheme 2). The shorter C–Au bond distance in **IIa**, with a donating chloride ligand, relative to that in the analogous cationic species with $P(OMe)_3$ as the ligand (2.00 versus 2.07 Å)[26] corresponds to a more metal-carbene-like structure for the neutral intermediate.[16a]

In summary, we have found a new method for the direct generation of fluxional barbaralyl cations either from readily prepared 7-alkynyl cyclohepta-1,3,5-trienes **5** or in one pot from aryl alkynes and 7-methoxycyclohepta-1,3,5-triene. These reactions are catalyzed by gold complexes under very mild conditions. In the absence of nucleophiles, substituted indenes are produced in good to high yields with catalyst-controlled regioselectivity. The nature of the gold catalyst affects the fluxionality and evolution the cationic intermediates. Such influence over the speciation of barbaralyl cations is unprecedented. Our methodology for the preparation of barbaralanes and barbaralyl cations may be of use in the field of shape-shifting molecules. We are therefore currently investigating the expansion of this methodology to the preparation of stabilized barbaralyl cations.

Received: September 23, 2012
Published online: November 19, 2012

Keywords: barbaralyl cations · cyclization · enynes · fluxionality · gold catalysis

[1] a) W. von E. Doering, W. R. Roth, *Tetrahedron* **1963**, *19*, 715 – 737; b) G. Schröder, *Angew. Chem.* **1963**, *75*, 722; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 481 – 482.
[2] a) R. V. Williams, *Chem. Rev.* **2001**, *101*, 1185 – 1204; b) M. He, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14752 – 14756.
[3] a) A. R. Lippert, V. L. Keleshian, J. W. Bode, *Org. Biomol. Chem.* **2009**, *7*, 1529 – 1532; b) K. M. Larson, M. He, J. F. Teichert, A. Naganawa, J. W. Bode, *Chem. Sci.* **2012**, *3*, 1825 – 1828.
[4] A. G. Campaña, A. Carlone, K. Chen, D. T. F. Dryden, D. A. Leigh, U. Lewandowska, K. M. Mullen, *Angew. Chem.* **2012**, *124*, 5576 – 5579; *Angew. Chem. Int. Ed.* **2012**, *51*, 5480 – 5483.
[5] S. Otto, *Acc. Chem. Res.* **2012**, DOI: 10.1021/ar200246j.
[6] J. B. Lambert, *Tetrahedron Lett.* **1963**, *4*, 1901 – 1906.
[7] D. Cremer, P. Svensson, E. Kraka, P. Ahlberg, *J. Am. Chem. Soc.* **1993**, *115*, 7445 – 7456.
[8] P. Ahlberg, D. L. Harris, S. Winstein, *J. Am. Chem. Soc.* **1970**, *92*, 4454 – 4456.
[9] a) H. E. Zimmerman, G. L. Grunewald, *J. Am. Chem. Soc.* **1966**, *88*, 183 – 184; b) N. H. Werstiuk, *Can. J. Chem.* **2010**, *88*, 1195 – 1204.
[10] W. von E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, M. Saunders, *Tetrahedron* **1967**, *23*, 3943 – 3963.
[11] a) P. Ahlberg, J. B. Grutzner, D. L. Harris, S. Winstein, *J. Am. Chem. Soc.* **1970**, *92*, 3478 – 3480; b) T. S. Abram, W. E. Watts, *J. Organomet. Chem.* **1976**, *105*, C16 – C18.
[12] a) H. Tsuruta, K. Kurabayashi, T. Mukai, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2822 – 2828; b) C. Engdahl, G. Jonsäll, P. Ahlberg, *J. Am. Chem. Soc.* **1983**, *105*, 891 – 897; c) C. Engdahl, P. Ahlberg, *J. Phys. Org. Chem.* **1990**, *3*, 349 – 357.
[13] a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211; b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333 – 346; c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351 – 3378; d) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766 – 1775; e) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239 – 3265; f) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350; g) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208 – 3221; h) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448 – 2462.
[14] C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456 – 2460; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402 – 2406.
[15] a) A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856 – 6858; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754 – 6756; b) P. Pérez-Galán, E. Herrero-Gómez, D. T. Hog, N. J. A. Martin, F. Maseras, A. M. Echavarren, *Chem. Sci.* **2011**, *2*, 141 – 149; c) P. Pérez-Galán, N. J. A. Martin, A. G. Campaña, D. J. Cárdenas, A. M. Echavarren, *Chem. Asian J.* **2011**, *6*, 482 – 486.
[16] a) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482 – 486; b) C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721 – 7730.
[17] L.-P. Liu, G. B. Hammond, *Chem. Soc. Rev.* **2012**, *41*, 3129 – 3139.
[18] C. R. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952 – 11955.
[19] For ligand-controlled selectivity in gold-catalyzed transformations, see Ref. [13c,16] and the following selected examples: a) D. Benitez, E. Tkatchouk, A. Z. Gonzalez, W. A. Goddard III, F. D. Toste, *Org. Lett.* **2009**, *11*, 4798 – 4801; b) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123 – 1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105 – 1109.
[20] P. K. Freeman, K. E. Swenson, *J. Org. Chem.* **1982**, *47*, 2040 – 2043.
[21] S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 6175 – 6178; *Angew. Chem. Int. Ed.* **2006**, *45*, 6029 – 6032.
[22] D. Bosse, A. de Meijere, *Tetrahedron Lett.* **1978**, *19*, 965 – 968.
[23] J. Siegwarth, J. Bornhöft, C. Näther, R. Herges, *Org. Lett.* **2009**, *11*, 3450 – 3452.
[24] Detailed procedures and characterization data are available in the Supporting Information. X-ray crystallography: CCDC 897922 (**16**/**16′**), 897923 (**17**), 897920 (**18**), and 897921 (**7v**; see the Supporting Information) 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.
[25] Although this cyclization could formally be seen as a direct 6-*endo*-dig process, calculations favor a cyclization involving the corresponding norcaradiene tautomer. See the Supporting Information for the reaction coordinate for the transformation of **Id** into **IId** ($L = PMe_3$) and for additional computational details.
[26] Similar minima were found for the phenylbarbaralyl gold species with AuCl, $AuCl_3$, $AuPMe_3$, and $AuP(OMe_3)$. In these structures, gold, rather than the phenyl substituent, stabilizes the carbocationic center.[25]

