Synthetic Methods

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Diastereoselective Gold-Catalyzed Cycloisomerizations of Ene-Ynamides**

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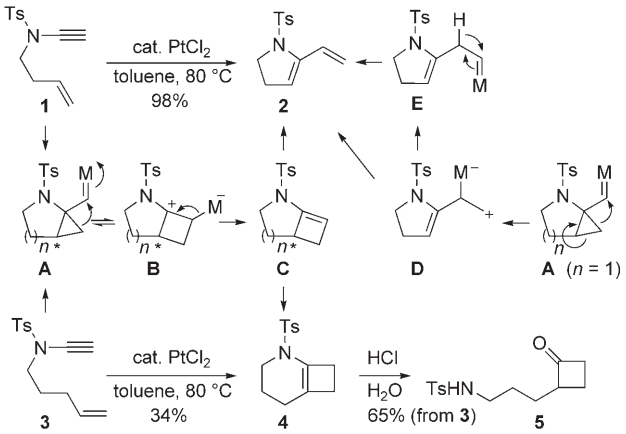
Metal-catalyzed cycloisomerizations of ene-ynes lie among the most powerful methods for the elaboration of cyclic or polycyclic organic compounds.[1] In recent years, achievements in the field of platinum-[2–6] and gold-catalyzed[7–14] cycloisomerizations of ene-ynes have been particularly noteworthy. As a result of their high reactivity and mild reaction conditions, gold(I) salts or complexes are currently emerging as the most promising catalysts for these reactions.[15] Whereas the gold-catalyzed cycloisomerizations of ene-ynes accommodate the presence of oxygen or nitrogen atoms in the tether,[7a–c] and enol ethers as nucleophilic partners,[7a,9b] ene-ynamines[5d,e] and ene-ynol ethers[10b] have been seldom considered as substrates. Herein, we report the first examples of gold-catalyzed cycloisomerizations of 1,6-ene-ynamides that lead to substituted cyclobutanones or azabicyclic compounds, depending on the substitution pattern, and proceed with high levels of diastereoselectivity.

The platinum(II)-catalyzed cycloisomerization of ene-ynamides has already been investigated.[5d,e] Little difference, in terms of reactivity relative to the non-heterosubstituted series, was apparent for the most simple 1,6-ene-ynamide **1**, which was converted into the so-called "formal metathesis product" **2** (98%).[16] By contrast, the platinum(II)-catalyzed cycloisomerization of the homologous 1,7-ene-ynamide **3** led to the cyclobutene intermediate **4**, which was isolated in rather low yield (34%), and the latter was therefore best hydrolyzed directly to the corresponding cyclobutanone **5** (65%).[5d,e] Compounds **2** and **4** were assumed to originate from a cyclopropyl platinum carbene intermediate of type **A** ($M = PtCl_2$).[3,4,14] The latter underwent ring expansion to the cyclobutylcation **B**, stabilized by the nitrogen atom,[17] and demetalation afforded the cyclobutene intermediate of type **C**. For 1,6-ene-ynamides such as **1**, it was suggested that the double bond in the cyclobutene of type **C** ($n = 1$) remained in the more stable *exo* position but that this intermediate underwent electrocyclic ring opening to afford the 1,3-diene **2**. However, recent mechanistic investigations suggest that the formation of 1,3-dienes, such as **2**, may result from the skeletal rearrangements of the cyclopropyl metal carbenes of type **A** ($n = 1$) via intermediates of type **D** and/or **E**.[14] In the case of 1,7-ene-ynamides such as **3**, the migration of the double bond to the more stable *endo* position took place, thus resulting in lower ring strain, and led to the cyclobutene **4**. As a consequence of the platinum-catalyzed reaction pathways, any stereocenter generated in the initial stages of the cycloisomerization in the metal carbene of type **A** would be lost in subsequent steps (Scheme 1).

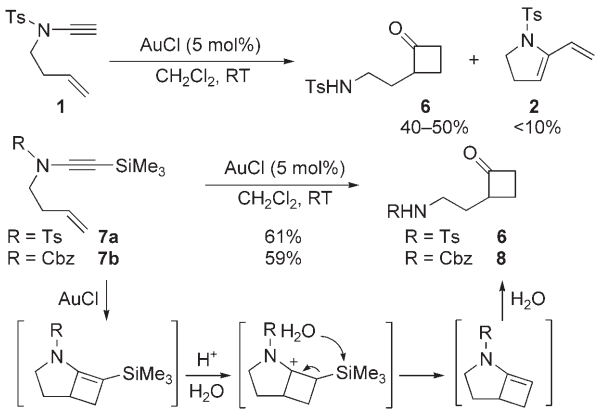
The use of milder reaction conditions should enable the rate of the skeletal rearrangements of the cyclopropyl metal carbene of type **A** to be decreased and/or avoid the electrocyclic ring opening of the intermediate cyclobutene of type **C**, both of which lead to the "formal metathesis product" **2**. To this end, we decided to investigate the gold-catalyzed cycloisomerizations of 1,6-ene-ynamides.



Scheme 1. Platinum(II)-catalyzed cycloisomerization of ene-ynamides. M = metal center, Ts = tosyl.

When the 1,6-ene-ynamide **1** was treated with AuCl (5 mol%) in CH_2Cl_2 at room temperature, a different reactivity profile was already apparent as the reaction led to the cyclobutanone **6** (40–50%), and the 1,3-diene **2** was only detected as a minor by-product (< 10%; Scheme 2).

Though the reaction was carried out under anhydrous conditions, subsequent exposure to atmospheric moisture during the workup seemed to be sufficient to promote the



Scheme 2. Gold-catalyzed cycloisomerization of ene-ynamides. Cbz = carbobenzyloxy.

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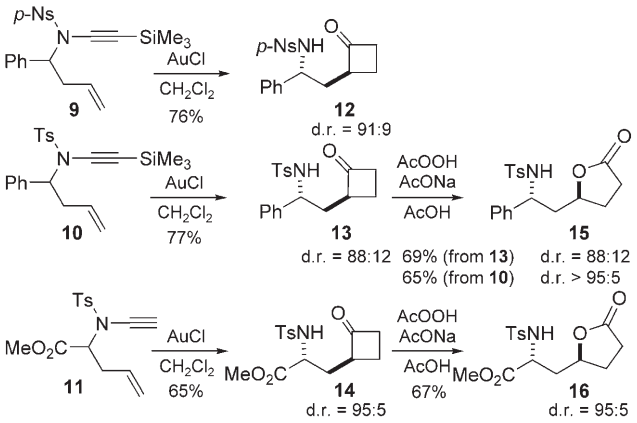
hydrolysis of the presumed cyclobutene intermediate of type **C** (M = AuCl) to the corresponding cyclobutanone **6**. Interestingly, the more stable ene-ynamides **7a** and **7b**, bearing either a tosyl or a benzyloxycarbonyl (Cbz) electron-withdrawing group on the nitrogen atom and a trimethylsilyl group as the alkyne substituent, also underwent gold-catalyzed cycloisomerizations to afford the cyclobutanones **6** (61%) and **8** (59%), respectively, without noticeable formation of the "formal metathesis" 1,3-diene by-products. As trimethylsilyl-ynamides do not undergo rapid protodesilylation in the presence of AuCl,[18] we propose that the loss of the trimethylsilyl group occurs during the hydrolysis process by protonation of the double bond of the initially formed trimethylsilyl-substituted cyclobutene intermediate with formation of trimethylsilanol (Scheme 2).

As a result of the milder reaction conditions, the cyclopropyl gold carbenes of type **A** (M = AuCl), generated by the gold-catalyzed cycloisomerizations of 1,6-ene-ynamides, do not seem to undergo skeletal rearrangements at a significant rate but instead undergo a preferential ring expansion to generate cyclobutenes of type **C** (Scheme 1; M = AuCl).[19] Although we have not been able, so far, to characterize the latter intermediates, presumably as a result of their sensitivity to moisture, they should retain any new stereogenic center created by the cycloisomerization process. Therefore, the previously unexplored opportunity of achieving diastereoselective cycloisomerizations of 1,6-ene-ynamides bearing stereogenic centers at the α or the β positions of the nitrogen atom could be investigated.

The 1,6-ene-ynamides **9**–**11** bearing a stereogenic center at the α position of the nitrogen atom[20] were subjected to a gold-catalyzed cycloisomerization (AuCl (5–20 mol%), CH_2Cl_2, room temperature). These reactions proceeded slowly (12–24 h) but efficiently and afforded the cyclobutanones **12** (76%), **13** (77%), and **14** (65%), respectively.[21] Examination of the ^{1}H NMR spectra of the crude materials indicated that the cycloisomerizations had proceeded with high levels of diastereoselection (d.r. > 95:5).[22,23] However, purification by flash chromatography on silica gel led to an erosion of the diastereoisomeric purity of the resulting cyclobutanones **12**–**14** (d.r. = 88:12–95:5). To avoid the purification of the latter sensitive cyclobutanones, their direct functionalization by a stereospecific transformation, such as a Baeyer–Villiger oxidation was envisaged.[24] Thus, treatment of cyclobutanone **13** (d.r. = 88:12) with peracetic acid (AcOOH, AcONa, AcOH, room temperature)[24b] provided the desired γ-lactone **15** (65%) without alteration of its diastereomeric purity owing to the well-known stereospecificity of the Baeyer–Villiger reaction (Scheme 3).[24,25]

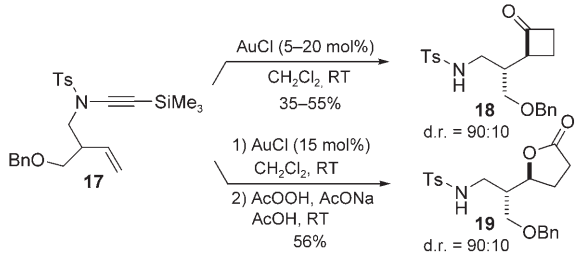
When the gold-catalyzed cycloisomerization and the Baeyer–Villiger oxidation were carried out subsequently starting from ynamide **10**, without purification of the intermediate cyclobutanone **13**, the resulting γ-lactone **15** was isolated in a satisfactory overall yield (65%) and as a single diastereomer (d.r. > 95:5), thereby indicating the intrinsic high diastereoselectivity of the gold-catalyzed cycloisomerization. Similarly, the Baeyer–Villiger oxidation of cyclobutanone **14** afforded the functionalized γ-lactone **16** (67%; Scheme 3).[25]



Scheme 3. Diastereoselective cycloisomerizations of ene-ynamides. *p*-Ns = $pNO_2(C_6H_4)SO_2$.

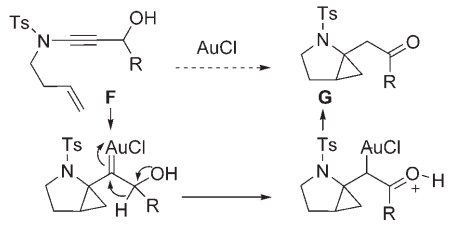
The cycloisomerization of the 1,6-ene-ynamide **17**, bearing a stereogenic center at the β position of the nitrogen atom, proceeded slowly (AuCl (5 mol%), CH_2Cl_2, room temperature), presumably as a result of the steric bulk around the nucleophilic alkene partner, and afforded the cyclobutanone **18** (d.r. = 90:10) in quite low yield (35%), which could be improved either by using a higher catalyst loading (20 mol%, 55% yield) or a more reactive cationic gold(I) complex (5 mol% $[Au(Ph_3P)(SbF_6)]$;[7a] 47% yield). When **17** was subjected to the cycloisomerization/Baeyer–Villiger rearrangement sequence, the γ-lactone **19** was obtained in satisfactory overall yield (56%, d.r. = 90:10; Scheme 4).

As the diastereoselectivity is set at the stage of the cyclopropyl gold carbene of type **A**, the possibility of retaining the interesting 2-azabicyclo[3.1.0]hexane substructure of the latter intermediate in the final cycloisomerization products was examined. Based on literature precedents disclosed in the non-heterosubstituted series,[8] the cycloisomerization of 1,6-ene-ynamides of type **F** bearing a propargylic alcohol moiety was investigated. For such substrates, the ring-expansion process should be diverted to an alternative event involving a 1,2-hydride shift followed by demetalation that leads to carbonyl derivatives of type **G** (Scheme 5).



Scheme 4. Diastereoselective cycloisomerization of ene-ynamide **17**. Bn = benzyl.

The ynamides **20**–**23** bearing a propargylic alcohol moiety[26] were treated with AuCl (5 mol%) in CH_2Cl_2 at room temperature. Under these conditions, the primary alcohol **20a** was smoothly converted into the aldehyde **24a** (40%), whereas the secondary alcohols **20b** and **20c** led to the

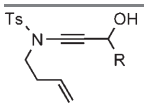
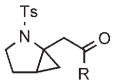
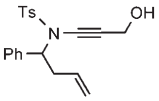
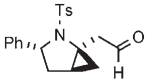
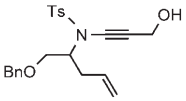
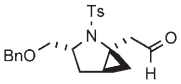
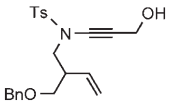


Scheme 5. Cycloisomerization of ene-ynamide bearing a propargylic alcohol moiety.

ketones **24b** (60%) and **24c** (42%), respectively. The ene-ynamides **21** and **22** bearing a stereocenter at the α position of the nitrogen atom were converted into the azabicylic aldehydes **25** (61%) and **26** (51%) with high diastereoselectivities (d.r. > 95:5). The cycloisomerization of the ene-ynamide **23** with a stereocenter at the β position of the nitrogen atom was also carried out, but the resulting aldehyde was directly reduced with $NaBH_4$ in MeOH to afford the alcohol **27** (60%, d.r. = 90:10; Table 1).[27]

We have reported the first examples of gold-catalyzed cycloisomerizations of 1,6-ene-ynamides, either unsubstituted or bearing a trimethylsilyl group at the acetylenic position, which led to cyclobutanones, or functionalized γ-lactones after a Baeyer–Villiger oxidation. High diastereoselectivities were observed for substrates bearing a stereocenter at the α or β positions of the nitrogen atom.[28] For 1,6-ene-ynamides bearing a propargylic alcohol moiety, the gold-catalyzed cycloisomerizations led to carbonyl compounds that incorporate a 2-azabicyclo[3.1.0]hexane framework. The gold-catalyzed cycloisomerization of other functionalized ynamides bearing different substitution patterns is currently under examination so that this methodology can be applied to natural and/or biologically active products.

Table 1: Cycloisomerization of ene-ynamides bearing a propargylic alcohol moiety.

Substrate		Product[a]		Yield [%][b]	d.r.
	**20a** R = H **20b** R = Me **20c** R = *i*Pr		**24a** R = H **24b** R = Me **24c** R = *i*Pr	40 60 42	–
	**21**		**25**	61	95:5
	**22**		**26**	51	95:5
	**23**		**27**	60[c]	90:10

[a] Treatment with AuCl (5 mol%) in CH_2Cl_2 at room temperature. [b] Yields of the isolated products as analytically pure materials. [c] Treatment with $NaBH_4$ in MeOH.

Experimental Section

4-Methyl-*N*-[(*R*)-2-{(2*S*)-2-oxocyclobutyl}-1-phenylethyl]benzenesulfonamide (**13**; representative procedure): AuCl (3.4 mg, 0.012 mmol, 0.05 equiv) was added to a solution of ynamide **10** (115 mg, 0.289 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was filtered through a short plug of celite (CH_2Cl_2) after 24 h, and the filtrate was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc = 80:20) to afford 77 mg (77%) of **13** as a colorless oil (88:12 mixture of diastereomers); IR $\tilde{\nu}_{max}$ = 3271, 1771, 1599, 1495, 1456, 1324, 1155, 1089, 813, 701, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (br d, J = 8.1 Hz, 2H), 7.16–7.14 (m, 3H), 7.11 (d, J = 8.1 Hz, 2H), 7.05–7.01 (m, 2H), 6.04 (br d, J = 8.5 Hz, 1H), 4.53 (ddd, apparent dt, J = 8.5 and 6.0 Hz, 1H), 3.14–3.05 (m, 1H), 2.99 (dddd, J = 19.1, 11.0, 8.5 and 2.5 Hz, 1H), 2.85 (dddd, J = 18.0, 9.5, 4.5, and 2.5 Hz, 1H), 2.34 (s, 3H), 2.09 (m, 1H), 2.04–1.90 (m, 2H), 1.61 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0 (s), 142.9 (s), 139.8 (s), 137.9 (s), 129.3 (d, 2C), 128.5 (d, 2C), 127.4 (d), 127.0 (d, 2C), 126.3 (d, 2C), 56.2 (d), 55.9 (d), 44.1 (t), 36.8 (t), 21.4 (q), 14.2 ppm (t); MS (70 eV): m/z (%): 343 (1) [M^+], 315 (4) [M^+−CO], 261 (17), 260 (100), 188 (15), 155 (58), 130 (10), 106 (11), 104 (12), 91 (84), 77 (9), 65 (12), 55 (8).

(1*R*,3*R*,5*R*)-3-Phenyl-2-(4-methylbenzenesulfonyl)-2-azabicyclo-[3.1.0]hex-1-yl]ethanal (**25**): IR $\tilde{\nu}_{max}$ = 1726, 1597, 1493, 1450, 1340, 1160, 1085, 1029, 961, 812, 760, 729, 699, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.96 (t, J = 1.6 Hz, 1H), 7.45 (br d, J = 8.1 Hz, 2H), 7.18–7.10 (m, 5H), 7.12 (br d, J = 8.1 Hz, 2H), 4.12 (dd, apparent t, J = 8.8 Hz, 1H), 3.83 (dd, apparent br d, J = 17.4 Hz, 1H), 2.33 (dd, J = 17.4 and 1.6 Hz, 1H), 2.31 (s, 3H), 2.27 (dd, J = 13.1 and 8.8 Hz, 1H), 2.16 (ddd, J = 13.1, 8.8, and 5.5 Hz, 1H), 1.42 (ddd, apparent dt, J = 8.8 and 6.6 Hz, 1H), 0.61 (dd, J = 8.8 and 6.6 Hz, 1H), 0.47 ppm (dd, J = 6.6 and 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8 (d), 143.8 (s), 141.6 (s), 134.3 (s), 129.3 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.3 (d), 126.8 (d, 2C), 65.0 (d), 48.1 (t), 45.1 (s), 37.8 (t), 21.9 (d), 21.5 (q), 14.9 ppm (t); MS (70 eV): m/z (%): 355 (1) [M^+], 327 (2) [M^+−CO], 263 (32), 262 (20), 200 (51), 172 (26), 155 (15), 132 (16),131 (78), 129 (16), 117 (19), 116 (16), 105 (21), 104 (21), 103 (16), 91 (100), 77 (11), 65 (14).

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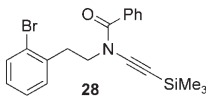
[14] For mechanistic studies, see: a) E. Soriano, P. Ballestros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3172 – 3181; b) C. Nieto-Oberhuber, S. López, M. P. Muñoz, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302 – 6304; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146 – 6148; c) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627 – 2635.

[15] a) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407 – 4409; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237 – 4239; b) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3 – 9; c) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51 – 65; d) A. Arcadi, S. Di Giuseppe, *Curr. Org. Chem.* **2004**, *8*, 795 – 812; e) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387 – 391; f) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150 – 7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990 – 6993; for a recent account, see: g) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206 – 209; *Angew. Chem. Int. Ed.* **2006**, *45*, 200 – 203.

[16] M. Mori, H. Wakamatsu, N. Saito, Y. Sato, R. Narita, Y. Sato, R. Fujita, *Tetrahedron* **2006**, *62*, 3872 – 3881.

[17] For a review on additions to *N*-acyliminium ions, see: H. Hiemstra, W. N. Speckamp in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1047 – 1082.

[18] Ynamide **28** was unaffected by treatment with AuCl.



28

[19] The AuCl-catalyzed cycloisomerization of the 1,7-enyne **3** afforded the cyclobutanone **5** in only 26% yield; for the cycloisomerization of this class of substrate, $PtCl_2$ seems to be a more efficient catalyst relative to AuCl.

[20] a) B. Witulski, T. Stengel, *Angew. Chem.* **1998**, *110*, 495 – 498; *Angew. Chem. Int. Ed.* **1998**, *37*, 489 – 492; b) B. Witulski, M. Gößmann, *Chem. Commun.* **1999**, 1879 – 1880.

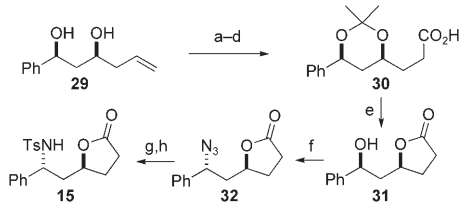
[21] Other gold(I) cationic catalysts such as $[Au(BF_4)(Ph_3P)]$[7a] and $[Au(NTf_2)(Ph_3P)]$[11] provided similar results.

[22] A 1:1 mixture of diastereomers was obtained by epimerization of the cyclobutanone **13** under alkaline conditions (K_2CO_3, MeOH, reflux).

[23] The Pt^{II}-catalyzed cycloisomerization of **10** ($PtCl_2$ (5 mol%), toluene, 80°C, 24 h) led to a mixture of compounds from which the cyclobutanone **13** was isolated in modest yield (39%) with low diastereoselectivity (d.r. = 55:45).

[24] a) G. R. Krow, *Org. React.* **1993**, *43*, 251 – 798; b) G. R. Krow, C. A. Johnson, J. P. Guare, D. Kubrak, K. J. Henz, D. A. Shaw, S. W. Szczepanski, J. T. Carey, *J. Org. Chem.* **1982**, *47*, 5239 – 5243.

[25] A chemical correlation from the 1,3-diol **29** (*syn*/*anti* = 70:30)[25a,b] was used to establish the relative configuration of compounds **15** and **13**; the relative configuration of the other cyclobutanones **12** and **14** was assumed to be similar.

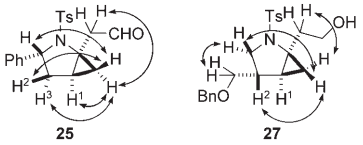


29 **30** **15** **32** **31**

Reagents and conditions: a) $Me_2C(OMe)_2$, cat. camphorsulfonic acid (CSA), acetone; b) BH_3·THF, THF then NaOH, H_2O_2; c) 2-iodoxybenzoic acid (IBX), THF/dimethyl sulfoxide (DMSO); d) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*BuOH; e) AcOH/H_2O, then toluene, cat. CSA, reflux (62% over 5 steps); f) $(PhO)_2P(=O)N_3$, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), THF (64%);[25c] g) PPh_3, NaOH, THF/H_2O; h) *para*-toluenesulfonyl chloride (TsCl), pyridine (31% over 2 steps); a) X. Wang, Q. Meng, A. J. Nation, J. L. Leighton, *J. Am. Chem. Soc.* **2002**, *124*, 10672 – 10673; b) G. W. Kabalka, C. Narayana, N. K. Reddy, *Tetrahedron Lett.* **1996**, *37*, 2181 – 2184; c) A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 5886 – 5888.

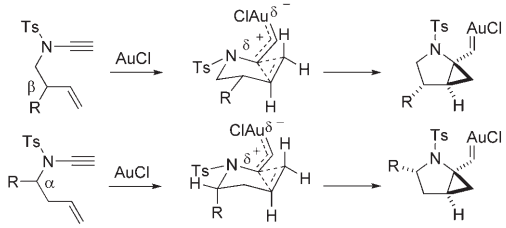
[26] a) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151 – 1154; b) D. Brückner, *Synlett* **2000**, 1402 – 1404.

[27] The following correlations observed in the NOESY spectra of **25** and **27** were used to assign their relative configurations. An *anti* relationship between H^1 and H^2 was also suggested by



the absence of coupling ($J^3(H^1–H^2) \approx 0$ Hz), see: S. F. Martin, M. R. Spaller, S. Liras, B. Hartmann, *J. Am. Chem. Soc.* **1994**, *116*, 4493 – 4494.

[28] The initial coordination of AuCl by the alkyne should result in charge build up on the triple bond. The observed stereochemical outcome has been tentatively rationalized by assuming that interaction with the double bond may proceed through the formation of a π complex of chairlike conformation by analogy with cyclizations involving *N*-acyliminium ions;[17] whereas a substituent at Cβ should preferentially occupy a pseudoequatorial position, a pseudoaxial positioning of the substituent at Cα may be preferred in the cyclic transition state to avoid a gauche



interaction with the *N*-tosyl substituent (similar to $A^{1,2}$ strain by assuming stabilization of the developing adjacent partial positive charge by the lone pair on the nitrogen atom).[17]