DOI: 10.1002/ejoc.200900745

Synthesis of Benzazepines by Gold-Catalysed Reactions of *N*-Allenylamides

Álvaro González-Gómez,[a] Gema Domínguez,[a] and Javier Pérez-Castells*[a]

Keywords: Gold / Cyclization / Allenes / Nitrogen heterocycles

The gold-catalysed reactions of alleneamides give different products depending on the substrate and the reaction conditions. In particular, *N*-(2-alkynylphenyl)-*N*-allenyltosylamides give benzazepines when using gold(III) catalysts in the presence of nucleophiles. This sequential process may follow two different reaction pathways, and these are discussed. Metal coordination to the alkyne followed by nucleophilic attack of the allene and trapping of the intermediate with NuH accounts for the formation of **4**, but coordination to the allene and addition of NuH to give **3**, which can decompose into other products and also form **4**, is postulated as a better explanation for these results.

Introduction

New reactions recently discovered in the field of gold catalysis have focused attention on this metal.[1] Gold(I) and gold(III) species catalyse the cycloisomerization of enynes and nucleophilic additions to π systems.[2] Allenes have been used in these reactions with alleneenes[3] and alleneynes[4] giving polyunsaturated carbo- and heterocycles upon reaction with gold chlorides and other modified salts such as Ph_3PAuX in a totally atom-economic manner. (Phosphite)-gold(I) monocations react with 1,6-alleneynes in an *exo* fashion to furnish vinyl-substituted benzocycles.[5] Various transition metals, for example, Rh, Pd and Pt, catalyse alleneyne cycloisomerization reactions, which generally involve the formation of metallacyclopentene intermediates.[6] On the other hand, in gold chemistry, the cyclization reactions of enynes and allenynes or allenenes are postulated to proceed by the addition of a double bond to a gold-complexed alkyne. A complete experimental and computational study with allenynes, disclosed recently by Toste and coworkers, proposes the addition of the allene to a (phosphane)gold-complexed acetylide, ruling out the complexation of the metal atom with the allene.[4a]

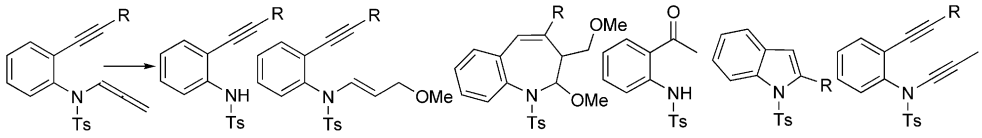
N-Allenylamides are an interesting group of substrates that are becoming useful in organic synthesis.[7] These allenes have found use in some reactions with electrophiles and in certain cyclization reactions.[8] We envisioned the possibility of promoting the cyclization reactions of *N*-(alkynylaryl)-*N*-allenylamides to furnish interesting heterocycles such as benzazepines. Some benzazepines have interesting biological properties. Examples are the vainilloid receptor subtype 1 (VR1) antagonist, capsazepine[9] or certain 1-benzazepines designed as potent and selective antagonists of the arginine vasopressin (AVP) V_{1A} receptor.[10] Herein we present a study of the cyclization reactions of *N*-(alkynylaryl)-*N*-allenylamides and other allenes by using gold catalysis.

Results and Discussion

Compound **1a**[11] was selected as a model compound and used in reactions performed under different conditions, as summarized in Table 1. The cycloisomerization reactions of allenynes previously described in the literature were postulated to occur by the coordination of the gold atom to the triple bond followed by nucleophilic attack of the internal allene bond to give a cationic species that undergoes a 1,5-hydrogen shift. The latter step is only possible with non-terminal allenes. With our substrate, the use of a nucleophile to trap the intermediate species was mandatory. Indeed, the reaction of **1a** with $AuCl_3$ in DCM produced extensive decomposition of the starting material and isolation of isomer **7a** in 25% yield (Entry 1, Table 1). Therefore, we added methanol to the reaction mixture, and we observed the formation of **4aa** and a new product **3aa** as a result of the addition of methanol to the allene (Entry 2). The reaction was completed within minutes, and we next explored different conditions in order to optimize the formation of **4aa**. The reaction temperature was critical for achieving high yields, and the best conditions for the synthesis of **4aa** were those of Entry 4 (–78 °C); **4aa** was obtained as only the *trans* diastereomer in 85% yield. For comparative reasons we performed the reaction with other metals as catalysts. Experiments with platinum salts led to the loss of the allene moiety and the formation of the ketone **5a** with subsequent cyclization to give the indole **6a**

[a] Departamento de Química, Facultad de Farmacia, Universidad San Pablo-CEU,
Urb. Montepríncipe, 28668 Boadilla del Monte, Madrid, Spain
Fax: +34-913510496
E-mail: jpercas@ceu.es
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900745.

Table 1. Reactions of **1a**–**d** with different catalysts under different conditions.

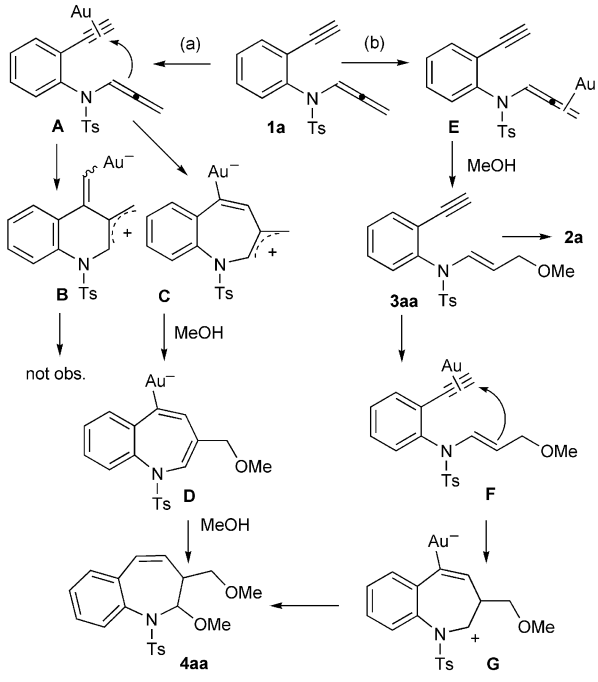


Entry	R	Substrate	Reaction conditions Catalyst[b]	Solvent	Time	Temp. [°C]	Product, yield[a] [%] 2	3	4	5	6	7
1	H	**1a**	$AuCl_3$	DCM	1 h	25						**7a**, 25
2	H	**1a**	$AuCl_3$	DCM/MeOH (9:1)	15 min	10		**3aa**, 18	**4aa**, 55			
3	H	**1a**	$AuCl_3$	DCM/MeOH (2:1)	15 min	10		**3aa**, 5	**4aa**, 71			
4	H	**1a**	$AuCl_3$	DCM/MeOH (2:1)	1 h	–78			**4aa**, 85			
5	H	**1a**	$PtCl_2$	DCM/MeOH (9:1)	24 h	10			**4aa**, 5	**5a**, 12	**6a**, 15	
6	H	**1a**	$PtCl_4$	DCM/MeOH (9:1)	24 h	10				**5a**, 17	**6a**, 40	
7	H	**1a**	$InBr_3$	$PhCH_3$/MeOH (9:1)	2 h + 24 h	10–80	**2a**, 60					
8	H	**1a**	AuCl	DCM/MeOH (2:1)	1.5 h	0	**2a**, 5				**6a**, 45	
9	H	**1a**	$(PPh_3)AuCl/AgSbF_6$	DCM/MeOH (9:1)	2 h	10	**2a**, 35					
10	Me	**1b**	$AuCl_3$	DCM/MeOH (2:1)	15 min	10			**4ba**, 55			
11	C_4H_9	**1c**	$AuCl_3$	DCM/MeOH (2:1)	1 h	10	**2c**, 18		**4ca**, 17			
12	C_4H_9	**1c**	$AuCl_3$	DCM/MeOH (2:1)	1 h	–78	**2c**, 18		**4ca**, 47			
13	Ph	**1d**	$AuCl_3$	DCM/MeOH (2:1)	4 h	–78					**6d**, 22	

[a] Yield of the isolated product. [b] 5 mol-% of catalyst.

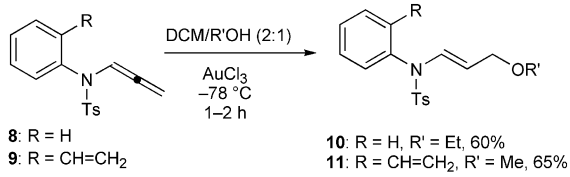
(Entries 5 and 6). With $PtCl_2$, a small amount of **4aa** was also isolated. Indium(III) bromide gave exclusively the product **2a** (Entry 7). We also studied the reactions of gold(I) species, which led to the cleavage of the allene or the formation of the indole **6a** in a moderate yield (Entries 8–9); alkynylamines are known to form indoles in the presence of gold and platinum catalysts, and **6a** is presumably formed by the cyclization of **2a**.[12] The reaction with $AuCl_3$ was then applied to the substrates **1b**–**d** with different substituents at the alkyne. Compound **1b** gave **4ba** in 55% yield as the only reaction product (Entry 10), whereas **1c** gave the corresponding **4ca** in low yield with a small amount of **2c** (Entry 11). For this reason we carried out the reaction at –78 °C and observed the yield of **4ca** to rise to 47% (Entry 12). Finally, **1d** did not cyclize and only gave **6d** in low yield (Entry 13). The increasing steric demand of the substituents at the triple bond is possibly responsible for these results.

The formation of **4aa** can be rationalized by two possible pathways according to proposals in the literature for similar reactions (Scheme 1). Although many gold-catalysed reactions can be explained by the complexation of the metal first with triple bonds (path a), in this case we have to consider coordination to the enriched allene (path b), which would also give a stable complex. If the gold atom prefers to coordinate to the alkyne first, the formation of intermediate **B** or **C** could be expected. As the formation of a six-membered ring was not observed under any of the reaction conditions, we assume that the aromatic ring is responsible for the regiochemical outcome of the nucleophilic attack and the formation of **C**. This path does not explain the formation of compound **3aa**. In addition, **7a** is the only isolated product in the reaction (in low yield) performed in the absence of a nucleophile (Entry 1), which indicates that the metal atom coordinates to the allene. Thus, path b accounts for the synthesis of **3aa**, which then acts as an intermediate. Nucleophilic attack on allenes catalysed by different metals is well documented and drives the reaction as it is more favourable than attack on a gold-complexed triple bond. Compound **3aa** may then evolve in two possible ways, that is, with the loss of the enamide group to give **2a** or by nucleophilic attack on the alkyne once it has coordinated to the gold atom. This latter step gives intermediate **G** leading to **4aa**.



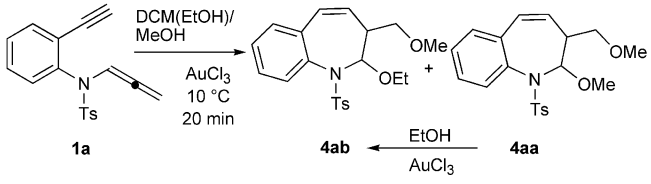
Scheme 1. Mechanism for the reaction of **1a**.

To support this pathway we isolated **3aa** and submitted it to a new reaction with $AuCl_3$ under the conditions described in Entry 3 (Table 1) and observed a total conversion into **4aa**. This result shows that path b is probably responsible for the formation of **4aa**. The electronic nature of the *N*-allenylamide and the type of nucleophile could affect the result of the reaction, favouring the formation of **4** or the evolution of **3** into **2** and from this *N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide the formation of **5** and **6**. In addition to this reaction, we submitted compounds **8** and **9** to our reaction conditions (Scheme 2). In the presence of DCM and an alcohol these compounds were converted into **10** and **11** in high yields.



Scheme 2. Reactions of compounds **8** and **9** with $AuCl_3$.

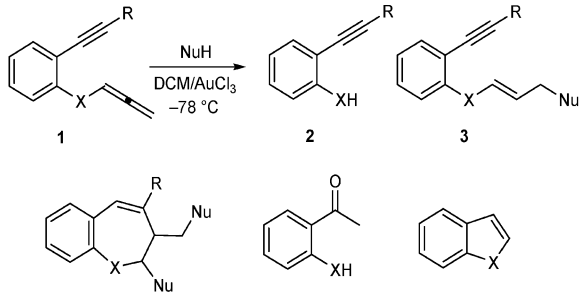
On the other hand, a curiosity we observed when performing the reaction of **1a** (Scheme 3) with undistilled DCM was the formation of compound **4ab** in 50% yield together with a small amount of **4aa**. As commercial DCM contains EtOH, the equilibrium between **4aa** and **4ab** must be displaced towards the latter compound during the workup. Thus, **4aa** would be converted into **4ab** when methanol is eliminated and ethanol is still in the mixture. To check this point we stirred **4aa** with ethanol, and after 18 h no changes were observed. On the other hand, **4aa** was completely converted into **4ab** after 20 min when stirred in ethanol in the presence of $AuCl_3$, which shows the positive effect of the metal on the transformation. As reported in the literature, the complex formed in situ with the alcohol [$AuCl_3$(ROH)] is possibly the acid catalyst responsible for this transformation.[13]



Scheme 3. Reaction of **1a** with $AuCl_3$ in undistilled DCM.

Our next aim was to study the scope of the cyclization reaction. Thus, we prepared allenyl ether **1e** and *N*-allenylamides **1f**–**i**, which were easily obtained by propargylation of *N*-protected 2-alkynylanilines followed by KO*t*Bu-mediated isomerization. The reaction of allenyl phenyl ether **1e** produced a rapid transformation to the corresponding phenol without the detection of any other products (Entry 1, Table 2). *N*-Allenylamides **1f**–**1h** bearing less withdrawing groups than tosyl at the nitrogen atom (acetyl or benzoyl) gave exclusively the products **2** and **3** (Entries 2–4). These results show the capacity of compounds **3** to lose the alkenyl group to form **2**. Indeed, when compound **3fa** was treated with $AuCl_3$ it gave **5f** (73%). On the other hand, the sulfonamide **1i** gave a mixture of diastereomers of **4ia** in good yield together with 11% of indole **6i** (Entry 5). The reaction of **1a** in the presence of other nucleophiles led to the isolation of compounds **4ac** and **4ad** in good yields (Entries 6 and 7). In contrast to the reactions with oxygen nucleophiles, in which only the *trans* isomers were formed, the reaction with EtSH gave a 1:1 mixture of isomers. The reaction in the presence of pyrrolidine gave exclusively the indole **6a** (Entry 8), and with TMSCN small amounts of **2a** and **3af** were obtained (Entry 9).

Table 2. Reactions of **1** with different NuH.



Entry	Reaction conditions					Product, yield [%]				
	X	R	Substrate	NuH	Time	**2**	**3**	**4**	**5**	**6**
1	O	H	**1e**	MeOH					**5e** 44	
2	NAc	H	**1f**	MeOH	10 min		**3fa** 54			
3	NAc	Me	**1g**	MeOH	4 h	**2g** 25	**3ga** 15			
4	NCOPh	H	**1h**	MeOH	4 h	**2h** 5	**3ha** 10			
5		H	**1i**	MeOH	4 h			**4ia** 46[a]		**6i** 11
6	NTs	H	**1a**	EtOH	1 h			**4ac** 81		
7	NTs	H	**1a**	EtSH	3 h			**4ad** 77[b]		
8	NTs	H	**1a**	pyrrolidine	30 min					**6a** 40
9	NTs	H	**1a**	TMSCN	1 h	**2a** 11	**3af** 14			

[a] 7:3 mixture of *trans* diastereoisomers. [b] 1:1 mixture of *cis* and *trans* isomers.

From the results shown herein it is clear that a highly electron-withdrawing group is necessary for the formation of benzazepines **4**. All the data point to a straightforward conversion of the starting allenes into addition products **3**, which partially decompose to the amides **2**, which undergo cyclization to indoles **6** or are converted into ketones **5**. This process is favoured with carboxylic amides and ethers. With sulfonamides, the corresponding compounds **3** undergo a cyclization reaction leading to **4**. The best nucleophiles are alcohols, which give the benzazepines **4** as only the *trans* isomers.

Conclusions

A novel cyclization process catalysed by gold species has been shown for *N*-allenylamides. The reaction is possible with *N*-allenylsulfonamides, whereas with other *N*-allenylamides a competitive nucleophilic addition to the allene is preferred. The results suggest a reaction pathway that involves the coordination of the metal atom to the allene followed by nucleophilic attack and cyclization. A complete study of the scope and limitations of these reactions and their further application in natural alkaloid synthesis is underway in our laboratory.

Experimental Section

((<=AUTHOR: Please give a brief paragraph describing makes and models of instruments used for characterization and from where chemicals were purchased with any relevant purification details!))

Typical Procedure for the Cyclization of 1: The catalyst (5 mol-%) was added to a solution of the *N*-(alkynylaryl)-*N*-allenylamide (1.0 mmol) in DCM/NuH (2:1, 2 mL), and the mixture was stirred until the reaction was complete (TLC). The crude mixture was extracted with water and ethyl acetate, the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

***N*-(2-Ethynylphenyl)-*N*-[(1*E*)-3-methoxyprop-1-enyl]-4-methylbenzenesulfonamide (3aa):** Table 1, Entry 2: reaction temperature, time: 10 °C, 15 min. Yield: 61 mg (18%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.97 (s, 1 H, HC≡), 3.25 (s, 3 H, OCH_3), 3.86 (d, J = 7.1 Hz, 2 H, CH_2), 4.30–4.40 (m, 1 H, CH=), 6.95–6.98 (m, 1 H, NCH=), 7.17 (d, J = 13.7 Hz, 1 H, ArH), 7.28 (d, J = 7.7 Hz, 2 H, ArH), 7.31–7.37 (m, 2 H, ArH), 7.55–7.58 (m, 1 H, ArH), 7.62 (d, J = 8.2 Hz, 2 H, ArH) ppm. IR (film): $\tilde{\nu}$ = 1650, 1600 cm^{-1}.

***N*-(2-Ethynylphenyl)-*N*-[(1*E*)-3-methoxyprop-1-enyl]acetamide (3fa):** Table 2, Entry 2: reaction temperature, time: –78 °C, 10 min. Yield: 124 mg (54%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, CH_3CO), 3.19 (s, 1 H, HC≡), 3.22 (s, 3 H, CH_3O), 3.82–3.93 (m, 2 H, CH_2), 4.36–4.45 (m, 1 H, CH=), 7.22 (dd, ^1J = 7.7, ^2J = 1.1 Hz, 1 H, NCH=), 7.39 (td, ^1J = 7.7, ^2J = 1.6 Hz, 1 H, ArH), 7.47 (td, ^1J = 7.7, ^2J = 1.6 Hz, 1 H, ArH), 7.63 (dd, ^1J = 7.7, ^2J = 1.6 Hz, 1 H, ArH), 7.65 (d, J = 14.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 57.1, 71.1, 78.7, 82.4, 108.5, 122.3, 128.8, 129.3, 130.4, 130.7, 134.1, 141.2, 168.6 ppm. IR (film): $\tilde{\nu}$ = 2100, 1680, 1660 cm^{-1}. $C_{14}H_{15}NO_2$ (229.27): calcd. C 73.34, H 6.59, N 6.11; found C 73.49, H 6.27, N 5.85.

***N*-[(1*E*)-3-Methoxyprop-1-enyl]-*N*-(2-prop-1-ynylphenyl)acetamide (3ga):** Table 2, Entry 3: reaction temperature, time: –78 °C, 4 h. Yield: 37 mg (15%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3C≡), 3.25 (s, 3 H, CH_3O), 3.85–3.96 (m, 2 H, CH_2), 4.38–4.48 (m, 1 H, CH=), 7.18 (dd, ^1J = 7.2, ^2J = 2.2 Hz, 1 H, NCH=), 7.33–7.42 (m, 2 H, ArH), 7.54 (dd, ^1J = 6.6, ^2J = 2.7 Hz, 1 H, ArH), 7.65 (d, J = 14.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.5, 22.8, 57.1, 71.3, 75.0, 91.4, 108.4, 124.2, 128.7, 129.1, 129.1, 130.9, 133.6, 140.5, 169.0 ppm. IR (film): $\tilde{\nu}$ = 1680, 1650 cm^{-1}. $C_{15}H_{17}NO_2$ (243.30): calcd. C 74.05, H 7.04, N 5.76; found C 73.80, H 7.18, N 5.88.

***N*-(2-Ethynylphenyl)-*N*-[(1*E*)-3-methoxyprop-1-enyl]benzamide (3ha):** Table 2, Entry 4: reaction temperature, time: –78 °C, 4 h. Yield: 27 mg (10%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27 (s, 1 H, HC≡), 3.29 (s, 3 H, CH_3O), 3.95 (br. s, 2 H, CH_2), 4.62–4.72 (m, 1 H, CH=), 7.21–7.49 (m, 10 H, NCH= and ArH) ppm. IR (film): $\tilde{\nu}$ = 2100, 1680, 1640 cm^{-1}.

***N*-[(1*E*)-3-Cyanoprop-1-enyl]-*N*-(2-ethynylphenyl)-4-methylbenzenesulfonamide (3af):** Table 2, Entry 9: reaction temperature, time: –78 °C, 1 h. Yield: 47 mg (14%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.96 (s, 1 H, HC≡), 3.04 (dd, ^1J = 6.8, ^2J = 1.5 Hz, 2 H, CH_2), 4.09–4.18 (m, 1 H, CH=), 7.00–7.03 (m, 1 H, NCH=), 7.17–7.23 (m, 1 H, ArH), 7.29 (d, J = 7.8 Hz, 2 H, ArH), 7.33–7.40 (m, 2 H, ArH), 7.54–7.57 (m, 1 H, ArH), 7.60 (d, J = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 21.6, 79.0, 82.3, 117.7, 123.8, 127.7, 128.2, 129.3, 129.7, 129.9, 130.8, 132.0, 134.5, 135.7, 137.2, 144.3 ppm. IR (film): $\tilde{\nu}$ = 2250 cm^{-1}. $C_{19}H_{16}N_2O_2S$ (336.41): calcd. C 67.84, H 4.79, N 8.33; found C 68.02, H 4.98, N 7.99.

2-Methoxy-3-(methoxymethyl)-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4aa): Table 1, Entry 4: reaction temperature, time: –78 °C, 1 h. Yield: 317 mg (85%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (br. s, 1 H, 3-H), 2.38 (s, 3 H, CH_3Ar), 3.36 (s, 3 H, CH_3OCH_2), 3.38–3.42 (m, 1 H, CH_2), 3.51–3.56 (m, 1 H, CH_2), 3.65 (s, 3 H, CH_3OCH), 5.61–5.62 (m, 2 H, 4-H and 5-H), 5.68 (d, J = 10.4 Hz, 1 H, 2-H), 6.93–6.96 (m, 1 H, ArH), 7.11 (d, J = 8.2 Hz, 2 H, ArH), 7.23 (d, J = 8.2 Hz, 2 H, ArH), 7.28–7.36 (m, 2 H, ArH), 7.55–7.58 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 43.5, 55.6, 59.2, 71.8, 98.7, 127.8, 128.0, 128.2, 128.6, 128.7, 129.9, 131.1, 133.5, 133.8, 136.0, 138.3, 143.0 ppm. IR (film): $\tilde{\nu}$ = 1620, 1580 cm^{-1}. $C_{20}H_{23}NO_4S$ (373.47): calcd. C 64.32, H 6.21, N 3.75; found C 64.52, H 6.07, N 3.93.

2-Methoxy-3-(methoxymethyl)-4-methyl-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4ba): Table 1, Entry 10: reaction temperature, time: 10 °C, 15 min. Yield: 213 mg (55%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3C=), 2.41 (s, 3 H, CH_3Ar), 2.76 (dd, ^1J = 9.8, ^2J = 6.1 Hz, 1 H, 3-H), 2.82 (s, 3 H, CH_3OCH_2), 2.93 (s, 3 H, CH_3OCH), 2.97 (dd, ^1J = 9.1, ^2J = 1.8 Hz, 1 H, CH_2), 3.18–3.25 (m, 1 H, CH_2), 5.46 (s, 1 H, 5-H), 5.88 (d, J = 12.8 Hz, 1 H, 2-H), 6.85–6.94 (m, 2 H, ArH), 7.00 (d, J = 7.9 Hz, 1 H, ArH), 7.12–7.38 (m, 4 H, ArH), 7.70 (d, J = 7.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 19.9, 21.5, 41.8, 58.4, 67.5, 70.2, 114.6, 126.3, 127.2, 128.7, 128.8, 129.9, 133.2, 134.6, 139.0, 140.9, 142.8, 144.7 ppm. IR (film): $\tilde{\nu}$ = 1600 cm^{-1}. $C_{21}H_{25}NO_4S$ (387.49): calcd. C 65.09, H 6.50, N 3.61; found C 64.83, H 6.78, N 3.47.

4-Butyl-2-methoxy-3-(methoxymethyl)-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4ca): Table 1, Entry 12: reaction temperature, time: –78 °C, 1 h. Yield: 200 mg (47%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.10–1.41 (m, 4 H, 2 CH_2), 1.94–2.20 (m, 2 H, CH_2C=), 2.49 (br. s, 1 H, 3-H), 2.39 (s, 3 H, CH_3Ar), 3.29 (s, 3 H, CH_3OCH_2), 3.50 (dd, ^1J = 9.3, ^2J = 2.4 Hz, 1 H, CH_2O), 3.59 (dd, ^1J = 9.3, ^2J = 2.0 Hz, 1 H, CH_2O), 3.63 (s, 3 H, CH_3OCH), 5.39 (br. s, 1 H, 5-H), 5.54 (d, J = 10.7 Hz, 1 H, 2-H), 6.94–6.97 (m, 1 H, ArH), 7.09 (d, J = 8.3 Hz, 2 H, ArH), 7.20 (d, J = 8.3 Hz, 2 H, ArH), 7.26–7.33 (m, 2 H, ArH), 7.53–7.57 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.5, 22.8, 29.5, 31.8, 45.9, 55.4, 58.7, 69.9, 97.7, 127.2, 127.3, 128.4, 128.5, 128.8, 129.8, 132.9, 133.4, 136.5, 138.7, 142.6, 142.9 ppm. IR (film): $\tilde{\nu}$ = 1600 cm^{-1}. $C_{24}H_{31}NO_4S$ (429.57): calcd. C 67.10, H 7.27, N 3.26; found C 66.84, H 7.42, N 3.46.

2-Ethoxy-3-(methoxymethyl)-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4ab): Reaction temperature: 10 °C, 20 min. Solvent: undistilled DCM/MeOH. Yield: 194 mg (50%). Yellow oil. ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 1.29 (t, J = 6.8 Hz, 3 H, CH_3CH_2O), 2.28 (br. s, 1 H, 3-H), 2.37 (s, 3 H, CH_3Ar), 3.35 (s, 3 H, CH_3O), 3.40 (dd, ^1J = 8.8, ^2J = 2.7 Hz, 1 H, CH_2OCH_3), 3.53 (dd, ^1J = 8.8, ^2J = 5.2 Hz, 1 H, CH_2OCH_3), 3.74–3.84 (m, 1 H, CH_3CH_2O), 4.06–4.16 (m, 1 H, CH_3CH_2O), 5.56–5.65 (m, 2 H, 4-H and 5-H), 5.78 (d, J = 10.4 Hz, 1 H, 2-H), 6.91–6.95 (m, 1 H, ArH), 7.09 (d, J = 8.2 Hz, 2 H, ArH), 7.22 (d, J = 8.2 Hz, 2 H, ArH), 7.27–7.34 (m, 2 H, ArH), 7.52–7.56 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 21.5, 43.5, 59.1, 63.1, 71.8, 97.2, 127.8, 128.0, 128.2, 128.5, 128.6, 129.8, 131.0, 133.4, 133.8, 136.0, 138.3, 142.9 ppm. IR (film): $\tilde{\nu}$ = 1590 cm^{-1}. $C_{21}H_{25}NO_4S$ (387.49): calcd. C 65.09, H 6.50, N 3.61; found C 65.31, H 6.26, N 3.86.

(1*S*)-1-({[2-Methoxy-3-(methoxymethyl)-2,3-dihydro-1*H*-1-benzazepinyl]sulfonyl}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (4ia): Table 2, Entry 5: reaction temperature, time: –78 °C, 4 h. Solvent: DCM (with ethanol traces)/MeOH. Yield: 205 mg (46%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of isomers, 7:3): δ = 0.72 (s, 0.9 H, CH_3camphor), 0.87 (s, 2.1 H, CH_3camphor), 0.96 (s, 0.9 H, CH_3camphor), 1.16 (s, 2.1 H, CH_3camphor), 1.23 (t, J = 7.1 Hz 3 H, CH_3CH_2O), 1.31–1.45 (m, 1 H, CH_2camphor), 1.81–2.05 (m, 2 H, CH_2camphor), 2.28–2.50 (m, 5 H, 3-H and CH_2camphor), 2.66 (d, J = 14.8 Hz, 0.3 H, SCH_2camphor), 2.77 (d, J = 14.8 Hz, 0.7 H, SCH_2camphor), 3.24 (d, J = 14.8 Hz, 0.7 H, SCH_2camphor), 3.35 (d, J = 14.8 Hz, 0.3 H, SCH_2camphor), 3.38 (s, 3 H, CH_3O), 3.45–3.52 (m, 1 H, CH_2OCH_3), 3.56–3.60 (m, 1 H, CH_2OCH_3), 3.63–3.74 (m, 1 H, CH_3CH_2O), 3.95–4.05 (m, 1 H, CH_3CH_2O), 5.63–5.66 (m, 1 H, 5-H), 6.11–6.20 (m, 1 H, 4-H), 6.67 (m, 1 H, 2-H), 6.72 (dd, ^1J = 10.4, ^2J = 2.2 Hz, 1 H, ArH), 7.21–7.41 (m, 2 H, Ar), 7.47–7.49 (m, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of isomers, 7:3): δ = 14.9, 19.6, 19.7, 20.0, 20.3, 25.0, 25.2, 26.7, 26.8, 42.4, 42.5, 42.7, 42.9, 44.3, 47.4, 47.6, 49.1, 49.2, 58.5, 58.6, 59.1, 59.2, 63.2, 71.9, 72.0, 96.9, 97.0, 128.0, 128.1, 128.6, 128.7, 128.8, 128.8, 130.6, 131.1, 132.6, 133.1, 133.2, 133.3, 134.3, 134.5, 137.4, 137.5, 191.9, 192.1 ppm. IR (film): $\tilde{\nu}$ = 1740, 1600 cm^{-1}.

2-Ethoxy-3-(ethoxymethyl)-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4ac): Table 2, Entry 6: reaction temperature, time: –78 °C, 1 h. Yield: 325 mg (81%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 6.8 Hz, 3 H, CH_3CH_2O), 1.28 (t, J = 6.8 Hz, 3 H, CH_3CH_2O), 2.28 (br. s, 1 H, 3-H), 2.36 (s, 3 H, CH_3Ar), 3.41–3.59 (m, 4 H, 2 CH_3CH_2O), 3.74–3.84 (m, 1 H, CH_2CH), 4.05–4.15 (m, 1 H, CH_2CH), 5.56–5.64 (m, 2 H, 4-H and 5-H), 5.80 (d, J = 10.3 Hz, 1 H, 2-H), 6.91–6.94 (m, 1 H, ArH), 7.09 (d, J = 8.3 Hz, 2 H, ArH), 7.23 (d, J = 8.3 Hz, 2 H, ArH), 7.27–7.31 (m, 2 H, ArH), 7.51–7.54 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 15.0, 21.4, 43.5, 63.0, 66.5, 69.4, 97.3, 127.6, 127.9, 128.1, 128.5, 128.6, 129.5, 131.3, 133.4, 133.9, 136.2, 138.2, 142.9 ppm. IR (film): $\tilde{\nu}$ = 1600 cm^{-1}. $C_{22}H_{27}NO_4S$ (401.52): calcd. C 65.81, H 6.78, N 3.49; found C 66.02, H 6.55, N 3.60.

2-(Ethylsulfanyl)-3-[(ethylsulfanyl)methyl]-1-tosyl-2,3-dihydro-1*H*-1-benzazepine (4ad): Table 2, Entry 7: reaction temperature, time: –78 °C, 3 h. Yield: 333 mg (77%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of isomers, 1:1): δ = 1.23–1.30 (m, 6 H, CH_3CH_2S), 1.55–1.67 (m, 1.5 H, CH_2CH), 1.75–1.89 (m, 0.5 H, CH_2CH), 2.29–2.76 (m, 4.5 H, CH_3CH_2S, CH), 2.41 (s, 3 H, CH_3Ar), 2.91–2.96 (m, 0.5 H, CH_3CH_2S), 5.48 (d, J = 8.8 Hz, 1 H, 5-H), 5.73 (dd, ^1J = 8.8, ^2J = 5.4 Hz, 1 H, 4-H), 6.88 (d, J = 7.8 Hz, 1 H, 2-H), 7.22–7.36 (m, 4 H, ArH), 7.45–7.51 (m, 1 H, ArH), 7.62–7.72 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO) (mixture of isomers, 1:1): δ = 14.6, 14.6, 14.7, 14.8, 21.1, 21.2, 24.5, 24.8, 25.0, 26.3, 27.9, 28.0, 34.4, 34.9, 65.3, 65.4, 125.9, 127.4, 127.9, 129.1, 129.4, 129.7, 130.0, 131.0, 133.5, 134.1, 134.2, 136.3, 136.7, 137.2, 143.8, 143.9 ppm. IR (film): $\tilde{\nu}$ = 1600 cm^{-1}.

2-Phenyl-1-tosyl-1*H*-indole (6d): Table 1, Entry 13: reaction temperature, time: –78 °C, 4 h. Yield: 76 mg (22%). Brown solid (m.p. 143–145 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3Ar), 6.56 (s, 1 H, ArH), 7.05 (d, J = 8.3 Hz, 2 H, ArH), 7.25–7.30 (m, 4 H, ArH), 7.37 (td, ^1J = 7.3, ^2J = 1.5 Hz, 1 H, ArH), 7.41–7.47 (m, 3 H, ArH), 7.51–7.55 (m, 2 H, ArH), 8.33 (d, J = 8.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 113.6, 116.6, 120.6, 124.3, 124.7, 126.7, 127.5, 128.6, 129.2, 130.3, 130.5, 132.4, 134.5, 138.2, 142.1, 144.5 ppm. IR (KBr): $\tilde{\nu}$ = 1590 cm^{-1}. $C_{21}H_{17}NO_2S$ (347.43): calcd. C 72.60, H 4.93, N 4.03; found C 72.83, H 4.68, N 4.24.

(1*S*)-1-[(1*H*-Indol-1-ylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]-heptan-2-one (6i): Table 2, Entry 5: reaction temperature, time: –78 °C, 4 h. Solvent: DCM (with ethanol traces)/MeOH. Yield: 36 mg (11%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, CH_3camphor), 1.18 (s, 3 H, CH_3camphor), 1.45–1.54 (m, 1 H, CH_2camphor), 1.76–1.85 (m, 1 H, CH_2camphor), 1.97 (d, J = 18.9 Hz, 1 H, CH_2camphor), 2.06–2.16 (m, 2 H, CH_2camphor), 2.39 (dt, ^1J = 18.3, ^2J = 3.0 Hz, 1 H, CH_2camphor), 2.51–2.61 (m, 1 H, CHcamphor), 3.08 (d, J = 14.6 Hz, 1 H, SCH_2camphor), 3.63 (d, J = 14.6 Hz, 1 H, SCH_2camphor), 6.72 (d, J = 3.0 Hz, 1 H, ArH), 7.32 (td, ^1J = 7.3, ^2J = 1.2 Hz, 1 H, ArH), 7.40 (td, ^1J = 7.9, ^2J = 1.2 Hz, 1 H, ArH), 7.48 (d, J = 3.7 Hz, 1 H, ArH), 7.65 (d, J = 7.3 Hz, 1 H, ArH), 8.01 (dd, ^1J = 7.9, ^2J = 1.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 19.9, 25.2, 26.9, 42.4, 42.8, 48.0, 50.5, 58.5, 108.4, 113.1, 121.5, 123.3, 124.8, 126.2, 130.6, 134.8, 193.0 ppm. IR (film): $\tilde{\nu}$ = 1740 cm^{-1}. $C_{18}H_{21}NO_3S$ (331.43): calcd. C 65.23, H 6.39, N 4.23; found C 65.39, H 6.16, N 3.94.

***N*-[(1*E*)-3-Ethoxyprop-1-enyl]-4-methyl-*N*-phenylbenzenesulfonamide (10):** Reaction temperature, time: –78 °C, 1 h. Yield: 198 mg (60%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 6.8 Hz, 3 H, CH_3CH_2), 2.43 (s, 3 H, CH_3Ar), 3.41 (q, J = 6.8 Hz, 2 H, CH_3CH_2), 3.89 (dd, ^1J = 1.0, ^2J = 6.8 Hz, 2 H, CH_2), 4.43–4.53 (m, 1 H, CH=), 6.97–7.00 (m, 2 H, NCH= and ArH), 7.22–7.28 (m, 3 H, ArH), 7.34–7.36 (m, 2 H, ArH), 7.55 (d, J = 8.3 Hz, 2 H, ArH), 7.57 (d, J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 21.6, 65.3, 69.3, 107.0, 127.5, 129.1, 129.5, 129.6, 130.3, 132.3, 135.7, 136.1, 144.0 ppm. IR (film): $\tilde{\nu}$ = 1600 cm^{-1}. $C_{18}H_{21}NO_3S$ (331.43): calcd. C 65.23, H 6.39, N 4.23; found C 64.89, H 6.07, N 4.45.

***N*-(3-Methoxyprop-1-enyl)-4-methyl-*N*-(2-vinylphenyl)benzenesulfonamide (11):** Reaction temperature, time: –78 °C, 2 h. Yield: 223 mg (65%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 3.23 (s, 3 H, CH_3O), 3.82–3.85 (m, 2 H, CH_2), 4.26–4.35 (m, 1 H, CH_2CH=), 5.21 (d, J = 11.2 Hz, 1 H, CH_2=CH), 5.71 (d, J = 17.5 Hz, 1 H, CH_2=CH), 6.66–6.75 (m, 2 H, CH_2=CH and NCH=), 7.16–7.22 (m, 2 H, ArH), 7.28 (d, J = 8.3 Hz, 2 H, ArH), 7.36 (t, J = 7.3 Hz, 1 H, ArH), 7.60 (d, J = 7.8 Hz, 2 H, ArH), 7.69 (d, J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 57.3, 70.9, 106.7, 116.2, 126.2, 127.5, 128.5, 129.5, 129.6, 130.0, 131.5, 132.1, 133.4, 135.9, 137.9, 144.1 ppm. IR (film): $\tilde{\nu}$ = 3050, 2920, 2820, 1650, 1600 cm^{-1}. $C_{19}H_{21}NO_3S$ (343.44): calcd. C 66.45, H 6.16, N 4.08; found C 66.63, H 5.97, N 4.29.

Supporting Information (see footnote on the first page of this article): Additional experimental procedures and characterization data for **8**, **1b**, **1g**, **1h**, **1i**, **1c**, **1d** and **9** and NMR spectra for all new compounds.

Acknowledgments

Funding of this project by the Spanish Ministerio de Educación y Ciencia (MEC) (Project No. CTQ2006-00601/BQU) is acknowledged. A. G. G. thanks the Ministerio de Educación y Ciencia (MEC) and the Fundación San Pablo-CEU for predoctoral fellowships.

[1] For recent reviews of gold-catalysed reactions, see: a) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; b) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; e) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; f) H. C. Shen, *Tetrahedron* **2008**, *64*, 7847–7870; g) R. Skouta, C. J. Li, *Tetrahedron* **2008**, *64*, 4917–4938; h) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; i) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; j) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; k) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; l) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; m) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936.

[2] See: a) R. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453; b) A. S. K. Hashmi, M. C. Blanco, D. Fischer, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387–1389; c) N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1897–1899.

[3] a) M. A. Tarselli, A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem. Int. Ed.* **2007**, *46*, 6670–6673; b) G. Lemière, V. Gandon, N. Agenet, J.-P. Goddard, A. de Kozak, C. Aubert, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2006**, *45*, 7596–7599; c) J. H. Lee, F. D. Toste, *Angew. Chem. Int. Ed.* **2007**, *46*, 912–914.

[4] a) P. H. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526; b) R. Zriba, V. Gandon, C. Aubert, L. Fensterbank, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1482–1491; c) C. Y. Yang, G. Y. Lin, H. Y. Liao, S. Datta, R. S. Liu, *J. Org. Chem.* **2008**, *73*, 4907–4914.

[5] G. Y. Lin, C. Y. Yang, R. S. Liu, *J. Org. Chem.* **2007**, *72*, 6753–6757.

[6] For a review see: V. Michelet, P. Y. Toullec, J. P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; for a computational study with Pt, see: E. Soriano, J. Marco-Contelles, *Chem. Eur. J.* **2005**, *11*, 521–533.

[7] L.-L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773–782.

[8] See: a) K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126–1136; b) H. Xiong, J. Huang, S. K. Ghosh, R. P. Hsung, *J. Am. Chem. Soc.* **2003**, *125*, 12694–12695.

[9] Y.-G. Suh, Y.-S. Lee, K.-H. Min, O.-H. Park, H.-S. Seung, H.-D. Kim, H.-G. Park, J.-Y. Choi, J. Lee, S.-W. Kang, U. Oh, J. Koo, Y.-H. Joo, S.-Y. Kim, J. K. Kimd, Y.-H. Park, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4389–4393.

[10] Y. Shimada, N. Taniguchi, A. Matsuhisa, H. Akane, N. Kawano, T. Suzuki, T. Tobe, A. Kakefuda, T. Yatsu, A. Tahara, Y. Tomura, T. Kusayama, K. Wada, J. Tsukada, M. Orita, T. Tsunodad, A. Tanakae, *Bioorg. Med. Chem.* **2006**, *14*, 1827–1837.

[11] A. González-Gómez, L. Añorbe, A. Poblador, G. Domínguez, J. Pérez-Castells, *Eur. J. Org. Chem.* **2008**, 1370–1377.

[12] M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem.* **2005**, *70*, 2265–2273.

[13] W. Robb, *Inorg. Chem.* **1967**, *6*, 382–386.

Received: July 6, 2009
Published Online: August 28, 2009

