Synthesis of 3-*exo*-Aroylhexahydroindoles via Sequential Gold(I)-Catalyzed Claisen-Type Rearrangement–Epimerization Reactions of *cis*-4-[*N*-Tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols

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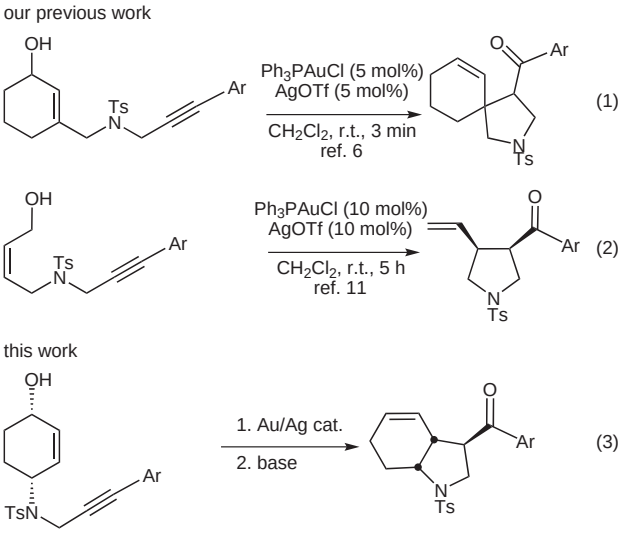
Received: 18.03.2014; Accepted after revision: 22.04.2014

Abstract: A two-step process for the synthesis of 3-*exo*-aroylhexahydroindoles is described. *cis*-4-[*N*-Tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols were cycloisomerized with a catalytic amount of chloro(triphenylphosphine)gold(I)/silver(I) hexafluoroantimonate ($AuPPh_3Cl/AgSbF_6$); subsequent base treatment of the crude mixture provided 3-*exo*-aroylhexahydroindoles in good yields and complete stereoselectivity. A key step involving a 9-*endo*-dig attack of the hydroxyl group onto the gold-activated alkyne is proposed. The resulting allyl vinyl ether intermediate underwent a gold-assisted [3,3]-sigmatropic rearrangement to form 3-*exo*-3-aroylhexahydroindole derivatives.

Key words: alcohols, alkynes, cyclization, ethers, indoles

Nitrogen-containing heterobicycles are of great interest because of their ubiquity and wide range of biological activities.[1] Transition metal-assisted hydroamination of unsaturated C–C bonds has been widely employed in the construction of hexahydroindole scaffolds. Several efforts towards the synthesis of hexahydroindoles include the zirconium-promoted reductive cyclization of *N*-benzyl-*N*-(cyclohex-2-enyl)propargylamines,[2] the palladium-catalyzed intramolecular olefin allylation of *N*-containing 1-acetoxy-2,7-dienes,[3a] the palladium-catalyzed coupling/cyclization reaction of cyclic *N*-containing 1,6-enynes with aryl halides,[3b] the nickel-catalyzed intramolecular allylation/carbonylation of *N*-containing dienyl acetates,[4] the gold(I)-catalyzed double cyclization of 3,7-dienylsulfonamide,[5a] and the gold(I)-catalyzed intramolecular 1,4-hydroamination of cyclic 1,3-dienes.[5b] In our previous study (Scheme 1),[6] we reported a gold-catalyzed Claisen-type rearrangement[7–10] of cyclic 8-aryl-5-aza-2-en-7-yn-1-ols, leading to azaspirocyclic ketones in 90% yield as a 1:1 mixture of diastereomers (1).[6] Similar results were obtained upon treatment of the acyclic analogues (*Z*)-8-aryl-5-azaoct-2-en-7-yn-1-ols with a catalytic amount of the gold cationic species, affording *cis*-3-acyl-4-alkenylpyrrolidines (2).[11] We envision that introducing an *N*-(3-arylpropargyl)-*N*-tosylamine tether at the C-4 position of the cyclohex-2-en-1-ol ring should lead to fused heterobicyclic skeletons under gold-catalyzed conditions (3). Herein, we describe a sequential gold(I)-catalyzed Claisen-type rearrangement–epimerization reaction to prepare 3-*exo*-aroylhexahydroindole derivatives from *cis*-4-[*N*-tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols (3). The reaction path leading to 3-aroylhexahydroindoles may be initiated with a nucleophilic 9-*endo*-dig addition of the hydroxy group onto the gold-activated alkyne,[12] providing an allyl vinyl ether intermediate which undergoes a gold-assisted [3,3]-sigmatropic rearrangement to furnish the heterobicyclic skeleton.



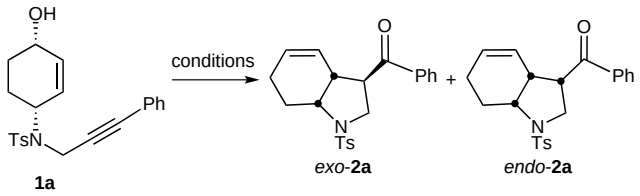
Scheme 1 Gold-catalyzed Claisen-type rearrangements of nitrogen-containing enynols

We began our studies with the parent *cis*-4-[*N*-tosyl-*N*-(3-phenylprop-2-ynyl)amino]cyclohex-2-en-1-ol (**1a**), which is available by epoxidation of cyclohexa-1,3-diene with *m*-chloroperoxybenzoic acid (see Supporting Information for details).[13–15] Compound **1a** was subjected to various catalysts and sets of conditions (Table 1). When exposed to chloro(triphenylphosphine)gold(I)/silver(I) trifluoromethanesulfonate ($AuPPh_3Cl$/AgOTf, 10 mol%) in dichloromethane at 20 °C for 24 hours, **1a** formed 3-benzoylhexahydroindole **2a** in only 5% isolated yield with low *exo*/*endo* stereoselectivity (*exo*-**2a**/*endo*-**2b** = 3:2, entry 1). Unfortunately, **1a** decomposed upon heating in the presence of the chloro(triphenylphosphine)gold(I)/silver(I) trifluoromethanesulfonate (10 mol%) catalyst system in dichloromethane at 40 °C (entry 2). No reaction occurred when chloro(triphenylphos-

SYNTHESIS 2014, 46, 2220–2224
Advanced online publication: 02.06.2014
DOI: 10.1055/s-0033-1339129; Art ID: ss-2014-f0190-op

phine)gold(I)/silver(I) bis(trifluoromethanesulfonyl)imide ($AuPPh_3Cl/AgNTf_2$, 10 mol%) was used as the catalyst system (entry 3). The use of silver(I) hexafluoroantimonate ($AgSbF_6$) as the silver salt additive with chloro(triphenylphosphine)gold(I) (10 mol%) in dichloromethane at 20 °C for 30 minutes delivered *exo*-**2a** and *endo*-**2b** in 55% yield (*exo*/*endo* = 1:1, entry 4). Delightfully, the cycloisomerization reaction was completed in four minutes when **1a** was reacted with chloro(triphenylphosphine)gold(I) and silver(I) hexafluoroantimonate (10 mol%) in dichloromethane at 40 °C, generating *exo*-**2a** and *endo*-**2b** with 2:3 *exo*/*endo* selectivity in 78% yield (entry 5). When **1a** was treated with the same catalyst system in dichloromethane at 0 °C, the reaction required a longer time (3 h) and produced the same amounts of *exo* and *endo* isomers in 68% yield (entry 6).

Table 1 Optimization of Catalyst and Conditions



1a *exo*-**2a** *endo*-**2a**

Entry	Catalyst (10 mol%)	Conditions	Yield (%)[a]	Ratio *exo*/*endo*[b]
1	$AuPPh_3Cl$, AgOTf	CH_2Cl_2, 20 °C, 24 h	5	3:2
2	$AuPPh_3Cl$, AgOTf	CH_2Cl_2, 40 °C, 6 h	0	–
3	$AuPPh_3Cl$, $AgNTf_2$	CH_2Cl_2, 20 °C, 12 h	0	–
4	$AuPPh_3Cl$, $AgSbF_6$	CH_2Cl_2, 20 °C, 30 min	55	1:1
5	$AuPPh_3Cl$, $AgSbF_6$	CH_2Cl_2, 40 °C, 4 min	78	2:3
6	$AuPPh_3Cl$, $AgSbF_6$	CH_2Cl_2, 0 °C, 3 h	68	1:1
7	$AuPPh_3Cl$, $AgSbF_6$	DCE, 25 °C, 2 h	44	3:2
8	$AuPPh_3Cl$, $AgSbF_6$	DCE, 80 °C, 2 min	77	2:3
9	$AuPPh_3Cl$, $AgSbF_6$	toluene, 25 °C, 5 h	22	3:2
10	$AuPPh_3Cl$, $AgSbF_6$	toluene, 80 °C, 2 min	39	3:2
11	$AuPPh_3Cl$, $AgPF_6$	DCE, 80 °C, 12 h	6	1:1
12	IPrAuCl, $AgSbF_6$	CH_2Cl_2, 40 °C, 24 h	30	1:1
13	Tf_2NH	CH_2Cl_2, 20 °C, 12 h	11	3:2
14	$AuCl_3$	CH_2Cl_2, 20 °C, 12 h	0	–
15	$AgSbF_6$	CH_2Cl_2, 40 °C, 24 h	0	–
16	$PtCl_2$	CH_2Cl_2, 20 °C, 24 h	0	–

[a] All reactions were conducted under N_2 and yields were obtained after flash column chromatography over silica gel.
[b] Determined by 400 MHz ^{1}H NMR analysis of the crude reaction mixture.

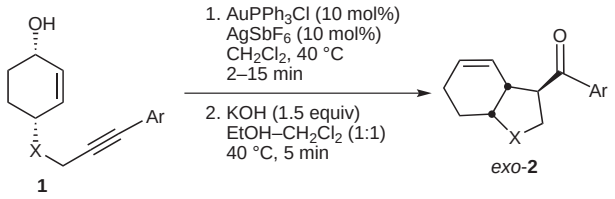
Changing the solvent to 1,2-dichloroethane afforded **2a** in 44% yield (*exo*:*endo* = 3:2) (Table 1, entry 7). Increasing the temperature to 80 °C in 1,2-dichloroethane provided **2a** in 2 min with a 2:3 *exo*/*endo* selectivity in 77% yield. (entry 8). The use of toluene at either 25 or 80 °C diminished the yield of **2a** (entries 9 and 10). Switching to silver(I) hexafluorophosphate (10 mol%) as the silver salt additive in 1,2-dichloroethane at 80 °C led to **2a** in only 6% yield (entry 11). Employing the *N*-heterocyclic carbene gold catalyst IPrAuCl [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] with silver(I) hexafluoroantimonate in dichloromethane at 40 °C for 24 hours failed to improve the yield and stereoselectivity of **2a** (entry 12). Moreover, the Brønsted acid trifluoromethanesulfonimide (Tf_2NH, entry 13), was ineffective and gave **2a** in only 11% yield. Subjecting **1a** to gold(III) chloride (10 mol%), silver(I) hexafluoroantimonate (10 mol%), or platinum(II) chloride (10 mol%) in dichloromethane at 40 °C led predominantly to the recovery of **1a** in each case (entries 14−16). Thus, entry 5 (10 mol% of $AuPPh_3Cl$ and $AgSbF_6$, CH_2Cl_2, 40 °C) was chosen as the optimal reaction conditions. It is of note that the corresponding *trans*-4-[*N*-tosyl-*N*-(3-phenylprop-2-ynyl)amino]cyclohex-2-en-1-ol (**3**) failed to undergo cycloisomerization with various gold(I)/silver(I) catalyst systems.

Although the *exo*/*endo* selectivity was poor in all cases, the mixture of *exo* and *endo* isomers can be separated easily by simple flash column chromatography over silica gel. Structural assignments for *exo*-**2a** and *endo*-**2a** were established by their ^{1}H NMR spectral data. The stereochemistry assignment for *endo*-**2a** was based on the characteristic upfield shift, δ = 4.96, of the vinyl proton at C-4, while the vinyl proton at C-4 of *exo*-**2a** appears at δ = 5.42. The observed upfield shift of the vinyl proton for *endo*-**2a** may result from a shielding effect of the *endo*-benzoyl moiety. These assignments were further secured by X-ray diffraction analysis of both *exo*-**2a** and *endo*-**2a**.[16]

Since *endo*-**2a** can be epimerized to the thermodynamically more stable *exo*-**2a** under basic conditions, it would be practical to obtain the *exo* isomer exclusively by treatment of the crude *exo* and *endo* mixture with base after the initial cycloisomerization reaction. Thus, **1a** was treated with the catalyst system (10 mol% $AuPPh_3Cl/AgSbF_6$) in dichloromethane at 40 °C for six minutes. The crude mixture was then filtered through a pad of Celite. The filter cake was eluted with dichloromethane (ca. 10 mL). The solvent was removed and the resulting residue was subjected to potassium hydroxide in dichloromethane–ethanol (1:1) at 40 °C for five minutes to give *exo*-**2a** as the only isomer in 73% yield after flash column chromatography (silica gel). As shown in Table 2, *exo*-**2a**–**l** were obtained in 55–83% yield (over two steps).

As shown in Table 2, substrates bearing an electron-neutral or -rich arene at the alkyne terminus were found to be successful, affording the desired 3-aroylhexahydroindoles *exo*-**2a**–**g** in yields of 55–78% over two steps (entries 1−7). It was found that a bromine atom at the C-4 position of the phenyl ring (**1h**) has no influence on the catalytic activity, as *exo*-**2h** was isolated in 83% yield (entry 8).

Table 2 Sequential Gold(I)-Catalyzed Cycloisomerization–Epimerization Reactions of **1**



Entry	Ar	Substrate	X	Yield (%)[a]
1	Ph	**1a**	NTs	73 (*exo*-**2a**)
2	4-MeC_6H_4	**1b**	NTs	75 (*exo*-**2b**)
3	3-MeC_6H_4	**1c**	NTs	58 (*exo*-**2c**)
4	4-PhC_6H_4	**1d**	NTs	55 (*exo*-**2d**)
5	1-naphthyl	**1e**	NTs	70 (*exo*-**2e**)
6	4-$MeOC_6H_4$	**1f**	NTs	57 (*exo*-**2f**)
7	3-$MeOC_6H_4$	**1g**	NTs	78 (*exo*-**2g**)
8	4-BrC_6H_4	**1h**	NTs	83 (*exo*-**2h**)
9	3-$EtO_2CC_6H_4$	**1i**	NTs	25 (*exo*-**2i**)[b]
10	4-$O_2NC_6H_4$	**1j**	NTs	15 (*exo*-**2j**)[b]
11	Ph	**1k**	NSO_2Ph	80 (*exo*-**2k**)
12	Ph	**1l**	NSO_2Mes	56 (*exo*-**2l**)

[a] Yields were obtained after column chromatography over silica gel.
[b] Products were obtained after gold-catalyzed cyclization followed by separation by column chromatography over silica gel.

However, the presence of an electron-withdrawing ester or nitro substituent on the phenyl ring, for example in **1i** and **1j**, resulted in the alkyne being less reactive, delivering the corresponding 3-aroylhexahydroindoles *exo*-**2i** and *exo*-**2j** in 25 and 15% yield, respectively, after gold-catalyzed cyclization/epimerization and purification by column chromatography over silica gel. (entries 9 and 10). Other nitrogen-protecting groups such as phenyl sulfonate, in **1k** (entry 11), and 2,4,6-trimethylphenyl sulfonate, in **1l** (entry 12), were readily allowed and afforded *exo*-**2k** and *exo*-**2l** in 80 and 56% yield, respectively. Unfortunately, treatment of substrates having a hydrogen or methyl group at the alkyne terminus, for example **1m** and **1n** (Figure 1), with the gold catalyst ($AuPPh_3Cl$ and $AgSbF_6$) in dichloromethane gave a complex mixture of unidentified products in both cases.

The postulated reaction path for the formation of **2** via gold(I)-catalyzed cycloisomerization of **1** is depicted in Scheme 2. First, coordination of the alkyne to the cationic gold center, generated from chloro(triphenylphosphine)gold(I) and silver(I) hexafluoroantimonate, forms the gold(I)–alkyne species. Attack of the *cis*-hydroxyl group onto the gold-activated alkyne in a 9-*endo*-dig fashion provides the allyl vinyl ether intermediate **4**. Therefore, the failure of gold-catalyzed cycloisomerization of

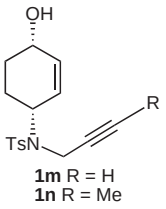
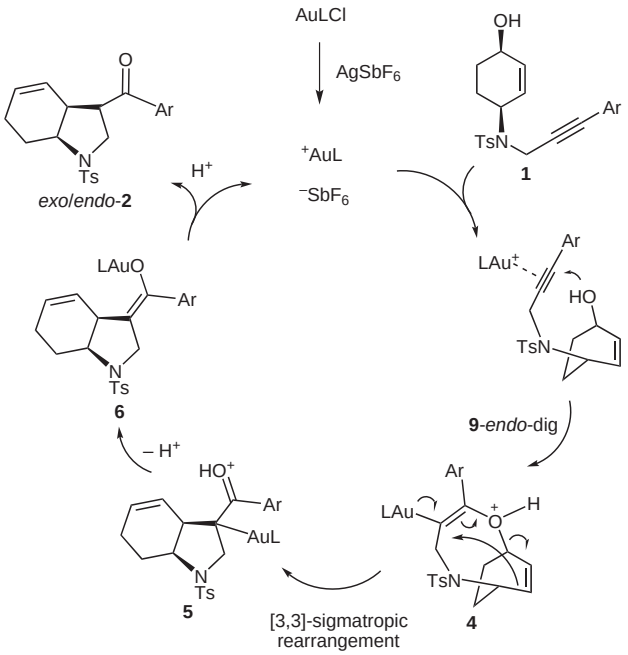


Figure 1 Structures of **1m** and **1n**

the *trans* isomer **3** indicates that the 9-*endo*-dig process could only take place when the hydroxyl and alkyne moieties are on the same face of the six-membered ring. Subsequently, a gold-assisted [3,3]-sigmatropic rearrangement of **4** gives the bicyclic intermediate **5** containing a carbon–gold bond at the α-position of the carbonyl group. The *cis* stereochemistry of the fused bicycle **5** is fixed by the vinylgold moiety aligned to the face of the six-membered ring where the tether resides. Deprotonation and tautomerization of **5** gives oxygen-bound gold enolate **6**. Protonation of enolate **6** provides hexahydroindole **2** as a mixture of *exo*/*endo* isomers and regenerates the gold(I) catalyst into the catalytic cycle. However, a stepwise reaction involving an activation of the allylic alcohol by gold(I) cannot be ruled out.[17] Addition of the allylgold moiety and the hydroxyl residue across the alkyne followed by tautomerization of the resulting enol furnishes *exo*/*endo*-**2**.

In summary, we have described a practical and convenient synthesis of 3-*exo*-aroylhexahydroindoles by gold-catalyzed cycloisomerization of 4-[*N*-tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols and subsequent epimerization with base. The advantages of this method are



Scheme 2 A plausible mechanism for the formation of hexahydroindole **2**

short reaction times, mild reaction conditions, and good yields. Further studies to reveal the reaction path are currently underway in our laboratory.

All reactions were performed with oven-dried glassware under a N_2 atmosphere. All organic solvents were dried by passing through a column of alumina. Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were obtained with 400 and 500 MHz spectrometers. The chemical shifts are reported in ppm with either TMS (δ = 0.00) or $CHCl_3$ (δ = 7.26) as internal standard. ^{13}C NMR spectra were recorded on 100 and 125 MHz spectrometers with $CDCl_3$ (δ = 77.0) as the internal standard. IR spectra were recorded of samples prepared as CH_2Cl_2 solutions. Mass spectra were determined by using a spectrometer operating at an ionization potential of 70 eV. High-resolution mass spectra were obtained on a double-focusing mass spectrometer.

Gold(I)-Catalyzed Cycloisomerization Reaction of *cis*-4-[*N*-Tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols; General Procedure (I)

To a solution solution of **1a** (80 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) were added Ph_3PAuCl (10 mg, 0.02 mmol) and $AgSbF_6$ (7 mg, 0.02 mmol) at 40 °C under an atmosphere of N_2. The reaction mixture was stirred until **1a** was consumed, as monitored by TLC. The reaction mixture was filtered through a bed of Celite and concentrated to give the crude mixture, which was purified by flash column chromatography (silica gel, EtOAc–hexanes, 5:95) to give *exo*-**2a** and *endo*-**2a**.

***exo*-3-Benzoyl-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole (*exo*-2a)**

Yield: 24 mg (0.063 mmol, 31%); white solid; mp 151−152 °C.

Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

IR (CH_2Cl_2): 3029, 2924, 1682, 1598, 1449, 1345, 1165, 1039 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88−7.84 (m, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.81 (dtt, *J* = 9.9, 2.5, 2.1 Hz, 1 H), 5.42 (d, *J* = 9.9 Hz, 1 H), 3.89−3.84 (m, 1 H), 3.84−3.77 (m, 2 H), 3.27 (t, *J* = 9.2 Hz, 1 H), 2.71 (br s, 1 H), 2.44 (s, 3 H), 2.25−2.15 (m, 2 H), 2.11−2.02 (m, 1 H), 1.85−1.76 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.7, 143.6, 136.1, 134.0, 133.8, 129.8, 129.6, 128.8, 128.5, 127.5, 125.1, 58.4, 51.2, 50.1, 41.7, 27.9, 23.0, 21.5.

ESI-MS: *m*/*z* = 404.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_3NaS$: 404.1297; found: 404.1305.

***endo*-3-Benzoyl-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole (*endo*-2a)**

Yield: 36 mg (0.094 mmol, 47%); white solid; mp 152−153 °C.

Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

IR (CH_2Cl_2): 3028, 2919, 1678, 1598, 1340, 1157, 1091 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82−7.77 (m, 4 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 5.93−5.85 (m, 1 H), 4.96 (d, *J* = 10.2 Hz, 1 H), 4.12 (br s, 1 H), 3.78 (t, *J* = 11.2 Hz, 1 H), 3.66 (dd, J = 11.8, 6.9 Hz, 1 H), 3.42 (dt, *J* = 10.6, 7.0 Hz, 1 H), 3.23 (br s, 1 H), 2.46 (s, 3 H), 2.37−2.30 (m, 1 H), 2.27−2.17 (m, 1 H), 1.90 (d, *J* = 17.2 Hz, 1 H), 1.67−1.59 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5, 143.5, 136.4, 135.4, 133.5, 132.2, 129.8, 128.8, 127.9, 127.5, 122.0, 59.5, 48.9, 48.9, 42.5, 26.0, 21.5, 19.6.

ESI-MS: *m*/*z* = 404.1 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_3NaS$: 404.1297; found: 404.1307.

Sequential Gold(I)-Catalyzed Cycloisomerization–Epimerization of *cis*-4-[*N*-Tosyl-*N*-(3-arylprop-2-ynyl)amino]cyclohex-2-en-1-ols; General Procedure (II)

To a solution of the crude mixture of *exo*-**2a** and *endo*-**2a**, obtained from General Procedure (I), in CH_2Cl_2 (2 mL) and EtOH (2 mL) was added KOH (0.017 g, 0.30 mmol) and then the mixture was heated to 40 °C. The mixture was stirred at 40 °C until no trace of the *endo* isomer was detected by TLC (ca. 5 min). The reaction mixture was then extracted with H_2O (5 mL) and CH_2Cl_2 (3 × 5 mL). The crude oil was purified by flash column chromatography (silica gel, EtOAc–hexanes, 1:20); this afforded *exo*-**2a** as the only product isolated.

Yield: 55 mg (0.145 mmol, 73%).

The analytical data of *exo*-**2a** are consistent with those obtained previously.

Acknowledgment

This work has been supported by the National Science Council (NSC 101-2113-M-003-002-MY3) and the National Taiwan Normal University.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084, including complete experimental procedures, analytical data, NMR spectra, and X-ray diffraction analyses.

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