Full Paper

Israel Journal of Chemistry

DOI: 10.1002/ijch.201300041

Nitrogen Nucleophiles in Au-Catalyzed Dehydrative Cyclization Reactions

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Abstract: Mild conditions for the gold-catalyzed dehydrative cyclization of carbamate-protected azaallylic alcohols to form saturated nitrogen heterocycles are reported. The cyclization reactions are high-yielding, operationally easy to perform, and provide heterocycles with a synthetically useful vinyl group, strategically located on the ring system, which can facilitate further transformations for target oriented synthesis. It is also demonstrated through chirality transfer experiments that the mechanism can be either cationic in nature or a Au-catalyzed addition/elimination sequence. The diverging mechanistic scenario is dependent on the nature of the substituents on the allylic alcohol and necessitates judicious substrate design.

Keywords: azacycles · dehydrative cyclizations · gold catalysis · heterocycles · S_N2'

Recently, there has been an influx of publications focused on transition metal-catalyzed allylic alkylation reactions using unactivated allylic electrophiles.[1] In 2008, our group reported the first intramolecular gold-catalyzed dehydrative cyclization of monoallylic diols, whereby a hydroxyl group acts as the formal leaving group.[2] Since that report, many extensions have been reported by our group,[3] as well as by many others.[4] With low catalyst loadings, facile substrate syntheses, and water as the only by-product, these methods have become powerful tools for the synthesis of complex heterocycles.

As an extension of our previously reported cyclization of monoallylic diols, we were interested in utilizing these cyclization reactions in the formation of nitrogen heterocycles. Recent work from Widenhoefer and co-workers has established conditions for a gold-catalyzed dehydrative cyclization, using basic nitrogen nucleophiles with chirality transfer, but these highly coordinating substrates usually required heating the reaction mixture to 100 °C.[4e] These pivotal reports prompted us to disclose our studies in this area. At the outset, the goal was to find general conditions for protected amine substrates, using a simple Au catalyst, at low temperature, and to study these conditions in chirality transfer reactions of non-racemic azaallylic alcohols. Herein, we report further development of our previously reported methodology,[2] to include the formation of nitrogen heterocycles, and discuss a surprising finding regarding the dichotomous nature of the mechanism with different substrates.

Although it is preferential to use the more synthetically versatile carbamate-protected amine substrates, initial experiments from our laboratory demonstrated that sulfonamides undergo cyclization much more readily than carbamates **1**. Furthermore, we have demonstrated that *Z*-allylic alcohols cyclize more readily than the corresponding *E*-allylic alcohols.[3e] Given these difficulties, we focused our efforts on finding conditions for the formation of piperidines **2** from the challenging carbamate-protected *E*-allylic alcohol substrate **1**. As was expected, treatment of **1** under our previously reported conditions for tetrahydropyran synthesis resulted in limited conversion to the desired product (Table 1, entry 1). Use of AuCl, or other phosphine supported catalysts, was met with similar results (entries 2–4). Much to our delight, switching to the catalyst system generated *in situ* from (IPr)AuCl and $AgBF_4$ gave the product **2** in 93% yield, after 20 hr at room temperature, in CH_2Cl_2, in the presence of molecular sieves (Table 1, entry 5). Removal of the molecular sieves from the reaction had little effect on the cyclization, giving the desired product in 87% yield, and a control experiment with $AgBF_4$ demonstrated that the cationic gold complex is indeed needed for the desired reaction (Table 1, entry 8).

It should be noted that no *gem*-disubstitution is needed for the reaction to proceed under these conditions. Interestingly, shortening the tether by one methylene unit appears to influence the reactivity, as revealed by comparison of entries 1 in Tables 1 and 2. As can be seen in Table 2, formation of pyrrolidine **4** from **3** proceeds both under our previously reported conditions (entry 1) and

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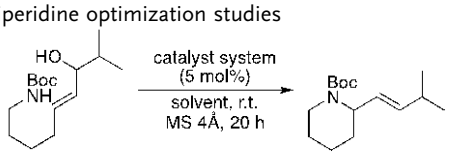
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ijch.201300041.

Table 1. Piperidine optimization studies

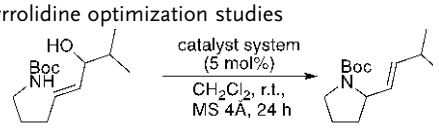


1 2

entry	Au complex	Ag salt	solvent	yield[a]
1	Ph_3PAuCl	AgOTf	CH_2Cl_2	<5[b]
2	AuCl	AgOTf	CH_2Cl_2	9
3	[(*o*-biphenyl)-di-*t*-butyl-P]AuCl	AgOTf	CH_2Cl_2	<5[b]
4	$(Ph_3PAu)_3O^+BF_4^-$	–	CH_2Cl_2	N.R.
5	(IPr)AuCl	$AgBF_4$	CH_2Cl_2	93
6	(IPr)AuCl	$AgBF_4$	CH_2Cl_2	87[c]
7	(IPr)AuCl	$AgBF_4$	THF	<5[b]
8	–	$AgBF_4$	CH_2Cl_2	N.R.

[a] Purified yields; [b] Conversion determined by ^{1}H NMR (300 MHz); [c] Molecular sieves omitted.

Table 2. Pyrrolidine optimization studies



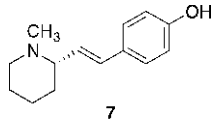
3 4

entry	Au complex	Ag salt	yield[a]
1	Ph_3PAuCl	AgOTf	62
2	(IPr)AuCl	$AgBF_4$	71
3	[(*o*-biphenyl)-di-*t*-butyl-P]AuCl	AgOTf	<5[b]

[a] Purified yields; [b] Conversion determined by ^{1}H NMR (300 MHz).

using (IPr)AuCl as the gold salt (entry 2). Since formation of both pyrrolidines and piperidines proceeded smoothly using the gold complex formed *in situ* from (IPr)AuCl/$AgBF_4$, these conditions were adopted as our standard conditions.

With the optimized conditions established, the substrate scope was then explored. In order to examine the role of nitrogen protecting groups, sulfonamides **5a** and **5b** were employed. These compounds readily cyclized, with catalyst loadings as low as 1 mol% at room temperature (Table 3, entries 1–3). When treated under the standard conditions, *E*-allylic alcohol **5c** gave little conversion to the desired piperazine **6c**; however, *Z*-allylic alcohol **5d** underwent smooth cyclization to give 89% of the product **6c**, after 16 hr at room temperature (Table 3, entries 4 and 5). The method also allows easy access to morpholines, such as **6d**, although the cyclization was again more facile when the *Z*-allylic alcohol isomer was used (Table 3, entries 6–8). Lastly, it was found that, while carbamates and sulfonamides readily undergo cyclization, substrates leading to lactams (i.e., **5g**→**6e**) were unreactive, even when higher temperatures and various substituents in the allylic position were employed.



7
Caulophyllumine B

Figure 1. Caulophyllumine B

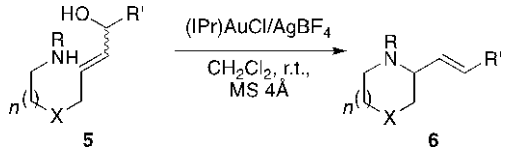
Given the ease of heterocycle formation under these conditions, we set out to study chirality transfer reactions using the synthesis of the relatively simple natural product caulophyllumine B (Figure 1) as a platform for our initial inquiries. Obtained from the blue cohosh plant, caulophyllumine B is a small alkaloid that piqued our interested because of its potential biological activity.[5] Although two total syntheses have been reported to date,[6] the substrate required for piperidine formation using this method should be readily available and also a good candidate for chirality transfer studies.

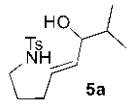
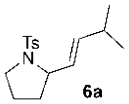
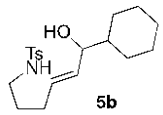
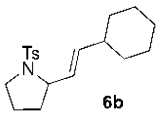
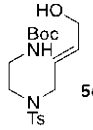
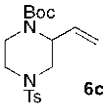
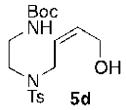
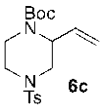
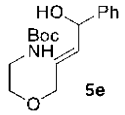
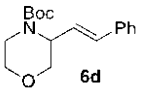
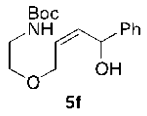
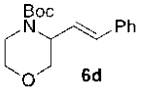
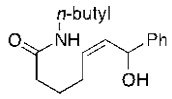
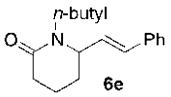
In a retrosynthetic sense, caulophyllumine B (**7**) should easily be prepared from the product of the gold-catalyzed cyclization of **8** (Scheme 1). We envisioned that **8** could be easily produced in a few simple steps, starting from commercially available 5-hexyn-1-ol, and would provide a short and direct stereoselective synthesis of the precursor to the natural product, using the present methodology..

The synthesis of the dehydrative cyclization precursor **8** commenced with the preparation of the protected propargyl alcohol **11** (Scheme 2). Treating **9** under the standard Carreira asymmetric alkynylation conditions,[7] with the pivaloyl protected 4-hydroxybenzaldehyde, gave the desired propargyl alcohol **11** in a reasonable yield and high enantiomeric excess (92% ee). Surprisingly, after partial hydrogenation under Lindlar conditions and deprotection of a single Boc group with LiBr, epimerization of the allylic alcohol stereocenter in **8** was observed. Since the enantiomeric excess of **8** was already relatively low, it was essential to find a new substrate that could be furnished in higher optical purity before cyclization.

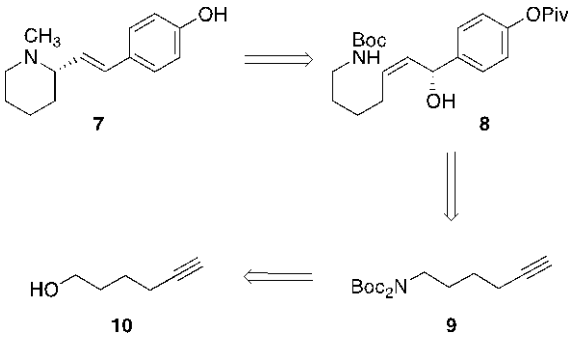
To accomplish this goal we turned to a more deactivating 4-bromo substituent, in hopes of circumventing the undesired epimerization of the allylic alcohol. Treatment of alkyne **9** under the standard Carreira alkynylation conditions with 4-bromobenzaldehyde gave the desired propargyl alcohol, **12**, in high yield, with 97% ee. Reduction of the alkyne, followed by partial deprotection of the biscarbamate, occurred with only minor epimerization of the desired substrate **13** and provided a substrate for our chirality transfer studies.[3d,g] Surprisingly, upon treatment of substrate **13** with the optimized conditions, the product **14** was formed in only one hour, but in an unanticipated 30% ee (Scheme 3). This result was somewhat contrary to the high chirality transfer observed in the formation of tetrahydropyrans.[3d,g] It is possible that carbamate-protected nitrogen nucleophiles function differently than hydroxyl groups and basic amines, which have been shown to transfer the allylic alcohol chirality.[3d,g,4e,k] At the outset, it was expected that they would behave similarly and that amine nucleophiles would access a pathway anal-

Table 3. Scope and limitations



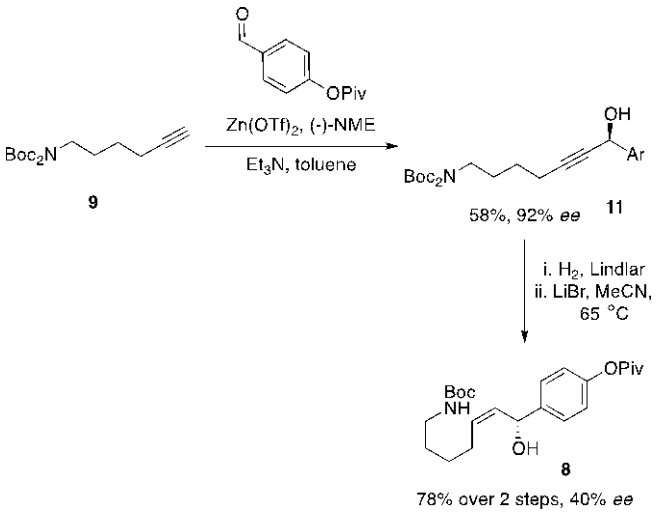
entry	substrate	mol (%)	time (h)	product	yield[a] (%)
1	 **5a**	1	20	 **6a**	71
2	 **5b**	2.5	6	 **6b**	88
3		5	1		92
4	 **5c**	5	16	 **6c**	<20[b]
5	 **5d**	5	16	 **6c**	89
6	 **5e**	5	24	 **6d**	30
7	 **5f**	5	7	 **6d**	51
8		5	24		81
9	 **5g**	5	24	 **6e**	n.r.[b,c]

[a] Purified yields; [b] Conversion by ^{1}H NMR (300 MHz); [c] No reaction.

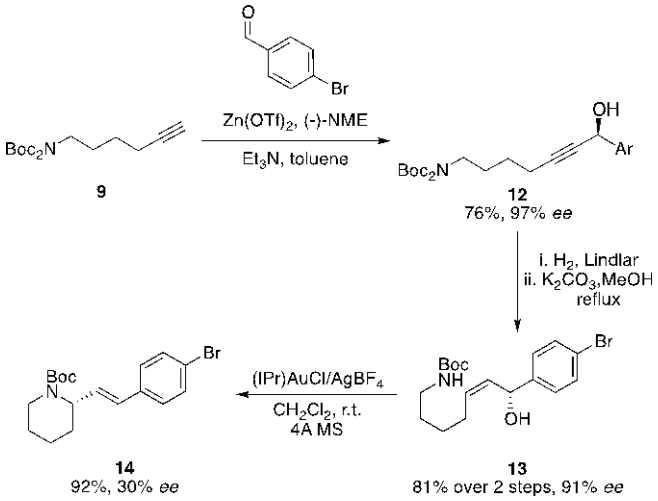


Scheme 1. Retrosynthetic analysis of caulophyllumine B

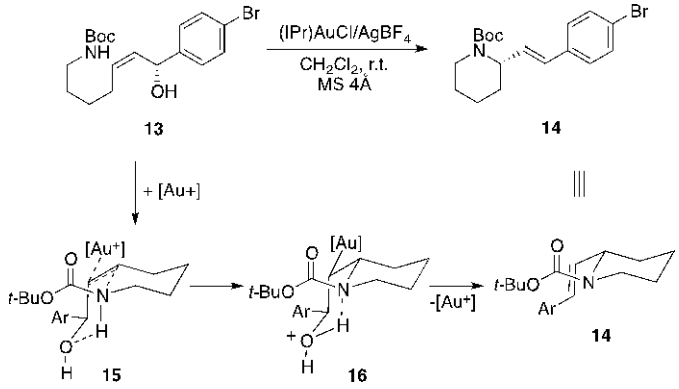
ogous to our previously reported transfer of chirality for monoallylic diols.[3g] In this mechanism (Scheme 4), the cationic Au catalyst coordinates to the double bond of **13**, forming a π-complex, thereby activating the olefin for nucleophilic attack. This then leads to transition state **15**, in which the hydrogen bonding interaction between the



Scheme 2. Synthesis of substrate **8**



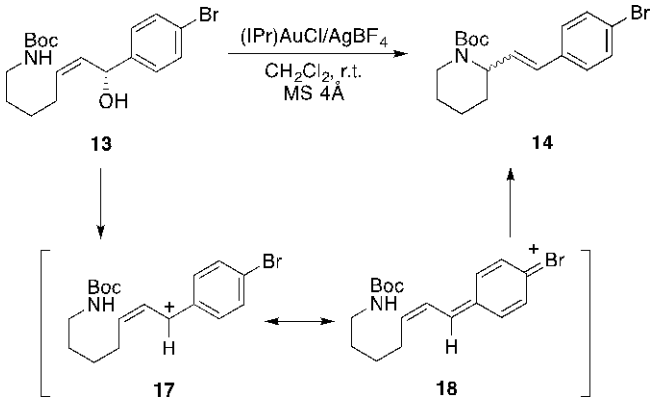
Scheme 3. Chirality transfer with aryl substituents



Scheme 4. Mechanism of chirality transfer

proton of the carbamate and the oxygen of the allylic alcohol should template the reaction, placing the aromatic group in a *pseudo*-equatorial position, thereby dictating the π-facial selectivity. After formation of the σ-complex, the hydroxyl group in **16** is activated by the formation of an O-H bond and the breaking the N-H bond, but hydrogen bonding is likely maintained. The oxonium leaving group, now perfectly aligned in an *anti*-periplanar fashion, allows for the facile dehydration of the allylic system in **16**, leading to **14**, after loss of water and catalyst turnover.

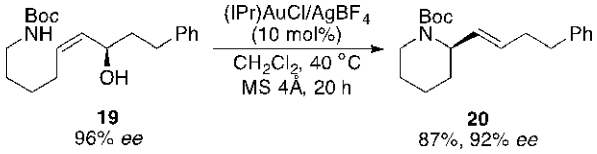
There are a number of possible reasons for such low optical purity in the recovered product **14**, but it would seem that the most plausible explanation for such a low transfer of chirality is that inclusion of an aromatic substituent facilitates a competing pathway involving a Au-catalyzed ionization of the allylic system and cyclization of the resulting achiral allylic cation. In this mechanistic scenario, the Au complex would need to act as a traditional oxophilic Lewis acid,[8] contrary to the now well documented carbophilic characteristic of Au catalysis.[9] This would involve ionization of **13** to form the resonance-stabilized cation **17**/**18** and, after cyclization, **14** with reduced optical purity (Scheme 5). It is possible that the catalyst



Scheme 5. Plausible cationic pathway

either directly ionizes the allylic alcohol and is turned over by loss of water or, alternatively, coordinates to the carbamate oxygen and acidifies the NH. The fact that **14** is obtained in 30% ee may suggest either that the two mechanisms are competing or that there is some memory of chirality with the counterion of **17**/**18** not being completely dissociated prior to cyclization.[10]

If electron rich aromatics are required for ionization to proceed via highly stabilized cations, it may follow that "non-stabilized" systems would indeed transfer chirality. To test this theory, we prepared a similar cyclization precursor, **19**, with an alkyl substituent in the allylic position. Gratifyingly, after treating carbamate **19** with the standard gold catalysis conditions, chirality transfer was achieved with only a small loss of enantiomeric excess (Scheme 6). This result demonstrates the first gold-cata-



Scheme 6. Chirality transfer with alkyl substrates

lyzed transfer of chirality using carbamate-protected nitrogen nucleophiles and should be a synthetically useful tool for the facile synthesis of heterocycles, without the complications of using a chiral gold complex with matched and mismatched substrate/catalyst pairs.[11]

Summary and Outlook

The preceding studies with nitrogen nucleophiles have given valuable insight into the delicate nature of the

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mechanism for gold-catalyzed dehydrative cyclization reactions. Substrates with electron rich substituents in the allylic position can follow a cationic pathway that provides the product with little transfer of chirality. This pathway becomes less competitive with substrates bearing substituents that have reduced electron donating capability, thereby giving rise to products with high enantiomeric excess by an olefin addition/elimination mechanism. Heterocycle formation under these conditions presents a mild and efficient route for the transfer of chirality without the need for a chiral metal complex and tolerates a broad range of functional groups. Furthermore, access to carbamate synthons via gold catalysis presents a versatile synthetic approach. Use of this method in the synthesis of complex natural products is underway in our laboratory and will be reported in due course.

Selected Experimental Data

General: All reactions were carried out under an atmosphere of dry nitrogen, unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried using an MBRAUN solvent purification system. 5-hexyn-1-ol, 6-chloro-1-hexyne, and N-(5-hexynyl)phthalimide were graciously donated to us by Petra Research, Inc. All other reagents were ordered from Sigma-Aldrich and used without any further purification. All Au and Ag catalysts were stored in and transferred to the reaction vessel in a glove box under a dry argon atmosphere.

Analytical thin layer chromatography (TLC) was performed using 250 μm silica gel 60 Å pre-coated plates (Whatman Inc.). Flash column chromatography was performed using 230–400 mesh 60 Å silica gel (Whatman Inc.). The eluents employed are reported as volume:volume percentages. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using Varian Unity Inova 500 MHz and Varian Mercury 300 MHz spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm) or $CDCl_3$ (7.26 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using Varian Unity Mercury 300 and 500 spectrometers at 75 MHz and 125 MHz, respectively. Chemical shift is reported in ppm relative to the carbon resonance of $CDCl_3$ (77.23 ppm). Infrared spectra were obtained on a PerkinElmer Spectrum RX1 FTIR spectrometer at 1.0 cm^{-1} resolution and are reported in wavenumbers. High resolution mass spectra (HRMS) were obtained by the Mass Spectrometry Core Laboratory of University of Florida, and are reported as m/e (relative ratio). Accurate masses are reported for the molecular ion (M+) or a suitable fragment ion.

Example procedure for the optimized gold-catalyzed dehydrative cyclizations: A test tube with a septum on top, containing 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.2 mg, 0.01 mmol, 5 mol%), silver tetrafluoroborate (1.9 mg, 0.01 mmol, 5 mol%), 4 Å molecular sieves (MS; previously activated by flame-drying under vacuum), and a stir bar, was taken from the glove box wrapped in aluminum foil and placed directly under dry nitrogen. A small portion of CH_2Cl_2 (0.2 mL) was added to the solid catalysts, and the mixture was left to stir at room temperature for 10 min, after which time a solution of the substrate (0.2 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture, all at once. The vessel was left to stir at room temperature. After TLC analysis had shown complete conversion, the reaction mixture was filtered through a short plug of silica with EtOAc, placed under vacuum to remove the solvents, and purified by flash column chromatography.

(*E*)-*tert*-butyl-(7-hydroxy-8-methylnon-5-en-1-yl)carbamate (2): Compound **2** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 1, entry 5), with **1** (39.4 mg, 0.14 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (4.7 mg, 0.008 mmol, 5 mol%), silver tetrafluoroborate (1.4 mg, 0.007 mmol, 5 mol%), 4 Å MS, and 1.0 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (5% EtOAc/hexanes), to yield the product as a clear oil (34.2 mg, 93%). $R_f = 0.47$ (10% EtOAc/hexanes). IR (neat) 2934, 2862, 1690, 1403, 1363, 1161 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48–5.28 (m, 2H), 4.72–4.71 (m, 1H), 3.96–3.84 (m, 1H), 2.81 (td, $J = 12.8$, 3.0 Hz, 1H), 2.28 (dq, $J = 13.1$, 6.6 Hz, 1H), 1.73–1.29 (m, 13H), 0.98 (d, $J = 6.8$, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 139.1, 125.1, 79.3, 52.2, 39.8, 31.2, 29.7, 28.7, 25.9, 22.8, 22.7, 19.7.

(*E*)-*tert*-butyl-(6-hydroxy-7-methyloct-4-en-1-yl)carbamate (4): Compound **4** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 2, entry 2), with **3** (76.8 mg, 0.3 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (9.3 mg, 0.015 mmol, 5 mol%), silver tetrafluoroborate (2.9 mg, 0.015 mmol, 5 mol%), 4 Å MS, and 1.5 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (5% EtOAc/hexanes), to yield the product as a clear oil (50.6 mg, 71%). $R_f = 0.70$ (20% EtOAc/hexanes). IR (neat) 2958, 2870, 1693, 1390, 1363, 1164, 1115 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46–5.36 (m, 1H), 5.29–5.20 (m, 1H), 4.16 (br s, 1H), 3.44–3.27 (m, 2H), 2.29–2.20 (m, 1H), 1.96 (br s, 1H), 1.87–1.73 (m, 2H), 1.67–160 (m, 1H), 1.42 (s, 10H), 0.96 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 137.5, 127.7, 79.0, 58.8, 46.3, 32.7, 30.9, 29.9, 28.7, 28.6, 22.8.

(*E*)-2-(3-methylbut-1-en-1-yl)-1-tosylpyrrolidine (6a)[12]: Compound **6a** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 3, entry 1), with **5a** (159.6 mg, 0.5 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (3.1 mg, 0.005 mmol, 1 mol%), silver tetrafluoroborate (1.0 mg, 0.005 mmol, 1 mol%), 4 Å MS, and 2.5 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (20–50% EtOAc/hexanes), to yield the product as a pale yellow oil (106.8 mg, 71%). All data matched that of the previously reported data.[12]

***E*)-2-(2-cyclohexylvinyl)-1-tosylpyrrolidine (6b)**: Compound **6b** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 3, entry 2), with **5b** (72.8 mg, 0.21 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (6.4 mg, 0.01 mmol, 5 mol%), silver tetrafluoroborate (2.0 mg, 0.01 mmol, 5 mol%), 4 Å MS, and 1.5 mL of CH_2Cl_2. The crude product was purified by flash column chromatography with a 20% EtOAc/hexanes solution, to yield the product as a clear oil (64.0 mg, 92%). $R_f = 0.60$ (20% EtOAc/hexanes). IR (neat) 3046, 2923, 2850, 1447, 1342, 1156 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 5.56 (ddd, $J = 15.4$, 6.4, 1.1 Hz, 1H), 5.27 (ddd, $J = 15.4$, 6.8, 1.4 Hz, 1H), 4.10 (td, $J = 7.1$, 3.9 Hz, 1H), 3.41 (ddd, $J = 9.7$, 7.3, 4.6 Hz, 1H), 3.29 (dt, $J = 9.9$, 7.1 Hz, 1H), 2.42 (s, 3H), 1.97–1.87 (m, 1H), 1.85–1.57 (m, 5H), 1.30–1.19 (m, 2H), 1.14 (qt, $J = 12.6$, 3.1 Hz, 1H), 1.08–0.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 137.7, 136.0, 129.6, 127.8, 127.7, 61.9, 48.7, 40.2, 33.0, 32.8, 26.4, 26.2, 26.1, 24.0, 21.7.

***tert*-butyl 4-tosyl-2-vinylpiperazine-1-carboxylate (6c)**: Compound **6c** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 3, entry 5), with **5d** (150.3 mg, 0.39 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (12.1 mg, 0.02 mmol, 5 mol%), silver tetrafluoroborate (3.8 mg, 0.02 mmol, 5 mol%), 4 Å MS, and 2.0 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (10–30% EtOAc/hexanes), with a 20% EtOAc/hexanes solution, to yield the product as a white solid (127.2 mg, 89%). $R_f =$ 0.80 (60% EtOAc/hexanes). IR (neat) 2976, 2930, 1702, 1455, 1415, 1342, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, $J = 8.2$ Hz, 2H), 7.34–7.26 (m, 2H), 5.70–5.55 (m, 1H), 5.23–5.10 (m, 2H), 4.79–4.68 (m, 2H), 3.81 (s, 2H), 3.47 (s, 2H), 3.32–3.19 (m, 2H), 2.42 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 154.9, 143.6, 136.8, 133.2, 130.0, 127.5, 119.6, 80.9, 51.9, 46.4, 45.8, 28.6, 21.8.

(*E*)-*tert*-butyl 3-styrylmorpholine-4-carboxylate (6d): Compound **6d** was made under the optimized gold-catalyzed dehydrative cyclization conditions (Table 3, entry 8), with **5f** (100.0 mg, 0.32 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (10.0 mg, 0.016 mmol, 5 mol%), silver tetrafluoroborate (3.1 mg, 0.016 mmol, 5 mol%), 4 Å MS, and 1.6 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (10–30% EtOAc/hexanes), with a 20% EtOAc/hexanes solution, to yield the product as an off-white solid (75.0 mg, 81%). $R_f = 0.85$ (60% EtOAc/hexanes). IR (neat) 2975, 2922, 2857, 1699, 1683, 1394, 1168 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.26 (m, 5H), 5.96–5.90 (m, 1H), 5.87–5.81 (m, 1H), 5.23 (d, $J = 6.1$ Hz, 1H), 4.90 (s, 1H), 4.00 (dt, $J = 5.0$, 0.9 Hz, 2H), 3.48 (t, $J = 5.2$ Hz, 2H), 3.35–3.19 (m, 2H), 2.25 (s, 1H), 1.44 (s, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 142.9, 135.4, 128.8, 128.0, 127.6, 126.5, 79.6, 74.7, 71.1, 69.6, 40.7, 28.7.

***N*,*N*-di-*tert*-butyloxycarbonyl-6-amino-1-hexyne (9):** To a flask containing di-(*tert*-butyl)-imidodicarbonate (3.1 g, 14.3 mmol, 1.2 eq.), a stir bar, and DMF (25 mL),NaH (60% in mineral oil, 0.399 g, 14.26 mmol, 1.4 eq.) was added, portion-wise, at room temperature. The solution was placed at 60 °C for 1 hr, then allowed to cool back to room temperature. The reaction mixture was then added to a solution of hex-5-yn-1-yl 4-methylbenzenesulfonate[13] (3.0 g, 11.9 mmol, 1.0 eq.) in DMF (10 mL), at room temperature. After stirring overnight, the reaction was placed at 0 °C, quenched with deionized water (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated under vacuum. The crude product was purified by flash column chromatography, using a solvent gradient (5–10% EtOAc/hexanes), to yield the product as an off-white solid (1.41 g, 40%). $R_f = 0.70$ (20% EtOAc/hexanes). IR (neat) 2980, 2935, 1744, 1696, 1368, 1139, 1114 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, $J =$ 6.9 Hz, 2H), 2.22 (dt, $J = 7.6$, 2.7 Hz, 2H), 1.94 (t, $J =$ 2.6 Hz, 1H), 1.75–1.64 (m, 2H), 1.62–1.45 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.8, 84.3, 82.3, 68.7, 46.0, 28.4, 28.3, 25.9, 18.4. HRMS (APCI) Calcd for $C_{16}H_{28}NO_4$ $(M+H)^+$: 298.2013; found 298.2000.

(*S*)-4-7-(*N*,*N*-di-*tert*-butyloxycarbonyl)-1-hydroxyhept-2-yn-1-yl)phenyl pivalate (11): The following compound was made using conditions similar to the standard Carreira asymmetric alkynylation conditions.[7] To a solution of $Zn(OTf)_2$ (1.2 g, 3.3 mmol, 1.1 eq.) and (−)-N-methylephedrine (0.54 g, 3.0 mmol, 1.0 eq.), in toluene (10 mL), Et_3N (0.46 mL, 3.3 mmol, 1.1 eq.) was added, and the solution was left to stir at room temperature for 2 hr, at which point **9** (892.2 mg, 3.0 mmol, 1.0 eq.), in toluene, (1 mL) was added to the mixture. The solution was left to stir for 20 min, and a solution of 4-(pivaloyloxy)benzaldehyde[14] (618.7 mg, 3.0 mmol, 1.0 eq.), in toluene, (1.0 mL) was added. The reaction mixture was left to stir at room temperature overnight, then quenched with NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated under vacuum. The crude product was purified by flash column chromatography, using

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a solvent gradient (10–25% EtOAc/hexanes), to yield the product as a translucent pale yellow oil (876.1 mg, 58%). $R_f = 0.64$ (30% EtOAc/hexanes). IR (neat) 3478, 2978, 2935, 1749, 1694, 1368, 1138, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, $J = 8.5$ Hz, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 5.37 (s, 1H), 3.54 (t, 2H), 2.25 (dt, $J = 7.0$, 2.0 Hz, 2H), 1.72–1.57 (m, 2H), 1.57–1.37 (m, 20H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 152.9, 151.0, 138.9, 127.8, 121.6, 87.0, 82.4, 80.7, 77.43, 64.2, 46.0, 39.2, 28.2, 27.3, 25.7, 18.6. HRMS (ESI) Calcd for $C_{28}H_{41}NNaO_7$ $(M+Na)^+$: 526.2775; found 526.2792. The enantiomeric excess (92%) was determined by HPLC analysis (Chiralpak IB, 5% *i*-PrOH in hexanes, 1.0 mL/min, 254 nm), t_r 7.7 (minor), 9.2 (major).

***(R,Z)*-4-(7-((*tert*-butoxycarbonyl)amino)-1-hydroxyhept-2-en-1-yl)phenyl pivalate (8)**: A two-necked flask containing **11** (503.6 mg, 1.0 mmol, 1.0 eq.), Lindlar's catalyst (100.0 mg, 20% by wt.), quinoline (100.0 mg, 20% by wt.), pentane:EtOAc (4.2 mL: 0.42 mL), and a stir bar was evacuated and backfilled with H_2 (g). The solution was stirred vigorously at room temperature, under the H_2 (g) atmosphere. The reaction was monitored by ^1H NMR of small aliquots of the reaction mixture. When the reaction was complete the mixture was filtered through a plug of cotton with EtOAc to remove the palladium, and the volatiles were removed under vacuum. The crude material was sufficient to use in the next step. To a flask containing the crude alkene (from reduction of **11**), acetonitrile (5 mL), and a stir bar, LiBr (260.5 mg, 3.0 mmol, 3.0 eq.) was added at room temperature. The reaction mixture was then placed at 65 °C and left to stir at this temperature overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL), and washed with 0.01 M HCl (3×20 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated under vacuum. The crude product was purified by flash column chromatography, using a solvent gradient (5–40% EtOAc/hexanes), to yield the product as a translucent pale yellow oil (315.9 mg, 78% over 2 steps). $R_f = 0.15$ (30% EtOAc/hexanes). $[\alpha]_D = -16.2$ (*c* 1.00, CH_2Cl_2). IR (neat) 3355, 2931, 1709, 1691, 1681, 1514, 1278, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, $J = 8.5$ Hz, 2H), 7.02 (d, $J = 8.6$ Hz, 2H), 5.71–5.45 (m, 3H), 4.66–4.49 (m, 1H), 3.25–2.98 (m, 1H), 2.57–2.45 (m, 1H), 2.40–2.25 (m, 1H), 2.22–2.06 (m, 1H), 1.56–1.37 (m, 14H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 156.3, 150.4, 141.3, 132.8, 131.6, 127.2, 121.6, 79.4, 69.1, 40.4, 39.2, 29.6, 28.6, 27.3, 27.1, 26.4. HRMS (ESI) Calcd for $C_{46}H_{70}N_2NaO_{10}$ $(2M+Na)^+$: 833.4923; found 833.4944. The enantiomeric excess (42%) was determined by HPLC analysis (Chiralpak IB, 10% *i*-PrOH in hexanes, 1.0 mL/min, 254 nm), t_r 7.8 (minor), 8.5 (major).

(*S*)-7-(*N*,*N*-di-*tert*-butyloxycarbonyl)-1-(4-bromophenyl)-hept-2-yn-1-ol (12): The following compound was made using conditions similar to the standard Carreira asymmetric alkynylation conditions.[7] To a solution of $Zn(OTf)_2$ (400.0 mg, 1.1 mmol, 1.1 eq.) and (−)-N-methylephedrine (180.0 mg, 1.0 mmol, 1.0 eq.), in toluene (4 mL), Et_3N (0.16 mL, 1.1 mmol, 1.1 eq.) was added, and the solution as left to stir at room temperature for 2 hr, at which point **9** (297.4 mg, 1.0 mmol, 1.0 eq.), in toluene (1 mL), was added to the mixture. The solution was left to stir for 20 min, and a solution of 4-bromobenzaldehyde (182.0 mg, 1.0 mmol, 1.0 eq.), in toluene (1.0 mL), was added. The reaction mixture was left to stir at room temperature overnight, then quenched with NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated under vacuum. The crude product was purified by flash column chromatography, using a solvent gradient (10–25% EtOAc/hexanes), to yield the product as a colorless oil (366.6 mg, 76%). $R_f = 0.32$ (20% EtOAc/hexanes). IR (neat) 3464, 2979, 2931, 1729, 1691, 1366, 1134, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47–7.43 (m, 2H), 7.39–7.35 (m, 2H), 5.38–5.31 (m, 1H), 3.59–3.52 (m, 2H), 2.74–2.70 (m, 1H), 2.29–2.22 (m, 2H), 1.73–1.61 (m, 2H), 1.57–1.41 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 140.5, 131.7, 128.5, 122.2, 87.3, 82.5, 80.5, 64.2, 46.0, 28.3, 28.1, 25.6, 18.6. HRMS (APCI) Calcd for $C_{23}H_{32}BrNNaO_5$ $(M+Na)^+$: 504.1379; found 504.1356. The enantiomeric excess (97%) was determined by HPLC analysis (Chiralpak IB, 5% *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), t_r 16.4 (major), 17.5 (minor).

(*R*,*Z*)-*tert*-butyl (7-(4-bromophenyl)-7-hydroxyhept-5-en-1-yl)carbamate (13): A two-necked flask containing **12** (366.6 mg, 0.76 mmol, 1.0 eq.), Lindlar's catalyst (73.3 mg, 20% by wt.), quinoline (73.3 mg, 20% by wt.), MeOH (4 mL), and a stir bar was evacuated and backfilled with H_2 (g). The solution was stirred vigorously at room temperature, under the H_2 (g) atmosphere. The reaction was monitored by ^1H NMR of small aliquots of the reaction mixture. When the reaction was complete, the mixture was filtered through a plug of cotton with EtOAc to remove the palladium, and the volatiles were removed under vacuum. The crude material was sufficient to use in the next step. To a flask containing the crude alkene (from reduction of **12**), MeOH (5 mL), and a stir bar, K_2CO_3 (525.2 mg, 3.8 mmol, 5.0 eq.) was added at room temperature. The reaction mixture was then placed at reflux and left to stir overnight. The reaction mixture was cooled to room temperature, the excess K_2CO_3 was filtered off, and the solution was placed under vacuum to remove the MeOH. The crude product was then diluted with EtOAc (30 mL) and washed with brine (2×10 mL). The organic phase was then dried over $MgSO_4$, filtered, and the solvents were evaporated under vacuum. The crude product was purified by flash column chromatography, using a solvent gradient (0–30% EtOAc/hexanes), to yield the product as a translucent pale yellow oil (245.9 mg, 81% over 2 steps). $R_f = 0.22$ (20% EtOAc/hexanes). $[\alpha]_D = -100.3$ (*c* 1.00, CH_2Cl_2). IR (neat) 3339, 2930, 1687, 1516, 1486, 1169 cm^{-1}. ^1H NMR (300 MHz,

$CDCl_3$): δ 7.47–7.41 (m, 2H), 7.28–7.22 (m, 2H), 5.61–5.44 (m, 3H), 4.65–4.45 (m, 1H), 3.24–3.10 (m, 1H), 3.10–2.97 (m, 1H), 2.76 (s, 1H), 2.42–2.23 (m, 1H), 2.20–2.04 (m, 1H), 1.58–1.31 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 142.9, 132.7, 131.8, 131.7, 127.9, 126.1, 121.3, 79.6, 68.9, 40.3, 29.5, 28.7, 27.0, 26.3. The enantiomeric excess (91 %) was determined by HPLC analysis (Chiralpak IB, 5 % *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), t_r 15.9 (major), 20.3 (minor).

(*S*,*E*)-*tert*-butyl-2-(4-bromostyryl)piperidine-1-carboxylate (14): Compound **14** was made under the optimized gold-catalyzed dehydrative cyclization conditions with **13** (20.0 mg, 0.05 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (1.6 mg, 0.0026 mmol, 5 mol %), silver tetrafluoroborate (0.5 mg, 0.0026 mmol, 5 mol %), 4 Å MS , and 1.0 mL of CH_2Cl_2. The crude product was purified by flash column chromatography, using a solvent gradient (0–5 % EtOAc/hexanes), to yield the product as a clear, colorless oil (16.8 mg, 92 %). R_f = 0.56 (20 % EtOAc/hexanes). $[\alpha]_D = -8.5$ (*c* 1.00, CH_2Cl_2). IR (neat) 2935, 2857, 1684, 1486, 1399, 1159 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.34 (dd, *J* = 16.2, 1.9 Hz, 1H), 6.20 (dd, *J* = 16.1, 4.8 Hz, 1H), 4.97 (s, 1H), 4.02 (d, *J* = 13.9 Hz, 2H), 2.91 (td, *J* = 13.0, 2.8 Hz, 1H), 1.88–1.74 (m, 2H), 1.72–1.61 (m, 2H), 1.61–1.37 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 136.2, 131.8, 129.9, 129.8, 128.0, 121.3, 79.8, 52.4, 40.2, 29.7, 28.7, 25.7, 19.9. The enantiomeric excess (30 %) was determined by HPLC analysis (Chiralpak IB, 0.5 % *i*-PrOH in hexanes, 0.8 mL/min, 254 nm), t_r 18.1 (minor), 20.3 (major).

(*R*,*E*)-*tert*-butyl 2-(4-phenylbut-1-en-1-yl)piperidine-1-carboxylate (20): The following compound was made under the optimized gold-catalyzed dehydrative cyclization conditions with **19** (13.0 mg, 0.04 mmol), 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride (2.4 mg, 0.004 mmol, 10 mol %), silver tetrafluoroborate (0.8 mg, 0.004 mmol, 10 mol %), 4 Å MS, and 1.0 mL of CH_2Cl_2, at 40 °C. The crude product was purified by flash column chromatography, using a solvent gradient (0–5 % EtOAc/hexanes), to yield the product as a white solid (10.4 mg, 87 %). R_f = 0.62 (20 % EtOAc/hexanes). $[\alpha]_D$ = 30.1 (*c* = 0.70, CH_2Cl_2). IR (neat) 2931, 2857, 1687, 1407, 1363, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.25 (m, 2H), 7.20–7.15 (m, 3H), 5.48 (dtd, *J* = 15.1, 6.6, 1.7 Hz, 1H), 5.41–5.35 (m, 1H), 4.72 (s, 1H), 3.88 (d, *J* = 13.5 Hz, 1H), 2.78–2.66 (m, 3H), 2.39–2.33 (m, 2H), 1.66–1.61 (m, 2H), 1.58–1.50 (m, 3H), 1.45 (s, 9H), 1.42- 1.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 142.0, 130.9, 129.4, 128.7, 128.5, 126.0, 79.4, 52.0, 39.8, 36.0, 34.5, 29.6, 28.7, 25.8, 19.6. The enantiomeric excess (92 %) was determined by HPLC analysis (Chiralcel OJ-H, 1.0 % *i*-PrOH in hexanes, 1.0 mL/min, 215 nm), t_r 8.8 (major), 13.2 (minor).

Acknowledgements

We gratefully acknowledge the Herman Frasch Foundation (647-HF07), the donors of the Petroleum Research Fund (47539-G1), and the James and Esther King Biomedical Research Program (09KN-01) for their generous support of our programs. F.S.P.C. thanks the NSF/FAPESP US/South America REU program for summer support. We thank Petra Research, Inc. for the gifts of 5-hexyn-1-ol, 5-chloro-1-hexyne, N-(5-hexynyl)phthalimide, and an unrestricted research award.

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Received: April 13, 2013
Accepted: June 13, 2013
Published online: August 23, 2013