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Gold-Catalyzed Intramolecular Allylic Amination of 2-Tosylaminophenylprop-1-en-3-ols. A Concise Synthesis of (±)-Angustureine

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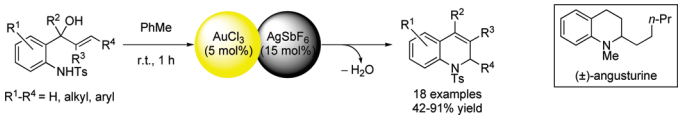

An efficient synthetic route to 1,2-dihydroquinolines that relies on $AuCl_3/AgSbF_6$-catalyzed intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols is described herein. Uniquely, the reactions were found to only proceed rapidly at room temperature in the presence of the gold and silver catalyst combination and produce the 1,2-dihydroquinoline products in yields of 40−91%. The method was shown to be applicable to a broad range of 2-tosylaminophenylprop-1-en-3-ols containing electron-withdrawing, electron-donating, and sterically demanding substrate combinations. The mechanism is suggested to involve activation of the alcohol substrate by the $AuCl_3/AgSbF_6$ catalyst. This is followed by ionization of the starting material, which causes intramolecular nucleophilic addition of the sulfonamide unit to the allylic cation moiety and construction of the 1,2-dihydroquinoline. The utility of this *N*-heterocyclic ring forming strategy as a synthetic tool that makes use of alcohols as pro-electrophiles was exemplified by its application to the synthesis of the bioactive tetrahydroquinoline alkaloid (±)-angustureine.

Introduction

Gold-catalyzed carbon−nitrogen bond formations have become a powerful and convenient synthetic route to amines and amine derivatives in recent years.[1−8] Generally, this type of reaction has relied upon the interaction of the gold catalyst with the π-bonds of alkenes, alkynes, and allenes followed by attack of a nitrogen nucleophile.[1−3] In contrast, the establishing of amination strategies in gold catalysis that make use of other functional groups as electrophiles has received much less attention and examples have remained sparse. In this regard, a recent notable advance is that by Campagne, Prim, and co-workers, who showed benzylation and propargylation of anilines, azides, and sulfonamides with benzylic and propargylic alcohols to proceed smoothly in the presence of $NaAuCl_4 \cdot 2H_2O$ as catalyst.[4] Following this seminal

(1) For recent reviews on gold-catalyzed reactions, see: (a) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (d) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (e) *Coinage Metals in Organic Synthesis*; Lipshutz, B. H., Yamamoto, Y., Eds. *Chem. Rev.* **2008**, *108*, 2793. (f) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817. (g) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (h) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (i) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (j) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. (k) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (l) Asao, N. *Synlett* **2006**, 1645. (m) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

(2) Selected examples: (a) Nishina, N.; Yamamoto, Y. *Tetrahedron* **2009**, *65*, 799. (b) Buzas, A.; Istrate, F.; Le Goff, X. F.; Odabachian, Y.; Gagosz, F. *J. Organomet. Chem.* **2009**, *694*, 515. (c) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (d) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672. (e) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (f) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Chem. Asian J.* **2008**, *3*, 285. (g) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 4148. (h) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (i) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (j) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, H.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (k) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Nass, A. R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 5376. (l) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905. (m) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, *20*, 4634. (n) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (o) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (p) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (q) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (r) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (s) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (t) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.

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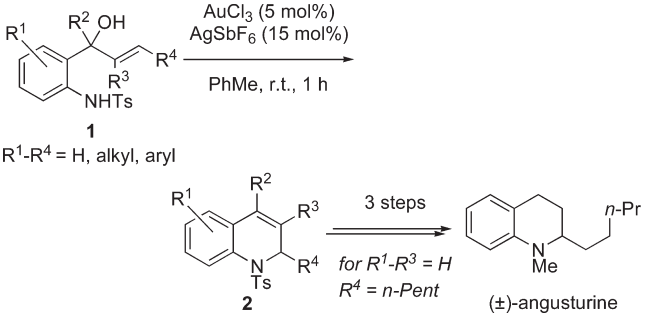
work, Liu and co-workers reported a similar efficient $AuCl_3$-mediated approach for the allylic alkylation of *p*-toluenesulfonamide with allylic alcohols.[5] More recently, we[6] and the groups of Liu[7] and Liang[8] described gold-catalyzed tandem amination/intramolecular hydroamination strategies for the synthesis of pyrrolidines and pyrroles from the respective cyclopropylmethanol and 1-en-4-yn-3-ol substrates could also be accomplished. In view of these works and an ongoing program on C−N bond formations,[6,9] we began to turn our attention to expanding the scope of gold-mediated reactions of alcohol pro-electrophiles as the basis for developing new strategies to 1,2-dihydroquinolines.

In addition to their presence in a myriad of bioactive natural products and therapeutics, partially hydrogenated quinolines are an immensely important class of building blocks in organic synthesis.[10] Although this has led to many synthetic methods[11] that has also recently included gold catalysis,[3] the reactions have been reported to usually require high temperatures and/or prolonged reaction times. In addition, limited examples demonstrating substrate scope, modest selectivities, and, in many cases, the need for more than stoichiometric amounts of various reagents and additives has lessened their utility in organic synthesis. We envisioned a gold-catalyzed strategy involving the use of alcohol pro-electrophiles[12,13] would be attractive from a synthetic standpoint as the ease of preparing the starting material provides the possibility to introduce a wide variety of substitution patterns in one step. Added to this is the potential formation of H_2O as the only side product. To our knowledge, while methods for quinoline synthesis from alcohols have been recently described,[14] the corresponding studies to 1,2-dihydroquinolines have been thus far limited to two reported literature methods. Lau and co-workers reported the thermolytic electrocyclization of *N*-methyl-2-hydroxyalkylanilines and found the reaction to only proceed at high temperatures (80−180 °C).[15] At about the same time, Kobayashi and co-workers showed that intramolecular cyclization of *o*-(1-hydroxy-2-alkenyl)phenyl isocyanides could be accomplished in the presence of $BF_3 \cdot Et_2O$ as catalyst at 0 °C.[16] However, these methods were shown to give low to good product yields and only applicable to a limited substrate scope. In this regard, it remains a challenge to develop catalytic systems that can effect efficient 1,2-dihydroquinoline formation for a wide variety of alcohol pro-electrophiles under ambient conditions. Herein, we report an efficient synthetic route to 1,2-dihydroquinolines involving intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols catalyzed by $AuCl_3$ with $AgSbF_6$ as a cocatalyst under mild conditions at room temperature (Scheme 1). Uniquely, the reaction was found to only efficiently proceed in the presence of a gold and silver catalyst combination and provide good to excellent product yields up to 91% for a wide variety of starting alcohols. The application of this catalytic 1,2-dihydroquinoline formation process to the synthesis of (±)-angustureine in four steps is also presented.

SCHEME 1. $AuCl_3/AgSbF_6$-Catalyzed Intramolecular Amination of 2-Tosylaminophenylprop-1-en-3-ols and Its Application to the Synthesis of (±)-Angustuerine



(3) (a) Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Gupta, M. K.; Sridhar, B. *J. Org. Chem.* **2008**, *73*, 6857. (b) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 2755. (c) Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159. (d) Godet, T.; Belmont, P. *Synlett* **2008**, 2513. (e) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821. (f) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645. (g) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811. (h) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2007**, *36*, 1422. (i) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203. (j) Arcadi, A.; Bianchi, G.; Di Guiseppe, S.; Marinelli, F. *Green Chem.* **2003**, *5*, 64.

(4) (a) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758. (b) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063.

(5) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964.

(6) Rao, W.; Chan, P. W. H. *Chem.—Eur. J.* **2008**, *14*, 10486.

(7) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 129.

(8) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 243.

(9) (a) Rao, W.; Zhang, X.; Sze, E. M. L; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 1740. (b) Chang, J. W. W.; Ton, T. M. U.; Zhang, Z.; Xu, Y.; Chan, P. W. H. *Tetrahedron Lett.* **2009**, *50*, 161. (c) Wu, W.; Rao, W.; Er, Y. Q.; Loh, K. J.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620; *Tetrahedron Lett.* **2008**, *49*, 4981. (d) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138. (e) Rao, W.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 3789. (f) Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245.

(10) (a) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor R. J. K., Eds.; Elsevier Science: Oxford, UK, 2008, Vol. 7. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (c) Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141. (d) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1987; Vol. 30, pp 251−377. (e) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329. (f) Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic: New York, 1981, Vol. 19, pp 1−80.

(11) (a) O'Byrne, A.; Evans, P. *Tetrahedron* **2008**, *64*, 8067. (b) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (c) Ryu, J.-S. *Bull. Korean Chem. Soc.* **2006**, *27*, 631. (d) Yi, C. S.; Yun, S. Y. *J. Am. Chem. Soc.* **2005**, *127*, 17000. (e) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *J. Am. Chem. Soc.* **2005**, *127*, 5782. (f) Williamson, N. M.; Ward, A. D. *Tetrahedron* **2005**, *61*, 155. (g) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017. (h) Ranu, B. C.; Hajra, A.; Dev, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813. (i) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621. (j) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807. (k) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807. (l) Arduini, A.; Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *Synthesis* **1981**, 975. (m) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279. (n) Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908. (o) Skraup, Z. H. *Ber.* **1880**, *13*, 2086. (p) Wahren, M. *Tetrahedron* **1964**, *20*, 2773. (q) Bischler, A.; Napieralski, B. *Ber.* **1893**, *26*, 1903.

(12) For recent reviews on the use of alcohols as pro-electrophiles, see ref 1a and the following: (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Kabalka, G. W.; Yao, M.-L. *Curr. Org. Synth.* **2008**, *5*, 28. (c) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (d) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (e) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647.

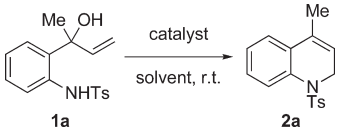
(13) For recent examples of amination of alcohol pro-electrophiles with metal-catalyzed systems other than gold, see: (a) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2009**, *11*, 2377. (b) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, *9*, 3371. (c) Piechaczyk, O.; Thoumazet, C.; Jean, Y.; le Floch, P. *J. Am. Chem. Soc.* **2006**, *128*, 14306. (d) Zhan, Z.-P.; Yu, J.-L.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem.* **2006**, *71*, 8298. (e) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085. (f) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (g) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1698. (h) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968.

Results and Discussion

Initially, we chose *N*-(2-(2-hydroxybut-3-en-2-yl)phenyl)-4-methylbenzenesulfonamide **1a** as the model substrate to establish the reaction conditions (Table 1). This revealed treatment of 1 equiv of **1a** with 5 mol % of $AuCl_3$ and 15 mol % of $AgSbF_6$ in toluene at room temperature for 1 h gave the best result (entry 1). Under these conditions, 4-methyl-1-tosyl-1,2-dihydroquinoline **2a** was furnished as the sole product in 87% yield. The 1,2-dihydroquinoline product was confirmed by ^{1}H NMR analysis and X-ray crystal structure determination of three closely related products vide infra. Lower product yields of 32−56% were obtained when the reaction was repeated with lower loadings of 5 or 10 mol % of $AgSbF_6$ or removing the AgCl formed in situ prior to use (entries 2−4). Similarly, a lower product yield of 58% was afforded when the reaction was performed in nitromethane in place of toluene as solvent (entry 5). In contrast, the analogous reactions in acetonitrile or 1,4-dioxane were found to result in trace product formation and near-quantitative recovery of the starting alcohol (entries 6 and 7). An inspection of entries 8−25 in Table 1 revealed the reaction also proceeded less effectively with other Lewis and Brønsted acid catalysts. In these reactions, the use of $AuCl_3$ in combination with AgOTf, AuCl with AgOTf or $AgSbF_6$, or Ph_3PAuCl with $AgSbF_6$ were the only instances that gave slightly lower product yields of 62−72% (entries 8−11). When we examined $AuCl_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $InCl_3$, $FeCl_3 \cdot 6H_2O$, $BF_3 \cdot Et_2O$, and *p*-TsOH·H_2O as the catalyst, markedly lower product yields of 7−18% were afforded (entries 12 and 19−24). However, changing the catalyst to AuCl, Ph_3PAuCl, $AgSbF_6$, AgOTf, $Bi(OTf)_3$, or $CuCl_2$ gave no reaction on the basis of ^{1}H NMR or TLC analysis of the crude mixtures (entries 13−18). On the other hand, when TfOH or HCl was employed as catalyst, the reaction was found to proceed to give a wide variety of side products that could not be separated by flash column chromatography or identified by ^{1}H NMR analysis of the crude mixtures (entries 25 and 26). The contrasting catalytic activities observed for the respective $AgSbF_6$- and TfOH-mediated reactions also provided evidence that the cationic Au(III) complex is the active species (entries 15 and 25). Additionally, the significantly poorer reactivities found for the respective reactions catalyzed by $AuCl_3$[5] and $Bi(OTf)_3$[17] are noteworthy as these catalysts were recently reported to efficiently mediate the allylic alkylation of sulfonamides with allylic alcohols (entries 12 and 17). Likewise, $BF_3 \cdot Et_2O$, which was found to catalyze the intramolecular cyclization of *o*-(1-hydroxy-2-alkenyl)phenyl isocyanides,[16] was shown to be less effective in this study (entry 23).

To define the scope of the present procedure, we next turned our attentions to the reactions of a variety of 2-tosylaminophenylprop-1-en-3-ols (Table 2). These experiments showed that with $AuCl_3/AgSbF_6$, starting alcohols

TABLE 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	catalyst	solvent	time (h)	yield (%)
1	$AuCl_3/AgSbF_6$	PhMe	1	87
2	$AuCl_3/AgSbF_6$	PhMe	4	55[b]
3	$AuCl_3/AgSbF_6$	PhMe	4	32[c]
4	$AuCl_3/AgSbF_6$	PhMe	16	56[d]
5	$AuCl_3/AgSbF_6$	$MeNO_2$	16	58
6	$AuCl_3/AgSbF_6$	MeCN	16	—[e]
7	$AuCl_3/AgSbF_6$	1,4-dioxane	16	—[e]
8	$AuCl_3$/AgOTf	PhMe	16	72
9	AuCl/$AgSbF_6$	PhMe	4	62
10	AuCl/AgOTf	PhMe	4	60
11	$Ph_3PAuCl/AgSbF_6$	PhMe	6	68
12	$AuCl_3$	PhMe	16	15
13	AuCl	PhMe	16	—[f]
14	Ph_3PAuCl	PhMe	16	—[f]
15	$AgSbF_6$	PhMe	16	—[f]
16	AgOTf	PhMe	16	—[f]
17	$Bi(OTf)_3$	PhMe	16	—[f]
18	$CuCl_2$	PhMe	16	—[f]
19	$Cu(OTf)_2$	PhMe	16	12
20	$Yb(OTf)_3$	PhMe	16	7
21	$InCl_3$	PhMe	16	11
22	$FeCl_3.6H_2O$	PhMe	16	18
23	$BF_3.Et_2O$	PhMe	16	16
24	*p*-TsOH.H_2O	PhMe	16	13
25	TfOH	PhMe	0.5	—[g]
26	HCl	PhMe	0.5	—[g]

[a]All reactions were performed at room temperature with 0.2 mmol of **1a** in the presence of 5 mol % of catalyst. [b]Reaction performed with 5 mol % of $AuCl_3$ and 10 mol % of $AgSbF_6$. [c]Reaction performed with 5 mol % of $AuCl_3$ and 5 mol % of $AgSbF_6$. [d]Reaction performed with 5 mol % of $AuCl_3$ and 15 mol % of $AgSbF_6$ with removal of AgCl prior to use. [e]Trace amount refers to less than 1% of product isolated after flash column chromatography. [f]No reaction based on TLC or ^{1}H NMR analysis of the crude mixture. [g]Mixture of unknown side products furnished based on ^{1}H NMR analysis of the crude mixture.

with a methyl- and/or phenyl-substituted terminal alkene moiety gave the corresponding products **2b**−**d** in excellent yields (entries 1−3). Similarly, the analogous reaction of **1e**, which contains a pendant *m*-toluidine ring unit, underwent intramolecular allylic amination and afforded **2e** in 86% yield (entry 4). Likewise, reaction of *p*-chloroaniline-substituted alcohol **1f** gave **2f** in 59% yield when subjected to the standard conditions, the yield of which could be increased to 68% on repeating with CH_2Cl_2 as the solvent at reflux (entry 5). The present procedure was also shown to work well for 2-tosylaminophenylprop-1-en-3-ols containing electron-withdrawing or electron-donating groups at the terminal position of the allylic alcohol moiety, giving **2i**−**l** in 58−90% yield (entries 8−11). Notably, these cyclizations also demonstrated that the electronic nature of the C=C bond could play a role since a gradual decrease in product yields from 78% to 58% was found and longer reaction times from 1 to 4 h were required as the electron-withdrawing ability of the substitutent increased on going from **1j** to **1l**. Substituted 2-tosylaminophenylprop-1-en-3-ols **1m**,**n** bearing a sterically bulky naphthylene and mesitylene group, respectively, were found to proceed well and afford **2m**,**n** in excellent yields (entries 12 and 13). However, moderate yields were obtained

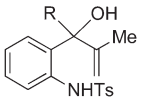
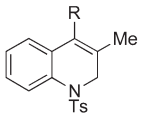
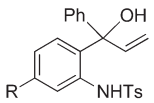
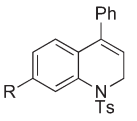
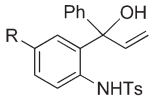
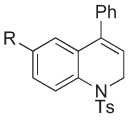
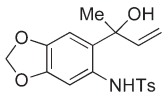
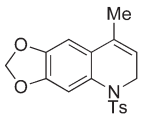
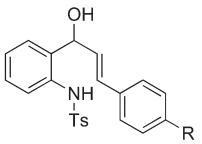
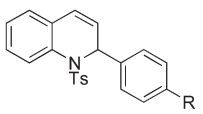
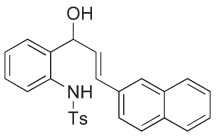
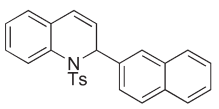
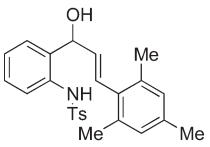
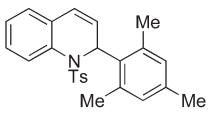
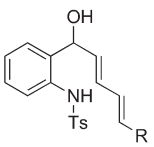
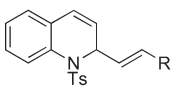
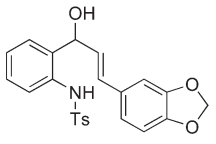
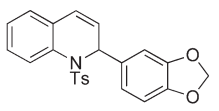
(14) For selected examples, see: (a) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778. (b) Mierde, H. V.; Voort, P. V. D.; Vos, D. D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, 1625. (c) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173. (d) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873. (e) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539.

(15) Migneault, D.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1995**, *73*, 1506.

(16) Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, *24*, 575.

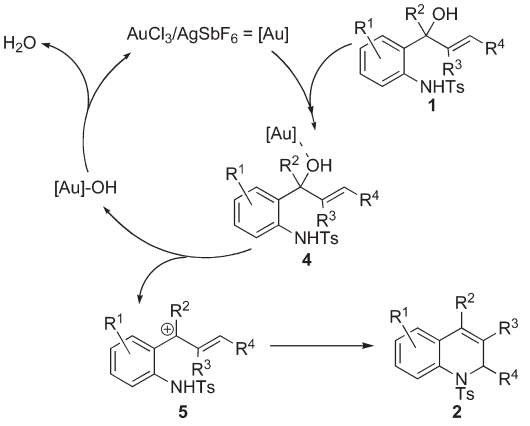
(17) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

TABLE 2. $AuCl_3/AgSbF_6$-Catalyzed Intramolecular Amination of 1b−q[a]

entry	alcohol	product		yield (%)
1			**2b**, R = Me	89
2	**1b-c**		**2c**, R = Ph	87
3			**2d**, R = H	86
4	**1d-e**		**2e**, R = Me	86
5			**2f**, R = Cl	68[b]
6	**1f-g**		**2g**, R = NO_2	-[c]
7	 **1h**		**2h**	45
8	 **1i-l**		**2i**, R = Me	90
9			**2j,** R = Br	78[d]
10			**2k**, R = Cl	62[e]
11			**2l**, R = F	58[e]
12	 **1m**		**2m**	85
13	 **1n**		**2n**	86
14			**2o**, R = Ph	62
15	**1o-p**		**2p**, R = *n*-Pr	69[f]
16	 **1q**		**2q**	42

[a]All reactions were performed in PhMe at room temperature for 1 h with $AuCl_3$:$AgSbF_6$:**1** ratio = 1:3:20. [b]Reaction conducted in CH_2Cl_2 as solvent at 40 °C. [c]No reaction based on ^1H NMR analysis of the crude mixture. [d]Reaction conducted for 2 h. [e]Reaction conducted for 4 h. [f]Reaction conducted with AuCl:AgOTf ratio = 1:3 as catalyst at reflux for 6 h.

SCHEME 2. Tentative mechanism for $AuCl_3/AgSbF_6$-Catalyzed Intramolecular Cyclization of 2-Tosylaminophenylprop-1-en-3-ols

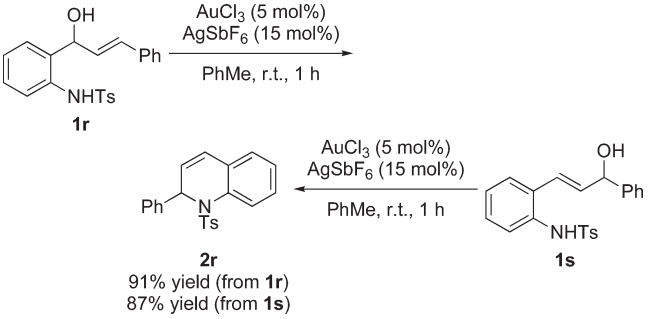


for intramolecular cyclizations of alcohols with a pendant benzo[*d*][1,3]dioxole group on the allylic moiety or as part of the aniline unit as in **1h** and **1q** (entries 7 and 16). On the other hand, reactions of alcohol substrates with pendant trans diene functionalities were found to proceed well when subjected to the standard conditions and give **2o**,**p** in good yields (entries 14 and 15). For the cyclization of **1p**, switching the catalyst to 5 mol % of AuCl and 15 mol % of AgOTf under reflux conditions was required to shorten the reaction time from 24 to 6 h. In our hands, reaction of **1g** containing a *p*-nitroaniline unit was the only case that was found to be ineffective with no product formation detected by ^{1}H NMR analysis of the crude mixture and near-quantitative recovery of the starting alcohol (entry 6).

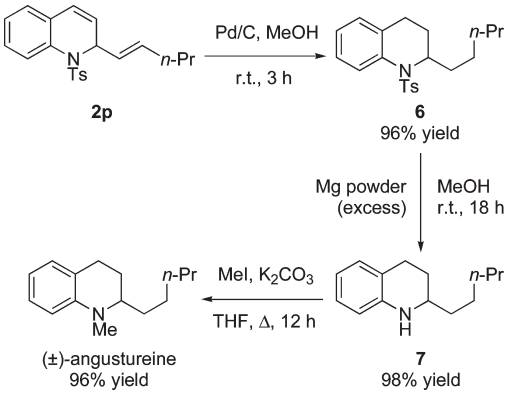
At this juncture, we would like to highlight the chemoselective nature of the present reaction. Consistent with our earlier findings for the intramolecular cyclization of **1a**, our studies found that the 1,2-dihydroquinolines described in Table 2 were obtained as the sole product in all except one case. As shown in Figures S41−44 in the Supporting Information, this was further confirmed by X-ray crystal structure determination of **2b** as well as that for **2c**, **2e**, and **2i**.[18] On the basis of ^{1}H NMR analysis of the crude mixtures, possible indole formation arising from competitive intramolecular hydroamination could not be detected under our experimental conditions. Similarly, a competitive Freidel−Crafts alkylation or hydroxyl group elimination process for substrates containing an aryl or alkyl group on the carbinol carbon that would give the respective indene and diene products was not found. Under the standard conditions, intramolecular cyclization of **1c** was the only instance in which the indene adduct **3**, determined by X-ray crystal analysis (please refer to Figure S45 in the Supporting Information), was also obtained as a minor side product in 3% yield.[18]

Although highly speculative, we propose the present $AuCl_3/AgSbF_6$-catalyzed 1,2-dihydroquinoline forming reaction to proceed by the mechanism outlined in Scheme 2. This could involve the gold and silver catalyst combination activating the alcohol substrate **1** by coordinating to the hydroxyl functionality. This delivers the Au(III)-coordinated intermediate **4** that can undergo elimination to give the carbocation species **5** and [Au]−OH, which releases the metal catalyst by protodemetalation.[19] It is possible that this newly formed cationic species promotes cyclization of the pendant sulfonamide group and subsequent delivery of the product **2**. The role of the catalyst in facilitating dehydroxylation of the alcohol substrate would account for our earlier results showing moderate yields for the reactions of **1h** and **1q** and no product formation for the cyclization of **1g** (entries 6, 7, and 16 in Table 2). It would not be inconceivable that such interactions are presumably weakened due to competitive coordination with a very electron-rich neighbor such as a 1,3-dioxole moiety or a strongly coordinating nitro substitutent on the alcohol substrate. The possible involvement of a resulting putative allylic carbocation species prior to formation of the new C−N bond to give the product is also supported by our findings for the reactions of **1r** and its regioisomer **1s**. Under the conditions described in Scheme 3, the 1,2-dihydroquinoline adduct **2r** was afforded as the sole product in both reactions in comparable yields of 91%

SCHEME 3. $AuCl_3/AgSbF_6$-Catalyzed Intramolecular Amination of 1r and 1s



SCHEME 4. Synthesis of (±)-Angustureine from 2p



(18) CCDC 720295−720297, 721703, and 724703 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336- 033; E-mail: deposit@ccdc.cam.ac.uk).

(19) A similar reaction mechanism has been suggested in related studies on gold-catalyzed reactions of alcohol pro-electrophiles, see refs 1a, 4−6 and the following: (a) Kothandaraman, P.; Rao, W.; Zhang, X.; Chan, P. W. H. *Tetrahedron* **2009**, *65*, 1833. (b) Arcadi, A.; Alfonsi, M.; Chiarini, M.; Marinelli, F. *J. Organomet. Chem.* **2009**, *694*, 576. (c) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426. (d) Dai, L.-Z.; Shi, M. *Chem.—Eur. J.* **2008**, *14*, 7011. (e) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3296. (f) Liu, J.; Muth, E.; Floerke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, G. *Adv. Synth. Catal.* **2006**, *348*, 456. (g) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

and 87% from **1r** and **1s**, respectively. The origin of the indene side product **3** could be due to competitive cyclization of this resulting carbocation species by the phenyl and *p*-tosylamino substituents on **1c**. What remains currently unclear is whether the gold center first coordinates to the C=C bond before hydroxyauration and elimination to give the allylic carbocation species and if subsequent coordination of this intermediate to the catalyst takes place prior to the ring-forming step.[20] Our earlier findings showing markedly poorer or lack of catalytic activity with other Lewis and Brønsted catalysts would certainly suggest that such interactions to be a possibility.

Having established a general and efficient synthetic route to 1,2-dihydroquinolines, we applied this new methodology to the synthesis of the biologically active tetrahydroquinoline alkaloid (±)-angustureine.[21] As shown in Scheme 4, Pd/C-mediated hydrogenation of **2p** in MeOH gave the tetrahydroquinoline **6** in 96% yield. Subsequent treatment of this newly formed intermediate with a methanolic solution containing an excess amount of magnesium powder furnished the detosylated tetrahydroquinoline **7** in 98% yield. Finally, *N*-methylation of this adduct with MeI and K_2CO_3 as base at reflux for 12 h gave (±)-angustureine in 96% yield. The ^{1}H and ^{13}C NMR spectra of (±)-angustureine prepared in this work are identical with the corresponding spectra of the authentic natural compound (see the Supporting Information for spectra).[21]

Conclusion

In summary, an efficient gold-catalyzed synthetic route to 1,2-dihydroquinolines based on intramolecular allylic amination of 2-tosylaminophenylprop-1-en-3-ols under mild conditions at room temperature has been reported. These results show the reaction to be applicable to a wide range of alcohol substrates containing electron-withdrawing, electron-donating, and sterically demanding substituents. Our studies also revealed the use of a gold and silver catalyst combination to be the only Lewis acid among the many examined in this work that can efficiently mediate the present cyclization process. The synthetic utility of the present method to this partially hydrogenated class of heterocycles was also demonstrated by further modifying one adduct obtained to the synthesis of the bioactive tetrahydroquinoline alkaloid (±)-angustureine. Efforts to develop an enantioselective approach to this synthetically useful building block are currently underway and will be reported in due course.

Experimental Section

Experimental Procedure for $AuCl_3/AgSbF_6$-Catalyzed Intramolecular Allylic Amination of 2-Tosylaminophenylprop-1-en-3-ols (1). A solution of $AuCl_3$ (15 μmol) and $AgSbF_6$ (47.3 μmol) was stirred in a solution of toluene (1.5 mL) at room temperature for 10 min. Then, a toluene solution (1.5 mL) containing **1** (0.31 mmol) was added slowly dropwise and the reaction mixture was stirred at room temperature and monitored to completion by TLC analysis. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (*n*-hexane/EtOAc 20:1 as eluent) to give the title compound **2**.

4-Methyl-1-tosyl-1,2-dihydroquinoline (2a):[11g] white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (1H, dd, J = 1.36, 8.2 Hz), 7.30 (1H, ddd, J = 1.8, 7.8, 7.7 Hz), 7.21−7.26 (3H, m), 7.12 (1H, dd, J = 1.36, 7.32 Hz), 7.06 (2H, d, J = 7.8 Hz), 5.31 (1H, m), 4.33 (2H, m), 2.33 (3H, s), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 136.1, 135.1, 131.6, 131.4, 128.8, 127.8, 127.4, 127.2, 126.7, 123.2, 120.3, 45.3, 21.4, 17.7; MS (ESI) m/z 300 $[M + H]^+$.

(*E*)-2-(Pent-1-enyl)-1-tosyl-1,2-dihydroquinoline (2p): colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (1H, d, J = 8.01 Hz), 7.22−7.29 (3H, m), 7.12 (1H, t, J = 7.52 Hz), 7.04 (2H, d, J = 8.19 Hz), 6.92 (1H, d, J = 8.42 Hz), 6.05 (1H, d, J = 9.54 Hz), 5.57−5.64 (2H, m), 5.26−5.34 (2H, m), 2.32 (3H, s), 1.83−1.92 (2H, m), 1.23−1.28 (2H, m), 0.71 (3H, t, J = 7.36 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.2, 136.4, 133.8, 133.1, 129.0, 128.6, 127.9, 127.4, 127.2, 126.9, 126.2, 126.2, 125.8, 124.5, 55.9, 34.0, 22.0, 21.5, 13.3; IR (NaCl, neat) ν 3025, 1596, 1478, 1342, 1216, 1165 cm^{-1}; MS (ESI) m/z 354 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{24}NO_2S$ (M^+ + H) 354.1528, found 354.1526.

(±)-Angustureine:[21] yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (1H, t, J = 7.8 Hz), 6.95 (1H, d, J = 6.88 Hz), 6.55 (1H, t, J = 7.32 Hz), 6.50 (1H, d, J = 8.24 Hz), 3.20−3.24 (1H, m), 2.91 (3H, s), 2.75−2.79 (1H, m), 2.62−2.67 (1H, m), 1.86−1.90 (2H, m), 1.53−1.58 (2H, m), 1.25−1.41 (6H, m), 0.87 (3H, t, J = 6.84 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.4, 128.6, 127.1, 121.9, 115.2, 110.4, 59.0, 38.0, 32.1, 31.2, 25.8, 24.4, 23.6, 22.7, 14,1; MS (ESI) m/z 218 $[M + H]^+$.

Acknowledgment. This work is supported by a University Research Committee Grant (RG55/06) and Supplementary Equipment Purchase Grant (RG134/06) from Nanyang Technological University.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for starting alcohols **1**, 1,2-dihydroquinolines **2**, **6**, and **7**, indene **3**, and (±)-angustureine, and CIF files of **2b**, **2c**, **2e**, and **2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) A similar mechanistic rationale for gold-catalyzed nucleophilic substitutions of propargylic alcohols with sulfonamides was put forward by Campagne and co-workers, see ref 4a.

(21) Please refer to refs 11a−c and the following: (a) Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; Pozo, C. D. *Chem.—Eur. J.* **2008**, *14*, 9868. (b) Shahane, S.; Louafi, F.; Moreau, J.; Hurvois, J.-P.; Renaud, J.-L.; Weghe, P.; Roisnel, T. *Eur. J. Org. Chem.* **2008**, 4622. (e) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577. (d) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260. (e) Theeraladanon, C.; Arisawa, M.; Nishida, A. *Tetrahedron: Asymmetry* **2005**, *16*, 827. (f) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (g) Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fouraste, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167.