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Gold Catalyzed Carbocyclization of Dienyl Acetates to Construct Mutifunctionalized 3-Vinyl Cyclohexanol Derivatives

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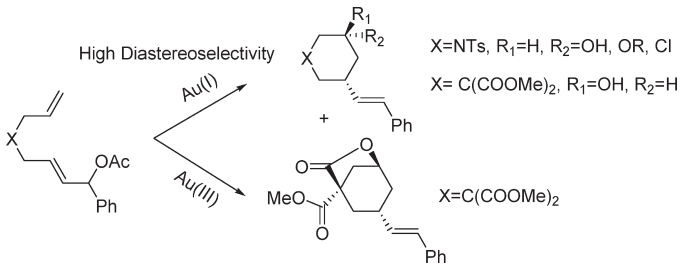
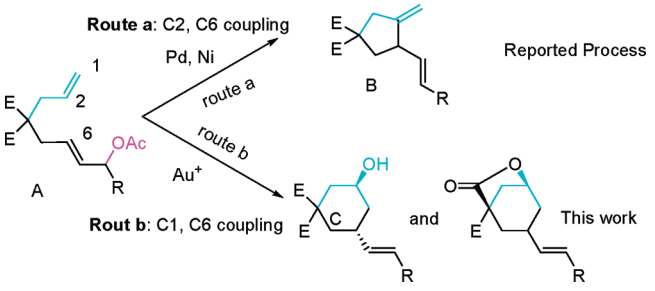


A convenient new method was developed to construct six-membered 3-vinylcyclohexanols (and piperidine products) and 6-oxabicyclo[3.2.1]octan-7-one derivatives with high diastereoselectivities from 1,6-dienyl acetates via gold catalysis. The reaction proceeded through the nucleophilic addition of the alkenes onto the allylic cation group via a 6-*endo*-*trig* process. The substrate's structure affected the configuration orientation of the allylic cation group in a boatlike transition state, which afforded either the *trans*-cyclohexanols or *cis*-piperidine derivatives.

Introduction

Regioselective cycloisomerization of polyunsaturated substrates is an efficient approach for the construction of cyclic molecules.[1] In this field, palladium(0)-catalyzed intramolecular carbocyclization of allylic acetates with alkenes in substrates of type A, as exemplified by the first route (route a) shown in Scheme 1, has been intensively studied to construct the five-membered hetero- or carbocycles of type B via a metallo−ene process.[2] Many transition metals (such as Pd, Ni, Rh, etc.) have been successfully utilized in this coupling reaction.[3] However, employing gold complexes[4] to catalyze the intramolecular nucleophilic addition of alkenes onto

SCHEME 1



(1) Ho, T. L. *Carbocycle Construction in Terpene Synthesis*; Wieley-VCH: Weinheim, 1988.

(2) (a) Oppolzer, W.; Gaudin, J.-M. *Helv. Chim. Acta* **1987**, *70*, 1477. (b) Oppolzer, W.; Gaudin, J.-M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (c) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (e) Oppolzer, W. In *Organometallic Reagents in Organic Synthesis*; Bateson, J. H., Mitchell, M. B., Eds.; Academic Press: London, 1994; p 161.

(3) (a) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883. (b) Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* **1993**, *76*, 2329.

(4) For recent general reviews, see: (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (f) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (h) Muzart, J. *Tetrahderon* **2008**, *64*, 5815.

(5) Recent examples of gold induced nucleophilic addition onto allylic acetate: (a) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653. (b) Gourlaouen, C.; Marion, N.; Nolan, S. P.; Maseras, F. *Org. Lett.* **2009**, *11*, 81. (c) Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1883. (d) Wang, Y. H.; Zhu, L. L.; Zhang, Y. X.; Chen, Z. *Chem. Commun.* **2010**, *46*, 577. (e) Chen, Z.; Zhang, Y.-X.; Wang, Y.-H.; Zhu, L.-L.; Liu, H.; Li, X.-X.; Guo, L. *Org. Lett.* **2010**, *12*, 3468.

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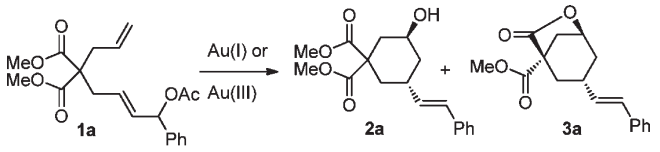
TABLE 1. Examination of the Gold-Catalyzed Reaction of Compound 1a[a]



	catalyst	loading (mol %)	time (h)	yield (%) of **2a**	yield (%) of **3a**
1	$AuPPh_3Cl/AgOTf$	1	24	35	10
2	AuCl	2	1.5	71	0
3	AuCl	5	1.5	79	0
4	$AuCl_3$	1	1	0	70
5	$AuCl_3/AgPF_6$[b]	1	1.5	trace	84
6	$AgPF_6$	1	1.5	15	45
7	HOAc	5	1.5	0	0
8	HCl	2	1.5	17	0
9	HOTf	2	1.5	35	0
10	$AuCl/K_2CO_3$[c]	1	24	30	0

[a]Unless noted, all reactions were carried out on a 0.2 mmol scale in DCE at rt with the addition of 1 equiv of H_2O. [b]The reaction temperature is 50 °C. [c]1 molar equiv of K_2CO_3 was added.

allylic acetates, to the best of our knowledge, has never been reported.[5−7]

Herein we describe a convenient new method to construct a series of six-membered 3-vinylcyclohexanols and 6-oxabicyclo-[3.2.1]octan-7-one derivatives with high diastereoselectivities from substrate A via gold catalysis (Scheme 1, route b). As compared with the palladium-catalyzed C2−C6 coupling reaction in route a, the new C−C bond was formed between C1 and C6 via a 6-*endo-trig* process.

We have recently reported on the diastereoselective γ-vinyl butyrolactone synthesis via gold-catalyzed intramolecular nucleophilic addition of an ester onto an allylic acetate.[5d] It was proposed that an allylic cation intermediate was formed as the key intermediate from allylic acetate, which was then trapped by the intramolecular nucleophilic addition of the ester carbonyl group. It seemed to us that the presence of the allylic cation intermediate might also promote the intramolecular C−C bond formation between alkenes and allylic acetates.

Results and Discussion

Dimethyl 2-(4-acetoxy-4-phenylbut-2-enyl)-2-allyl malonate **1a** was chosen as the model system for our initial investigation. As shown in Table 1, when **1a** was treated with 1 mol % equiv of $AuPPh_3Cl/AgOTf$ in CH_2Cl_2 at rt for 24 h, to our surprise, two products were separated in a total yield of 45% (**2a**/**3a** = 3.5/1). Their NMR spectral data (^1H and ^{13}C NMR) were quite similar. The structure of **3a** was identified to be a bicyclic lactone through X-ray crystallography.[8] It was found that the vinyl group was located on the opposite side of the lactone. Compound **2a** can be transformed into **3a** in the condition of $AuCl_3/AgPF_6$, indicating that two products have the same stereochemistry. Therefore, the structure of **2a** was deduced to be a *trans*-3-vinylcyclohexanol derivative.[9]

Considering the importance of the synthesis of six-membered carbocycles in chemistry, and the ample functionalities present in **2a** and **3a**, optimizations of the reaction condition were then performed and some representative results were summarized in Table 1. Initial solvent screening established dichloroethane as the best choice. Different gold catalysts were tested. Treating **1a** with 2 mol % equiv (with respect to **1a**) of AuCl and 1 molar equiv of H_2O in DCE provided product **2a** in 71% yield, without the formation of **3a** (Table 1, entry 2). Addition of too much H_2O would prolong the reaction time. Using 5 mol % equiv of AuCl as the catalyst enhanced the reaction yield (Table 1, entry 3, conditions A). However, when $AuCl_3$ was used as the catalyst, only product **3a** was obtained in 70% yield (Table 1, entry 4). Combination of $AuCl_3$ with $AgPF_6$ enhanced the reactivity, which gave **3a** in 84% yield after 1.5 h at 50 °C (Table 1, entry 5, conditions B). In control experiments, acetic acid afforded no product, HCl and HOTf gave **2a** in low yields (Table 1, entries 7−9), which provided the evidence that Lewis acidic gold(I) complex is the catalytically active species to promote this reaction. In addition, when **1a** was treated with 1 mol % of AuCl under the basic conditions (1 equiv K_2CO_3 was added), compound **2a** could be obtained in 30% yield after 24 h (Table 1, entry 10).

Using the conditions from entry 3 in Table 1, the scope and limitations of this reaction were explored. A number of 1,6-dienyl acetate substrates with different substitution patterns at the double bonds as well as at the allyl carbon were prepared from the simple starting materials by utilizing −C(COOMe) or TsN− as the linker group. Table 2 shows some representative examples for the preparation of 3-vinylcyclohexane derivatives **2** using a variety of differently substituted substrates **1a**−**n**. The influence of the substitutes (R_3 and R_4) at the allyl carbon (C8 position, Table 2 reaction scheme) was

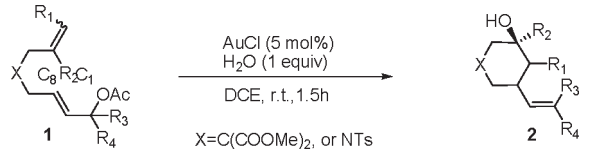
(6) Gold-catalyzed reaction of allenyl carbinol esters or allyl alcohols: (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985. (b) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (c) Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947. (d) Rao, W. D.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426. (e) Kothandaraman, P.; Rao, W. D.; Zhang, X. X.; Chan, P. W. H. *Tetrahedron* **2009**, *65*, 1833. (f) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1.

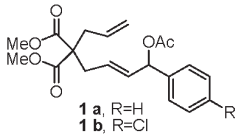
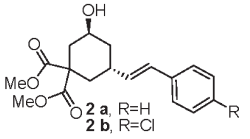
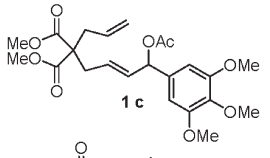
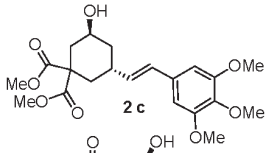
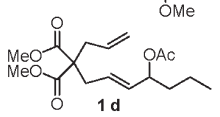
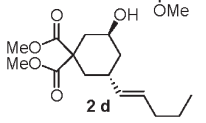
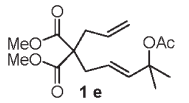
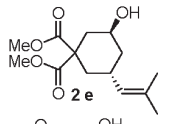
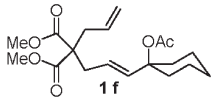
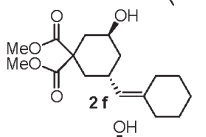
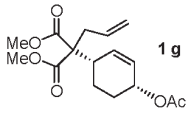
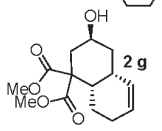
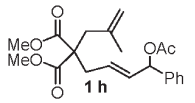
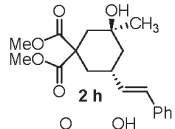
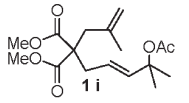
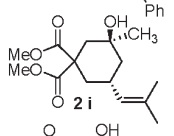
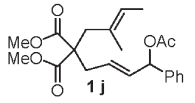
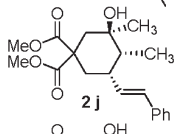
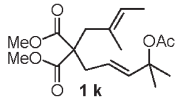
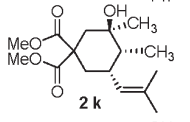
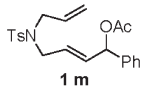
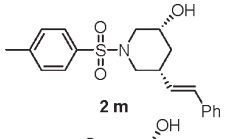
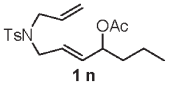
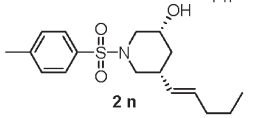
(7) Gold-catalyzed reaction of enynols: (a) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409. (b) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839. (c) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964. (d) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Syn. Catal.* **2009**, *351*, 129. (e) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Syn. Catal.* **2009**, *351*, 517.

(8) See the Supporting Information for the details of the NOESY spectral data of compounds **2a** and **6** and the X-ray crystallography of compound **3a** and compound **8**. CCDC no. for compound **3a**: 776682. CCDC no. for compound **8**: 800366.

(9) Compound **2a**'s *trans* configuration has been proven by its NOESY spectral data.

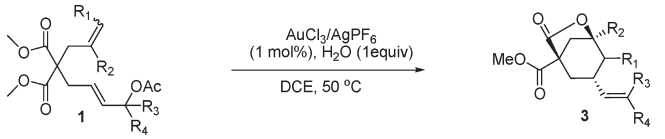
TABLE 2. Preparation of a Series of 3-Vinylcyclohexanols and 5-Vinylpiperidin-3-ol Derivatives under Gold Catalyst Conditions[a]

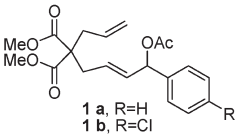
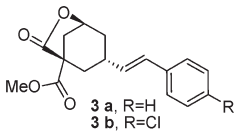
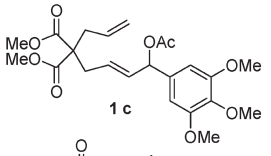
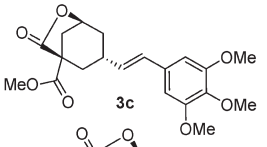
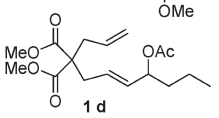
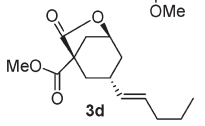
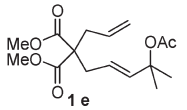
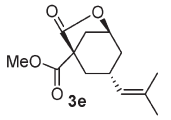
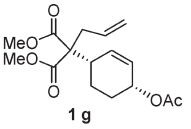
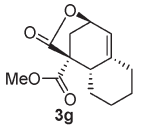
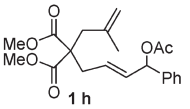
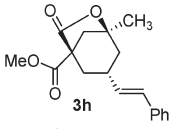
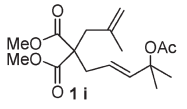
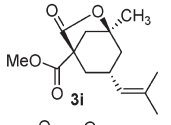
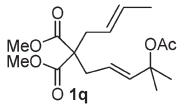
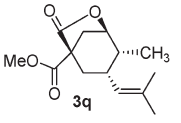


Entry	Dienyl acetate **1**	Product **2**	Time(h)	Yield(%)[b] /dr [c]
1	 **1 a**, R=H **1 b**, R=Cl	 **2 a**, R=H **2 b**, R=Cl	1.5	79%, dr = 50:1
2			1.5	77%, dr = 40:1
3	 **1 c**	 **2 c**	1.5	91 %, dr >99:1
4	 **1 d**	 **2 d**	12	52 %, dr > 99:1
5	 **1 e**	 **2 e**	1.5	86 %, dr > 99:1
6	 **1 f**	 **2 f**	2	79%, dr = 46:1
7	 **1 g**	 **2 g**	12	48 %, dr > 25:1
8	 **1 h**	 **2 h**	1.5	71 %, dr = 32:1
9	 **1 i**	 **2 i**	1.5	69 %, dr = 20:1
10	 **1 j**	 **2 j**	1.5	38 %, d.r. = 25:1
11	 **1 k**	 **2 k**	1.5	59 %, dr = 17:1
12 [d]	 **1 m**	 **2 m**	0.5	69 %, dr > 30:1
13 [d]	 **1 n**	 **2 n**	0.5	52 %, dr > 20:1

[a]Unless noted, all reactions were carried out on a 0.2 mmol scale in DCE at rt with AuCl as catalyst (conditions A). [b]Separated yields. [c]Ratio was determined by ^{1}H NMR spectral data. [d]$AuPPh_3Cl/AgSbF_6$ was used as catalyst.

TABLE 3. Preparation of Bicyclic 3-Vinyl-6-oxabicyclo[3.2.1]octan-7-one Derivatives 3[a]



Entry	Enyne **1**	Product **3**	Time(h)	Yield(%)[b] /d.r.[c]
1	 **1 a**, R=H **1 b**, R=Cl	 **3 a**, R=H **3 b**, R=Cl	1.5	84%, d.r.= 66:1
2			1.5	98%, d.r.>99:1
3	 **1 c**	 **3c**	1.5	82 %, d.r.>99:1
4	 **1 d**	 **3d**	1.5	84 %, d.r.> 99:1
5	 **1 e**	 **3e**	1.5	79 %, d.r.> 99:1
6	 **1 g**	 **3g**	3	57%, d.r.> 99:1
7	 **1 h**	 **3h**	1.5	79 %, d.r.= 17:1
8	 **1 i**	 **3i**	1.5	81 %, d.r. = 25:1
9	 **1q**	 **3q**	7	42 %, d.r. = 13:1

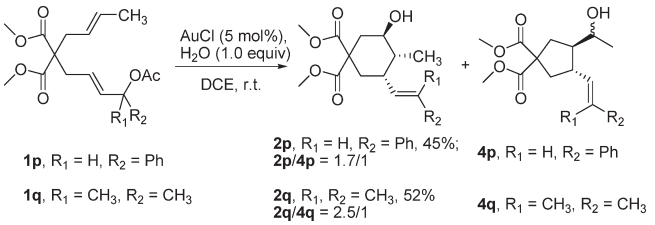
[a]Unless noted, all reactions were carried out on a 0.2 mmol scale in DCE at 50 °C with $AuCl_3/AgPF_6$ as catalyst (conditions B). [b]Separated yields. [c]Ratio was determined by ^1H NMR spectral data.

first studied by using monosubstituted terminal alkene (C1, C2 position) as the intramolecular nucleophile (**1a**−**d**). Almost all substrates, which bear phenyl groups (**1a**−**c**) or alkyl groups at the C8 carbon, gave the desired products in moderate to high yields with high diastereoselectivities. Among these examples, substrate **1c**, which contained an electrodonating trimethoxy phenyl group (Table 2, entry 3), worked better than **1b** (substituted with an electrowithdrawing *p*-chlorophenyl group) and **1a** (Table 2, entries 1 and 2). Similarly, substrates **1e** and **1f**, which had dialkyl groups at the C8 position (Table 2, entries 5 and 6), performed better than **1d** (substituted with a monoalkyl group, Table 2, entry 4). The cyclic substrate **1g** afforded **2g** in a low yield (48% yield) with a diastereoselectivity of 25/1 (Table 2, entry 7).

The influence of the double-bond substitution pattern (C1, C2 position) upon cycloisomerization was also investigated. When *gem*-disubstituted isobutene was used as the nucleophile (**1h**, **i**), intramolecular carbocyclization proceeded very well, giving products **2h** and **2i** in satisfactory yields with dr values of 32/1 and 20/1 (Table 2, entries 8 and 9). However, trisubstituted isopentene-bearing substrates (**1j**,**k**) afforded the desired products with reduced yields (Table 2, entries 10 and 11) because of the formation of a mixture of elimination products.

Substrates with −NTs as the linker groups were then studied. As compared with the results obtained in substrates **1a** and **1d**, TsN-containing substrates **1m** and **1n** gave the desired products in relative low yields (Table 2, entries 12 and 13), with the phenyl-containing substrate **1m** being superior to

SCHEME 2. Examination of the Reaction of Compounds 1p and 1q



1n. It was interesting that, in compound **2m** and **2n**, the hydroxyl group and the vinyl group have a "*cis*" structure.[10]

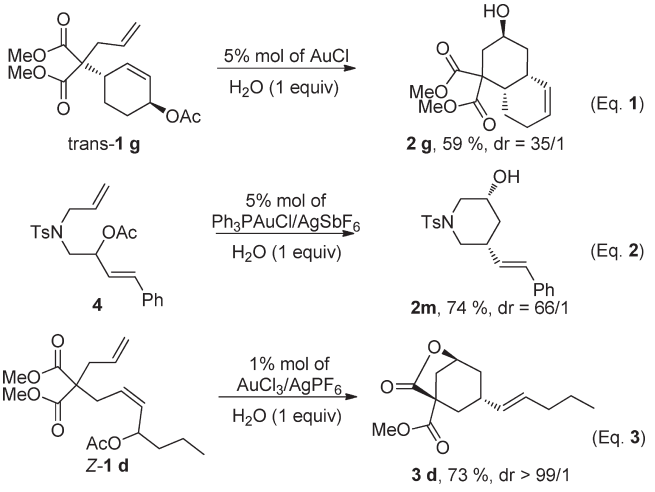
A number of 3-vinyl bicyclic lactone derivatives **3** can also be prepared from these substrates by using $AuCl_3/AgPF_6$ as the catalyst (condition B, Table 3). Under these conditions, substrate **1b**, which had an electron-withdrawing phenyl group, worked better than its electron-rich analoges (**1a**,**c**) (the reaction yield of **3b** is higher than **3a** and **3c**). Substrate **1d**, containing a monoalkyl group at the C8 carbon, performed better than the dialkyl analogue **1e** did (Table 3, entries 4 and 5). With a 1,1-disubstituted alkene as the intramolecular nucleophile, **3h** and **3i** were obtained in 79% and 81% yields with high dr values (Table 3, entries 7 and 8). The reaction yields of substrates **1g** and **1q** were quite low, giving products **3g** and **3q** in 57% and 42% yields, respectively.[11]

We then turned to investigate the reaction of substrates **1p** and **1q**, which contained a 1,2-disubstituted alkene as the intramolecular nucleophile. As shown in Scheme 2, when compound **1p** was treated with 5 mol % equiv of AuCl in DCE at rt, 3-vinylcyclohexanol product **2p** was obtained in 45% yield with a high diastereoselectivity. Nevertheless, a mixture of 5-membered vinylcyclopentylethanol side product **4p** was also separated from the reaction. The ratio of **2p** to **4p** was equal to 1.7/1. The reaction of **1q** under the same reaction conditions afforded the desired cyclohexanol **2q** and a mixture of five-membered analogues **4q** with a ratio of **2q/4q** equal to 2.5/1 (Scheme 2). These results indicated that the intramolecular carbocyclization preferred to proceed via a 6-*endo*-*trig* process to afford the six-membered products.[12]

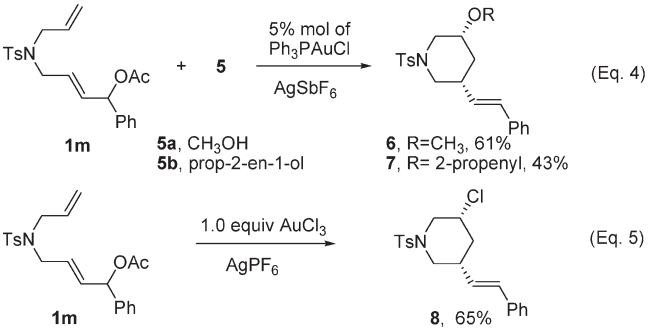
To determine the effect of the substrate's stereochemistry on the reaction yield, *trans*-**1g** and compound **4** (regioisomer of **1m**) were prepared and treated with AuCl and $Ph_3PAuCl/AgSbF_6$ in DCE, respectively, which gave **2g** in 59% yield and **2m** in 74% yield (Scheme 3, eqs 1 and 2), while the reaction of *Z*-**1d** under $AuCl_3/AgPF_6$ conditions afforded **3d** in 73% yield with a high diastereoselectivity (Scheme 3, eq 3). These results are similar to those of *cis*-**1g**, **1m** (Table 2, entries 7 and 12), and **1d** (Table 3, entry 4).

The reaction of substrate **1m** with other nucelophiles was then tested. As shown in Scheme 4, the reaction of **1m** with methanol afforded the methoxy adduct **6** in 61% yield, while the reaction of prop-2-en-1-ol **5b** provided the corresponding product **7** in 43% yield. In compound **6**, a "*cis*" configuration of the methoxy group and the vinyl group was determined by NOESY spectrum.[8] When substrate **1m** was treated with 1.0

SCHEME 3. Examination of the Reaction of Compounds 4, *trans*-1g, and *Z*-1d



SCHEME 4. Examination of the Reaction of Compound 1m with Other Nucelophiles



equiv of $AuCl_3$ in DCE, a chloropiperidine product **8** was obtained in 65% yield (Scheme 4, eq 5), in which the *cis* stereochemistry was determined by its crystal structure.[8]

A plausible mechanism was proposed. The intramolecular carbocyclization started from the formation of an allylic cation intermediate,[13] which was then attacked by the alkene via a 6-*endo*-*trig* process through a boatlike transition state. The in situ generated carbon cation was then trapped by H_2O to give the desired product **2**. In order to avoid the 1,3-diaxial steric interaction with the ester group in the transition state II, allylic cation group was favored to take the equatorial position in transition state I, which therefore afforded the *trans*-configuration 3-vinyl cyclohexanol product **2** and **3** (Scheme 5).[14] Direct trapping allylic cation with ester groups through route b or c seems unlikely because of unfavored stereoelectronic effect in route c and the long distance of the pseudoequatorial ester in route b. Therefore, product **3** should be derived from **2** under the Au(III) catalyst conditions

(10) The relative stereochemistry of compounds **2m** and **2n** are deduced from the structure of compounds **6** and **8**.

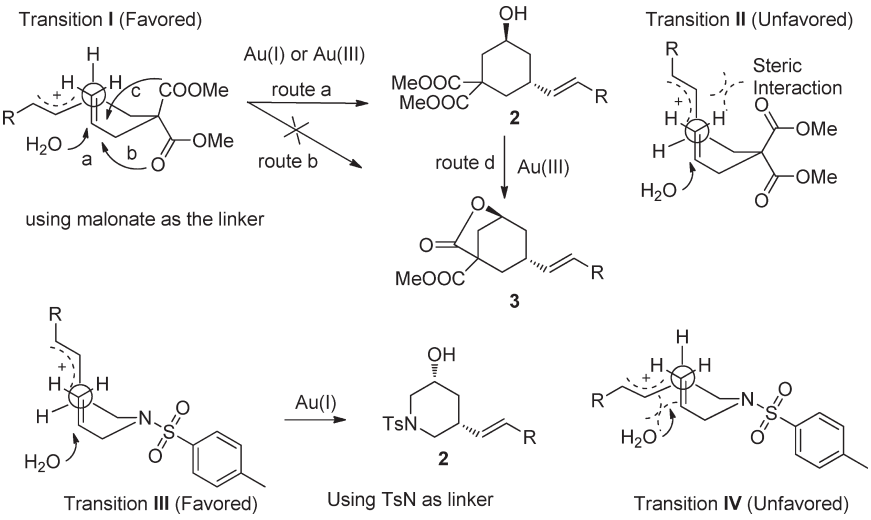
(11) The low reaction yield of **3g** and **3q** might be due to the formation of the elimination products and the five-membered regioisomers.

(12) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

(13) (a) Lin, C.-C.; Teng, T.-M.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2007**, *129*, 3798. (b) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2091. (c) Barluenga, J.; Fernández, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2009**, *15*, 11660.

(14) There are two steric interactions in transition state **I** and **II**: (i) the steric interaction between the allylic cation group and the vinyl group in transition state **I**; (ii) 1,3-diaxial steric interaction between allylic cation group and the ester group in transition state **II**. The formation of the *anti* stereochemistry in **2a** might be mainly affected by the latter interaction.

SCHEME 5. Plausible Mechanism To Give *Trans* Configuration 3-Vinylcylohexanol 2 and Bicyclic Lactone 3 with High Diastereoselectivity



(route d). In the reaction of **1m** and **1n**, the allylic cation group, however, is favored to take an axial position (transition state III) to avoid the steric interaction with the vinyl group (transition state IV), which therefore afforded the *cis* piperidine products.

Conclusion

We have developed an efficient and simple method to construct polysubstituted 3-vinylcyclohexanols (and piperidine products) and the bicyclic lactone derivatives with high diastereoselectivities through gold-catalyzed intramolecular carbocyclization of alkenes onto allylic acetates. The reaction proceeded via 6-*endotrig* process through a boatlike transition state. In the reaction of the malonate containing substrates, the allylic cation group was favored to take the pseudoequatorial position to give the *trans* configuration cyclohexanol products. However, in the reaction of TsN-bearing substrates, the allylic cation group preferred to take the pseudo axial position to give the *cis*-piperidine products.

Experimental Section

Typical Procedure for the Gold Catalyzed Carbocyclization of Allylic Acetates with Alkenes. Procedure A. To a solution of AuCl (0.05 equiv) in 1 mL of 1, 2-dichloroethane was added a solution of substrate **1a** (0.2 mmol) in 2 mL of 1,2-dichloroethane and H_2O (1.0 equiv) under N_2. The reaction mixture was stirred under room temperature, until complete consumption of the starting material with TLC monitoring. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography on silica gel to afford compound **2a** in 79% yield.

Procedure B. The gold catalyst was generated in an oven-dried Schlenk tube containing a magnetic stir bar under N_2 by addition of $AgPF_6$ (0.01 equiv), $AuCl_3$ (0.01 equiv), and 1,2-dichloroethane (1 mL). After the catalyst mixture was stirred at room temperature for 2 min, a solution of **1a** (0.2 mmol) in 1,2-dichloroethane (2 mL) and H_2O (1.0 equiv) was added. The reaction mixture was heated to 50 °C and maintained until complete consumption of starting material. The solvent was then removed by rotary evaporation, and the residue was purified by column chromatography on silica gel to afford the compound **3a** in 84% yield.

(3*S,5*R**)-Dimethyl 3-hydroxy-5(*E*)-styrylcyclohexane-1,1-dicarboxylate (2a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 7.1 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.21 (t, J = 7.1 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0, 7.0 Hz, 1H), 4.30−4.27 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 2.92−2.84 (m, 1H), 2.59 (d, J = 14.6 Hz, 1H), 2.53 (d, J = 13.7 Hz, 1H), 2.21(br, 1H), 2.00 (dd, J = 14.7, 2.9 Hz, 1H), 1.95 (d, J = 13.9 Hz, 1H), 1.53 (d, J = 12.9 Hz, 1H), 1.40 (td, J = 13.0, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.3, 137.4, 134.0, 128.9, 128.5, 127.1, 126.0, 65.5, 52.9, 52.8, 52.7, 38.1, 36.6, 36.3, 31.1; IR (neat) 3520, 3468, 3447, 2951, 2928, 2851, 1734, 1449, 1433, 1313, 1250, 1213, 1184, 1126, 968, 746, 694 cm^{-1}; MS (m/z, rel intensity) 318 (M^+, 1), 300 (30), 286 (8), 240 (67), 181 (100), 129 (18), 115 (15), 91 (17), 69 (5), 59 (6); HRMS (EI) calcd for $C_{18}H_{22}O_5$ [M^+] 318.1467, found 318.1463.

(3*R,5*S**)-Dimethyl 3-(*E*)-(4-chlorostyryl)-5-hydroxycyclohexane-1,1- dicarboxylate (2b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 4H), 6.39 (dd, J = 16.0, 1.2 Hz, 1H), 6.08 (dd, J = 16.0, 7.0 Hz, 1H), 4.30−4.26 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.92−2.84 (m, 1H), 2.59 (dd, J = 14.7, 2.9 Hz, 1H), 2.53 (td, J = 13.5, 1.6 Hz, 1H), 2.17 (br, 1H), 1.99 (dd, J = 14.7, 3.0 Hz, 1H), 1.94 (d, J = 13.6, 1.7 Hz, 1H), 1.53 (t, J = 12.9 Hz, 1H), 1.40 (td, J = 13.0, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 136.0, 134.7, 132.7, 128.6, 127.8, 127.2, 65.4, 52.9, 52.8, 52.7, 38.0, 36.5, 36.4, 31.1; IR (neat) 3523, 3468, 2951, 2997, 1732, 1490, 1452, 1313, 1251, 1213, 1126, 1091, 968 cm^{-1}; MS (m/z, rel intensity) 352 (M^+, 1), 334 (35), 320 (12), 277 (12), 276 (22), 275 (28), 274 (75), 217 (28), 215 (100), 179 (21), 125 (21), 97 (6), 69 (5), 59 (7); HRMS (EI) calcd for $C_{18}H_{21}O_5{}^{35}Cl$ [M^+] 352.1078, found 352.1076.

(3*R,5*S**)-Ddimethyl 3(*E*)-(3,4,5-trimethoxystyryl)-5-hydroxycyclohexane-1,1- dicarboxylate (2c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 2H), 6.37 (d, J = 15.9 Hz, 1H), 6.03 (dd, J = 15.9, 7.0 Hz, 1H), 4.29−4.27 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 2.92−2.84 (m, 1H), 2.59 (d, J = 14.8 Hz, 1H), 2.53 (d, J = 13.5 Hz, 1H), 2.19 (br, 1H), 1.99 (dd, J = 14.7, 2.9 Hz, 1H), 1.96 (d, J = 13.6 Hz, 1H), 1.53 (d, J = 12.9 Hz, 1H), 1.40 (td, J = 12.9, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 153.3, 133.6, 133.2, 128.9, 103.1, 65.4, 60.9, 56.1, 52.9, 52.8, 38.2, 36.7, 36.4, 31.0; IR (neat) 3520, 3468, 2953, 2941, 1726, 1581, 1240, 1125, 968 cm^{-1}; MS (m/z, rel intensity) 408 (M^+, 100), 390 (30), 376 (67), 330(32), 299 (28), 271 (18), 239 (18), 181 (39), 97 (4), 59 (5); HRMS (EI) calcd for $C_{21}H_{28}O_8$ [M^+] 408.1784, found 408.1762.

(3*S,5*R**)-Dimethyl 3-hydroxy-5-((*E*)-pent-1-enyl)cyclohexane-1,1-dicarboxylate (2d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (td, J = 15.8, 6.4 Hz, 1H), 5.30 (dd, J = 15.6, 6.7 Hz, 1H), 4.22 (br, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.67−2.59 (m, 1H), 2.54 (dd, J = 14.7, 2.6 Hz, 1H), 2.40 (dd, J = 13.5, 1.4 Hz, 1H), 2.20 (br, 1H), 1.98−1.91 (m, 3H), 1.84 (td, J = 13.6, 1.6 Hz, 1H), 1.44−1.31 (m, 3H), 1.30−1.23 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.5, 134.1, 129.5, 65.6, 52.9, 52.8, 52.7, 38.5, 37.0, 36.4, 34.7, 30.5, 33.6, 13.6; IR (neat) 3520, 3468, 3447, 2954, 2931, 2872, 1734, 1433, 1313, 1247, 1215, 1184, 1145, 1124 cm^{-1}; MS (m/z, rel intensity) 285 ([M + 1]$^+$, 1), 267 (4), 266 (8), 252 (10), 221 (10), 208 (20), 207 (96), 206 (100), 147 (85), 105 (20), 91 (42), 59 (18); HRMS (EI) Calcd for $C_{15}H_{24}O_5$ [M + 1]$^+$ 285.1702, found 285.1705.

(3*S,5*R**)-Dimethyl 3-hydroxy-5-(2-methylprop-1-enyl)cyclohexane-1,1- dicarboxylate (2e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (d, J = 8.6 Hz, 1H), 4.22−4.20 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.96−2.88 (m, 1H), 2.53 (dd, J = 14.6, 2.2 Hz, 1H), 2.30 (d, J = 13.5 Hz, 1H), 2.05 (br, 1H), 1.97 (dd, J = 14.6, 2.5 Hz, 1H), 1.77 (d, J = 13.6 Hz, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.33 (t, J = 12.8 Hz, 1H), 1.24 (td, J = 13.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.5, 132.4, 128.4, 65.7, 52.7, 52.6, 38.5, 37.1, 36.3, 27.0, 25.6, 18.0; IR (neat) 3525, 3468, 3447, 2953, 2929, 2857, 1734, 1435, 1311, 1242, 1213, 1193, 1174, 1121 cm^{-1}; MS (m/z, rel intensity) 270 (M$^+$, 1), 253 (8), 252 (29), 239 (4), 221 (7), 207 (9), 194 (17), 193 (100), 192 (85), 177 (28), 149 (27), 133 (81), 105 (12), 91 (22), 59 (12); HRMS (EI) calcd for $C_{14}H_{22}O_5$ [M$^+$] 270.1467, found 270.1464.

(3*R,5*S**)-Dimethyl 3-(cyclohexylidenemethyl)-5-hydroxycyclohexane-1,1-dicarboxylate (2f):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 8.6 Hz, 1H), 4.22−4.20 (m, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.00−2.91 (m, 1H), 2.52 (dd, J = 14.6, 2.9 Hz, 1H), 2.28 (td, J = 13.6,1.8 Hz, 1H), 2.21−2.19 (m, 2H), 2.05−2.00 (m, 3H), 1.97 (dd, J = 14.6, 2.9 Hz, 1H), 1.77 (d, J = 13.7 Hz, 1H), 1.54−1.50 (m, 6H), 1.34 (t, J = 12.9 Hz, 1H), 1.26 (td, J = 12.8, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.5, 140.7, 125.2, 65.8, 52.8, 52.7, 52.6, 38.9, 37.7, 37.0, 36.3, 29.2, 28.7, 28.1, 26.9, 26.0; IR (neat) 3520, 2926, 2851, 1732, 1433, 1242, 1213, 1194, 1179, 1138, 1119 cm^{-1}; MS (m/z, rel intensity) 310 (M$^+$, 1), 292 (30), 278 (18), 260 (8), 234 (22), 233 (72), 217 (13), 174 (18), 173 (100), 172 (28), 151 (32), 137 (31), 97 (23), 95 (28), 93 (33), 91 (75), 79 (71), 67 (52), 59 (81), 41 (74); HRMS (EI) calcd for $C_{17}H_{26}O_5$ [M$^+$] 310.1780, found 310.1778.

(3*S,4a*R**,8a*S**)-Dimethyl 2,3,4,4a,8,8a-hexahydro-3-hydroxynaphthalene-1,1(7*H*)-dicarboxylate (2g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (d, J = 3.0 Hz, 2H), 4.18−4.14 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.91 (d, J = 13.0 Hz, 1H), 2.69 (d, J = 13.4 Hz, 1H), 2.45 (d, J = 14.8 Hz, 1H), 2.14−2.04 (m, 3H), 1.73 (d, J = 14.2 Hz, 1H), 1.52−1.47 (m, 1H), 1.40 (td, J = 14.1, 2.6 Hz, 1H), 1.10−1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.6, 131.5, 125.8, 65.6, 55.9, 52.5, 52.4, 36.7, 34.8, 32.9, 27.9, 26.2, 19.4; IR (neat) 3522, 3435, 3018, 2945, 2936, 1732, 1435, 1267, 1238, 1194, 1178, 1159, 1117, 1072, 1053 cm^{-1}; MS (m/z, rel intensity) 268 (M$^+$, 20), 267 (71), 252 (20), 251 (100), 250 (21), 235 (25), 219 (28), 207 (40), 192 (12), 191 (62), 187 (22), 175 (18), 147 (19), 105 (14), 85 (9), 71 (12), 57 (11), 43 (6); HRMS (EI) calcd for $C_{14}H_{20}O_5$ [M$^+$] 268.1311, found 268.1313.

(3*S,5*R**)-Dimethyl 3-hydroxy-3-methyl-5(*E*)-styrylcyclohexane-1,1-dicarboxylate (2h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5H), 6.44 (d, J = 15.9 Hz, 1H), 6.10 (dd, J = 16.0, 7.0 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.95−2.86 (m, 1H), 2.54 (td, J = 13.3, 1.7 Hz, 1H), 2.48 (td, J = 14.4, 2.2 Hz, 1H), 1.89 (d, J = 14.4 Hz, 1H), 1.82 (td, J = 13.4, 1.7 Hz, 1H), 1.69 (br, 1H), 1.40 (t, J = 12.8 Hz, 1H), 1.30 (s, 3H), 1.26 (t, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 172.5, 137.6, 134.1, 128.9, 128.5, 127.1, 126.0, 69.5, 53.8, 52.8, 52.7, 44.2, 42.0, 36.4, 33.0, 31.7; IR (neat) 3520, 2953, 2926, 2849, 1732, 1449, 1433, 1377, 1314, 1252, 1217, 1179, 1150, 966, 746, 694 cm^{-1}; MS (m/z, rel intensity) 332 (M$^+$, 1), 314 (48), 300 (5), 254 (67), 239 (5), 223 (18), 195 (100), 176 (15), 163 (21), 129 (32), 115 (28), 104 (29), 91 (63), 77 (12), 59 (19), 43 (85), 29 (6); HRMS (EI) calcd for $C_{19}H_{24}NaO_5$ [M$^+$] 355.1516, found 355.1515.

(3*S,5*R**)-Dimethyl 3-hydroxy-3-methyl-5-(2-methylprop-1-enyl)cyclohexane-1,1- dicarboxylate (2i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.99−2.89 (m, 1H), 2.41 (td, J = 14.4, 2.3 Hz, 1H), 2.31 (td, J = 13.3, 1.8 Hz, 1H), 1.86 (d, J = 14.4 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.65−1.62 (m, 2H), 1.25 (s, 3H), 1.18 (t, J = 12.8 Hz, 1H), 1.11 (t, J = 12.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.6, 132.4, 128.4, 69.5, 53.8, 52.7, 52.5, 44.6, 41.9, 36.9, 31.7, 29.0, 25.6, 18.0; IR (neat) 3525, 2960, 2927, 2852, 1728, 1433, 1379, 1250, 1171, 1138, 943 cm^{-1}; MS (m/z, rel intensity) 285 ([M + 1]$^+$, 100), 270 (61), 252 (29), 267 (38), 253 (5), 236 (1), 224 (1), 218 (1), 180 (1), 168 (1); HRMS (EI) calcd for $C_{15}H_{24}O_5$ [M + 1]$^+$ 285.1702, found 285.1688.

(3*R,5*S**)-Dimethyl 3-hydroxy-3,4- dimethyl-5(*E*)-styrylcyclohexane-1,1-dicarboxylate (2j):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 7.1 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 5.93 (dd, J = 15.8, 9.1 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 2.64−2.55 (m, 1H), 2.50 (dd, J = 14.5, 2.6 Hz, 1H), 2.44 (td, J = 13.3, 3.1 Hz, 1H), 2.02 (d, J = 14.5 Hz, 1H), 1.55 (br, 1H), 1.51 (t, J = 12.4 Hz, 1H), 1.27 (s, 3H), 0.94 (dd, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 172.5, 137.6, 133.8, 131.1, 128.5, 127.1, 126.1, 71.0, 53.2, 52.8, 52.5, 44.3, 43.8, 40.5, 37.8, 29.3, 12.2; IR (neat) 3530, 2954, 2926, 1730, 1447, 1250, 1177, 1150, 746, 694 cm^{-1}; MS (m/z, rel intensity) 346 (M$^+$, 1), 329 (19), 328 (78), 314 (34), 313 (8), 282 (9), 270 (19), 269 (100), 268 (57), 253 (17), 237 (55), 209 (87), 208 (49), 177 (23), 145 (18), 129 (33), 128 (18), 91(21), 77 (4), 59 (6), 43 (12); HRMS (EI) calcd for $C_{20}H_{26}O_5$ [M$^+$] 346.1780, found 346.1784.

(3*R,5*S**)-Dimethyl 3-hydroxy-3,4-dimethyl-5-(2-methylprop-1-enyl)cyclohexane-1,1-dicarboxylate (2k):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, J = 9.2 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.69−2.60 (m, 1H), 2.45 (dd, J = 14.4, 2.6 Hz, 1H), 2.27 (td, J = 13.4, 3.2 Hz, 1H), 1.98 (d, J = 14.4 Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.43 (br, 1H), 1.26 (t, J = 12.7 Hz, 1H), 1.24 (s, 3H), 1.18−1.10 (m, 1H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.6, 132.6, 128.7, 71.1, 53.2, 52.7, 52.4, 44.8, 43.8, 37.6, 35.4, 29.3, 25.7, 18.2, 11.8; IR (neat) 3527, 2962, 2926, 2878, 2857, 1732, 1442, 1248, 1194, 1171, 1140 cm^{-1}; MS (m/z, rel intensity) 298 (M$^+$, 1), 281 (7), 280 (20), 266 (10), 265 (6), 234 (10), 222 (17), 221 (100), 220 (35), 205 (24), 177 (13), 165 (62), 145 (83), 119 (13), 113 (16), 83 (19), 81 (9), 79 (7), 55 (7), 43 (14); HRMS (EI) calcd for $C_{16}H_{26}O_5$ [M$^+$] 298.1780, found 298.1782.

(3*R,5*S**)-Dimethyl 3-hydroxy-4-methyl-5(*E*)-styrylcyclohexane-1,1-dicarboxylate (2p): .** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 5.95 (dd, J = 15.8, 8.9 Hz, 1H), 3.99−3.96 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.67 (td, J = 14.6, 2.8 Hz, 1H), 2.59 (d, J = 11.9 Hz, 1H), 2.45 (td, J = 13.6, 2.9 Hz, 1H), 2.07 (dd, J = 14.6, 2.6 Hz, 1H), 1.91 (br, 1H), 1.56 (t, J = 12.8 Hz, 1H), 1.47−1.39 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 172.5, 137.6, 133.8, 131.1, 128.5, 127.1, 126.1, 71.0, 53.2, 52.8, 52.5, 44.3, 43.8, 40.5, 37.8, 29.3, 12.2; IR (neat) 3540, 3469, 3024, 2955, 2930, 2872, 1732, 1447, 1302, 1248, 1204, 1167, 1130, 1063, 966, 932, 746, 694 cm^{-1}; MS (m/z, rel. intensity) 332 (M$^+$, 1), 315 (17), 314 (59), 300 (21), 269 (5), 256 (9), 255 (44), 254 (100), 239 (18), 223 (19), 196 (14), 195 (87), 179 (26), 165 (12), 145 (14), 129 (41), 115 (37), 91(29), 77 (7), 59 (13), 41 (5); HRMS (EI) calcd for $C_{19}H_{24}O_5$ [M$^+$] 332.1624, found 332.1620.

(3*R,4*R**,5*S**)-Dimethyl 3-hydroxy-4-methyl-5-(2-methylprop-1-en-1-yl)cyclohexane-1,1-dicarboxylate (2q):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 9.2 Hz, 1H), 3.95−3.92 (m, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.70−2.59 (m, 2H), 2.27 (td, J = 13.5, 3.3 Hz, 1H), 2.04

(dd, J = 14.6, 2.6 Hz, 1H), 1.80 (br, 1H), 1.70 (d, J = 1.3 Hz, 3H), 1.69 (d, J = 1.2 Hz, 3H), 1.33−1.27 (m, 2H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.6, 132.9, 128.1, 70.2, 52.7, 52.5, 52.4, 40.8, 37.6, 33.3, 25.7, 18.2, 15.9; IR (neat) 3537, 2959, 2930, 2872, 1734, 1447, 1242, 1207, 1163, 1128,1069 cm^{-1}; MS (m/z, rel intensity) 284 (M^+, 1), 267 (8), 266 (30), 252 (4), 227 (5), 209 (6), 208 (13), 207 (87), 206 (100), 191 (27), 175 (10), 151 (25), 147 (58), 145 (19), 119 (11), 113 (14), 105 (16), 91 (12), 69 (10), 59 (12); HRMS (EI) calcd for $C_{15}H_{24}O_5$ [M^+] 284.1624, found 284.1627.

(3*S,5*R**)-5(*E*)-Styryl-1-tosylpiperidin-3-ol (2m):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.32−7.21 (m, 5H), 6.46 (d, J = 16.0 Hz, 1H), 5.98 (dd, J = 16.0, 7.1 Hz, 1H), 3.96−3.88 (m, 2H), 3.78 (dd, J = 11.2, 3.6 Hz, 1H), 2.63−2.56 (m, 1H), 2.44 (s, 3H), 2.18−2.15 (m, 1H), 2.05 (d, J = 10.6 Hz, 1H), 2.00 (d, J = 11.2 Hz, 1H), 1.70 (br, 1H), 1.15 (q, J = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 136.8, 133.4, 131.1, 129.8, 129.3, 128.6, 127.6, 126.1, 66.7, 52.2, 50.5, 39.2, 37.9, 21.5; IR (neat) 3369, 2955, 2924, 2857, 1726, 1163, 912, 746 cm^{-1}; MS (m/z, rel intensity) 357 (M^+, 100), 340 (5), 326 (1), 312 (1), 297 (5), 286 (5), 284 (14), 271 (5), 222 (10), 220 (22), 184 (22), 156 (8), 155 (33), 130 (9), 129 (13), 115 (14), 91 (34), 65 (5), 43 (2); HRMS (EI) calcd for $C_{20}H_{23}NO_3S$ [M^+] 357.1399, found 357.1401.

(3*S,5*R**)-5-((*E*)-Pent-1-enyl)-1-tosylpiperidin-3-ol (2n):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.51 (td, J = 14.4, 6.8 Hz, 1H), 5.16 (dd, J = 15.4, 7.0 Hz, 1H), 3.91−3.82 (m, 2H), 3.67 (dd, J = 11.4, 4.1 Hz, 1H), 2.44 (s, 3H), 2.40−2.35 (m, 1H), 2.06−2.02 (m, 1H), 2.00−1.86 (m, 4H), 1.64 (d, J = 4.2 Hz, 1H), 1.35 (sext, J = 7.4 Hz, 2H), 1.00 (dd, J = 23.0, 12.0 Hz, 1H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 133.5, 132.0, 129.7, 129.6, 127.6, 66.8, 52.2, 50.7, 39.5, 37.5, 34.6, 22.4, 21.5, 13.6; IR (neat) 3261, 2918, 2931, 2855, 1342, 1165, 1090, 1042, 988, 810, 664, 576 cm^{-1}; MS (m/z, rel intensity) 323 (M^+, 61), 306 (14), 286 (19), 284 (58), 271 (12), 198 (39), 186 (80), 155 (38), 150 (28), 91 (78), 79 (21), 65 (17), 55 (8), 42 (13); HRMS (EI) calcd for $C_{17}H_{25}NO_3S$ [M^+] 323.1555, found 323.1551.

(1*R,3*R**,5*S**)-Methyl 7-oxo-3(*E*)-styryl-6-oxabicyclo[3.2.1]-octane-1-carboxylate (3a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 6.44 (d, J = 15.8 Hz, 1H), 6.08 (dd, J = 15.8, 7.2 Hz, 1H), 4.96 (t, J = 5.4 Hz, 1H), 3.81 (s, 3H), 2.96−2.92 (m, 1H), 2.51 (dd, J = 13.3, 5.8 Hz, 1H), 2.24 (td, J = 10.6, 4.8 Hz, 1H), 1.94 (d, J = 11.6 Hz, 1H), 1.71 (t, J = 13.0 Hz, 1H), 1.49 (t, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.6, 136.8, 131.2, 130.2, 128.6, 127.5, 126.1, 76.2, 52.8, 52.5, 40.9, 35.2, 34.3, 34.1; IR (neat) 3520, 3468, 2955, 2922, 2851, 1776, 1730, 1443, 1252, 1119, 972, 749, 694 cm^{-1}; MS (m/z, rel intensity) 286 (M^+, 100), 258 (4), 242 (5), 240 (32), 226 (33), 208 (10), 183 (9), 182 (13), 181 (71), 180 (21), 141 (18), 129 (31), 91 (21), 77 (5), 59 (3); HRMS (EI) calcd for $C_{17}H_{18}O_4$ [M^+] 286.1205, found 286.1168.

(1*R,3*R**,5*S**)-Methyl 3(*E*)-(4-chlorostyryl)-7-oxo-6-oxabicyclo-[3.2.1]octane-1-carboxylate (3b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H), 6.40 (dd, J = 15.8, 1.0 Hz, 1H), 6.05 (dd, J = 15.8, 7.2 Hz, 1H), 4.96 (t, J = 5.4 Hz, 1H), 3.81 (s, 3H), 2.94 (tdd, J = 11.5, 6.2, 2.2 Hz, 1H), 2.79−2.69 (m, 1H), 2.51 (dd, J = 13.3, 5.8 Hz, 1H), 2.27−2.21 (m, 1H), 1.94 (d, J = 11.6 Hz, 1H), 1.69 (t, J = 12.8 Hz, 1H), 1.48 (t, J = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.6, 135.3, 133.1, 131.9, 129.1, 128.7, 127.4, 76.1, 52.9 52.5, 40.9, 35.1, 34.3, 34.0; IR (neat) 3524, 3468, 2951, 2897, 1732, 1491, 1452, 1435, 1314, 1252, 1213, 1184, 1126, 1092, 968, cm^{-1}; MS (m/z, rel intensity) 352 (M^+, 1), 336 (11), 334 (31), 320 (10), 289 (4), 277 (9), 276 (22), 275 (27), 274 (74), 260 (7), 239 (9), 217 (29), 215 (100), 214 (11), 179 (23), 138 (14), 125 (23), 97 (5), 69 (4), 59 (6); HRMS (EI) calcd for $C_{18}H_{21}O_5$ ^{35}Cl [M^+] 352.1078, found 352.1076.

(1*R,3*R**,5*S**)-Methyl 3(*E*)-(3,4,5-trimethoxystyryl)-7-oxo-6-oxabicyclo[3.2.1]octane-1-carboxylate (3c):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 2H), 6.37 (d, J = 15.7 Hz, 1H), 6.00 (dd, J = 15.8, 7.2 Hz, 1H), 4.97 (t, J = 5.2 Hz, 1H), 3.8 (s, 6H), 3.84 (s, 3H), 3.81 (s, 3H), 2.97−2.92 (m, 1H), 2.80−2.69 (m, 1H), 2.52 (dd, J = 13.2, 5.9 Hz, 1H), 2.28−2.22 (m, 1H), 1.94 (d, J = 11.6 Hz, 1H), 1.71 (t, J = 12.8 Hz, 1H), 1.49 (t, J = 12.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 169.6, 153.4, 132.5, 130.7, 130.2, 103.5, 76.1, 60.9, 56.2, 52.9, 52.6, 41.0, 35.3, 32.3, 34.2; IR (neat) 2955, 2928, 1778, 1732, 1582, 1246, 1125 cm^{-1}; MS (m/z, rel intensity) 376 (M^+, 100), 361 (9), 334 (11), 326 (8), 285 (8), 245 (5), 231 (9), 218 (11), 181 (14), 153 (3), 115 (3), 91 (3), 59 (1); HRMS (EI) calcd for $C_{20}H_{24}O_7$ [M^+] 376.1522, found 376.1516.

(1*R,3*R**,5*S**)-Methyl 7-oxo-3-((*E*)-pent-1-enyl)-6-oxabicyclo-[3.2.1]octane-1-carboxylate (3d):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (td, J = 15.3, 6.8 Hz, 1H), 5.29 (dd, J = 15.3, 7.0 Hz, 1H), 4.90 (t, J = 5.4 Hz, 1H), 3.79 (s, 3H), 2.92−2.86 (m, 1H), 2.57−2.46 (m, 1H), 2.40 (dd, J = 13.3, 5.8 Hz, 1H), 2.16−2.10 (m, 1H), 1.96 (dd, J = 14.0, 7.0 Hz, 2H), 1.88 (d, J = 11.5 Hz, 1H), 1.56 (t, J = 12.8 Hz, 1H), 1.41−1.32 (m, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.8, 131.6, 131.1, 52.8, 52.6, 41.0, 35.6, 34.5, 34.4, 34.0, 22.4, 13.5; IR (neat) 3530, 3429, 2953, 2926, 1730, 1437, 1244, 1217, 1120 cm^{-1}; MS (m/z, rel intensity) 252 (M^+, 72), 235 (2), 234 (10), 221 (20), 209 (28), 208 (78), 206 (100), 193 (82), 192 (78), 177(87), 149 (39), 147 (86), 137 (71), 107 (28), 105 (41), 91 (50), 79 (41), 67 (28), 54 (16), 41 (25); HRMS (EI) calcd for $C_{14}H_{20}O_4$ [M^+] 252.1362, found 252.1359.

(1*R,3*R**,5*S**)-Methyl 3-(2-methylprop-1-enyl)-7-oxo-6-oxabicyclo[3.2.1]octane-1-carboxylate (3e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, J = 8.6 Hz, 1H), 4.89 (t, J = 5.4 Hz, 1H), 3.79 (s, 3H), 2.91−2.87 (m, 1H), 2.82−2.71 (m, 1H), 2.32 (dd, J = 13.5, 5.5 Hz, 1H), 2.07 (td, J = 13.6, 5.5 Hz, 1H), 1.89 (d, J = 11.5 Hz, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.49 (t, J = 12.8 Hz, 1H), 1.27 (t, J = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.8, 133.6, 126.3, 76.5, 52.8, 52.6, 41.0, 35.6, 34.4, 30.1, 25.7, 17.9; IR (neat) 3454, 2957, 2924, 1780, 1738, 1737, 1440, 1249, 1115, 1055, 1022, 974 cm^{-1}; MS (m/z, rel intensity) 238 (M^+, 100), 224 (2), 223 (8), 207 (12), 195 (18), 194 (48), 179 (69), 178 (42), 177 (33), 163 (52), 151 (21), 137 (52), 133 (71), 119 (23), 107 (34), 93 (40), 91 (54), 82 (69), 79 (42), 67 (51), 53 (23), 41 (38); HRMS (EI) calcd for $C_{13}H_{18}O_4$ [M^+] 238.1205, found 238.1196.

(1*S,4*S**,5*aR**,9*aS**)-Methyl 2-oxo-1,2,4,5,5a,8,9,9a-octahydro-1,4-methanobenzo[*d*]oxepine-1-carboxylate (3g):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77−5.75 (m, 1H), 5.59−5.56 (m, 1H), 4.85 (t, J = 5.4 Hz, 1H), 3.81 (s, 3H), 2.76 (dd, J = 12.2, 6.1 Hz, 1H), 2.62−2.57 (m, 1H), 2.51−2.44 (m, 1H), 2.17−2.08 (m, 4H), 1.57−1.44 (m, 2H), 1.37 (t, J = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 169.1, 128.6, 127.3, 76.3, 57.3, 52.9, 37.1, 33.9, 31.8, 30.6, 25.4, 20.1; IR (neat) 2951, 2928, 1776, 1736, 1256, 1238, 1155, 964 cm^{-1}; MS (m/z, rel. intensity) 236 (M^+, 10), 219 (4), 218 (18), 205 (15), 190 (10), 186 (17), 177 (12), 163 (8), 161 (17), 160 (25), 158 (100), 140 (54), 133 (41), 131 (33), 118 (31), 108 (23), 92 (8), 91 (53), 79 (27), 77 (18), 59 (8), 53 (6); HRMS (EI) calcd for $C_{13}H_{16}O_4$ [M^+] 236.1049, found 236.1051.

(1*R,3*R**,5*S**)-Methyl 5-methyl-7-oxo-3(*E*)-styryl-6-oxabicyclo-[3.2.1]octane-1- carboxylate (3h):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 6.44 (d, J = 15.8 Hz, 1H), 6.06 (dd, J = 15.9, 7.2 Hz, 1H), 3.81 (s, 3H), 2.75−2.65 (m, 2H), 2.51 (dd, J = 13.2, 5.7 Hz, 1H), 2.09 (dd, J = 13.8, 5.8 Hz, 1H), 1.92 (d, J = 11.6 Hz, 1H), 1.64 (t, J = 12.7 Hz, 1H), 1.55 (s, 3H), 1.47 (t, J = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.6, 136.9, 131.2, 130.3, 128.6, 127.5, 126.2, 83.6, 55.1, 52.8, 46.4, 40.4, 35.3, 34.7, 24.9; IR (neat) 2974, 2953, 2930, 2853, 1776, 1738, 1449, 1331, 1260, 1246, 1134, 1113, 1018, 964, 750, 694 cm^{-1}; MS (m/z, rel intensity) 300 (M^+, 100), 285 (1), 269 (5), 268 (10), 256 (22), 254 (25), 241 (31), 223 (13), 211 (28), 195 (61), 181 (11), 169 (12), 165 (17), 141 (18), 130 (39), 129 (52), 115 (41), 104 (16), 91 (40), 77 (11), 59 (8), 51 (3); HRMS (EI) calcd for $C_{18}H_{20}O_4$ [M^+] 300.1362, found 300.1350.

(1*R,3*R**,5*S**)-Methyl 5-methyl-3-(2-methylprop-1-enyl)-7-oxo-6-oxabicycle[3.2.1]octane-1-carboxylate (3i):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, J = 8.8 Hz, 1H), 3.78 (s, 3H), 2.77−2.66 (m, 1H), 2.61 (td, J = 11.5, 2.3 Hz, 1H), 2.31 (dd, J = 13.2, 5.2 Hz, 1H), 1.91 (dd, J = 13.9, 6.0 Hz, 1H), 1.87 (d, J = 11.5 Hz, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.49 (s, 3H), 1.42 (t, J = 12.8 Hz, 1H), 1.25 (t, J = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 169.7, 133.5, 126.3, 55.2, 52.7, 46.4, 40.8, 35.0, 31.1, 25.6, 24.8, 17.9; IR (neat) 2972, 2955, 2930, 1778, 1738, 1281, 1261, 1142, 1115, 1018 cm^{-1}; MS (*m*/*z*, rel intensity) 252 (M^+, 61), 238 (2), 237 (12), 222 (4), 221 (17), 220 (59), 208 (57), 193 (100), 192 (29), 191 (12), 177 (43), 163 (95), 151 (55), 149 (52), 147 (32), 135 (22), 121 (20), 107 (32), 91 (28), 82 (51), 67 (23), 59 (9), 43 (21); HRMS (EI) calcd for $C_{14}H_{20}O_4$ [M^+] 252.1362, found 252.1356.

(1*R,3*S**,4*R**,5*R**)-Methyl 4-methyl-3-(2-methylprop-1-en-1-yl)-7-oxo-6-oxabicyclo[3.2.1]octane-1-carboxylate (3q): .** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, J = 9.0 Hz, 1H), 4.61 (d, J = 6.3 Hz, 1H), 3.78 (s, 3H), 2.91 (ddd, J = 11.6, 6.3, 2.7 Hz, 1H), 2.35−2.24 (m, 2H), 1.93 (d, J = 11.6 Hz, 1H), 1.71 (s, 3H), 1.60 (s, 3H), 1.53−1.46 (m, 1H), 1.44−1.40 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 169.8, 134.5, 126.1, 81.5, 52.8, 52.6, 41.2, 39.6, 37.3, 35.4, 25.8, 18.2, 16.8; IR (neat) 2959, 2916, 2874, 2851, 1773, 1319, 1296, 1256, 1238, 1126, 1088, 964, 932, 920 cm^{-1}; MS (*m*/*z*, rel intensity) 252 (M^+, 100), 237 (4), 221 (15), 220 (17), 208 (44), 193 (64), 192 (38), 177 (43), 165 (63), 151 (51), 147 (41), 137 (21), 121 (25), 109 (38), 93 (38), 82 (77), 81 (32), 67 (28), 55 (16), 41 (17); HRMS (EI) calcd for $C_{14}H_{20}O_4$ [M^+] 252.1362, found 252.1364.

(3*S,5*R**)-3-Methoxy-5-((*E*)-styryl)-1-tosylpiperidine (6):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.34−7.27 (m, 6H), 7.25−7.22 (m, 1H), 6.45 (d, J = 15.9 Hz, 1H), 5.97 (dd, J = 16.0, 7.2 Hz, 1H), 4.08 (dd, J = 10.8, 4.6 Hz, 1H), 3.80 (dd, J = 11.4, 4.2 Hz, 1H), 3.48−3.43 (m, 1H), 3.41 (s, 3H), 2.60−2.52 (m, 1H), 2.44 (s, 3H), 2.24 (d, J = 12.4 Hz, 1H), 1.96 (d, J = 11.1 Hz, 1H), 1.91 (d, J = 10.4 Hz, 1H), 1.04 (q, J = 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ143.7, 136.8,133.3, 131.0, 129.7, 129.4, 128.6, 127.6, 126.2, 75.3, 56.7, 50.9, 49.6, 37.9, 36.3, 21.5; IR (neat) 2924, 2851, 1346, 1170, 1155, 1090, 748, 662 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}NO_3S$ [$M + 1$]$^+$ 372.1633, found 372.1636.

(3*S,5*R**)-3-(Allyloxy)-5-((*E*)-styryl)-1-tosylpiperidine (7):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.34−7.27 (m, 6H), 7.24−7.21 (m, 1H), 6.44 (d, J = 16.0 Hz, 1H), 6.00 (dd, J = 15.9, 7.2 Hz, 1H), 5.94−5.85 (m, 1H), 5.29 (dd, J = 17.2, 1.5 Hz, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H), 4.07 (dd, J = 5.6 Hz, 2H), 4.05 (dd, J = 11.6, 8.2 Hz, 1H), 3.80 (dd, J = 11.3, 4.1 Hz, 1H), 3.62−3.55 (m, 1H), 2.60−2.52 (m, 1H), 2.43 (s, 3H), 2.22 (d, J = 12.4 Hz, 1H), 1.99 (d, J = 10.6 Hz, 1H), 1.93 (d, J = 11.3 Hz, 1H), 1.10 (q, J = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ143.7,136.8, 134.6, 133.3, 131.0, 129.7, 129.4, 128.6, 127.6, 126.2, 117.3, 73.3, 70.0, 50.9, 50.0, 38.0, 36.7, 21.5; IR (neat) 2925, 2854, 1344, 1169, 1157, 1090, 991, 912, 699 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{28}NO_3S$ [$M + 1$]$^+$ 398.1790, found 398.1793.

(3*S,5*S**)-3-Chloro-5-((*E*)-styryl)-1-tosylpiperidine (8):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.31−7.21 (m, 5H), 6.45 (d, J = 16.0 Hz, 1H), 5.93 (dd, J = 16.0, 7.3 Hz, 1H), 4.15 (dd, J = 11.3, 4.7 Hz, 1H), 4.04−3.97 (m, 1H), 3.86 (dd, J = 11.6, 4.2 Hz, 1H), 2.68−2.58 (m, 1H), 2.45 (s, 3H), 2.42−2.38 (m, 1H), 2.27 (t, J = 11.2 Hz, 1H), 2.00 (t, J = 11.5 Hz, 1H), 1.15 (q, J = 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 136.6, 133.6, 131.6, 129.9, 128.6, 128.4, 127.8, 126.2, 76.7, 53.1, 52.7, 50.4, 40.7, 39.6, 21.5; IR (neat) 2955, 2924, 2857, 1726, 1163, 912, 749 cm^{-1}; MS (*m*/*z*, rel intensity) 375 (M^+, 100), 340 (5), 284 (12), 220 (21), 184 (21), 155 (32), 129 (11), 115 (13), 91 (32), 65 (3), 43 (5); HRMS (EI) calcd for $C_{20}H_{22}ClNO_2S$ [M^+] 375.1060, found 375.1.

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Supporting Information Available: Detailed experimental procedures, detailed spectral data for products, and two crystal structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.