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$Hg(OTf)_2$-Catalyzed Vinylogous Semi-Pinacol Rearrangement Leading to 1,4-Dihydroquinolines

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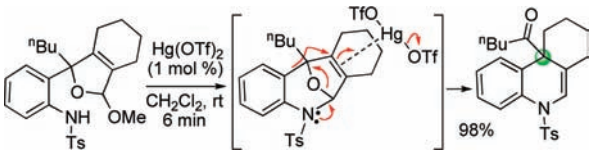
ABSTRACT



An efficient method for the construction of dihydroquinoline derivatives possessing a quaternary carbon center is developed by an application of $Hg(OTf)_2$-catalyzed vinylogous semi-pinacol-type rearrangement. The reaction was found to be specifically catalyzed by mercury salt and to proceed via a bicyclic aminal.

Catalytic synthesis of hydroquinoline derivatives, which are commonly found in biologically active compounds, is of great interest for academic and industrial research.[1] The transition-metal-catalyzed syntheses of hydroquinoline derivatives have been mainly based on (i) a direct addition of the anilino nitrogens to inner alkynes and alkenes,[2] (ii) aza-Michael addition of anilinoenone derivatives,[3] (iii) Friedel–Crafts type cyclization of *N*-alkenyl and alkynyl anilines,[4] (iv) intramolecular coupling of 2-haloaniline derivatives,[5] and so on[6] (Scheme 1). We also recently reported the $Hg(OTf)_2$-catalyzed cyclization of *N*-tosylanilino allylic alcohol or methyl vinyl ether giving rise to 1,2,3,4-tetrahydroquinoline derivatives or 1,4-dihydroquinoline derivatives, respectively.[7] However, although the 1,2,3,4-tetrahydroquinoline derivatives were obtained in excellent yield at room temperature, the cyclization reaction leading to 1,4-dihydroquinoline derivative did not proceed smoothly even at 110 °C in toluene. Similarly, although many examples of the catalytic synthesis of hydroquinoline derivatives have been reported,[2−6] there have been few examples of the 1,4-dihydroquinoline derivatives.[8]

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(1) (a) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5.06, p 245. (b) Patil, N. T.; Singh, V. *J. Organomet. Chem.* **2011**, *696*, 419. (c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(2) For selected recent examples: (a) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron* **2011**, *67*, 1501. (b) Okuro, K.; Alper, H. *Tetrahedron Lett.* **2010**, *51*, 4959. (c) Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010**, *12*, 4110. (d) Han, Z.-Y.; Chen, Z.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182.

(3) For selected recent examples: (a) Liu, X.; Lu, Y. *Org. Lett.* **2010**, *12*, 5592. (b) Saito, A.; Kasai, J.; Fukaya, H.; Hanazawa, Y. *J. Org. Chem.* **2009**, *74*, 5644. (c) Lee, J. I.; Youn, J. S. *Bull. Korean Chem. Soc.* **2008**, *29*, 1853. (d) Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63.

(4) (a) Giera, D. S.; Schneider, C. *Org. Lett.* **2010**, *12*, 4884. (b) Sizhuo, K. X.; Li, W. P.; Li, X.; Yang, Z.; An, X.; Guo, C.-C.; Tan, Z. *Tetrahedron Lett.* **2010**, *51*, 4466. (c) Youn, S. W.; Pastline, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

(5) For selected recent examples: (a) Lu, Z.; Hu, C.; Guo, J.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 480. (b) Liu, P.; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 2307. (c) Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72. (d) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

(6) (a) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (b) Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87.

(7) Namba, K.; Nakagawa, Y.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Synlett* **2008**, 1719.

(8) (a) Watanabe, T.; Oishi, T.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821. (b) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494.

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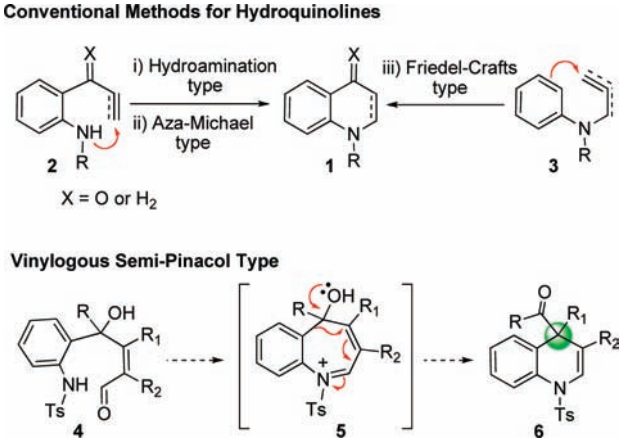
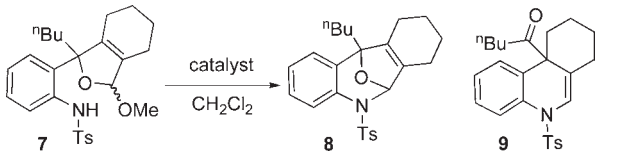
Furthermore, a common synthetic method based on the reduction of the quinolines can only be applied to a limited range of substrates.[9] Therefore, we attempted to establish an efficient catalytic method for the preparation of 1,4-dihydroquinoline derivatives using a new approach distinct from the conventional methods described above. Our plan was to apply vinylogous semi-pinacol rearrangement[10] to *N*-tosylanilinoenal derivatives **4**. It was expected that the metal-catalyzed direct addition of a sulfonamide group to the alkene would be prevented due to the steric hindrance, and seven-membered ring intermediate **5** would be formed by the condensation of sulfonamide with aldehyde. The iminium cation **5** was considered to have undergone the rearrangement to give the 1,4-dihydroquinoline derivatives **6** as depicted in Scheme 1. It is especially noteworthy that the rearrangement reaction simultaneously constructed a quaternary carbon center at the C4 position. Although there have been several examples of the synthesis of 1,4-dihydroquinolines possessing a quaternary carbon center at the C4 position,[11] the development of the catalytic synthesis is a challenging subject. Thus, we describe herein the efficient catalytic synthesis of 1,4-dihydroquinoline derivatives possessing a quaternary carbon center.

Scheme 1. Synthetic Approach to the 1,4-Dihydroquinolines



We began the investigation of the vinylogous semi-pinacol rearrangement reaction with acetal **7** due to its ready availability. In fact, we were able to obtain acetal **7** from 2-cyano-*N*-tosylaniline in just two steps (see Supporting Information). Treatment of the acetal **7** with 10 mol % of $TiCl_4$ as a typical Lewis acid at 40 °C afforded a hemiaminal **8** in quantitative yield, and the rearrangement product **9** was not detected (Table 1, entry 1). Although the $TiCl_4$ induced

Table 1. Investigation of the Catalysts Leading to 1,4-Dihydroquinoline **9**



					yield[a]	
entry	catalyst	mol %	temp (°C)	time (h)	**8**	**9**
1	$TiCl_4$	10	40	6	quant	
2	$EtAlCl_2$	5	40	6.5	81	
3	$BF_3 \cdot OEt_2$	10	40	6	81	
4[c]	TMSOTf	10	40	4.5	82	8
5	$Sc(OTf)_3$	5	40	11	98	
6	$Cu(OTf)_2$	5	40	6	95	
7	AgOTf	10	40	7	96	
8[b,c]	$PdCl_2(MeCN)_2$	50	70	28	67	33
9	$Hg(OTFA)_2$	10	40	9		90
10	$Hg(OTf)_2$	1	rt	0.1		98
11	TfOH	1	rt	5.5	80	
12	$AuClPPh_3/AgSbF_6$	5	rt	24	89	

[a] Isolated yield. [b] The reaction was conducted in THF. [c] NMR yield using pyrazine as an internal standard.

the condensation to give hemiaminal **8**, formation of the iminium cation **5** was not straightforward. Similarly, the use of other catalysts such as $EtAlCl_2$, $BF_3 \cdot OEt_2$, $Sc(OTf)_3$, $Cu(OTf)_2$, and AgOTf also gave only hemiaminal **8** (entries 2, 3, 5, 6, 7), and the case of TMSOTf and 50 mol % of $PdCl_2(MeCN)_2$ at 70 °C provided a small amount of **9** along with hemiaminal **8** (entries 4, 8). In clear contrast, treatment of the acetal **7** with 10 mol % of mercury trifluoroacetate at 40 °C afforded **9** in 90% yield (entry 9). Furthermore, when $Hg(OTf)_2$ was used as a highly reactive mercury salt, the rearrangement reaction proceeded smoothly even under the condition of 1 mol % of $Hg(OTf)_2$ at room temperature to give **9** in 98% yield (entry 10). Additionally, treatment of **7** with 1 mol % of TfOH afforded only hemiaminal **8**, indicating that the $Hg(OTf)_2$ is the real catalytic species of this rearrangement reaction (entry 11). Finally, we examined a gold catalyst because its reactivity is similar to that of the mercury catalyst. However, the gold catalyst gave only the hemiaminal **8**, and the formation of **9** was not detected (entry 12). Therefore, we found that the rearrangement reaction of acetal **7** leading to dihydroquinoline derivatives **9** is the particular reaction of mercury catalysts. Recently, mercury catalysis has demonstrated their unieque powerfulness in a variety of transformations.[12] This vinylogous semi-pinacol

(9) Rabideau, P. W.; Marcinow, Z. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1992; 42, pp 3−320.

(10) For selected examples of semi-pinacol rearrangement: (a) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523. (b) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed* **2009**, *48*, 8572. (c) Wang, B.; Tu, Y.-Q. *Acc. Chem. Res.* **2011**, *44*, 1207.

(11) (a) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673. (b) Lin, H.; Ng, F. W.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 549. (c) Otsuji, Y.; Yutani, K.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 520.

(12) For a review, see: Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511. For selected recent examples: (a) Zhou, F.; Cao, Z.-Y.; Zhang, J.; Yang, H.-B.; Zhou, J. *Chem. Asisan J.* **2012**, *7*, 233. (b) Cao, Z.-Y.; Zhang, Y.; Ji, C.-B.; Zhou, J. *Org. Lett.* **2011**, *13*, 3178. (c) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178. (d) Yamamoto, H.; Sasaki, I.; Hirai, Y.; Namba, K.; Imagawa, H.; Nishizawa, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1244. (e) Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem.—Eur. J.* **2009**, *15*, 6560.

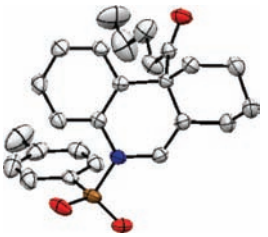
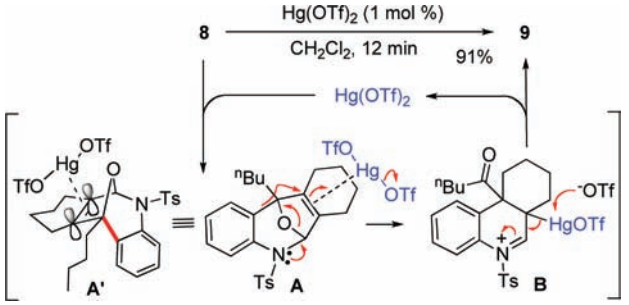


Figure 1. ORTEP of the molecular structure of **9**.

rearrangement reaction is also a good example of usefulness of mercury catalyst. The structure of **9** was unambiguously confirmed by an X-ray diffraction study (Figure 1).

Meanwhile, treatment of hemiaminal **8** with 1 mol % of $Hg(OTf)_2$ afforded **9** in 91% yield, and **8** was proven to be the intermediate of the vinylogous semi-pinacol rearrangement reaction (Scheme 2). Therefore, we proposed that the reaction is likely to be initiated from a π-complex **A**. The migration of an aryl group assisted by the electron donation of the hemiaminal moiety leads to organomercuric tosyl iminium cation **B**, which undergoes the smooth demercuration to regenerate $Hg(OTf)_2$ catalyst, and the 1,4-dihydroquinoline derivative **9** is obtained. The conformation of hemiaminal **8** is considered to be suitable for the rearrangement of aryl group due to the better orbital overlap depicted as **A′** in Scheme 2.

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Attempts at Performing Rearrangement Reactions without the Formation of Cyclic Hemiaminal

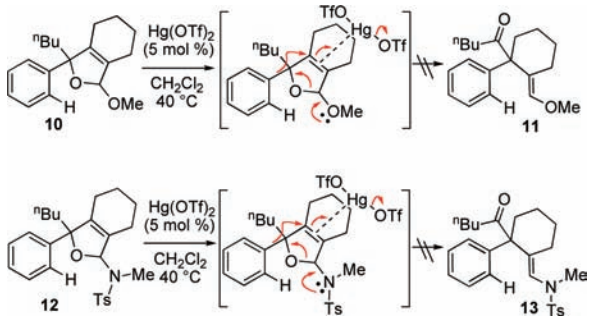
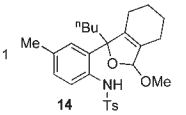
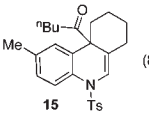
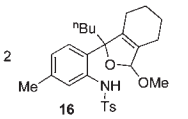
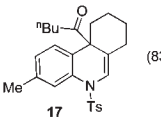
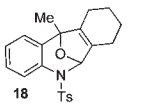
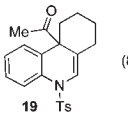
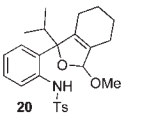
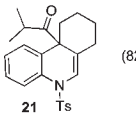
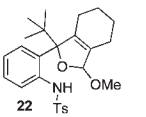
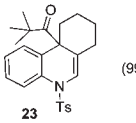
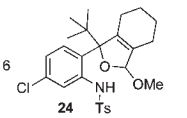
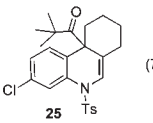
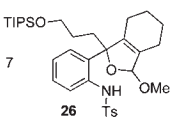
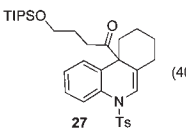
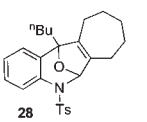
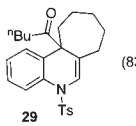
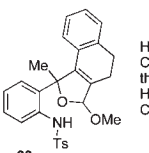
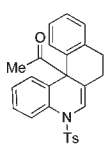
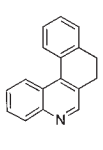
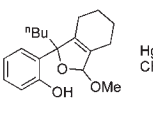
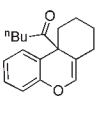
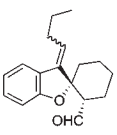
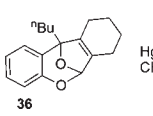


Table 2. $Hg(OTf)_2$-Catalyzed Vinylogous Semi-Pinacol Type Rearrangement of the Various Substrates

entry	substrate	condition	product (yield)	
1	 **14**	$Hg(OTf)_2$ (3 mol %) CH_2Cl_2, rt, 30 min	 **15**	(84%)
2	 **16**	$Hg(OTf)_2$ (3 mol %) CH_2Cl_2, rt, 30 min	 **17**	(83%)
3	 **18**	$Hg(OTf)_2$ (2 mol %) CH_2Cl_2, rt, 1 h	 **19**	(84%)
4	 **20**	$Hg(OTf)_2$ (2 mol %) CH_2Cl_2, rt, 1.5 h	 **21**	(82%)
5	 **22**	$Hg(OTf)_2$ (4 mol %) CH_2Cl_2, rt, 2.5 h	 **23**	(99%)
6	 **24**	$Hg(OTf)_2$ (10 mol %) toluene, 110 °C, 5 h	 **25**	(70%)
7	 **26**	$Hg(OTf)_2$ (3 mol %) $ClCH_2CH_2Cl$, 60 °C 16 min	 **27**	(40%)
8	 **28**	$Hg(OTf)_2$ (5 mol %) CH_2Cl_2, rt, 3 h	 **29**	(83%)
9	 **30**	$Hg(OTf)_2$, (1 mol %) CH_2Cl_2, rt, 30 min then $Hg(OTf)_2$, (3 mol %) CH_2Cl_2, 40 °C, 8 h	 **31** (37%)	 **32** (5%)
10	**30**	$Hg(OTf)_2$, (2 mol %) CH_2Cl_2, rt, 50 min vacuum then $Hg(OTf)_2$, (3 mol %) CH_2Cl_2, 40 °C, 30 min	**31** (85%)	**32**(ND)
11	 **33**	$Hg(OTf)_2$, (3 mol %) CH_2Cl_2, 40 °C, 3.5 h	 **34** (10%)	 **35** (43%) (E/Z = 4/1)
12	 **36**	$Hg(OTf)_2$, (3 mol %) CH_2Cl_2, rt, 3 min	**34** (97%)	**35** (trace)

Thus, we investigated the necessity of cyclic hemiaminal formation for the rearrangement (Scheme 3). Treatment of acetal **10**, not possessing a tosylamide group, with 5 mol %

of $Hg(OTf)_2$ at 40 °C for 1.5 h did not afford a rearrangement product **11**, and the starting compound **10** was recovered in 59% yield after 1.5 h. The similar reaction of hemiacetal analogue **12** also did not proceed to give **13**, although a similar electron donating effect was expected. Therefore, we confirmed that the formation of the seven-membered cyclic hemiacetal played a significant role for the rearrangement leading to the dihydroquinoline derivatives possessing a quaternary carbon center.

Having established an optimized condition for the vinylogous semi-pinacol rearrangement, we next examined the reactions with various substrates (Table 2).

The reactions of similar analogues that possess a methyl group on the aromatic ring (**14** and **16**) and other side chains such as a methyl group (**18**),[13] isopropyl group (**20**), and *tert*-butyl group (**22**) also provided the corresponding rearrangement products in good yields, although the slightly more than 1 mol % of $Hg(OTf)_2$ was needed to complete the conversion (entries 1−5). The reaction of **24** possessing an electron-withdrawing group was slow, and treatment of 10 mol % of $Hg(OTf)_2$ at 110 °C afforded the ketone **25** in 70% yield (entry 6). The reaction of triisopropylsilyl ether derivatives **26** gave the desired **27** in 40% yield, along with the byproducts derived from the desilylation of **27** (entry 7). The reaction of the seven-membered ring fused system **28** needed 5 mol % of $Hg(OTf)_2$ to give **29** in 83% yield (entry 8). The reaction of an aryl fused system **30** with 2 mol % of $Hg(OTf)_2$ at room temperature stopped at the hemiaminal due to the stability of the conjugated alkene, and an additional treatment of $Hg(OTf)_2$ at 40 °C afforded a mixture of the desired **31** and 7,8-dihydrobenzo[*k*]phenanthridine **32**[14] (entry 9). Thus, in situ-generated methanol was evacuated by a vacuum after the formation of hemiaminal, and then treatment of the additional 3 mol % of $Hg(OTf)_2$ in dichloromethane at 40 °C gave **31** in 85% yield (entry 10). Finally, we examined a similar rearrangement reaction of phenol derivatives. Treatment of **33** with 3 mol % of $Hg(OTf)_2$ afforded a small amount of rearrangement product **34** and benzofuran derivative **35** as a major product, in later of which was formed by a direct oxymercuration reaction (entry 11). Thus, the phenol **33** was first converted to bicyclic acetal **36** by treatment with PPTS before the rearrangement reaction. Treatment of bicyclic acetal **36** with 3 mol % of $Hg(OTf)_2$ at room temperature induced only the rearrangement reaction to give the desired chromene derivative **34** in 97% yield (entry 12). Thus, the rearrangement reaction of the phenol derivative was also proven to proceed via bicyclic acetal as an intermediate.

In this study, an efficient method for the construction of 1,4-dihydroquinoline and 4*H*-chromene derivatives possessing a quaternary carbon center was established. We elucidated that the reactions proceed via seven-membered bicyclic hemiaminal and are specifically catalyzed by mercury salt. Our current study clearly demonstrated that this catalytic rearrangement protocol is applicable to the various tosylanilinoallyl acetals and is a powerful synthetic method for the construction of complex carbon frameworks with similarities to natural products. The application of this rearrangement reaction is currently underway in our laboratory.

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Supporting Information Available. Experimental details, and ^1H and ^{13}C NMR spectra of each each rearrangement product. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) The methyl analogue automatically formed the cyclic hemiaminal **18** just after synthesis of the starting material.

(14) Addition of methanol to the methyl ketone moiety of **31** was assumed to induce the aromatization to give **32**. For the spectral data of **32**, see: Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2741–2744.