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A $Hg(ClO_4)_2 \cdot 3H_2O$ Catalyzed Sakurai–Hosomi Allylation of Isatins and Isatin Ketoimines Using Allyltrimethylsilane

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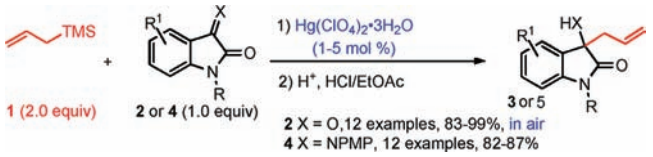
ABSTRACT



It is reported that $Hg(ClO_4)_2 \cdot 3H_2O$ could efficiently activate the cheap but less reactive allyltrimethylsilane for the allylation of isatins or isatin ketoimines, with catalyst loading down to 0.1 mol %. This is the first example of Sakurai–Hosomi allylation of ketoimines using allyltrimethylsilane. A rare example of chiral mercury catalysis is also reported.

The exploration of new catalytic properties of cheap and easily available metal salts such as iron, bismuth, and copper salts is of current interest in organic synthesis. In contrast, limited attention was paid to mercury catalysis, mainly because of the worry about its toxicity.[1] This is to some extent perplexing because mercury is still widely used for gauges, barometers, high-intensity discharge lamps, electrodes, electrical switches, and extraction of gold.[1a] In addition, mercury amalgam is a common tooth filling, and thimerosal is still used in vaccines in many countries.[1a] No convincing proof revealed that mercury-containing vaccines and mercury amalgams lead to adverse health effects.[1]

Recent studies have shown that mercury compounds have interesting properties worthwhile to explore.[2] For example, Barron reported that a stabilized arene–mercury complex could efficiently catalyze H/D exchange of C_6D_6 with arenes.[2a,b] Nishizawa had identified $Hg(OTf)_2$ as a powerful catalyst for a series of transformations,[2c,d] which had been applied to natural product synthesis. A recent example was the synthesis of hippuristanol via $Hg(OTf)_2$-catalyzed spiroketalization by Deslongchamps.[2f]

In light of these facts, we believe the discovery of new catalytic properties of mercury, an "element of mystery",[1a] is still needed. During our efforts in the synthesis of 3,3-disubstituted oxindoles for biological evaluation,[3] we had developed a highly efficient Friedel–Crafts reaction of 3-substituted 3-hydroxyoxindoles and aromatic compounds catalyzed by $Hg(ClO_4)_2 \cdot 3H_2O$.[3d] Its high efficiency results from aromatic mercuration that produces a strong acid to facilitate the generation of carbocationic intermediate and simultaneously forms the more reactive nucleophile aryl mercural. Here, we wish to report that $Hg(ClO_4)_2 \cdot 3H_2O$ could activate allyltrimethylsilane for a highly efficient allylation of isatins and isatin derived ketoimines.

The Sakurai–Hosomi allylation reaction is very useful for the synthesis of homoallylic alcohols or amines from inexpensive and nontoxic allylsilanes.[4] Although significant achievements have been made in allylation reactions

(1) (a) Clarkson, T. W.; Magos, L. *Crit. Rev. Toxicol.* **2006**, *36*, 609. (b) Doja, A.; Roberts, W. *Can. J. Neurol. Sci.* **2006**, *33*, 341.

(2) (a) Borovik, A. S.; Barron, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 3743. (b) Branch, C. S.; Barron, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 14156. (c) Yamamoto, H.; Sasaki, I.; Hirai, Y.; Namba, K.; Imagawa, H.; Nishizawa, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1244. (d) Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem.—Eur. J.* **2009**, *15*, 6560. (e) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178. (f) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420. For a review, see: (g) Nishizawa, M.; Imagawa, H.; Yamamoto, H. *Org. Biomol. Chem.* **2010**, *8*, 511.

(3) (a) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753. (b) Liu, Y.-L; Wang, B.-L.; Cao, J.-J; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176. (c) Ding, M.; Zhou, F.; Liu, Y.-L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Chem. Sci.* **2011**, *2*, 2035. (d) Zhou, F.; Cao, Z.-Y.; Zhang, J.; Yang, H.-B.; Zhou, J. *Chem.—Asian J.* 2011, in press.

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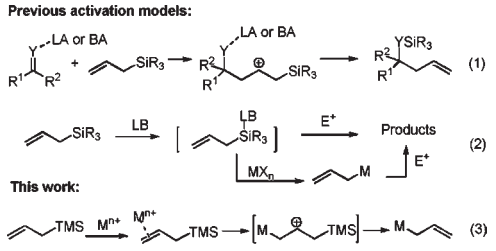
by Leighton, using strain-release-activated silane reagents, the activation of less reactive allysilanes for reaction design is still needed.[4k,l] In this context, two activation models have been adopted: one is to activate the electrophile by an acid to react with allylsilane (eq 1),[4b] and the other is to activate allylsilanes by a Lewis base to directly react with electrophiles[4c] or to help the formation of reactive allyl metallic species (eq 2).[4h−j] Despite achievements, efficient allylation of ketones or ketoimines is very limited, which often relies on the dual activation of both reaction partners and using allyltrimethoxysilane or specially designed allylsilanes that can be easily activated by Lewis base to form reactive allylmetallic species.[4h−j] As far as we knew, the catalytic allylation of ketoimines using cheaper but less reactive allyltrimethylsilane **1** was not reported yet,[4] and no catalytic asymmetric allylation of ketones using allyltrimethylsilane was reported.[4]



To activate the less reactive allyltrimethylsilane **1** for reaction development, we considered a new approach: the direct activation of silane **1** by a Lewis acid. It was postulated that the interaction of a carbophilic Lewis acid with the double bond of **1** might form an intermediate carbocation, which was stabilized by hyper-conjugative overlap with the adjacent carbon−silicon bond, followed by the cleavage of the silyl electrofuge to afford a reactive allylic metallic species for further transformations (eq 3). To test this hypothesis, we first analyzed the interaction between silane **1** and Lewis acids (10 mol %) by NMR analysis under N_2. We found that hard Lewis acids such as $Sc(OTf)_3$ and $In(ClO_4)_3 \cdot 8H_2O$ have no obvious interaction

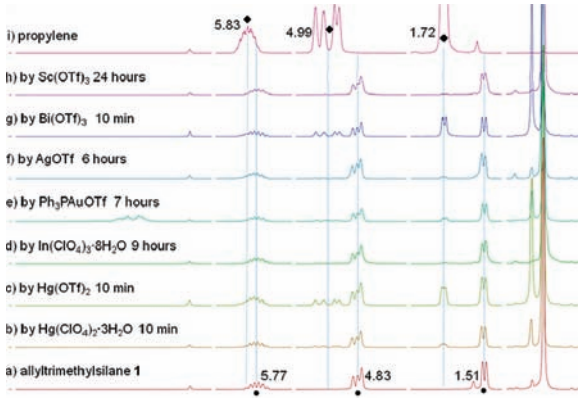
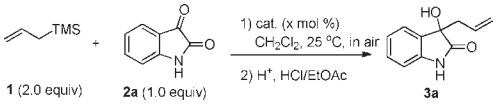


Figure 1. NMR analysis of the interaction between selected Lewis acids and silane **1**.

Table 1. Comparing Different Lewis Acids



entry[a]	cat.	×	time (h)	yield[b] (%)
1	$Sc(OTf)_3$	2	48	31
2	$In(ClO_4)_3 \cdot 8H_2O$	2	48	75
3	$Ph_3PAuCl + AgOTf$	2	48	10
4	$Bi(OTf)_3$	2	48	50
5	$Hg(OTf)_2$	2	1	99
6	$Hg(ClO_4)_2 \cdot 3H_2O$	2	2	95
7	$Hg(ClO_4)_2 \cdot 3H_2O$	1	4	98
8[c]	$Hg(ClO_4)_2 \cdot 3H_2O$	0.3	12	93
9[d]	$Hg(ClO_4)_2 \cdot 3H_2O$	0.1	144	71

[a] On a 0.40 mmol scale. [b] Isolated yield. [c] On a 7.0 mmol scale. [d] On a 20.0 mmol scale, with 23% of **2a** recovered.

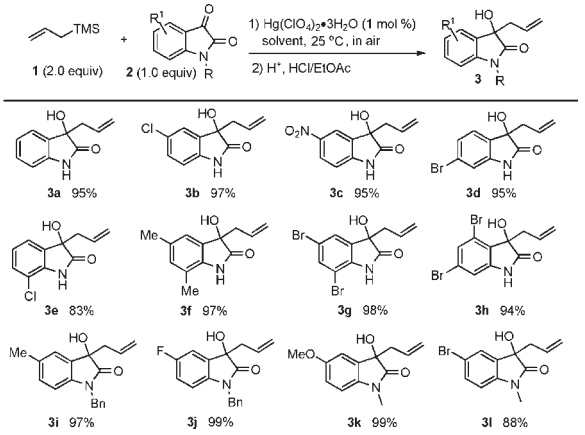
with silane **1** after several hours (Figure 1). Soft Lewis acids such as $Ph_3PAuOTf$ and AgOTf could interact with **1** slowly. However, borderline Lewis acid $Bi(OTf)_3$ and soft Lewis acid $Hg(ClO_4)_2 \cdot 3H_2O$ or $Hg(OTf)_2$ could rapidly interact with silane **1** within 10 min, and the generation of propylene was observed by NMR analysis. Next, we examined the performance of these Lewis acids in the reaction of silane **1** and isatin **2a** in CH_2Cl_2 at 25 °C, with 2 mol % catalyst. Some typical results were shown in Table 1 (for details about NMR studies, screened Lewis acids, and optimization, see the Supporting Information). Of hard Lewis acids screened, $In(ClO_4)_3 \cdot 8H_2O$ and $Sc(OTf)_3$, which failed to activate silane **1**, catalyze this reaction slowly (Table 1, entries 1 and 2), possibly through the activation of isatin **2a**. Of Lewis acids interacting with silane **1**, $Ph_3PAuOTf$ and $Bi(OTf)_3$ catalyze the reaction slowly, giving product **3a** in 10 and 50% yield after 2 days, respectively (Table 1, entries 3 and 4).

In contrast, $Hg(OTf)_2$ and $Hg(ClO_4)_2 \cdot 3H_2O$ enable the completion of reaction within 2 h to afford **3a** in 99 and 95% yield, respectively (Table 1, entries 5 and 6). Although $Hg(OTf)_2$ was more reactive, cheap and easy to handle, $Hg(ClO_4)_2 \cdot 3H_2O$[5] was chosen as the optimum. The catalyst loading could be reduced to 0.3 mol % for a 7.0 mmol scale reaction, which finished within 12 h to give **3a** in 93% yield

(4) For reviews, see: (a) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. Also see: (e) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *33*, 3043. (f) Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 4233. (g) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett.* **2001**, 1851. (h) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (i) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. (j) Kamei, T.; Fujita, K.; Itami, K.; Yoshida, J.-I. *Org. Lett.* **2005**, *7*, 4725. For the use of strained silacycles, see: (k) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (l) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596.

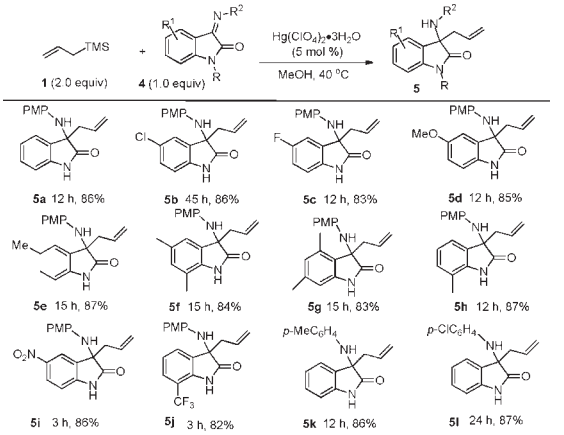
(5) For a review about metal perchlorate hydrates, see: Dalpozzo, R.; Bartoli, G.; Sambri, L.; Melchiorre, P. *Chem. Rev.* **2010**, *110*, 3501.

Scheme 1. Allylation of Isatins **2** Using Allyltrimethylsilane **1**[a,b]



[a] On a 0.40 mmol scale. [b] Isolated yield.

Scheme 2. Allylation of Isatin Derived Ketoimine **4**[a,b]



[a] On a 0.40 mmol scale. [b] Isolated yield.

(Table 1, entry 8). Further lowering the catalyst loading to 0.1 mol % for a 20.0 mmol scale reaction, product **3a** could still be obtained in 71% yield after 6 days, with 23% of **2a** recovered. As far as we know, this is the lowest catalyst loading for the allylation of ketones using allylsilane.

We further examined the substrate scope by running the reaction in CH_2Cl_2 with 1 mol % of $Hg(ClO_4)_2 \cdot 3H_2O$ (THF was used when unprotected isatins dissolved poorly in CH_2Cl_2). The nature and the position of the substituents on isatin had no obvious influence, and all the desired products **3a**–**l** were obtained in high yield (Scheme 1). These products are very useful.[6k] For example, product **3a** can be used for the synthesis of CPC-1,[6b] donaxaridine, and dioxibrassinine,[6i] and product **3h** for convolutamydine A, B, and E.[6i] In the total synthesis of perophoramidine,[6f] Qin used 6.0 equiv of allylmagnesium bromide to react with 6-bromoisatin to ensure the high yield of product **3d**; our method is obviously a good alternative.

We next tried the $Hg(ClO_4)_2 \cdot 3H_2O$ catalyzed allylation of isatin derived ketomines **4** using silane **1**. As far as we knew, the use of allyltrimethylsilane **1** for allylation of ketoimines was unknown, and the limited reports on Sakurai–Hosomi allylation of ketomines were based on the more reactive but expensive allyltrimethoxysilane or special allylsilanes.[4h,j] We were pleased to find that different substituted isatin ketoimine **4** worked well in MeOH at 40 °C, using 5 mol % of $Hg(ClO_4)_2 \cdot 3H_2O$ as the catalyst (Scheme 2). It should also be noted that aminooxindoles **5** were very useful building blocks for a number of bioactive compounds,[6a] but synthetic methods to 3-allyl-3-aminooxindoles were very limited.[7]

In the NMR studies, we observed that $Bi(OTf)_3$ could interact with allyltrimethylsilane **1** as rapidly as $Hg(OTf)_2$, but it catalyzed the allylation of isatin **2** very slowly (entry 4 vs 5, Table 1). During our work, Meshram also reported that the use of 5 mol % $Bi(OTf)_3 \cdot 4H_2O$ was necessary to catalyze the allylation of isatin **2**, with slow addition at −78 °C and then warmed to 20 °C.[6j] Although less reactive than $Hg(OTf)_2$, $Hg(ClO_4)_2 \cdot 3H_2O$ is obviously more efficient than $Bi(OTf)_3 \cdot 4H_2O$ for this reaction, and the catalyst loading could be down to 0.1 mol %.

We further compared both catalysts (Scheme 3). First, $Bi(OTf)_3$ failed to catalyze the allylation of ketoimine **4a** under the same conditions. Although Ollevier reported that the allylation of compound **6** only gave the desired product **7** in 16% yield with carbamate **8** in 36% yield,[8] even using 5 mol % of $Bi(OTf)_3 \cdot 4H_2O$ and 5.0 equiv of silane **1** in refluxing CH_2Cl_2, we found that the use of 5 mol % of $Hg(ClO_4)_2 \cdot 3H_2O$ and only 2.0 equiv of **1** could afford the desired product **7** in 70% yield at room temperature.

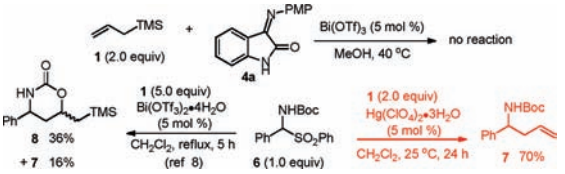
The catalytic asymmetric allylation of isatins is of great interest because enantioenriched 3-allyl-3-hydroxyoxindoles are very useful.[6a] Although Krische have already developed a highly enantioselective allylation of *N*-benzyl isatins using allylacetate,[6d] the allylation of *unprotected* isatins waited for development,[6] and only 42% ee was obtained when using tetraallylstannane.[6b] In the Pd-catalyzed asymmetric allylation of unprotected isatin **2a** using allyl alcohol and Et_3B, Zhou found the nitrogen of the

(6) For a comprehensive review, see: (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. For methods to 3-allyl 3-hydroxyoxindoles, see: (b) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199. (c) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744. (d) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (e) Qiao, X.-C.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2009**, *20*, 1254. (f) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052. (g) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453. (h) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (i) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493. (j) Meshram, H. M.; Ramesh, P.; Reddy, C. B.; Kumar, G. S. *Chem. Lett.* **2011**, *40*, 357. (k) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346. (l) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (m) Bui, T.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2010**, *132*, 5574. (n) Zheng, K.; Yin, C.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573.

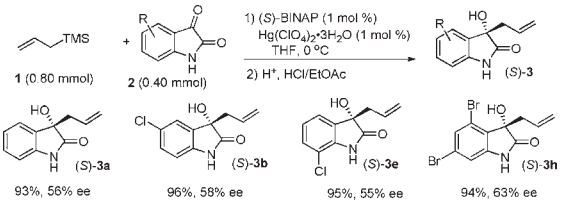
(7) (a) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Eur. J. Org. Chem.* **2010**, 2845. (c) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. For reviews: (d) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. *Chem. Rev.* **2011**, *111*, 2626. (e) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2011**, *2*, No. DOI:10.1039/C1SC00544H.

(8) Ollevier, T.; Li, Z. *Adv. Synth. Catal.* **2009**, *351*, 3251.

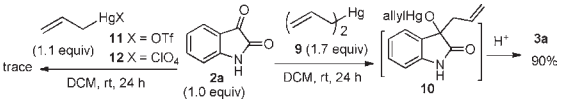
Scheme 3. Comparing $Bi(OTf)_3$ with $Hg(ClO_4)_2 \cdot 3H_2O$



product was also masked with an allyl group.[6e] Although chiral mercury catalysis was rare,[9] we found that at 0 °C in THF, 1.0 mol % of (*S*)-BINAP/$Hg(ClO_4)_2 \cdot 3H_2O$ could give the *S*-enantiomer of product **3** in excellent yield with up to 63% ee. Although there has much room for improvement, this is the first example of catalytic asymmetric allylation of ketones using allyltrimethylsilane.[4]

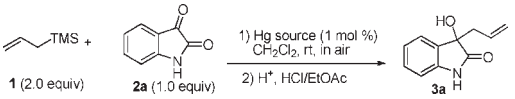


To gain more insight into the mechanism, we first tried NMR studies and observed little interaction between Hg^{2+} and *N*-methylisatin, suggesting $Hg(ClO_4)_2 \cdot 3H_2O$ might not act as a Lewis acid to activate isatin (see the Supporting Information). Since diallylmercury **9** could react with aldehydes in water,[10] we tried the reaction of **9** and **2a**, which worked slowly, and found 1.7 equiv of **9** was need to ensure 90% yield of product **3a** after 24 h. We also prepared allylmercury triflate **10** or perchlorate **11**, from anion exchange of allylmercury chloride **13** using AgOTf or $AgClO_4 \cdot H_2O$, to react with **2a** but found that no reaction took place.



To probe if diallylmercury **9** was the key intermediate for allylation of isatin, we tried using different Hg(II) sources to mediate the reaction of isatin **2a** with silane **1**. Although the use of 1 mol % of **9** or 2 mol % of TMSOTf failed to initiate the reaction (Table 2, entries 1 and 2), the combination of both resulted in high reactivity (Table 2, entry 3). The possible role of TMSOTf was to cleave the Hg−O bond of adduct **10** to release O-TMS protected product **15** and allylmercury triflate **11**, which further interact with silane **1** to give diallylmercury **9**. Indeed, the in situ prepared triflate **11** or perchlorate **12** initiated the reaction well (Table 2, entries 6 and 7), though allylmercury chloride **13** failed to initiate the reaction (Table 2, entry 5). These results were also in

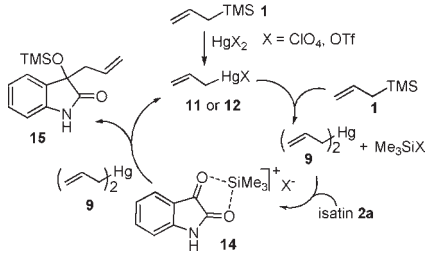
Table 2. Control Experiments



entry	Hg source	additive	time (h)	yield[a] (%)	ee[b] (%)
1	**9**	no	48	trace	
2	no	TMSOTf[c]	48	trace	
3	**9**	TMSOTf[c]	2	91	
4	**9**	TMSOTf[c] and (*S*)-BINAP[d]	72	84	57
5	**13**	no	24	trace	
6	**13**	AgOTf[e]	4	90	
7	**13**	$AgClO_4 \cdot H_2O$[e]	4	91	

[a] Isolated yield. [b] By HPLC analysis. [c] 2.0 mol %. [d] 1.0 mol %, in THF at 0 °C. [e] 1.1 mol %; both silver salts could not catalyze the reaction (**13**: allylmercury chloride).

accordance with NMR studies that the in situ generated **11** or **12** could react with silane **1** as quickly as $Hg(OTf)_2$ or $Hg(ClO_4)_2 \cdot 3H_2O$. These results also confirmed that weak-coordinating counteranions such as OTf^- and ClO_4^- were key to ensure the high Lewis acidity of Hg(II) to activate silane **1**. A possible catalytic cycle was then proposed as below (for more details and discussion, please see the Supporting Information).



In conclusion, we have demonstrated that $Hg(OTf)_2$ and $Hg(ClO_4)_2 \cdot 3H_2O$ could activate allyltrimethylsilane for a highly efficient allylation of isatins and isatin ketoimines. The catalyst loading could be down to 0.1 mol %, the lowest known for a Sakurai−Hosomi allylation reaction. Our results further demonstrated that mercury salts had some interesting catalytic properties worthwhile to explore.[2,11] Efforts to develop a highly enantioselective version are now in progress in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China (20902025, 21172075), Shanghai Pujiang Program (10PJ1403100), and 973 Program (2011CB-808600) for the financial support, which is highly appreciated.

Supporting Information Available. Experimental procedures and characterizations, copies of ^1H NMR and ^{13}C NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) Only two examples were reported by now: (a) Yamamoto, H.; Ho, E.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem.—Eur. J.* **2010**, *16*, 11271. (b) Oh, T.; Lopez, P.; Reilly, M. *Eur. J. Org. Chem.* **2000**, 2901.

(10) Hashmi, A. S. K.; Schwarz, L.; Bolte, M. *Tetrahedron Lett.* **1998**, *39*, 8969.

(11) As suggested by one reviewer, we checked the Hg contamination level of product **3a** by both CVAFS and ICP-MS analysis, which gave consistent results that ca. 3.0% of Hg of catalyst remained in product **3a**. For details, please see the Supporting Information.