$Hg(OTf)_2$-Catalyzed Cyclization of *N*-Tosylanilinoallylic Alcohols to 2-Vinylindolines

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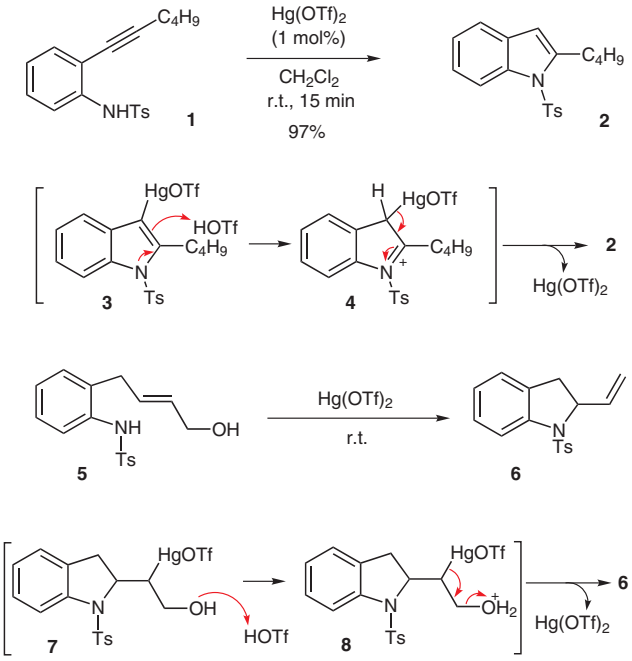
Received 21 March 2008

Abstract: The $Hg(OTf)_2$-catalyzed cyclization of *N*-tosylanilinoallylic alcohols giving rise to vinyl-substituted indolines has been developed. The reaction takes place with a highly efficient catalytic turnover (up to 1000 times) under mild conditions. The hydroxyl group of the organomercuric intermediate is protonated by in situ formed TfOH generating an oxonium cation, which regenerates the catalyst after demercuration.

Key words: $Hg(OTf)_2$, *N*-tosylanilinoallylic alcohol cyclization, 2-vinylindoline, 2-vinylpyrrolidine, 2-vinylpiperidine

Transition-metal-catalyzed cyclization of alkynyl and alkenyl amine derivatives leading to nitrogen heterocycles is of great interest for both academic and industrial research.[1] In particular, catalytic hydroamination[2] as well as indole syntheses have been intensively investigated.[3] Recently, we also reported the $Hg(OTf)_2$-catalyzed cycloisomerization of alkynyl aniline derivatives giving rise to indoles, with very high catalytic turnover (up to 400 times), under very mild reaction conditions.[4] For example the reaction of alkynyl aniline derivative **1** with 1 mol% of $Hg(OTf)_2$ in dichloromethane at room temperature for 15 minutes generates indole **2** in 97% yield. When vinyl mercuric intermediate **3** is formed, it is protonated with in situ formed TfOH generating iminium ion **4**, which undergoes smooth demercuration to give **2** while regenerating catalyst $Hg(OTf)_2$.[5] If the corresponding alkenyl aniline derivatives were treated with $Hg(OTf)_2$, a stable sp^3 C–Hg bond would be formed in an essentially stoichiometric reaction.[6] We expected to overcome this drawback by introducing an oxygen-containing group as a protonation site thereby triggering a smooth demercuration step. Therefore, the reaction of anilino allyl alcohol **5** with a catalytic amount of $Hg(OTf)_2$ afforded indoline derivative **6** in quantitative yield. An organomercuric intermediate **7** should be protonated by in situ formed TfOH and generate oxonium ion **8**. The latter leads to a smooth demercuration step giving rise to indoline **6** and the regenerated catalyst (Scheme 1). Described herein is the synthesis of 2-vinyl-substituted indoline derivatives as well as tetrahydroquinoline, pyrrolidine, and piperidine derivatives by means of $Hg(OTf)_2$-catalyzed cyclization of *N*-tosylanilino- and *N*-tosylaminoallylic alcohol derivatives. The vinyl functionality maintained in the product should be useful for further molecular modification such as hydroboration, ozonolysis, and metathesis. Although Pd and Ni complex catalyzed nitrogen allyl alcohol cyclizations were reported, catalytic turnover was not very high.[7,8] Quite recently Au-salt-catalyzed cyclization of monoallylic diol to give 2-vinylpyrane has reported by Aponick and co-workers.[9]



Scheme 1 $Hg(OTf)_2$-catalyzed cyclization of alkynyl and alkenyl aniline derivatives

First, we examined the reaction of (*E*)-*N*-[2-(4-hydroxy-2-butenyl)phenyl]benzenesulfonamide (**5**)[10] with 1 mol% of $Hg(OTf)_2$ in MeCN at room temperature for 20 hours, and the expected vinylindoline derivative **6** was obtained in 84% yield after column chromatography on silica gel (Table 1, entry 1).[10] This reaction was sensitive to solvent effect, and $MeNO_2$ and $CHCl_3$ were shown to not be satisfactory enough (entries 2 and 3). Since the substrate **5** was not soluble at all in toluene, the reaction did not proceed in this solvent (entry 4). CH_2Cl_2 was shown to be the solvent of choice, and afforded **6** in quantitative yield within 30 minutes using 1 mol% of $Hg(OTf)_2$ (entry 5). Although catalyst loading of 0.1 mol% gave rise to **6** in 98% yield within an acceptable reaction time (24 h),[11] 0.05 mol% was not enough to complete the reaction (entries 6 and 7). The reactions were also examined using 2

SYNLETT 2008, No. 11, pp 1719–1723
Advanced online publication: 11.06.2008
DOI: 10.1055/s-2008-1077881; Art ID: U02408ST

Table 1 $Hg(OTf)_2$-Catalyzed Cyclization of **5** to **6**

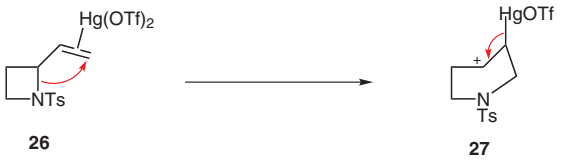
		$Hg(OTf)_2$		Yield (%)[a]	
Entry	Solvent	(mol%)	Time	**6**	**5**
1	MeCN	1	20 h	84	–
2	$MeNO_2$	1	48 h	53	42
3	$CHCl_3$	1	24 h	88	11
4	toluene[b]	1	24 h	–	95
5	CH_2Cl_2	1	30 min	99	–
6	CH_2Cl_2	0.1	24 h	98	–
7	CH_2Cl_2	0.05	24 h	14	80
8	CH_2Cl_2	1[c]	24 h	3	84
9	CH_2Cl_2	1[d]	24 h	27	63

[a] Isolated yield.
[b] Compound **5** did not dissolve at all in toluene.
[c] Reaction was carried out with 2 mol% of $Hg(OTFA)_2$.
[d] Reaction was carried out with 1 mol% of TfOH.

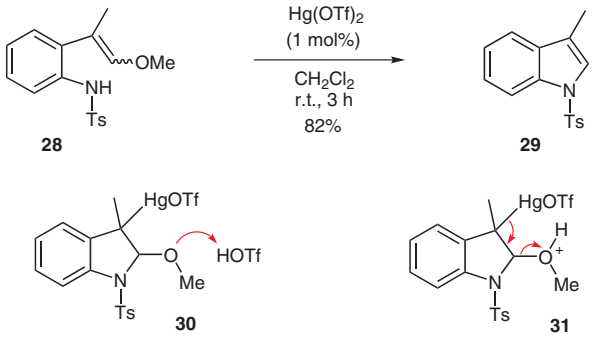
mol% of $Hg(OTFA)_2$ and 1 mol% of TfOH as catalyst at room temperature for 24 hours in CH_2Cl_2, but the yield of **6** were only 3% and 27%, respectively (entries 8 and 9). These results suggested that the transformation of **5** to **6** in the presence of $Hg(OTf)_2$ is not an acid-catalyzed S_N2' reaction, and involves organomercuric intermediates **7** and **8**.

The second substrate to be examined was (*E*)-*N*-[2-(4-methoxy-2-butenyl)phenyl]-4-methylbenzenesulfonamide (**9**). Although the reaction of **9** with 1 mol% of $Hg(OTf)_2$ at room temperature was slower than the reaction of **5**, 2-vinylindoline **6** was obtained in 87% yield after one hour at room temperature (Table 2). The corresponding acetate **10**,[12] however, did not react with $Hg(OTf)_2$ (2 mol%) at room temperature, and most of the starting materials were recovered after two days. Reaction of methyl-substituted *E*-allylalcohol **11** with 1 mol% of $Hg(OTf)_2$ at room temperature for two hours afforded **12** in 79% yield. Thus the procedure is suitable for the formation of a quaternary carbon center. *Z*-Isomer **13** also afforded **12** in 88% yield indicating that the reactivity is not dependent on the stereochemistry of the double bond. Although the reaction of 5-hydroxy-3-pentenyl derivative **14** with 1 mol% of $Hg(OTf)_2$ at room temperature was slower than the reaction of **5**, tetrahydroquinoline derivative **15** was obtained in 52% yield after two hours at room temperature.[13] Reaction at reflux temperature in CH_2Cl_2, however, afforded **15** in 96% yield after one hour. In contrast, reaction of the corresponding 6-hydroxy-3-hexenyl derivative **16** in $(CH_2Cl)_2$ at 80 °C for 30 minutes afforded the seven-membered ring product **17** in only 25% yield,[12] together with an unexpected carbocyclization product **18** in 30% yield and an alternative tetrahydroquinoline **19** in 34% yield.[13] Reaction of amino allyl alcohol **20** with 0.1 mol% of $Hg(OTf)_2$ in $(CH_2Cl)_2$ at room temperature was examined and the expected 2-vinylpyrrolidine **21** was obtained in quantitative yield after 30 minutes.[10] Amino allyl alcohol **22** reacted with 0.3 mol% of $Hg(OTf)_2$ affording 2-vinylpiperidine **23** in 65% yield.[7] Reaction of amino allyl alcohol **24** with 1 mol% of $Hg(OTf)_2$ was also examined, however instead of the expected 2-vinylazetidine, 1-tosyl-1,2,3,6-tetrahydropyridine (**25**) was obtained as the major product in 41% yield. $Hg(OTf)_2$ probably acts as the catalyst for the ring enlargement as seen in **26** and following smooth demercuration from the cation **27** (Scheme 2) leads to **25**.

If aniline derivatives such as **28**, containing a vinylmethoxy moiety, are cyclized by reaction with $Hg(OTf)_2$, generating intermediate **30**, the methoxy group should act as the protonation site. Thus, in situ generated TfOH could protonate **30** leading to oxonium cation **31** (Scheme 3). The latter should undergo smooth demercuration to regenerate $Hg(OTf)_2$ and afford indole **29**. Thus, an *E*/*Z* (1:1) mixture of **28** was treated with 1 mol% of $Hg(OTf)_2$ in CH_2Cl_2, and 3-methylindole derivative **29** was obtained in 82% yield after three hours at room temperature.



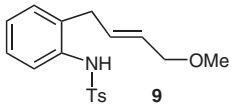
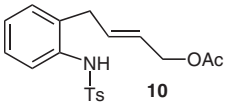
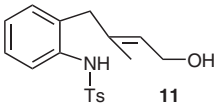
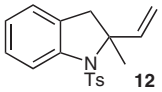
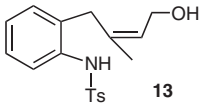
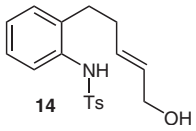
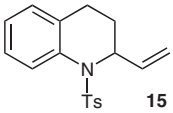
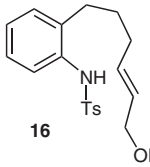
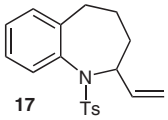
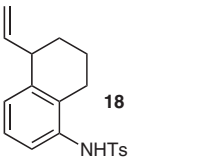
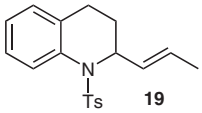
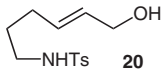
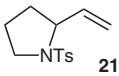
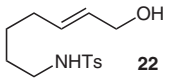
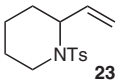
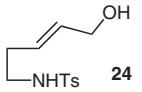
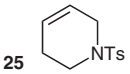
Scheme 2 Reaction intermediates to give **25**



Scheme 3 $Hg(OTf)_2$-catalyzed cyclization of methoxyvinyl aniline

The corresponding butyl homologue **32** afforded **33** in quantitative yield under similar conditions (Table 3). Reaction of **34** with 1 mol% of $Hg(OTf)_2$ afforded the six-membered ring product **35** in 40% yield after heating to 120 °C for three hours in toluene. Attempted synthesis of the corresponding seven-membered ring by the reaction of **36** with 2 mol% of $Hg(OTf)_2$ in toluene at room temperature for five minutes resulted in the methoxylated product **38** as the major product (66%), while the same reaction in toluene at 100 °C for ten minutes afforded **37** in 52% yield along with 15% of **38**. Neither eight- nor nine-membered rings were accessible using this methodology.

Table 2 Hg(OTf)$_2$-Catalyzed Cyclization of Amino Allylic Alcohols

Substrate	Hg(OTf)$_2$ (mol%)	Solvent	Temp	Time	Product	(Yield%)[a]
 **9**	1	CH_2Cl_2	r.t.	1 h	**6**	87%
 **10**	2	CH_2Cl_2	r.t.	2 d	**6**	0
 **11**	1	CH_2Cl_2	r.t.	2 h	 **12**	79
 **13**	1	CH_2Cl_2	r.t.	3 h	**12**	88
 **14**	1	CH_2Cl_2	r.t.	2 h	 **15**	52
	1	CH_2Cl_2	40 °C	1 h		96
 **16**	1	$(CH_2Cl)_2$	80 °C	30 min	 **17**	25
					 **18**	30
					 **19**	34
 **20**	0.1	$(CH_2Cl)_2$	r.t.	30 min	 **21**	99
 **22**	0.3	$(CH_2Cl)_2$	r.t.	10 h	 **23**	65
 **24**	1	CH_2Cl_2	r.t.	66 h	 **25**	41

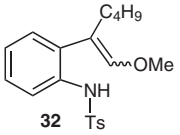
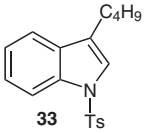
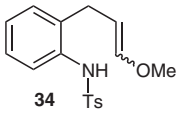
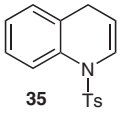
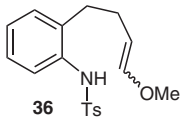
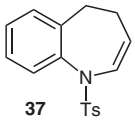
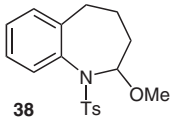
[a] Isolated yield.

Thus, we have established a Hg(OTf)$_2$-catalyzed anilino olefin cyclization reaction using neighboring oxygen functionality as the protonation site, facilitating the regeneration of the catalyst. The procedure should be of use in a wide variety of carbocyclizations as well as heterocycle synthesis.

Acknowledgment

This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government, and a MEXT.HAITEKU, 2003–2007.

Table 3 $Hg(OTf)_2$-Catalyzed Cyclization of Methoxyvinyl Anilines

Substrate	$Hg(OTf)_2$ (mol%)	Solvent	Temp	Time	Product	Yield (%)[a]
 **32**	1	CH_2Cl_2	40 °C	16 h	 **33**	99
 **34**	2	toluene	120 °C	3 h	 **35**	40
 **36**	1 1	toluene toluene	r.t. 100 °C	5 min 10 min	 **37**  **38**	0 (**37**), 66 (**38**) 52 (**37**), 15 (**38**)

[a] Isolated yield.

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(11) **Typical Experiment Procedure**: To a solution of **5** (20 mg, 0.063 mmol) in CH_2Cl_2 (0.6 mL) was added mercury triflate (0.01 M solution in MeCN, 6.3 μL, 0.063 μmol) at r.t., and the mixture was stirred for 24 h. After addition of sat. $NaHCO_3$ solution, the dried and concentrated residue was subjected to a column chromatography on silica gel using hexane–EtOAc (12:1) as eluent to give **6** (18.4 mg, 98%) as a colorless powder; mp 111 °C. IR (neat): 3066, 1598, 1354, 1165 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.1 Hz, 1 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 7.21 (m, 1 H), 7.17 (d, *J* = 8.1 Hz, 1 H), 7.01–7.07 (m, 2 H), 6.99 (dd, *J* = 0.9, 7.5 Hz, 1 H), 5.91 (ddd, *J* = 6.3, 10.2, 16.8 Hz, 1 H), 5.39 (dt, *J* = 1.2, 16.8 Hz, 1 H), 5.15 (dt, *J* = 1.5, 10.2 Hz, 1 H), 4.74 (m, 1 H), 2.95 (dd, *J* = 9.9, 15.9 Hz, 1 H), 2.64 (dd, *J* = 3.3,

15.9 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 141.4, 137.6, 135.3, 131.2, 129.5, 127.7, 127.1, 125.1, 124.5, 116.8, 115.7, 63.8, 34.9, 21.5. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{19}NO_3S^+$: 299.0980; found: 299.0999.

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