Carbon–Nitrogen Bond Formation between Allyl Silyl Ether and Hydrazide Promoted by Mercuric Triflate Catalyst

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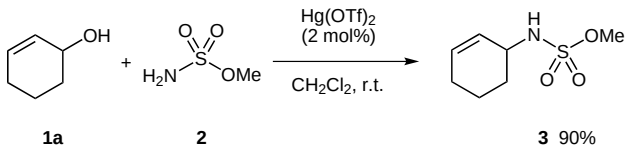
Abstract: An efficient method for carbon–nitrogen bond formation between ally silyl ethers and *N*,*N*-acyltosylhydrazine was developed under very mild conditions using 2 mol% of mercuric triflate [$Hg(OTf)_2$] as a catalyst. This method does not require the use of any ligand system or supplementary additives and is applicable to the preparation of various *N*-allylhydrazides with good to excellent yields.

Key words: allylation, amination, hydrazine, silyl ether, mercury

Tuji–Trost-type amination of allyl halides, carbonates, carboxylates, or phosphonates with amine nucleophiles has served as a pivotal reaction in a number of syntheses of nitrogen-containing natural products and pharmaceuticals.[1] Indeed, a variety of allylamine units have been efficiently constructed using a catalytic amount of palladium,[2] iridium,[3] or some other reagent.[4] Recently, we found remarkable catalytic activity in $Hg(OTf)_2$ for the allylic amination of allyl alcohols and 'soft' nitrogen nucleophiles such as sulfamates or sulfonamides.[5] For example, the reaction of 2-cyclo-1-hexen-1-ol (**1a**) with methyl sulfamate (**2**) using 2 mol% of $Hg(OTf)_2$ affords **3** in excellent yield at room temperature (Scheme 1).[5b]



1a **2** **3** 90%

Scheme 1 $Hg(OTf)_2$-catalyzed allylic amination

As part of our ongoing studies of carbon–nitrogen bond-forming reactions, we have been exploring the use of hydrazines instead of methyl sulfamate. Although the nitrogen–nitrogen linkage of hydrazines is an important structural unit in organic chemistry,[6] there have been only a few examples of Tuji–Trost-type reactions using hydrazines as the nitrogen nucleophile: For the synthesis of alkyl- or allyl-substituted hydrazine derivatives, classical S_N2-type reaction using halogenated compounds under severe conditions has traditionally been used.[6a] A pioneering study of hydrazines being employed as the nucleophile for Tuji–Trost-type reactions was performed by Lee and co-workers in 2005.[7] This reaction of allylic carbonates with *t*-Boc-protected hydrazine proceeded at room temperature in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ complex and pyridine ligand; however, the additions of Et_2Zn (0.25–0.5 equiv)[8] and NH_4I (1 equiv)[9] are essential to induce the reaction. Herein is proposed a new and simple protocol for the catalytic synthesis of allylhydrazine derivatives.

Namba, Tanino, and co-workers most recently reported the efficient preparation of *N*,*N*-acyltosylhydrazine (**4**) using a catalytic amount of 4-aminopyridine.[10] Although N,N-diprotected hydrazines including **4** have almost never been employed as key synthons for organic synthesis,[11] the structure of **4** has a clear advantage in achieving selective allylation at only one of two nitrogens. Moreover, **4** is expected to function as a mild nitrogen nucleophile as a result of having two electron-withdrawing groups on the same nitrogen atom. Thus we hypothesized that **4** would be a suitable nitrogen source for a $Hg(OTf)_2$-catalyzed carbon–nitrogen bond-forming reaction.

Initially, the reaction of commercially available **1a** with **4** was examined, using 2 mol% of $Hg(OTf)_2$ in CH_2Cl_2 (Table 1, entry 1). However, in contrast to the allylic amination with methyl sulfamate, the reaction conditions only gave a small quantity of the desired product **5**, along with dimerized **6** as a byproduct after 48 hours. MeCN and toluene were also poor solvents, affording **5** in 10% and 15% yield, respectively. A better result was obtained by switching to $MeNO_2$, but the yield was still only 25% (Table 1, entry 4). Thus, other conditions using allyl alcohol derivatives **1b**–**h** as allyl sources were examined. When allyl acetate **1b** and carbonate **1c** were used, no reaction resulted upon addition of **4** (Table 1, entries 5 and 6). Methyl ether **1d** was also ineffective at inducing the reaction, giving only a trace amount of **5** after 24 hours (Table 1, entry 7). In contrast, interestingly, trimethylsilyl (TMS) ether **1e** showed remarkable reactivity, giving rise to the desired adduct in 50% yield in six hours (Table 1, entry 8). However, cleavage of the siloxy group in **1e** took place simultaneously under the reaction conditions, confirming the tendency of some silyl ethers to find a more ideal leaving group. For *tert*-butyldimethylsilyl (TBS) ether **1f**, the reactivity was slightly increased compared to that of **1e**,

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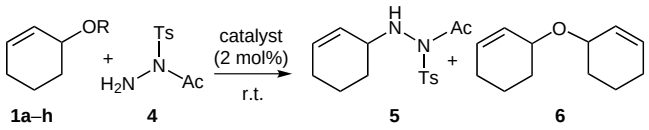
Table 1 Optimization of the $Hg(OTf)_2$-Catalyzed Amination of **1** with **4**



1a–h **4** **5** **6**

Entry	Catalyst	Solvent	**1** R	Time (h)	Yield of **5** (%)[a]
1	$Hg(OTf)_2$	CH_2Cl_2	**1a** H	48	12/22[b]
2	$Hg(OTf)_2$	MeCN	**1a** H	48	10/20[b]
3	$Hg(OTf)_2$	PhMe	**1a** H	48	25/38[b]
4	$Hg(OTf)_2$	$MeNO_2$	**1a** H	8	25/25[b]
5	$Hg(OTf)_2$	$MeNO_2$	**1b** Ac	0.5	0
6	$Hg(OTf)_2$	$MeNO_2$	**1c** CO_2Me	24	0
7	$Hg(OTf)_2$	$MeNO_2$	**1d** Me	24	trace
8	$Hg(OTf)_2$	$MeNO_2$	**1e** TMS	6	50
9	$Hg(OTf)_2$	$MeNO_2$	**1f** TBS	6	52
10	$Hg(OTf)_2$	$MeNO_2$	**1g** TIPS	6	62
11	$Hg(OTf)_2$	$MeNO_2$	**1h** TBDPS	4	88/82[c]
12[d]	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	**1c** CO_2Me	24	0
13[d]	$[Pd(C_3H_5)Cl]_2$	CH_2Cl_2	**1c** CO_2Me	24	0
14[d]	$Pd_2(dba)_3CHCl_3$	CH_2Cl_2	**1c** CO_2Me	24	0
15[e]	PhHgOTf	$MeNO_2$	**1h** TBDPS	24	trace
16	AuCl	$MeNO_2$	**1h** TBDPS	24	42
17[f]	PPh_3AuCl	$MeNO_2$	**1h** TBDPS	24	57
18	$AuCl_3$	$MeNO_2$	**1h** TBDPS	24	trace
19	$In(OTf)_3$	$MeNO_2$	**1h** TBDPS	24	23
20	HOTf	$MeNO_2$	**1h** TBDPS	24	trace

[a] Yield was determined by comparison of the ^1H NMR integration of the crude mixture to an internal standard (CH_2Br_2).
[b] Yield of homodimer **6**.
[c] Yield of isolated product **5**.
[d] Reaction carried out using Ph_3P (4 mol%) at reflux.
[e] Catalyst was prepared from PhHgOAc (2 mol%) and HOTf (2 mol%).
[f] Reaction carried out using AgOTf (2 mol%).

giving **5** in 52% yield (Table 1, entry 9). Triisopropylsilyl (TIPS) ether **1g** was even more suitable to the catalytic system, as **5** was obtained in 62% yield (Table 1, entry 10). Among the siloxy groups evaluated, *tert*-butyldiphenylsilyl (TBDPS) ether **1h** showed the best reactivity, affording **5** in 88% yield after four hours (Table 1, entry 11).[12,13] The isolated product **5** was characterized by NMR and IR spectroscopy, mass spectrometry, and X-ray crystallography. Figure 1 illustrates the molecular structure of **5**,[14] which was crystallized from a mixture of hexane and ethyl acetate (3:1) at room temperature.

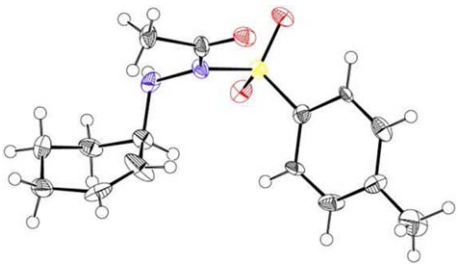
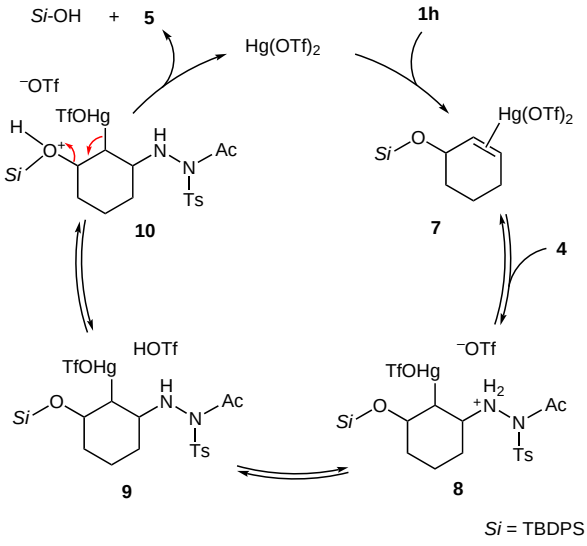


Figure 1 ORTEP plot of the molecular structure **5**

Next, an attempt was made to find an effective palladium catalyst leading to **5**, since the hydrazide **4** is thought to react with a π-allylpalladium intermediate (Table 1, entries 12–14). However, reaction with **4** was unsuccessful under the general allylic amination reaction conditions using allyl carbonate derivatives,[2a] and the majority of **1c** decomposed after 24 hours. After several other attempts using phenyl mercuric triflate (PhHgOTf),[15] gold catalysts,[16] and $In(OTf)_3$,[17] all known to have reactivity similar to $Hg(OTf)_2$, the combination of $Hg(OTf)_2$ and the TBDPS group was found to be the most suitable for the carbon–nitrogen bond formation using **4** (Table 1, entries 15–20).

A plausible mechanism for the $Hg(OTf)_2$-catalyzed reaction of **1h** with **4** is depicted in Scheme 2. Nucleophilic attack of **4** is promoted by complexation of **1h** with $Hg(OTf)_2$, producing the organomercuric intermediate **9**. Then, incidental protonation of the siloxy moiety in **9** by in situ generated TfOH leads to product **5** via demercuration step **10**. Although the exact effect of TBDPS group is unclear, it is likely that its bulkiness enhances the leaving ability of siloxy group. However, more detailed investigation is required for full elucidation of the role.



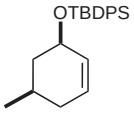
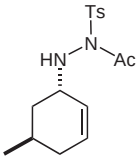
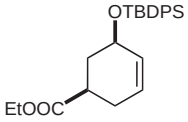
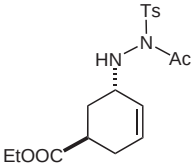
Scheme 2 Proposed mechanism of $Hg(OTf)_2$-catalyzed reaction of **1h** with **4**

As shown in Table 2, this procedure is applicable to the reaction of both cyclic and acyclic ethers. In the case of the 2-cyclopentenyl derivative **11** (Table 2, entry 1), the reactivity was dramatically increased compared to that of **1h**, as the reaction was induced even at 0 °C. Acyclic **13**, **15**, and **17** also gave the corresponding desired adducts **14**, **16**, and **18** in acceptable yields (Table 2, entries 2–4). The conjugated diene **19** and nonconjugated **21** afforded the same conjugated product **20** as a single *E*-isomer, as detected by X-ray crystal structure analysis (Table 2, entries 5 and 6). This result is similar to that of the $Hg(OTf)_2$-catalyzed allylic amination with methyl sulfamate,[5b] and suggests that an equilibrium between **20** and **22** exists under the reaction conditions. Therefore, the formation of the more stable conjugated isomer **20** should prevail over the formation of **22**. The reaction of phenyl-substituted **23** also proceeded regioselectively to afford **24** in good yield (Table 2, entry 7). Even with **25** and **27** as the unsymmetrical substrates, single products **26** and **28** were formed in excellent yields, respectively (Table 2, entries 8 and 9).

Table 2 $Hg(OTf)_2$-Catalyzed Allylic Amination of Allyl Silyl Ethers with **4**

Entry	Substrate	Adduct	Time (min)	Yield (%)[b]
1	**11**	**12**	30	78
2	**13**	**14**	180	76
3	**15**	**16**	60	70
4	**17**	**18**	60	84
5	**19**	**20**	20	85
6	**21**	**22**	30	83
7	**23**	**24**	30	86
8	**25**	**26**	60	88
9	**27**	**28**	10	88

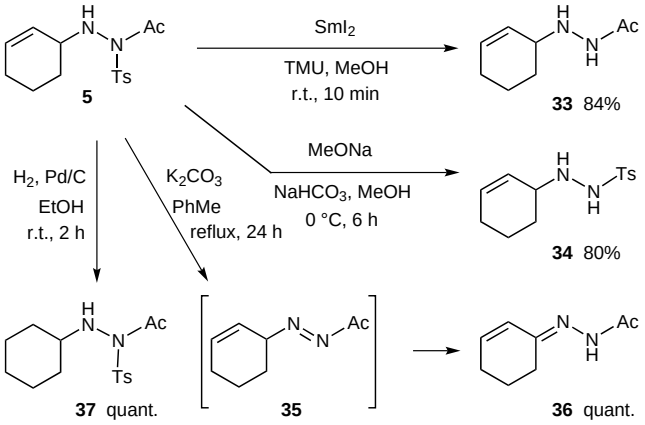
Table 2 $Hg(OTf)_2$-Catalyzed Allylic Amination of Allyl Silyl Ethers with **4** (continued)

Entry	Substrate	Adduct	Time (min)	Yield (%)[b]
10	**29** 	**30** 	10	92
11	**31** 	**32** 	10	63

[a] Except for entries 1, 10 and 11, reactions were carried out with $Hg(OTf)_2$ (2 mol%) in $MeNO_2$ at r.t.
[b] Yield of isolated product.
[c] Reaction was carried out at 0 °C.
[d] Yield of isolated conjugated product **20**.
[e] Reaction was carried out at reflux.
[f] Reaction was carried out using $Hg(OTf)_2$ (5 mol%) at reflux.

The reactions using diastereomerically pure *cis*-5-substituted **29** and **31** were sluggish, and required reflux to reach completion within a reasonable reaction time (Table 2, entries 10 and 11). However, thermodynamically stable diastereoisomers **30** and **32** were obtained in good to excellent yields within 10 minutes under reflux.

The utility of the *N*,*N*-acyltosylhydrazine functionality is demonstrated by the various divergent transformations from product **5** (Scheme 3). Treatment with SmI_2 in the presence of tetramethylurea (TMU) gave **33** in 84% yield. The selective deprotection of the acyl group also succeeded upon using ten equivalents of $NaHCO_3$ and 0.4 equivalents of MeONa. Furthermore, conversion to the hydrazone **36** was easily achieved via unstable intermediate **35** by treatment with K_2CO_3 in toluene. Moreover, catalytic hydrogenation using Pd/C afforded **37** quantitatively, without disruption of the nitrogen–nitrogen linkage.



Scheme 3 Reactivity of *N*,*N*-acetyltosylhydrazine adduct **5**

In summary, a $Hg(OTf)_2$-catalyzed carbon–nitrogen bond-forming reaction between allyl silyl ethers and *N*,*N*-acyltosylhydrazine has been developed. In many cases, the reaction can be performed with as little as 2 mol% of catalyst at room temperature, giving excellent yields. To the best of our knowledge, the present method is the first example employing siloxy functionality as a leaving group for allylic amination. Furthermore, the application of *N*,*N*-acyltosylhydrazine highlights the utility of the reaction. Thus, the present method constitutes a reasonable alternative for the preparation of various hydrazine derivatives.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure:** To a solution of TBDPS ether **1h** (1 g, 3.0 mmol) and *N*,*N*-acyltosylhydrazine (**4**, 1.01 g, 4.5 mmol) in $MeNO_2$ (15 mL) was added a 0.1 M MeCN solution of $Hg(OTf)_2$ (0.6 mL, 0.06 mmol) at r.t. under argon atmosphere. After stirring for 4 h at r.t., the reaction mixture was quenched with sat. aq $NaHCO_3$. The organic materials were extracted with EtOAc, and then washed with brine. The organic phase was dried over Na_2SO_4, and the filtrates were concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane and EtOAc (8:1) to give *N*,*N*-acyltosylhydrazine adduct **5** (754 mg, 82%) as a white solid.
Analytical Data for Compound 5: white solid. FTIR (neat): ν_{max} = 3314, 3068, 3025, 2935, 2862, 2835, 1706, 1596 cm^{-1}. ^1H NMR (400 MHz, DMSO, 60 °C): δ = 1.50 (2 H, m), 1.68 (2 H, m), 1.97 (2 H, m), 2.13 (3 H, s), 2.40 (3 H, s), 3.83 (1 H, m), 5.57 (1 H, m), 5.84 (1 H, ddt, *J* = 10.4, 3.6, 1.6 Hz), 6.21 (NH, br d, *J* = 2.0 Hz), 7.40 (2 H, br d, *J* = 8.4 Hz), 7.85 (2 H, br d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, DMSO, 60 °C): δ = 18.88, 21.42, 23.76, 25.29, 27.10, 54.42, 125.87, 128.77, 128.84, 129.68, 129.78, 131.26, 136.78, 144.85, 172.99. MS (CI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{21}O_3N_2S$: 309.1273; found: 309.1274.

(13) When using optically active ether **1h** (97% ee), the racemic product **5** was obtained.

(14) CCDC 852683 contains the supplementary crystallographic data. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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