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$Hg(OTf)_2$–BINAPHANE-Catalyzed Enantioselective Anilino Sulfonamide Allyl Alcohol Cyclization

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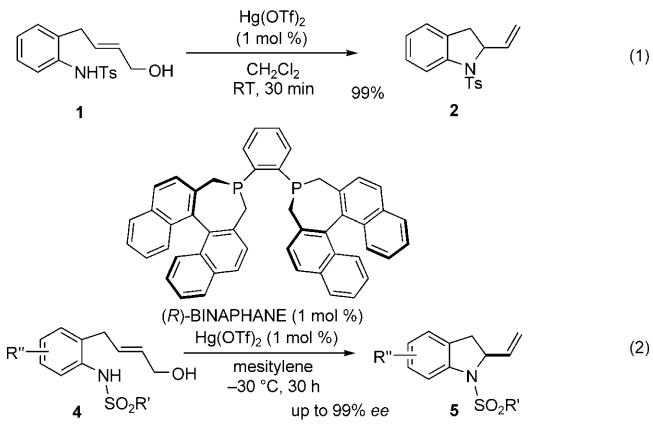
Direct allylic amination of allylic alcohols with amine nucleophiles to produce water as the only byproduct is one of the most attractive reactions in modern organic synthesis.[1] Therefore, significant resources have been devoted to developing the latent ability of transition-metal reagents with the aim of achieving allylic amination from allylic alcohols in high catalytic turnover.[2,3] Recently, Shibasaki, Matsunaga, and co-workers reported the direct allylic amination with sulfonamides by using a catalytic amount of $Bi(OTf)_3$ and KPF_6 under mild reaction conditions.[2b] Although intermolecular allylic aminations are well-established reactions, $[PdCl_2(MeCN)_2]$ has been used exclusively as the catalyst for intramolecular N-cyclization of amino allylic alcohols.[4] Moreover, no catalytic enantioselective cyclization of amino allylic alcohol has been reported thus far.[5]

We have developed mercuric triflate $[Hg(OTf)_2]$ as a key catalyst for organic synthesis[6] by achieving the hydration of terminal alkynes to methyl ketones in high catalytic turnover.[7] Indeed, enyne cyclization, arylyne cyclization, and indole synthesis have been developed based on the significant affinity of $Hg(OTf)_2$ for the alkyne group.[8] Recently the procedure has expanded to include alkene cyclization by the introduction of an allylic hydroxyl moiety as the leaving group, thereby triggering the smooth demercuration step that regenerates the catalyst.[9] The reaction of anilino sulfonamide allyl alcohol **1** with 1 mol% of $Hg(OTf)_2$ was completed within 30 min at room temperature to give 2-vinyl indoline **2** in 99% yield [Eq. (1), Scheme 1]. Because a new chiral center is generated, we decided to perform the reaction in the presence of chiral auxiliaries. We found that BINAPHANE[10] provides effective chiral induction (up to 99% *ee*) during the conversion of **4** to **5** [Eq. (2)]. Although asymmetric oxymercuration of alkene has already been reported,[11] mercuric salt catalyzed asymmetric reactions are seldom described in the literature.[12]



Scheme 1. Catalytic cyclization of anilino sulfonamide allylic alcohol to 2-vinyl indoline derivative. Tf = trifluoromethanesulfonyl; Ts = *para*-toluenesulfonyl. R′ = alkyl, phenyl; R″ = alkyl, methoxy, bromo.

Our initial studies focused on the asymmetric cyclization of **1** in the presence of 5 mol% of $Hg(OTf)_2$ and a variety of chiral auxiliaries (5 mol%). As shown in Table 1, reactions with BINAP[13a] gave enantioenriched **2** in only 34% *ee* at room temperature using CH_2Cl_2 for 60 min in 90% yield (entry 1). PHANEPHOS,[13d] SDP,[13e] tol-SDP,[13e] and NORPHOS[13f] also afforded some chiral inductions (entries 5–7 and 9). However, BINAPHANE afforded the best result (40% *ee*) under the same conditions (entry 10). It is particularly noteworthy that the BINAPHANE–$Hg(OTf)_2$ complex was highly reactive and 1 mol% was enough to

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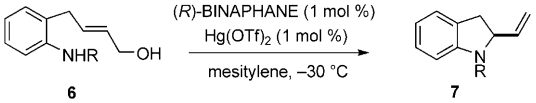
Table 1. $Hg(OTf)_2$-catalyzed enantioselective cyclization of **1** to **2**.

Entry	Auxiliary	Solvent	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]
1[c]	BINAP	CH_2Cl_2	RT	1	90	34
2[c]	CHIRAPHOS	CH_2Cl_2	RT	1	>95	9
3[c]	Et-DUPHOS	CH_2Cl_2	RT	1	>95	2
4[c]	Me-DUPHOS	CH_2Cl_2	RT	1	>95	4
5[c]	PHANEPHOS	CH_2Cl_2	RT	1	>95	18
6[c]	SDP	CH_2Cl_2	RT	1	>95	22
7[c]	tol-SDP	CH_2Cl_2	RT	1	>95	19
8[c]	xyl-SDP	CH_2Cl_2	RT	1	95	11
9[c]	NORPHOS	CH_2Cl_2	RT	1	92	23
10[c]	BINAPHANE	CH_2Cl_2	RT	0.25	>95	40
11[d]	BINAPHANE	CH_2Cl_2	RT	0.3	>95	32
12[d]	BINAPHANE	toluene	RT	0.3	>95	47
13[d]	BINAPHANE	*p*-xylene	RT	0.3	>95	55
14[d]	BINAPHANE	mesitylene	RT	0.3	>95	59
15[d]	BINAPHANE	mesitylene	0	0.6	>95	62
16[d]	BINAPHANE	mesitylene	−30	40	>95/99[e]	74

[a] Yield was determined by comparison of the integration in ^1H NMR spectrum of the crude mixture with CH_2Br_2, which was used as an internal standard. [b] Determined by HPLC analysis using a CHIRALCEL OJ-H column. [c] Reaction carried out using 5 mol% of $Hg(OTf)_2$ and 5 mol% of chiral auxiliary. [d] Reaction carried out using 1 mol% of $Hg(OTf)_2$ and 1 mol% of chiral auxiliary. [e] Yield of isolated product.

Table 2. Optimization of anilino sulfonamide **6** in the enantioselective cyclization.



6 **7**

Entry	**6**, R	t [h]	**7**	Yield [%][a]	*ee* [%][b]
1	**6a**, SO_2Ph	48	**7a**	98	60
2	**6b**, $SO_2C_6H_3$-3,5-Me	48	**7b**	97	54
3	**6c**, $SO_2C_6H_2$-2,4,6-Me	48	**7c**	97	67
4	**6d**, $SO_2C_6H_4$-4-Ph	48	**7d**	92	70
5	**6e**, $SO_2C_6H_4$-4-*t*Bu	24	**7e**	95	74
6	**6f**, SO_2Me	30	**7f**	60	71
7	**6g**, SO_2Et	30	**7g**	78	76
8	**6h**, SO_2*i*Pr	30	**7h**	99	78
9	**6i**, SO_2*t*Bu	12	**7i**	99	78
10[c]	**6i**, SO_2*t*Bu	30	**7i**	97	80
11[d]	**6i**, SO_2*t*Bu	48	**7i**	trace	n.d.
12	**6j**, Boc	48/6[e]	**7j**	trace/72[e]	41[e]

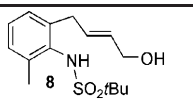
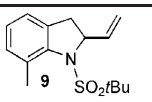
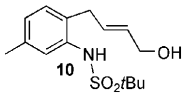
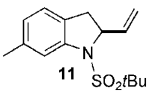
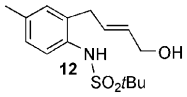
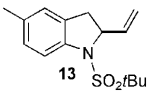
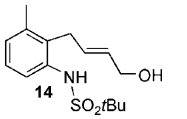
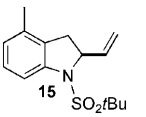
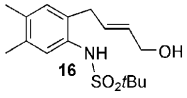
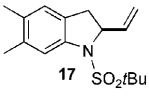
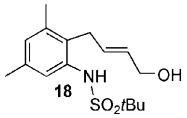
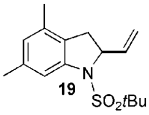
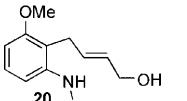
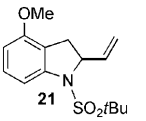
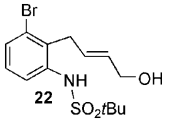
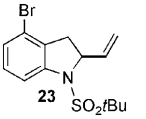
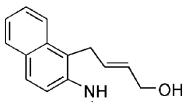
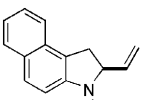
[a] Yield of isolated product. [b] Determined by HPLC using CHIRALCEL AD-H and OJ-H columns. [c] Reaction carried out at −45°C. [d] Reaction carried out using 1 mol% of $Hg(OTf)_2$ and 2 mol% of chiral auxiliary at −30°C. [e] Reaction carried out at RT. Boc = *tert*-butoxycarbonyl.

complete the reaction within 20 min (entry 11).[14] Mesitylene was the solvent of choice to give **2** in 59% *ee* (entry 14). Moreover, an improved *ee* (i.e., 74% *ee*) was achieved when the reaction was carried out at lower temperature (−30°C), although the reaction time had to be extended (entry 16).

Next, we investigated the effect of the protecting group on the nitrogen. The phenylsulfonamide group gave a lower enantioselectivity than the tosyl group when the reaction was carried out using 1 mol% of $Hg(OTf)_2$ in the presence of (*R*)-BINAPHANE (1 mol%) in mesitylene at −30°C (Table 2, entry 1). 3,5-Di- as well as 2,4,6-trimethylarylsulfonyl groups were also less effective (entries 2 and 3).

4-Phenyl and 4-*tert*-butyl substituted arylsulfonamide group afforded **7d** and **7e** in 70 and 74% *ee*, respectively (entries 4 and 5). Alkylsulfonamide derivatives were found to show higher enantioselectivity, with the bulkiness of the alkyl group contributing to *ee* (entries 6–8). *tert*-Butyl-substituted sulfonamide derivative **6i** induced the highest *ee* of 78%, when the reaction was conducted at −30°C for 12 h (entry 9), and 80% *ee* when the reaction was performed at a lower temperature of −45°C for 30 h (entry 10). The structures and absolute configurations of the products **2** and **7a–j** were confirmed by preparation of authentic samples from (*S*)-indoline-2-carboxylic acid via **7k** (R = H) according to the reported procedure.[15]

Table 3. Catalytic enantioselective cyclization of sulfonamide allyl alcohols.

Entry[a]	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	 **8**	 **9**	91	72
2	 **10**	 **11**	98	79
3	 **12**	 **13**	95	84
4	 **14**	 **15**	96	99
5	 **16**	 **17**	93	83
6	 **18**	 **19**	99	93
7	 **20**	 **21**	92	76
8	 **22**	 **23**	91	92
9	 **24**	 **25**	97	88

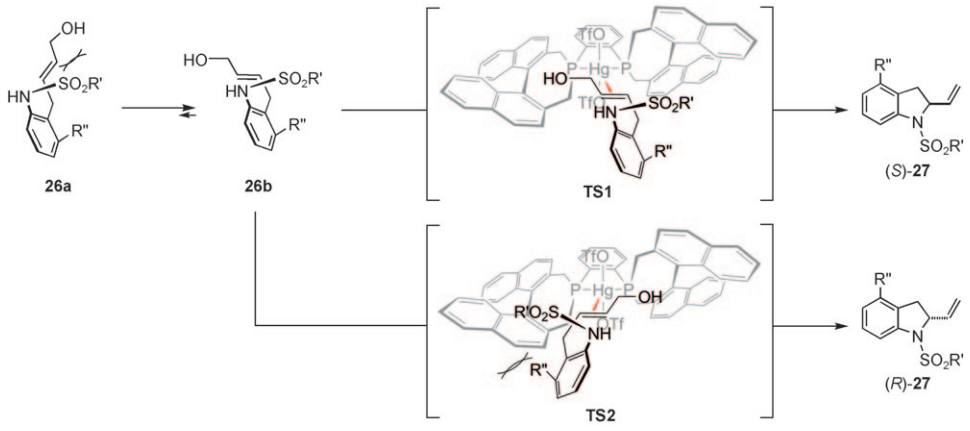
[a] All reactions were carried out with (*R*)-BINAPHANE (1 mol%) and $Hg(OTf)_2$ (1 mol%) in mesitylene for 30 h at −30°C. [b] Yield of isolated product. [c] Determined by HPLC using CHIRALCEL AD-H and OJ-H columns.

Table 3 shows the generality of the present asymmetric catalysis using a variety of *tert*-butyl sulfonamide derivatives. The substituted methyl group at the aromatic ring of aniline had a dramatic effect on the enantioselectivity. Reaction of the 6-methylaniline derivative **8** afforded the corresponding indoline **9** in 72% *ee* (entry 1). 5-Methyl-substituted **10** and 4-methyl-substituted **12** provided indolines **11** and **13**, in 79 and 84% *ee*, respectively. The 3-methyl derivative **14** gave **15** in the highest (99%) *ee* (entry 4). The *ee* obtained using 4,5-dimethyl substituted **16** and 3,5-dimethyl derivative **18** was 83 and 93%, respectively. Although 3-methoxy-substituted **20** resulted in moderate enantioselectivity (i.e., only up to 76% *ee*), the 3-bromoaniline derivative **22** gave 2-vinyl indoline in 92% *ee*. Naphthalene derivative **24** also behaved as a suitable precursor to afford **25** in excellent enantioselectivity.

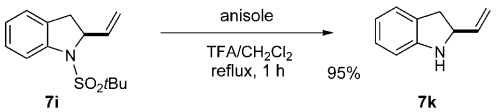
A conceivable mechanism for inducing the enantioselective formation of 2-vinyl indoline derivative is depicted in Scheme 2. Generation of two plausible transition-state models TS1 and TS2 are estimated from the interaction of (*R*)-BINAPHANE–Hg(OTf)$_2$ complex[16] with regard to the stable conformation **26b**.[17] The effect of steric repulsion between the substituted aromatic ring of **26b** and the naphthylmethyl moiety of (*R*)-BINAPHANE is clear in TS2. In comparison to sterically strained transition-state TS2, the reaction proceeds through the well-matched overlapping transition-state TS1, thereby predominantly affording (*S*)-**27**.

Cleavage of *tert*-butyl sulfonamide group in cyclic products was easily achieved under acidic conditions (Scheme 3).[18] Treatment of **7i** with anisole in the presence of TFA under reflux conditions gave (*S*)-2-vinylindoline **7k** in 95% yield without isomerization of the chiral center.

In summary, we found that the novel combination of chiral ligand BINAPHANE with Hg(OTf)$_2$ acts as a highly efficient chiral inducing agent for the dehydrative N-cyclization of anilino allyl alcohol derivatives giving rise to 2-vinyl indoline with excellent selectivity. The present method is useful for syntheses of various indoline derivatives, which are important structural units for drug development.



Scheme 2. Proposed transition state of **26** with (*R*)-BINAPHANE and Hg(OTf)$_2$. R′ = alkyl, phenyl; R″ = methyl, methoxy, bromo.



Scheme 3. Deprotection of *tert*-butyl sulfonamide group. TFA = trifluoroacetic acid.

Experimental Section

General procedure for the catalyzed enantioselective cyclization of (*E*)-*N*-[2-(4-hydroxybut-2-enyl)phenyl]-4-methylbenzenesulfonamide (1) (in Table 1, entry 16): A 0.1 M CH_3CN solution of Hg(OTf)$_2$ (30 μL, 3.0 μmol) was added to a dried two-neck flask under an atmosphere of argon, and the CH_3CN was evacuated under vacuum. To this was added mesitylene (3.0 mL) and (*R*)-BINAPHANE (2.0 mg, 3.0 μmol). After stirring for 5 min at room temperature, a solution of **1** (100 mg, 315 μmol) was added to the mixture, which was then stirred for 40 h at −30 °C. The reaction mixture was immediately subjected to column chromatography on silica gel (hexane/ethyl acetate 5:1) to give compound **2** (93 mg, 99%, 74% *ee*) as a white solid. Enantiomeric purity was determined by HPLC analysis using a DAICEL CHIRALCEL OJ-H column (ϕ 0.46×25 cm), *n*-hexane/*i*PrOH 9:1, flow rate: 3.0 mL min^{-1}, detection at 245 nm: t_R = 3.7 min (*S*, major) and 4.7 min (*R*, minor).

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Keywords: alcohols · allylic compounds · cyclization · enantioselectivity · mercury

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[17] The stable conformation **26b** was proven by single X-ray crystallographic analysis of **14**. CCDC-775612 contains the supplementary crystallographic data. These 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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