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Lewis acid-catalyzed intramolecular amination via 1,3-chirality transfer

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ABSTRACT

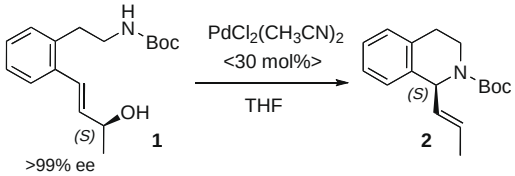
Direct intramolecular amination of the chiral non-racemic allylic alcohol **1** conjugated with a benzene ring afforded the tetrahydroisoquinoline **2** possessing a newly formed alkene in the presence of a catalytic amount of Lewis acid.

An acid-catalyzed direct substitution of an allylic alcohol has attracted a considerable amount of attention from organic chemists over recent years.[1] However, because the hydroxy moiety is a poor leaving group, this process has been largely restricted to multistep syntheses. Thus, the hydroxy group must be transformed into a better leaving group, such as a halide, carboxylate, carbonate, phosphonate, or sulfonate, and then treated with the corresponding nucleophiles (amine or amide) in the presence of a stoichiometric amount of base for amino substitution.[2] Direct amino substitution of alcohols has emerged as an attractive area of research because this approach is considered to be more efficient.[3] Although there are many catalysts for direct amino substitution or amination of allylic alcohols reported in the literature, only a few reports involve chiral transfer with a chiral secondary allylic alcohol as a substrate.[3,4] In most examples, the racemic amine and amide were afforded by passing through the cationic intermediate.[4e,g] Therefore, selective direct amino substitution or amination of chiral allylic alcohols might appear challenging.

We have previously reported the Pd(II)-catalyzed stereoselective cyclization of substrate possessing a chiral allylic alcohol to form the oxaheterocycles via a 1,3-chirality transfer process.[5] In this reaction, the newly formed chiral center is produced by a syn S_N2' process. The reaction proceeds smoothly at 0 °C with excellent stereoselectivity in the absence of any oxidants such as CuCl. During the course of our study on the Pd(II)-catalyzed cyclization of chiral allylic alcohols, we have expanded to apply this method to the synthesis of azahetero cyclic compounds. Recently, we found that azapalladation[6] also took place to form piperidines in the same process.[6c] However, in contrast to oxypalladation, the lower nucleophilicity of nitrogen caused reduced reactivity. In order to investigate the stereoselectivity on the direct intramolecular amination of chiral allylic alcohol, the amino allylic alcohol **1**[7] conjugated with a benzene ring was utilized to afford a tetrahydroisoquinoline that can be found as a core structure in a number of biologically important natural and medicinal products. In this Letter, we report that $Bi(OTf)_3$ catalyzes the direct intramolecular amination of chiral allylic alcohol with high stereoselectivity to construct tetrahydroisoquinoline.

Initially, our developed Pd(II)-catalyzed cyclization was employed as shown in Scheme 1. In the presence of 30 mol % of $PdCl_2(CH_3CN)_2$ at 0 °C in THF, the aza-palladation reaction of amino allylic alcohol **1** proceeded smoothly and the tetrahydroisoquinoline **2** possessing (*E*)-alkenyl moiety was obtained in 74% yield. The ratio of **2**(*S*) and **2**(*R*) was determined as 77:23 by HPLC analysis using a chiral column.[11] At −20 °C, it is noteworthy that the selectivity was increased significantly to 92:8 though the yield dropped down to be 22%. We thought that $PdCl_2(CH_3CN)_2$ might have a limitation in terms of catalyzing direct amino substitution. We therefore decided to explore Lewis acid catalysts for intramolecular amino substitution of the chiral allylic alcohol. The screening of Lewis acids for the cyclization is shown in Table 1.

$NiCl_2$ and Au(I), soft metals, with lower LUMO energy, which are able to provide π-complexes with carbon–carbon multiple bonds (accepter), did not catalyze the cyclization (entries 1 and 2). Furthermore, intramolecular amino mercuration[12] by Hg(II) did not occur with allylic alcohol **1** (entry 3). However, $SnCl_4$, a comparatively hard metal, having relatively higher LUMO energy and strong interaction with heteroatoms, catalyzed the cyclization reaction. Tetrahydroisoquinoline, possessing an (*E*)-alkenyl moiety **2,** was obtained in 83% yield with moderate selectivity (71:29) (entry 4). Comparison of soft and hard metals indicates that a borderline metal[13] possessing both functions was worth examining. $FeCl_3$ efficiently catalyzed the cyclization reaction to afford **2** in 89%



Scheme 1. Pd(II)-catalyzed intramolecular direct amination reaction.

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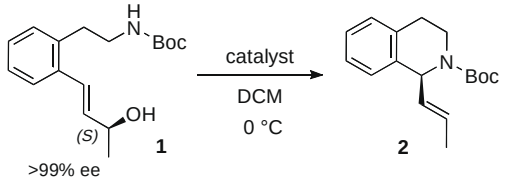
yield with good selectivity (83:17) (entry 5). $Cu(OTf)_2$ did not catalyze the reaction and the starting material **1** was completely recovered (entry 6). $AuCl_3$ promoted cyclization and **2** was obtained in 68% yield with good selectivity (84:16) (entry 7). $SbCl_3$, $GaCl_3$, $InCl_3$, and $BiBr_3$ catalyzed the reaction to afford **2**(*S*) with the same level of stereoselectivity (entries 8–11). The more cationic $In(OTf)_3$ and $Bi(OTf)_3$, compared with the corresponding $InCl_3$ and $BiBr_3$, gave product in higher yield and selectivity in the presence of MS-4 Å (entries 12–13). In contrast, $Bi(OTf)_3$ catalyzed the reaction in high yield with excellent stereoselectivity (94:6) (entry 13). To compare entries 13 and 14, the presence of MS-4 Å was essential to afford the product with high yield in the Bi-catalyzed reaction. Finally, the amino allylic alcohol **1** was cyclized in the presence of 10 mol % of $Bi(OTf)_3$ and MS-4 Å in DCM at -15 °C to afford **2** in 83% yield with the highest level of 1,3-chirality transfer (98:2) (entry 15) via an S_N2'-type reaction.[14] Shibasaki and coworkers reported that $Bi(OTf)_3$ with KPF_6 catalyzed intermolecular direct amination to afford the product as a racemic compound from chiral non-racemic allylic alcohol.[4e] Therefore, it is noteworthy that the intra-molecular amination of **1** catalyzed by $Bi(OTf)_3$ proceeded with an excellent level of 1,3-chirality transfer.

Table 2 shows the effect of solvent on the $Bi(OTf)_3$-catalyzed cyclization. Under the optimized reaction conditions, several solvents were examined. In nonpolar aprotic solvents, such as toluene, the reactivity and selectivity were lower than those in DCM (entries 1 and 2). In CH_3NO_2, a polar solvent, the reactivity decreased and a cyclized product was obtained in low yield (entry 3). No reactions were detected using THF and dioxane (entries 4 and 5). MeOH, a protic solvent, gave no reaction (entry 6).

The scope of the reaction with respect to the substituent on the nitrogen atom was examined with a catalyst (Table 3). The methyl carbamate was less reactive in terms of cyclization than the Boc group. Indeed, the cyclized product was obtained in 65% yield with good selectivity (90:10) (entries 1 and 2). When the Ns (2-nitrobenzenesulfonyl) substituent was used, the reaction was complete within 30 minutes and the corresponding cyclized amide was obtained in 91% yield with moderate selectivity (entry 3). The *p*-methoxybenzyl (PMB) amine did not cyclize at all (entry 4). The amide (Piv) was examined (entry 5). However, no cyclized product was detected and only the starting material was recovered.

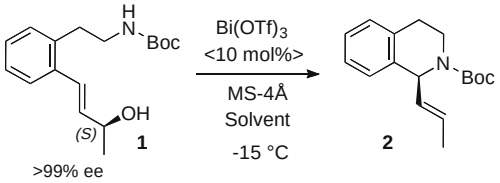
Table 1
Screening of catalysts for the intramolecular direct amination reaction



Entry	Catalyst	Loading (mol %)	Time (h)	Yield (%)	Ratio[a] (2*S*:2*R*)
1	$NiCl_2$	30	24	0	—
2	$AuCl{\cdot}PPh_3$	30	24	0	—
3[b]	$HgCl_2$	30	7	0	—
4[c]	$SnCl_4$	10	0.5	83	71:29
5	$FeCl_3$	10	4	89	83:17
6[c]	$Cu(OTf)_2$	30	3	0	—
7[c]	$AuCl_3$	30	2.5	68	84:16
8[c]	$SbCl_3$	30	1	69	81:18
9[c]	$GaCl_3$	10	0.5	89	84:16
10	$InCl_3$	30	9.5	22	83:17
11	$BiBr_3$	20	9.5	31	81:19
12[c]	$In(OTf)_3$	10	0.75	53	86:14
13[c]	$Bi(OTf)_3$	10	0.5	82	94:6
14	$Bi(OTf)_3$	10	0.5	27	94:6
15[c,d]	$Bi(OTf)_3$	10	0.5	83	98:2

[a] Determined by chiral HPLC.
[b] THF was used as a solvent.
[c] MS-4 Å was added.
[d] At −15 °C.

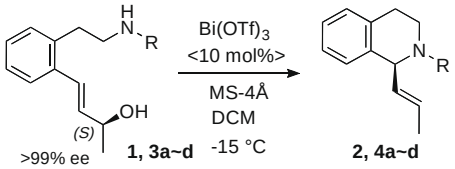
Table 2
Solvent effects on the cyclization



Entry	Solvent	Time (h)	Yield (%)	Ratio[a] (2*S*:2*R*)
1	DCM	0.5	83	98:2
2	Toluene	0.5	67	88:12
3[b]	CH_3NO_2	12	29	83:17
4[c]	THF	24	0	—
5[c]	Dioxane	24	0	—
6[c]	MeOH	8	0	—

[a] Determined by chiral HPLC.
[b] The reaction was allowed to warm to 0 °C.
[c] The reaction was allowed to warm to 23 °C.

Table 3
Effects on the substitution of the amino group



Entry	Compound	R	Product	Time (h)	Yield (%)	Ratio[a] (*S*: *R*)
1	**1**	Boc	**2**	0.5	83	98:2
2	**3a**	CO_2Me	**4a**	1	65	90:10
3	**3b**	Ns	**4b**	1	91	70:30
4[b]	**3c**	PMB	**4c**	24	0	—
5[b]	**3d**	Piv	**4d**	24	0	—

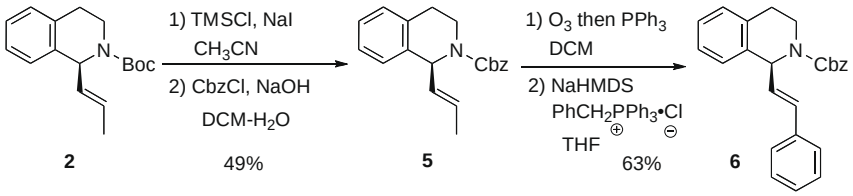
[a] Determined by chiral HPLC.
[b] The reaction was allowed to warm to 23 °C.

In order to determine the absolute configuration of the cyclized product, compound **2** (88% ee) was converted to the known compound (*S*)-**6** (Scheme 2). The Boc group of **2** was replaced by Cbz upon treatment with TMSCl and NaI in acetonitrile followed by treatment with Cbz-Cl in aqueous DCM (49% yield in two steps). Ozonolysis of **5** followed by treatment of the resultant ozonide with PPh_3, and Wittig reaction with benzyl triphenylphosphonium bromide and NaHMDS afforded **6** ($[\alpha]_D^{20}$ +137, *c* 0.25, MeOH) in 63% yield in two steps. The absolute configuration of **6** was confirmed by comparing the sign of its specific optical rotation with the reported data ($[\alpha]_D^{25}$ +155.7, *c* 0.26, MeOH, 96% ee) in the literature.[15]

As shown in Table 4 (entry 1), $Bi(OTf)_3$ was efficient for substrates comprising a substituted methyl group on the benzene ring to afford **8** in 74% yield with a ratio of (*S*)-isomer and (*R*)-isomer of 95:5. However, the allylic alcohol **9** with a tri-substituted group gave **10** possessing a tetra-substituted carbon in 60% yield with a moderate level of 1,3-chirality transfer (entry 2).

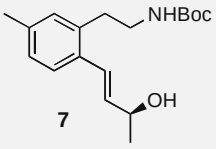
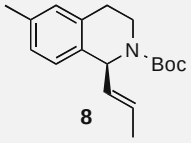
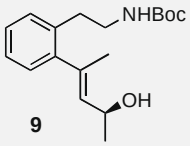
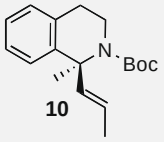
Based on the results, we propose that the reaction intermediate involves interaction between parts of the allylic alcohol and NH-Boc on the central Bi atom, which promotes the intramolecular syn S_N2' amino substitution via 1,3-chirality transfer (Fig. 1).

In summary, we have succeeded in developing a Lewis acid to promote intramolecular syn S_N2' amino substitution of a chiral amino allylic alcohol via 1,3-chiral transfer. The high level of 1,3-chiral transfer was accomplished in the presence of 10 mol % of $Bi(OTf)_3$ in excellent yield. Further investigations on the scope and mechanism of this process are currently underway.



Scheme 2. Determination of the absolute configuration of the cyclized product

Table 4
Scope of the intramolecular amination

Entry	Substrate	Product	Yield (%)	Ratio[a] (*S*:*R*)
1			74	95:5
2			65	74:26

[a] Determined by chiral HPLC.

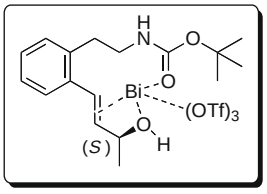


Figure 1. Proposed chelation intermediate.

Acknowledgments

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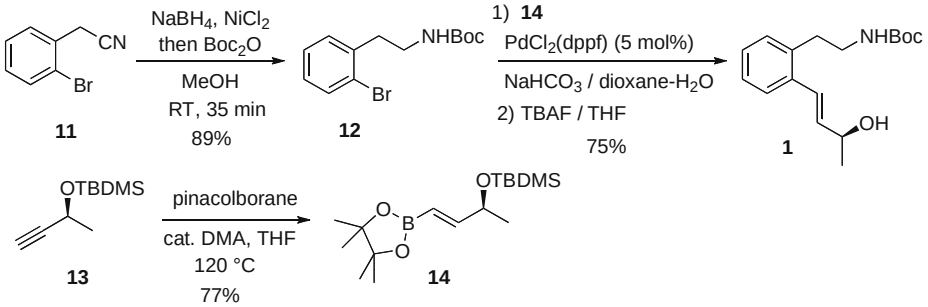
7. Synthesis of the precursor for intramolecular amination of amino allylic alcohol **1** is shown in the following. The carbamate **12** was prepared from the nitrile **11**[8] by reductive protection with $NiCl_2$ and $NaBH_4$, Boc_2O in dioxane. The chiral alkenyl borate **14**[9] was synthesized by hydroboration of the alkyne **13**[10] derived from ethyl L-(*S*)-lactate by the conventional method. The Suzuki cross coupling with bromobenzene **12** and alkenyl borate **14** took place in the presence of $PdCl_2$(dppe) and Et_3N in dioxane and H_2O followed by deprotection of the silyl group by TBAF in THF giving the alcohol **1** in 75% yield in two steps.



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14. *Experimental procedure*: to a flame-dried flask, MS-4 Å (58 mg), $Bi(OTf)_3$ (6.5 mg, 0.01 mmol), and DCM (3 mL) were added. To the mixture was added a solution of **1** (29 mg, 0.1 mmol) in DCM (2 mL) at −15 °C. The reaction mixture was stirred for 30 min at the same temperature, quenched with aqueous saturated $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by PTLC developed with 20% EtOAc in hexane gave **2** (22.7 mg, 0.083 mmol) in 83% yield. ^1H NMR ($CDCl_3$) δ 1.49 (9H, s), 1.68 (3H, d, J = 6.0 Hz), 2.68–2.76 (1H, m), 2.85–2.96 (1H, m), 3.20 (1H, br s), 4.10 (1H, br s), 5.45–5.64 (3H, m), 7.10–7.21 (4H, m).
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