CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201103646

Bismuth Triflate-Catalyzed Asymmetric Allylation of Aromatic Aldehydes

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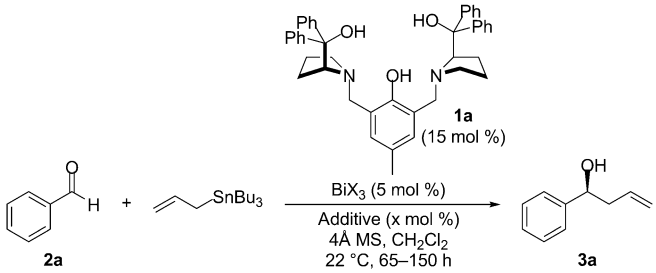
The allylation reaction of carbonyl compounds is well-recognized as one of the most powerful synthetic tools for fast carbon–carbon bond formation.[1] The enantioselective synthesis of homoallylic alcohols is an essential objective in asymmetric synthesis. Enantioenriched homoallylic alcohols are important building blocks for the construction of biologically active compounds.[2] In addition to the processes using stoichiometric chiral reagents or mediators,[3] several catalytic asymmetric methods have been developed, either by using chiral Lewis and Brønsted acids or bases.[4] With the chiral Lewis acid approach, many reactions using allyltributylstannane involve various metal–chiral ligand complexes, in which the catalyst loading is typically 10–20 mol%. This drawback, in addition to the use of expensive or toxic metals, strongly reduces the interest of such methods. However, catalytic enantioselective allylation by using a chiral bismuth(III) complex has never been explored, even though Bi^{III}-derived Lewis acid catalysts have gained widespread use as efficient catalysts for numerous synthetic transformations.[5] Bismuth salts have recently attracted attention due to their low toxicity, low cost, and environmentally benign character.

We describe herein a new method for the enantioselective allylation of aromatic aldehydes using allyltributylstannane and a novel chiral $Bi(OTf)_3$–Trost's (*R*,*R*)-ProPhenol **1a** complex. This phenol ligand, initially reported by Trost,[6] has been used for various reactions.[7]

Our initial studies began with the model coupling of benzaldehyde with allyltributylstannane using a catalytic amount of a bismuth salt and (*R*,*R*)-ProPhenol ligand **1a**. The chiral complex was prepared by reacting BiX_3 (5 mol%) and (*R*,*R*)-ProPhenol **1a** (15 mol%) in dichloromethane in the presence of molecular sieves. After 5.5 h of stirring, benzaldehyde **2a** was added to the pre-catalyst followed by allyltributylstannane. The results are summarized in Table 1. Additives, such as Proton sponge or Hünig's base, were used to avoid any trace of triflic acid released from the hydrolysis of $Bi(OTf)_3$ in the medium.[8] A good level of enantioselectivity was already reached without the use of a base (Table 1, entry 1). However, such additives led to an increase in the enantioselectivity of the homoallylic alcohol **3a** (Table 1, entries 2 and 3), with the two bases being equally efficient. Upon bismuth salt screening, we found that $Bi(OTf)_3$ was more efficient than $Bi(ONf)_3$ or $BiBr_3$ (Table 1, entries 4–7). $Bi(OTf)_3$ used in conjunction with 50 mol% Hünig's base afforded homoallylic alcohol **3a** with the highest enantioselectivity (Table 1, entries 4 and 5). Additionally, the use of anhydrous $Bi(OTf)_3$ led to an increase in yield and a slightly better enantioselectivity was observed (Table 1, compare entry 5 vs. entry 4).

Table 1. Selected optimization experiments illustrating the effects of the bismuth salt and additive used in the enantioselective allylation of benzaldehyde.[a]



Entry	BiX_3	Additive [mol%]		Yield **3a** [%]	*er*[b]
1	$Bi(OTf)_3{\cdot}4H_2O$	–		70	82:18
2	$Bi(OTf)_3{\cdot}4H_2O$	Proton sponge	15	69	92:8
3	$Bi(OTf)_3{\cdot}4H_2O$	Hünig's base	15	53	92:8
4	$Bi(OTf)_3{\cdot}4H_2O$	Hünig's base	50	62	93:7
5	$Bi(OTf)_3$	Hünig's base	50	76	94:6
6	$Bi(ONf)_3{\cdot}4H_2O$	Hünig's base	15	46	89:11
7	$BiBr_3$	Hünig's base	50	42	88:12

[a] Conditions: aldehyde (0.5 mmol), allyltributylstannane (1.2 equiv), 4 Å MS (30 mg). [b] Determined by chiral HPLC analysis.

The influence of the solvent and the ligand structure was evaluated under the optimum conditions cited in Table 1. Reactions conducted in THF, in PhMe or neat were not as efficient as those in CH_2Cl_2 (Table 2, entries 1–4). Under the best conditions in CH_2Cl_2, but using differently substituted (*R*,*R*)-ProPhenol ligands, the corresponding homoallylic alcohol was obtained with a slightly eroded enantioselectivity (Table 2, entries 1, 5–7). Additionally, it appeared that a 1:1 or 1:2 versus 1:3 metal/ligand ratio led to a slight decrease of the enantioselectivity.[9]

In our optimized procedure, the chiral catalyst is prepared by stirring a mixture of $Bi(OTf)_3$ with **1a** in a 1:3 ratio with

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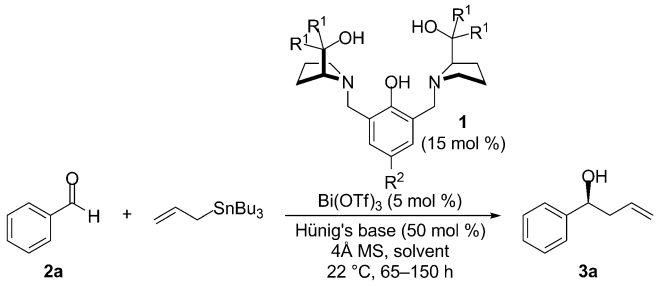
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103646.

Table 2. Influence of the solvent and the structure of (*R*,*R*)-ProPhenol ligand on the model reaction.[a]



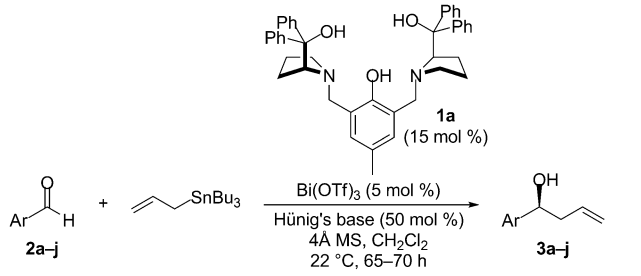
Entry	R^1	R^2	Solvent	Yield **3a** [%]	*er*[b]
1	Ph	Me	CH_2Cl_2	76	94:6
2	Ph	Me	THF	55	85:15
3	Ph	Me	PhMe	5	77:23
4	Ph	Me	–	47[c]	81:19
5	1-naphthyl	Me	CH_2Cl_2	30	90:10
6	Ph	F	CH_2Cl_2	61	91:9
7	Ph	*t*Bu	CH_2Cl_2	82	93:7

[a] Conditions: aldehyde (0.5 mmol), allyltributylstannane (1.2 equiv), 4 Å MS (30 mg). [b] Determined by chiral HPLC analysis. [c] Proton sponge used as the additive.

powdered 4 Å molecular sieves at room temperature in dichloromethane for 5.5 h; upon addition of Hünig's base, the mixture was further stirred for 0.75 h.

The optimal conditions established for the enantioselective allylation of benzaldehyde **2a** were applied to aldehydes **2b–j** (Table 3). The desired homoallylic alcohols **3b–j** were generated in mostly good yields with high enantioselectivities ranging from 93:7 to 96:4 enantiomer ratio (*er*). The reaction also proved to proceed in good yield and high enantioselectivity using naphthyl carboxaldehydes as electrophiles (Table 3, entries 7–9). Our conditions were further applied to a heteroaromatic aldehyde, such as 2-thionyl carboxaldehyde, affording the corresponding homoallylic alcohol in a lower yield but in high enantioselectivity (Table 3, entry 10).

Table 3. Bismuth triflate-catalyzed enantioselective allylation of aromatic aldehydes.[a]



Entry	Ar	Product	Yield **3** [%]	*er*[b]
1	Ph	**3a**	76	94:6
2	4-Me-C_6H_4	**3b**	69	95:5
3	4-MeO-C_6H_4	**3c**	56	93:7
4	2-MeO-C_6H_4	**3d**	76	93:7
5	4-*n*BuO-C_6H_4	**3e**	54	94:6
6	4-Cl-C_6H_4	**3f**	77	94:6
7	1-naphthyl	**3g**	84	96:4
8	2-naphthyl	**3h**	78	94:6
9	4-methyl-1-naphthyl	**3i**	79	95:5
10	2-thionyl	**3j**	65	95:5

[a] Conditions: aldehyde (0.5 mmol), allyltributylstannane (1.2 equiv), 4 Å MS (30 mg). [b] Determined by chiral HPLC analysis.

^{1}H NMR analysis of the formation of $Bi(OTf)_3$-**1a** complexes with different ratios of $Bi(OTf)_3$ and **1a** was studied (Figure 1). We focused our study on a specific region of the ^{1}H NMR spectra (3.7–5.0 ppm), in which two out of the four

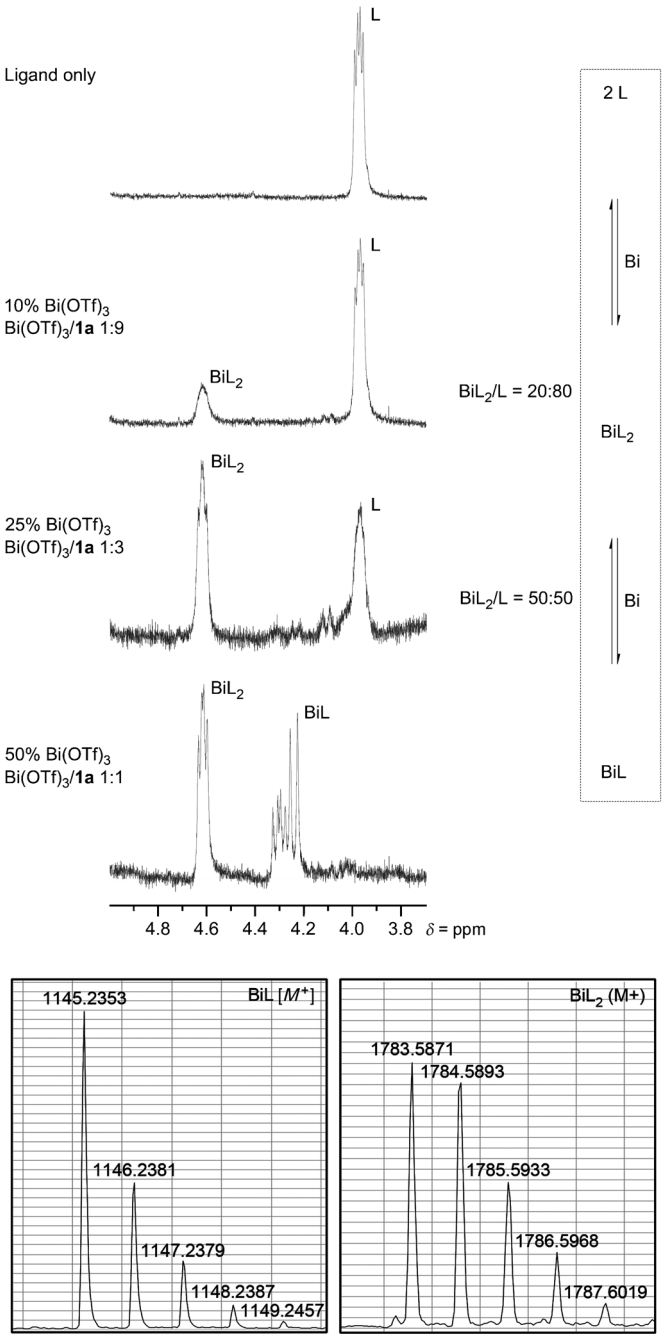


Figure 1. Characterization of the chiral bismuth complexes.

diastereotopic benzylic protons of the ligand can be observed. When 10% $Bi(OTf)_3$ was added to a solution of **1a** ($Bi(OTf)_3$/**1a** 1:9), a new signal at $\delta = 4.6$ ppm appeared. This important deshielding of the benzylic protons would suggest a strong interaction between Bi and ArOH. The relative integrations between this new signal and that of the ligand appeared to be proportionally related in a 2:1 ratio to the amount of bismuth introduced. These results indicated that two equivalents of **1a** (Ligand (L)) and 1 equivalent of $Bi(OTf)_3$ afforded a BiL_2 complex. Adding more bismuth from a mixture containing 25% $Bi(OTf)_3$ ($Bi(OTf)_3$/**1a** 1:3) resulted in the appearance of another signal at $\delta = 4.3$ ppm corresponding to a BiL complex. The hypothesis of these BiL and BiL_2 complexes was further evidenced by HRMS analyses of the mixture containing 50% $Bi(OTf)_3$ ($Bi(OTf)_3$/**1a** 1:1), showing BiL and BiL_2 both as mono-cationic complexes with the loss of one triflate counter-anion.[10] NMR results also allowed us to corroborate our results regarding the Bi/L ratio. Indeed, the best selectivities were obtained with a $Bi(OTf)_3$/**1a** ratio of 1:3 (25% $Bi(OTf)_3$), corresponding to the presence of complex BiL_2 only. Increasing the amount of bismuth resulted in the appearance of complex BiL, which seems detrimental to the selectivity ($Bi(OTf)_3$/**1a** 1:1; 76:24 *er*).[9]

In summary, the catalytic enantioselective allylation reaction of various aromatic aldehydes with allyltributylstannane has been achieved with $Bi(OTf)_3$ and the chiral (*R*,*R*)-ProPhenol ligand. To the best of our knowledge, this method is the first allylation reaction of an aldehyde using a chiral Bi^{III} complex. High enantioselectivities and good chemical yields have been obtained with aromatic and heteroaromatic aldehydes. The conditions have also been applied to aliphatic aldehydes. In preliminary experiments, enantioselectivities up to 96:4 have been obtained.[11] Preliminary characterization including ^{1}H NMR spectroscopy and mass spectrometry data has been provided as first evidence of the pre-catalyst structure. The process has the desirable feature of using a low catalyst loading of an environmentally benign Lewis acid. In addition, both the Lewis acid and the chiral ligand are commercially available. The chiral ligand is also easily recycled. Further studies to clarify the precise mechanism are now in progress.

Experimental Section

General procedure: In a flame dried vial (12×35 mm, 0.5 dr) equipped with triphenylbismuthine (11.1 mg, 0.025 mmol) in freshly distilled CH_2Cl_2 (0.25 mL) was added freshly distilled trifluoromethanesulfonic acid (6 μL, 0.068 mmol). The solution was stirred for 4.5 h at room temperature under argon atmosphere. Then this catalyst solution was transferred into a flame dried test tube filled with (*R*,*R*)-ProPhenol ligand **1a** (49.1 mg, 0.075 mmol) and 4 Å MS (30 mg) in freshly distilled CH_2Cl_2 (0.25 mL). The obtained mixture was stirred for 5.5 h at room temperature followed by addition of Hünig's base (44 μL, 0.25 mmol). After 0.75 h, the aldehyde (0.5 mmol) and allyltributylstannane (185 μL, 0.6 mmol) were added to the above mixture. The reaction was stirred at room temperature for 65–70 h and quenched by addition of saturated $NaHCO_3$ (0.5 mL). The contents were stirred for another 1 h and then poured over $MgSO_4$ and filtered through a plug of Celite. The crude material was purified by silica gel chromatography (Hexanes/EtOAc) to afford the desired homoallylic alcohol. The enantiomeric excess of the product was determined by chiral HPLC analysis. The HPLC conditions and the spectral data of all compounds are provided in the Supporting Information.

Acknowledgements

This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT, Québec, Canada), the Centre in Green Chemistry and Catalysis (CGCC), the Canada Foundation for Innovation, and Université Laval.

Keywords: allylation · asymmetric catalysis · bismuth · homoallylic alcohols · Lewis acids

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[10] BiL: HRMS (ESI-TOF) calcd for $C_{45}H_{46}BiF_6N_2O_9S_2^+$: 1145.2347 $[LBi(OTf)_2]^+$; found: 1145.2353. BiL_2: HRMS (ESI-TOF) calcd for $C_{88}H_{92}BiF_6N_4O_{12}S_2^+$: 1783.5856 $[L_2Bi(OTf)_2]^+$; found: 1783.5871.

[11] The same conditions have been applied without further optimization to aliphatic aldehydes. In preliminary experiments, the reaction of allyltributylstannane with cyclohexanecarboxaldehyde and 2-(benzyloxy)acetaldehyde furnished the corresponding homoallylic alcohol with good selectivities (88:12 and 96:4, respectively) and unoptimized yields (45 and 28%, respectively).

Received: November 18, 2011
Published online: February 15, 2012

