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Direct Catalytic Asymmetric Aminoallylation of Aldehydes: Synergism of Chiral and Nonchiral Brønsted Acids

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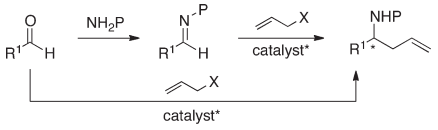
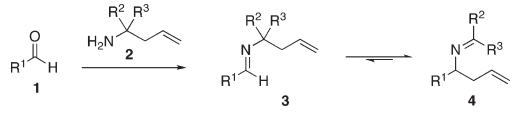
Supporting Information

ABSTRACT: The development of a catalytic asymmetric method for the direct aminoallylation of aldehydes is described that gives high asymmetric inductions for a broad range of substrates including both aromatic and aliphatic aldehydes. This method allows for direct isolation of unprotected analytically pure homoallylic amines without chromatography. The unique catalyst system developed for this process involves the synergistic interaction between a chiral and a nonchiral Brønsted acid.

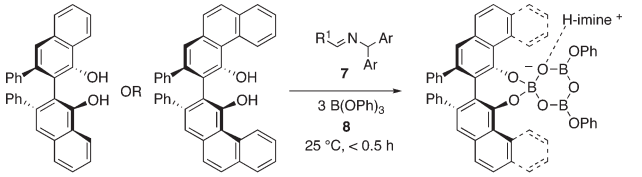
Of the known catalytic asymmetric methods for the synthesis of homoallylic amines[1] from aldehydes, the most popular is a two-step method that involves the formation of an imine and then catalytic asymmetric allylation of the imine or imine derivative.[2] Due to the low reactivity of C=N bonds, activating groups or reactive organometallic reagents are necessary. In contrast, there is only a single report on the catalytic asymmetric synthesis of homoallylic amines directly employing aldehydes as substrates.[3] We report here the development of a new method for the catalytic asymmetric synthesis of homoallylic amines directly from aldehydes that is based on a chiral polyborate catalyst generated from the vaulted biaryl ligand VANOL. This method is scalable since it is chromatography free and it gives rise to unprotected homoallylic amines with excellent asymmetric inductions over a broad range of substrates including both aromatic and aliphatic aldehydes.



Our approach builds on the method developed by Kobayashi[4] and Rueping[3] involving the aza-Cope rearrangement of imines **3** derived from 3-butenyl-1-amines of type **2**. With proper control of the nature of the substituents R^2 or R^3 on amine **2**, they were able to either sterically[4,5] or electronically[3] drive the reversible Cope rearrangement to isomer **4**.[6] In the study by Rueping it was found that two phenyl groups (R^2, R^3) were sufficient to drive the equilibrium to isomer **4**.



We recently identified the boroxinate−iminium complex **9**[7] as the active catalyst in the aziridination of imines[8,9] and the heteroatom Diels−Alder reactions of imines.[10] This catalyst is an entirely new class of chiral Brønsted acids that in the cases of the boroxinate **9** exists as an ion pair consisting of a chiral boroxinate anion derived from either the VANOL or VAPOL ligand and a protonated iminium. In the development of these reactions it was found that a diphenylmethyl group on the imine nitrogen was important for high asymmetric inductions.[7,9] It was furthermore found that both the rates and inductions for the reaction could be increased with the proper substitution pattern in the two aryl groups in **7**.[8h,j] Most interestingly, the boroxinate catalyst **9** only forms when the imine substrate is added.[7a,b] Boroxinate assembly can be induced by the imine either from the ligand and commercial $B(OPh)_3$ or from the ligand and $BH_3 \cdot SMe_2$, phenol, and H_2O.[7a,b,8i] Characterization of this chemzyme−substrate complex **9** (from VAPOL) by X-ray diffraction revealed the presence of several noncovalent interactions including an H-bond of the iminium to one of the boroxinate oxygens as well as a $\pi-\pi$ stacking and a series of CH−π interactions.[7b] These interactions between the substrate and the catalyst added to the understanding of how certain groups on the benzhydryl substituent can affect the binding and the outcome of the aziridination reaction.



(*S*)-VANOL **5** (*S*)-VAPOL **6** **9** B3 catalyst

We hoped to take advantage of what we learned about the interactions of the imines **7** and the boroxinate catalyst; however, initial results were not encouraging since the VAPOL B3 catalyst **9** gave the Cope product **12a** in 2% ee and the VANOL B3 catalyst gave 19% ee (Table 1, entries 1 and 3).[11] During the course of optimization, it was found that the rearrangement of imine **10a** prepared from a sample of benzaldehyde that had not been distilled for 2 weeks led to a slightly higher induction with the VANOL catalyst (27% vs 19% ee). It was speculated that a small amount of benzaldehyde was oxidized to benzoic acid and that its presence in a catalytic amount was responsible for the enhanced asymmetric induction. To test this assumption, 10 mol % benzoic acid was added to the reaction mixture. While a negligible effect was observed for the VAPOL catalyst (entry 2), a significant increase in ee was observed for the VANOL catalyst (entry 4).

Attention was then turned to the imine **11a** in which the aryl groups are both 3,5-dimethylphenyl substituents. This substitution pattern was found to increase the asymmetric

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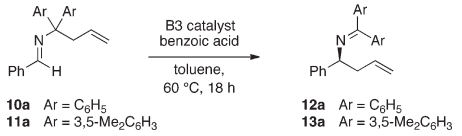
Table 1. Effects of Ligand and Benzoic Acid on the Aza-Cope Reaction[a]



10a Ar = C_6H_5
11a Ar = 3,5-$Me_2C_6H_3$

12a Ar = C_6H_5
13a Ar = 3,5-$Me_2C_6H_3$

entry	imine	ligand	mol % catalyst	mol % $C_6H_5CO_2H$	% yield **12a**/**13a**[b]	% ee **12a**/**13a**[c]
1	**10a**	(*R*)-VAPOL	20	0	67	2
2	**10a**	(*R*)-VAPOL	20	10	67	4
3	**10a**	(*R*)-VANOL	20	0	80	19
4	**10a**	(*R*)-VANOL	20	10	78	45
5	**10a**	(*R*)-VANOL	10	5	76	42
6	**10a**	none	0	10	NR	—
7	**11a**	(*R*)-VANOL	10	0	77	25
8	**11a**	(*R*)-VANOL	10	1	80	40
9	**11a**	(*R*)-VANOL	10	5	85	69
10	**11a**	(*R*)-VANOL	10	10	81	72
11	**11a**	(*R*)-VANOL	10	15	81	72
12	**11a**	(*R*)-VANOL	10	20	83	70
13	**11a**	(*R*)-VANOL	10	40	84	68
14	**11a**	(*R*)-VANOL	10	60	84	66
15	**11a**	(*R*)-VANOL	10	10	89	78[d]
16	**11a**	(*R*)-VAPOL	10	5	84	9
17	**11a**	(*R*)-BINOL	10	0	63	15[e]
18	**11a**	(*R*)-BINOL	10	10	78	36[e]
19	**11a**	(*R*)-3,3-Ph_2BINOL	10	0	78	13[e]
20	**11a**	(*R*)-3,3-Ph_2BINOL	10	10	62	−7[e]

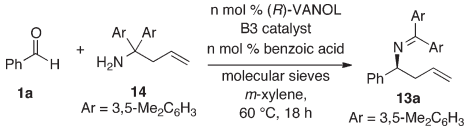
[a] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine for 18 h and went to 100% completion at 60 °C. The precatalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \cdot SMe_2$, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg. [b] Isolated yield after silica gel chromatography. [c] Chiral HPLC. [d] Solvent is *m*-xylene. [e] Reaction time is 44 h.

induction and the rate (10×) over that of the unsubstituted benzhydryl group in aziridinations of imines of type **7**.[8h] The induction was found to increase for the aza-Cope rearrangement from 42% ee for **10a** (entry 5) to 69% ee with **11a** (entry 9). The difference between VANOL and VAPOL was significant also with imine **11a**, the former giving 69% ee and the latter 9% ee under identical conditions (entries 9 vs 16). This is in stark contrast to the aziridination reaction where these two ligands were equipotent.[8g,h,j] Neither the catalyst derived from BINOL nor 3,3′-diphenylBINOL proved to be effective for the Cope rearrangement of **11a** (entries 17−20).[12]

A survey of the effect of added benzoic acid on the induction (entries 7−14) reveals that the optimal amount is 1 equiv relative to the boroxinate catalyst. A number of other carboxylic acids were also screened including substituted benzoic acids and aliphatic acids, but none proved superior to benzoic acid (see Supporting Information (SI)). Most of the reactions in Table 1 were performed in toluene, but upon screening many different solvents (see SI) it was found that *m*-xylene gave the highest induction (entry 15).

Orthogonal interplay of chiral and nonchiral Brønsted acids was reported by Rueping's group[13] in 2006 and Antilla's group in 2009.[14] In the former reaction, the two Brønsted acids were

Table 2. Direct Aminoallylation of Benzaldehyde[a]



1a + **14** Ar = 3,5-$Me_2C_6H_3$ → **13a** Ar = 3,5-$Me_2C_6H_3$

entry	*n* mol %	mol sieves	MS loading	% yield **13a**[b]	% ee **23a**[c]
1[d]	10	4 Å	300	10[e]	—
2[d]	10	5 Å	300	84	71
3	10	5 Å	100	82	76
4	10	5 Å	10	72	53
5	5	5 Å	100	82	75
6	5	5 Å	50	92	80
7	0	5 Å	300	15[e]	—

[a] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in *m*-xylene at 0.2 M in amine **14** with 1.1 equiv of aldehyde **1a** for 18 h and went to 100% completion at 60 °C. The precatalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \cdot SMe_2$, 2 equiv of 2,4,6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg. [b] Isolated yield after silica gel chromatography. [c] Chiral HPLC. [d] Molecular sieves added after stirring VANOL B3 catalyst and amine for 30 min at 60 °C. [e] Percent completion of the reaction as determined by the ^1H NMR spectrum of the crude.

involved in two parallel steps, while, for the latter, an achiral Brønsted acid was utilized to maintain a sufficient concentration of iminium. In neither report was the addition of the achiral acid observed to affect the asymmetric induction. However, in the present case, the addition of benzoic acid led to not only a rapid color change of the reaction mixture from beige to bright yellow but also more importantly a *significant enhancement* in the enantioselection (Table 1, entries 7 and 10), which clearly indicates a synergistic interaction of these two Brønsted acids. Akiyama has reported a related observation,[15] which, to the best of our knowledge, is the only other example of a nonorthogonal, or synergistic coexistence of a chiral and an achiral strong Brønsted acid in asymmetric catalysis where the result is an increase in asymmetric induction.[16,17]

At this point, it was decided to determine whether the conditions that have been optimized for the Cope rearrangement of imine **11a** could be translated to a direct aminoallylation of benzaldehyde. The initial answer was no. The reaction of benzaldehyde **1a** with amine **14** in the presence of 4 Å molecular sieves to absorb the water only went to 10% completion in 18 h with 10 mol % catalyst (Table 2, entry 1). Remarkably, when 5 Å sieves were employed, the reaction went to completion to give the homoallyic imine **13a** in 84% yield and 71% ee.[18] The optimal procedure gave 92% yield and 80% ee with 5 mol % catalyst[19,20] and 50 mg of 5 Å molecular sieves (entry 6).

The scope of the asymmetric catalytic aminoallylation of aromatic aldehydes with the VANOL boroxinate catalyst was probed with the 12 substrates indicated in Table 3. All of the reactions in Table 3 were performed on gram scale (4.0 mmol) to facilitate the isolation of the homoallylic amine product. The amines **15** were purified by dissolution into aqueous acid and then extraction of the impurities with ethyl acetate. This simple procedure is not scale limited and leads to the isolation of analytically pure hydrochloride salts suitable for prolonged storage or immediate

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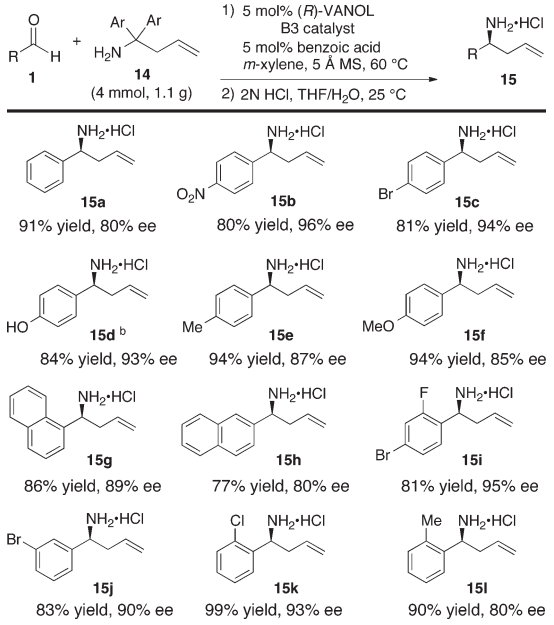
Table 3. Asymmetric Catalytic Aminoallylation of Aromatic Aldehydes[a]



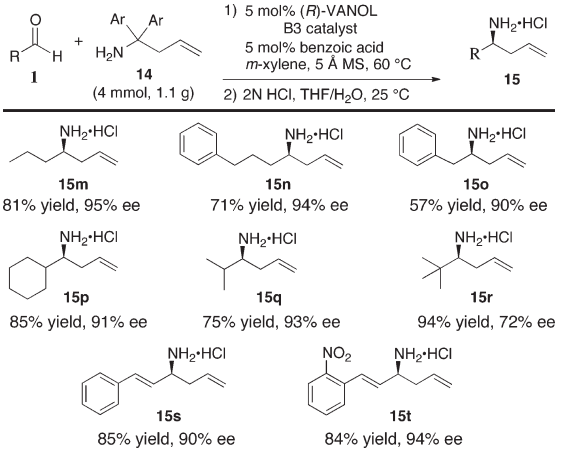
[a] Unless otherwise specified, all reactions were performed as described in Table 2 (entry 6) on a 4.0 mmol scale and went to completion in 18−30 h except the reaction of aldehyde **1f** which required 55 h. The hydrolysis step required 3−18 h for completion. The asymmetric inductions are the average of two runs, one each with (*R*)- and (*S*)-VANOL. The inductions were measured on the corresponding Cope rearrangement product **13** except where indicated in the Supporting Information. The yields are based on amine **14** and are of salt **15** purified by dissolution into aqueous acid and extraction of impurities with ethyl acetate. [b] Reaction on *p*-acetoxybenzaldehyde.

use. Slightly higher inductions were obtained with aryl aldehydes with electron-withdrawing substituents; nonetheless, *p*-methoxybenzaldehyde **1f** reacts to give the amine **15f** in 94% yield and 85% ee. As a surrogate for *p*-methoxybenzaldehyde, *p*-acetoxybenzaldehyde **1d** will give the homoallylic amine **15d** in an improved induction of 93% ee. The asymmetric inductions were measured in a separate reaction in which the corresponding imine **13** was isolated and fully characterized (see SI).

A lacuna in the only existing method for the asymmetric catalytic amino-allylation of aldehydes is the subclass of aliphatic aldehydes.[3] Thus, we were pleased to find that the optimized protocol developed for the aromatic aldehydes in Table 3 could be directly applied to aliphatic aldehydes and excellent asymmetric inductions (90−95% ee) for a variety of unbranched and α-branched aliphatic aldehydes were observed (Table 4). The only limitation encountered was with an α,α-doubly branched aldehyde where the amine **15r** was obtained in only 72% ee.

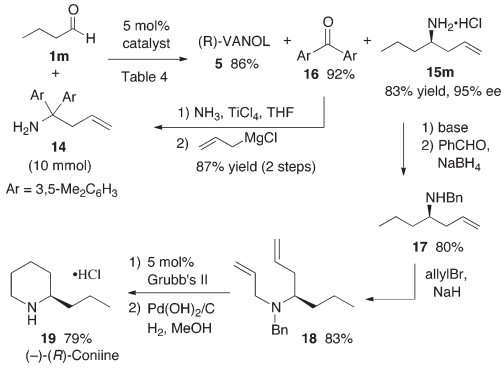
Coniine, the hemlock alkaloid, contains a piperidine ring, and in Scheme 1 we illustrate how the asymmetric catalytic amino-allylation of *n*-butanal can be utilized in its synthesis. The chiral center is installed in acyclic amine **15m**, and the piperidine ring is closed using a metathesis reaction. The ring-closing metathesis reaction has been previously employed in the synthesis of coniine; however, in all of those syntheses, the chiral center was installed via a chiral auxiliary.[21] Reductive cleavage of the benzyl group and saturation of the double bond

Table 4. Aminoallylation of Aliphatic and Alkenyl Aldehydes[a]



[a] Unless otherwise specified, all reactions were performed as described in Table 2 (entry 6) on a 4.0 mmol scale and went to completion in 18−30 h. The hydrolysis step required 6−10 h for completion. The asymmetric inductions are the average of two runs, one each with (*R*)- and (*S*)-VANOL. The inductions were measured on the corresponding Cope rearrangement product **13** except where indicated in the SI. The yields are based on amine **14** and are of the salt **15** purified by dissolution in aqueous acid and extraction of impurities with ethyl acetate.

Scheme 1



gives coniine in 78% yield for the last three steps. This synthesis was also chosen to demonstrate how the amine **14** and the VANOL ligand can be recycled. The amino-allylation of *n*-butanal was carried out on 10 mmol scale, and after the hydrolysis of the imine **13m**, the aryl ketone **16** was isolated from the reaction in 92% yield and the VANOL could be recovered in 86% yield. **16** could be converted back to **14** in 87% yield in one pot where an allyl Grignard was added directly to the N−H imine which was generated in situ by treatment of **16** with ammonia and titanium tetrachloride.[22]

The spiro-boroxinate **9** is the catalyst for aziridinations and heteroatom Diels−Alder reactions of imines,[7] but in the present case it is suspected that the catalyst for the aminoallylation is a boroxinate that has incorporated a molecule of benzoic acid. Further studies are ongoing to determine not only the structure and function of the active catalyst for the aminoallylation but also the synthetic applications of this practical method for the catalytic asymmetric aminoallylation of aldehydes.

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■ ASSOCIATED CONTENT

Supporting Information. Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(11) The catalyst is prepared from 1 equiv of VANOL, 3 equiv of $BH_3 \cdot SMe_2$, 2 equiv of phenol, and 3 equiv of H_2O as described in the Supporting Information and in ref 8i.

(12) We are currently examining the structures of the catalysts from these ligands produced under the same conditions that give the boroxinates **9** for VANOL and VAPOL.

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(16) For an example where a protic solvent can accelerate the rate of a reaction, see: Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631–3634.

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(18) We thank Professor David MacMillan for suggesting the use of 5 Å molecular sieves.

(19) The catalyst prepared from 2,4,6-trimethylphenol gives slightly higher inductions than the same catalyst prepared from phenol. For example, the catalyst from 2,4,6-trimethylphenol gives an 83% ee and 79% yield under the conditions in entry 15 of Table 1.

(20) It has been shown that boroxinate formation can be induced by amines: Hu, G., Ph. D. Thesis, Michigan State University, 2007.

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