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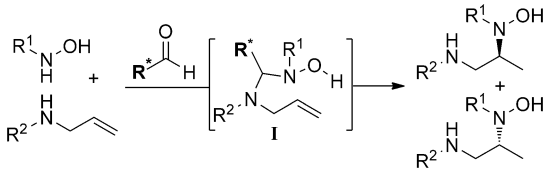
Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts

Melissa J. MacDonald,[a] Colin R. Hesp,[a] Derek J. Schipper,[a] Marc Pesant,[b] and André M. Beauchemin*[a]

Asymmetric catalysis is of enormous academic and industrial importance as a highly efficient approach to enantioenriched organic molecules. Enzymes and bifunctional catalysts are among the most efficient systems available to perform difficult intermolecular reactions with nearly perfect stereocontrol. This efficiency stems from their ability to perform substrate activation while favoring substrate preassociation and preorganization. However, highly efficient asymmetric catalysis does not require both activation methods. Many asymmetric catalysts achieve high enantioselectivities by performing substrate activation in a chiral environment alone. In contrast, and despite the possibility of accelerating intermolecular reactions by a factor of 10^4 to 10^8 through substrate preassociation,[1] catalytic reactions relying exclusively on temporary intramolecularity are rare, and highly efficient examples of such asymmetric catalysis have not been reported.[2] Herein, we show that chiral aldehydes are capable tethering asymmetric catalysts, leading to highly enantioenriched vicinal diamine motifs through temporary intramolecularity alone.

Recently, we reported that aldehydes catalyze intermolecular Cope-type hydroaminations of allylic amines via the formation of a temporary tether [(Eq. (1)].[3,4] In contrast to common tethering strategies,[5] which rely on the stepwise assembly and cleavage of a tether, this approach uses aldehydes as catalysts to access a transient mixed aminal in situ and thus allow a facile "intramolecular" hydroamination. Although encouraging enantioselectivities suggested that transfer of stereochemical information from chiral aldehydes was possible (4 examples, 47–87% *ee*), initial efforts were thwarted by catalyst epimerization and reproducibility issues. Seeking to develop an enantioselective hydroamination[6,7] approach to synthetically useful vicinal diamines[8] and to establish that highly efficient stereoinduction is possible by means of tethering catalysis, we embarked on a systematic survey of chiral aldehyde catalysts and reaction conditions (selected data shown in Table 1).

In a previous communication, we had shown that commercially available (*R*)-glyceraldehyde acetonide (**1a**) led to

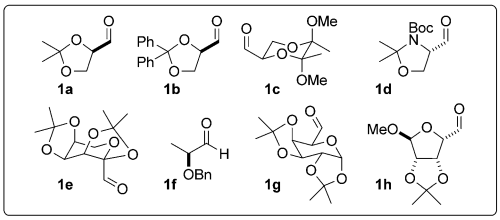


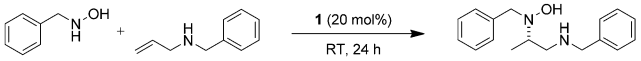
(1)

Efficient enantioinduction via stereocontrolled formation of **I**

21 examples, up to **97% *ee***
Access to both enantiomers with appropriate R*CHO

Table 1. Representative results of chiral aldehyde screening[a]





Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a**	C_6H_6	93	75
2	**1b**	C_6H_6	91	88
3	**1c**	C_6H_6	16	37
4	**1d**	C_6H_6	12	9
5	**1e**	C_6H_6	5	3
6	**1f**	C_6H_6	16	9
7	**1g**	C_6H_6	51	−85
8	**1h**	C_6H_6	41	−94
9	**1f**	C_6H_6	34	8[d]
10	**1g**	C_6F_6	54	−94[d]
11	**1h**	C_6F_6	46	−93[e]
12	**1b**	C_6F_6	91	97[d]

[a] Performed with hydroxylamine (1 equiv), allylamine (1.5 equiv), and catalyst **1a–h** (0.2 equiv) in a solvent (1 M) under argon, for 24 h at room temperature. [b] Determined by ^{1}H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard. [c] Determined by chiral HPLC analysis of derivatized products (see the Supporting Information). [d] Catalyst was added to the reaction mixture last. [e] At 10 mol%, catalyst **1h** gave 89% *ee* with a 43% NMR yield in 72 h.

[a] M. J. MacDonald, C. R. Hesp, D. J. Schipper, Prof. A. M. Beauchemin
Centre for Catalysis Research and Innovation
Department of Chemistry, University of Ottawa
10 Marie-Curie, Ottawa, ON K1N 6N5 (Canada)
E-mail: andre.beauchemin@uottawa.ca

[b] M. Pesant
Boehringer Ingelheim (Canada) Ltd
2100 Cunard Street, Laval, QC, H7S 2G5 (Canada)

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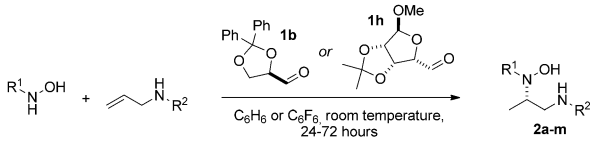
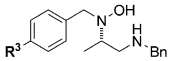
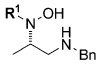
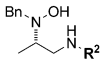
enantioenriched products with moderate enantiocontrol (3 examples, 45–78% *ee*; Table 1, entry 1). However, this aldehyde is notorious for its ready epimerization, and preliminary efforts thus focused on the identification of a more robust aldehyde. Increased enantioselectivity was observed with the more easily handled diphenyl analogue **1b** (88% *ee*; Table 1, entry 2), but an early screening of the substrate scope showed that this procedure was not general and was plagued by some catalyst epimerization. Unfortunately, the Ley aldehyde[9] (**1c**), the Garner aldehyde[10] (**1d**), and an aldehyde lacking an α proton (**1e**) led to poor reactivity and enantiocontrol (Table 1, entries 3–5). The low yields obtained with these aldehyde catalysts suggest that their steric bulk has a negative impact on the preassociation step, which involves the formation of the mixed aminal **I**. However, the acyclic aldehyde **1f** also showed poor reactivity (Table 1, entry 6), which highlights the benefits associated with the cyclic structures present in **1a** and **1b**. It is also worth noting that catalysts **1a–d** and **1f** had the common problem that epimerization (via enamine formation, for example) would lead to catalyst racemization. In contrast, the bicyclic aldehydes **1g** and **1h** possess several stereocenters embedded in a rigid bicyclic structure that could help prevent epimerization and help ensure retention of the original chirality.[11] Encouragingly, high enantioselectivities were observed with both the 6- and 5-membered bicyclic aldehydes **1g** (85% *ee*; Table 1, entry 7) and **1h** (94% *ee*; Table 1, entry 9). Catalyst **1h** showed remarkable stability as the reaction proceeds in 72 h with high selectivity. In addition, these catalysts led to the *R* enantiomer of the diamine, which complements the ability of catalyst **1b** to provide access to the *S* enantiomer. Fortunately, two additional observations were made during this screening process that led to higher enantioselectivities with catalyst **1b**. We found that addition of the catalyst last proved optimal, and higher enantioselectivities were obtained with C_6F_6 as solvent. By following this revised procedure, catalyst **1b** afforded the *S* enantiomer in 97% *ee* (Table 1, entry 11)!

With efficient conditions giving access to either enantiomer of the diamine motifs with catalysts **1b** and **1h**,[12] the applicability of this enantioselective reaction was evaluated (Table 2). Electron-rich and electron-poor benzylic hydroxylamines displayed excellent enantioselectivity with benzylallylamine as substrate (Table 2, entries 1–6). In contrast, reduced enantioselectivity was seen with two aliphatic hydroxylamines (Table 2, entries 7–9). To determine if this effect was steric or electronic in nature, the reaction of benzylhydroxylamine and methylallylamine was also performed. This reaction led to reduced enantioselectivity (56% *ee*; Table 2, entry 10), which suggests that the size of the allylic amine is important for high enantioselectivity. Additionally, the lower enantioselectivity could result from reduced diastereoselectivity in the formation of the mixed aminal **I** or from an amine-catalyzed aldehyde epimerization process (see below). To probe this, many secondary allylic amines were reacted with benzylhydroxylamine and catalysts **1b** and **1h** (Table 2, entries 11–20). Collectively, these results reveal

Table 2. Scope of asymmetric hydroamination with chiral aldehydes[a]



Entry	Product	Catalyst	Yield [%][b]	*ee* [%][c]
				
1	R^3 = H (**2a**)	**1b**	91	97
2	R^3 = H (**2a**)	**1h**	79	−88
3	R^3 = Cl (**2b**)	**1b**	81	94
4	R^3 = OMe (**2c**)	**1b**	86	92
				
5	R^1 = 3,5-$(CF_3)_2$Bn (**2d**)	**1b**	82	82
6	R^1 = 3,5-$(CF_3)_2$Bn (**2d**)	**1h**	74	−92
7	R^1 = *i*Pr (**2e**)	**1b**	60	60
8	R^1 = $(CH_2)_3$Ph (**2f**)	**1b**	63	71
9	R^1 = $(CH_2)_3$Ph (**2f**)	**1h**	60	−77
				
10	R^2 = Me (**2g**)	**1b**	91	56
11	R^2 = allyl (**2h**)	**1b**	85	82
12	R^2 = allyl (**2h**)	**1h**	76	−88
13	R^2 = *p*-NO_2Bn (**2i**)	**1b**	83	95
14	R^2 = BrBn (**2j**)	**1b**	81	90
15	R^2 = $CH_2CH(OEt)_2$ (**2k**)	**1b**	62	60
16	R^2 = $CH_2CH(OEt)_2$ (**2k**)	**1h**	51	−88
17	R^2 = CH_2CO_2Et (**2l**)	**1b**	75	72
18	R^2 = CH_2CO_2Et (**2l**)	**1h**	71	−91
19	R^2 = $(CH_2)CO_2Me$ (**2m**)	**1b**	73	82
20	R^2 = $(CH_2)CO_2Me$ (**2m**)	**1h**	66	−90

[a] Performed with hydroxylamine (1 equiv), allylamine (1.5 equiv), and catalyst (0.2 equiv) in solvent (1 M) under argon, for 24 h with catalyst **1b** (and 72 h with **1h)** at room temperature. [b] Yields of the isolated product. [c] Determined by chiral HPLC analysis of derivatized products (see the Supporting Information).

that the enantioselectivities obtained with catalyst **1b** are quite sensitive to the structure of the allylic amine (Table 2, entries 10, 11, 13, 15, 17, and 19), and that the lowest enantioselectivities are observed with the least nucleophilic amines (60–95% *ee*; Table 2, entries 15 and 17 vs. 19). In contrast, **1h** afforded the enantiomeric products reliably in high enantioselectivities (88–91% *ee*; Table 2, entries 12, 16, 18, and 20). Overall, the enantioselectivities obtained are, in many cases, the highest obtained for intermolecular hydroaminations of unactivated alkenes by any method[7i,j] (including metal-catalyzed reactions) and clearly validate the tethering strategy as an effective method in asymmetric organocatalysis.

The enantioselectivity trend highlighted above for aldehyde **1b** suggests that catalyst epimerization occurs under the reaction conditions. To probe this, the aldehyde was separately exposed to catalytic amounts of each reagent and the enantiopurity of the catalyst was determined after 24 h (Figure 1). Both experiments showed significant epimeriza-

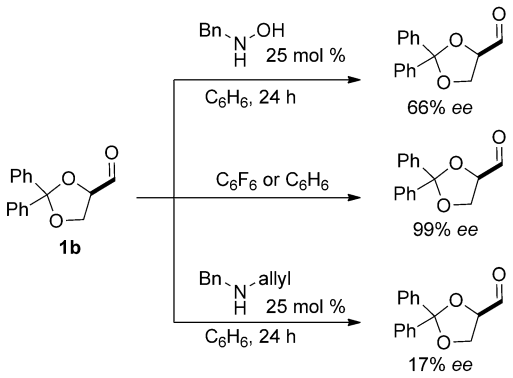


Figure 1. Probing the source of epimerization for catalyst **1b**.

tion, with benzylallylamine (25 mol%) leading to almost complete racemization and benzylhydroxylamine (25 mol%) leading to recovered aldehyde in 66% *ee*. Control experiments also showed that no epimerization of the catalyst occurred simply upon stirring in benzene or hexafluorobenzene. In agreement with this, the highest enantioselectivities observed with catalyst **1b** involve the fastest reactions.[13]

With less nucleophilic amines, catalyst racemization is a competing side reaction, leading to formation of the desired adduct in 60 and 72% *ee* (Table 2, entries 15 and 17). Because aldehyde **1b** epimerizes over time, even if stored neat under argon at reduced temperatures (7–14 d, depending on the batch), oxidation of the commercially available alcohol precursor prior to each reaction proved a reliable experimental procedure. In contrast, catalyst **1h** is more robust, because of its bicyclic nature, and affords the enantiomeric products in high *ee* (Table 2, entries 16 and 18). In agreement with this observation, the nitrone derived from **1h** proved remarkably stable toward epimerization in the presence of either excess hydroxylamine or amine (NMR spectra are provided in Figure S1 of the Supporting Information).

The proposed mechanism is presented in Figure 2, and has been thoroughly examined for the related racemic reactions involving α-benzyloxyacetaldehyde.[14] Condensation of the hydroxylamine and the aldehyde precatalyst affords a nitrone, which is rapidly attacked by an allylic amine to form a transient, chiral mixed aminal **I** (likely with high stereocontrol). This stereocenter is then efficiently transferred[5,15] through the bicyclic transition state associated with a Cope-type hydroamination. With α-benzyloxyacetaldehyde, the latter step was shown to be rate determining.[14] Thus it is not clear if, in this system, the stereoinduction results from the stereoselective formation of aminal **I** because of a preference for one of the two diastereomeric transition states for the Cope-type hydroamination, or from the synergy between these two steps. Experiments are underway to determine the origin of enantioinduction in this system.

In summary, we have shown that aldehydes catalyze the intermolecular hydroamination of unactivated alkenes in high enantiomeric excess. Both enantiomers of the hydroamination products containing the 1,2-diamine motif can be synthesized in high enantioselectivity by using two different chiral aldehydes catalysts. This work highlights the fact that simple chiral α-oxygenated aldehydes are effective organocatalysts capable of efficiently inducing asymmetry through temporary intramolecularity. Advanced scope, further catalyst design, and mechanistic insights will be presented in due course.

Experimental Section

A round-bottom flask (5 mL) was charged with a stirring bar, hydroxylamine (1 equiv; typically 1 mmol), degassed solvent (1.0 M with respect to hydroxylamine), amine (1.5 equiv), and lastly, catalyst (0.2 equiv). The reaction was stirred at room temperature for 24–72 h. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give the corresponding *N,N*-dialkylhydroxylamine products. To determine the *ee*, the hydroamination product (**2a**–**2m**; 1 equiv) was dissolved in CH_2Cl_2 (0.5 M) then 1,1′-carbonyldiimidazole (CDI; 1.5–2.5 equiv) was added and the reaction stirred for 3–24 h. After completion, the reaction mixture was concentrated under reduced pressure, purified by column chromatography and analyzed by HPLC with an appropriate chiral column. See the Supporting Information for details.

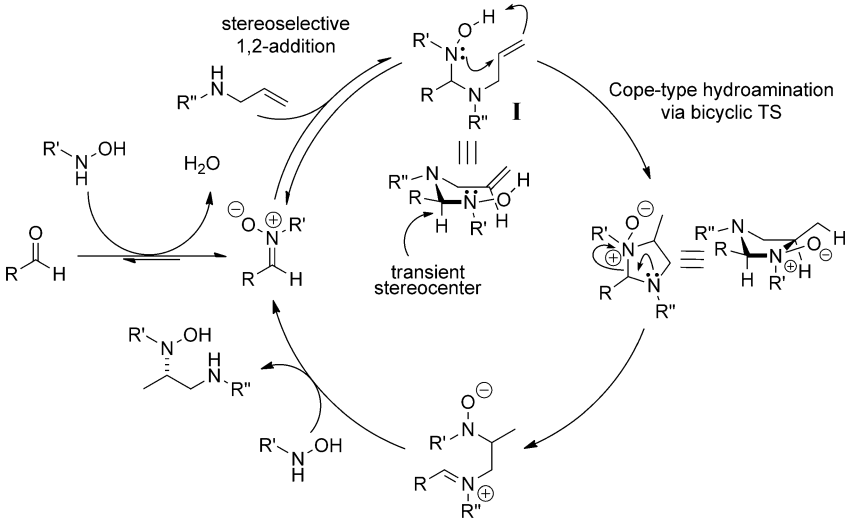


Figure 2. Enantioselective hydroamination by temporary intramolecularity, with stereocontrol originating from a transient stereocenter formed by a stereoselective 1,2-addition reaction.

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Keywords: asymmetric catalysis · hydroamination · hydroxylamines · tethered reactions · vicinal diamines

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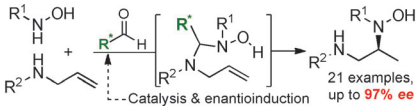
Organocatalyzed Hydroamination

*M. J. MacDonald, C. R. Hesp, D. J. Schipper, M. Pesant, A. M. Beauchemin** ..... ■■■–■■■

Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts



Chirally LinkedIn: Chiral aldehydes are effective tethering catalysts for enantioselective intermolecular hydroamination, which provides access to vicinal diamine motifs in good yields and excellent enantioselectivities (see scheme). This work highlights simple chiral α-oxygenated aldehydes as effective organocatalysts capable of efficiently inducing asymmetry through transient intramolecularity.