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Formaldehyde as Tethering Organocatalyst: Highly Diastereoselective Hydroaminations of Allylic Amines

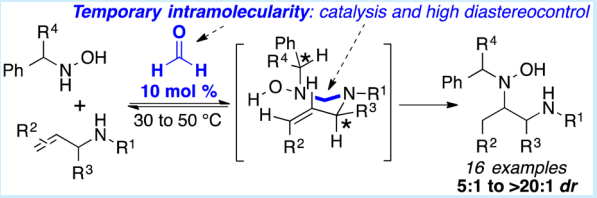
Colin R. Hesp,[†,§] Melissa J. MacDonald,[†,§] M. Mehdi Zahedi,[†] Didier A. Bilodeau,[†] Shu-Bin Zhao,[†] Marc Pesant,[‡] and André M. Beauchemin*[,†]

[†]Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie-Curie, Ottawa, ON K1N 6N5, Canada

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

Supporting Information

ABSTRACT: Catalysts possessing sufficient activity to achieve intermolecular alkene hydroaminations under mild conditions are rare, and this likely accounts for the scarcity of asymmetric variants of this reaction. Herein, highly diastereoselective hydroaminations of allylic amines utilizing hydroxylamines as reagents and formaldehyde as catalyst are reported. This catalyst induces temporary intramolecularity, which results in high rate accelerations, and high diastereocontrol with either chiral allylic amines or chiral hydroxylamines. The reaction scope includes internal alkenes. Overall this work provides a new, stereocontrolled route to form complex vicinal diamines.

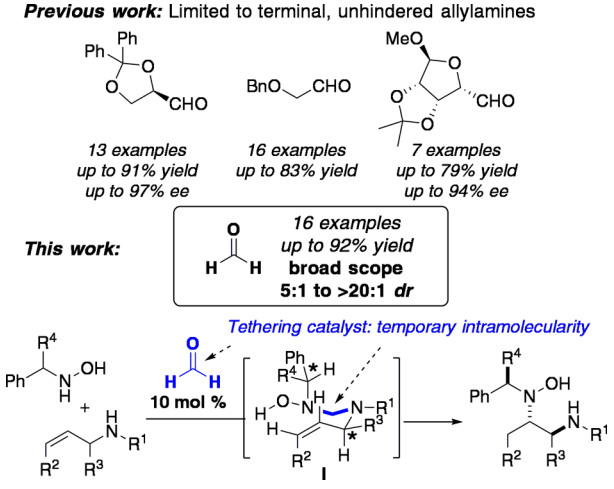


Efficient stereoselective C−N bond forming reactions are of high interest due to the importance of chiral nitrogen-containing molecules. While many asymmetric reactions have been developed to form chiral amines, asymmetric alkene hydroaminations suffer from narrow applicability, despite intense efforts toward enantioselective variants.[1] Asymmetric intramolecular reactions are often limited to five-membered ring cyclizations of biased substrates (Thorpe−Ingold activation or terminal alkenes). Until recently, highly enantioselective (>80% ee) intermolecular reactions had only been reported for three alkene types: strained alkenes, styrenes, and cyclic dienes.[1,2] Highly diastereoselective variants are even more rare, especially catalytic intermolecular examples.[3] We were thus drawn to this issue as part of our efforts on the catalysis of difficult reactions via temporary intramolecularity.[4] Indeed, a *catalytic* tethering strategy should allow for high diastereocontrol through temporary intramolecularity. In addition, this would circumvent the additional steps of tether formation and tether cleavage that are inherent to stoichiometric diastereoselective tethered reactions.[5] Herein, we report a remarkably simple catalytic system that allows a highly stereocontrolled synthesis of vicinal diamines in which either reagent controls the stereochemical outcome of the reaction.

We have recently reported that aldehydes catalyze metal-free Cope-type hydroaminations via transient formation of an aminal intermediate (**I**), in which temporary intramolecularity is achieved.[6,7] Notably, chiral aldehydes were efficient organocatalysts and provided the 1,2-diamine motif in up to 97% *ee* (Scheme 1). Although the use of unbiased alkenes was achieved and selectivity was high, this reactivity was limited to terminal allylamines and sensitive to steric hindrance.

Given that our recent mechanistic studies identified formaldehyde as a superior preassociation catalyst,[8] we speculated

Scheme 1. Temporary Intramolecularity Now Allows Diastereoselective Hydroaminations



that its activity and minimal size could tolerate the increased substitution inherently required for a diastereoselective variant. To perform reaction development, a less reactive internal alkene was used with the goal to control alkene facial selectivity using *N*-(1-phenylethyl)hydroxylamine.[9] Encouragingly, we observed and improved a rare example of an asymmetric intermolecular hydroamination reaction in which the amine reagent controls the stereochemical outcome (Table 1).

Optimization began with *N*-(1-phenylethyl)hydroxylamine since this chiral reagent can be reliably obtained in optically

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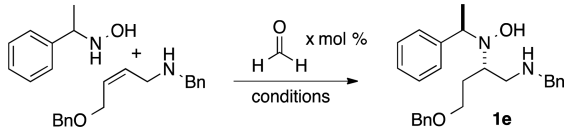
Table 1. Optimization of Formaldehyde-Catalyzed Asymmetric Intermolecular Hydroamination[a]



entry	catalyst (x mol %)	temp (°C)	time (h)	yield (%)[b]	dr
1	10	30	24	10	>20:1
2	10	50	24	58	>20:1
3	10	50	48	42[c]	>20:1
4	10	80	24	41	>20:1
5	5	50	24	39	>20:1
6	0	50	24	0	—

[a]Conditions: Hydroxylamine (1 equiv), allylic amine (1.0 equiv), formaldehyde (x mol %, from 37 wt % aqueous solution; see Supporting Information), in t-BuOH (1 M) under Ar. [b]^{1}H NMR yield, determined using 1,4-dimethoxybenzene as internal standard. [c]Product degradation was observed.

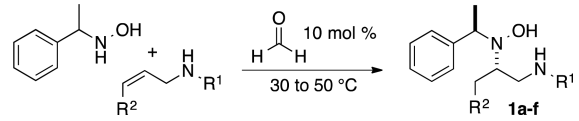
pure form by the method of Fukuyama.[9] We speculated that a chiral center on the periphery of the bicyclic Cope-type hydroamination transition state could allow stereocontrol. Initial efforts rapidly identified t-BuOH as an ideal solvent to ensure solubility of aqueous formaldehyde.[8] The diastereoselectivity was greater than 20:1; however, the conversions obtained were quite low (Table 1, entry 1). Increasing the temperature to facilitate the hydroamination step greatly increased the yield without impacting the selectivity (entry 2). A moderate conversion and diastereomeric ratio were observed with only 5 mol % of catalyst (entry 5), and no background reaction was detected in the absence of formaldehyde (entry 6). With optimized conditions in hand (entry 2), the scope of this hydroamination was investigated (Table 2).

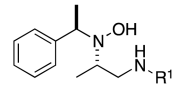
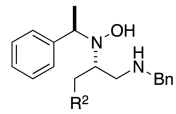
N-(1-Phenylethyl)hydroxylamine was reacted with several secondary allylic amines (Table 2). We observed that terminal alkenes react with moderate to good yields (47−85%, entries 1−4) and consistent diastereoselectivity (ca. 5−6:1 dr). Electron-rich allylic amines likely favor the formation of the mixed aminal intermediate **I**,[8] thus leading to an increased yield (entry 1 vs 2; 3 vs 4). The reactions of internal alkenes showed very high diastereoselectivity (>20:1 dr, entries 5−6). The favored anti stereochemistry was confirmed with an X-ray structure (**1a**) and proves to be consistent with the proposed transition state model (see Figure 1 below). Overall, these results show that the use of a chiral hydroamination reagent can lead to high diastereocontrol in the formation of 1,2-diamine motifs.

We then sought to explore if the chirality present on the allylic amine could be used to achieve stereoinduction in the synthesis of vicinal diamine motifs. A similar but stoichiometric approach had been previously investigated by Knight and coworkers, using nitrones and allylic amines as reagents to form six-membered heterocycles via an aminal formation/hydroamination/ring-opening/ring-closing sequence.[10,11] Excellent diastereoselectivities were observed and suggested that a catalytic variant could be very effective. Again using formaldehyde as a catalyst, intermolecular hydroaminations were performed using *N*-benzylhydroxylamine with several chiral allylic amines (Table 3).

Encouragingly, using *N*-benzylbut-3-en-2-amine **2a** as a substrate, near perfect diastereoselectivity was observed

Table 2. Diastereoselective Hydroamination Using a Chiral Hydroxylamine[a]



entry	product	yield (%)[b]	dr[c]
			
1	R^1 = Bn (**1a**)	83	6.1:1[d]
2	R^1 = PMB (**1b**)	47	5.0:1
3	R^1 = CH_2CO_2Me (**1c**)	50	5.7:1
4	R^1 = $(CH_2)_2CONMe_2$ (**1d**)	85	5.9:1
			
5[e]	R^2 = CH_2OBn (**1e**)	42	>20:1
6[e]	R^2 = CH_2allyl (**1f**)	57	>20:1[e]

[a]Conditions: Hydroxylamine (1 equiv), allylic amine (1.5 equiv), formaldehyde (10 mol %, from 37 wt % aqueous solution, see Supporting Information), in t-BuOH (1 M) under Ar, at 30 °C, 24 h. [b]Isolated yields (mixture of diastereoisomers). [c]Determined by ^{1}H NMR of unpurified reaction mixture. [d]Stereochemistry of major diastereomer assigned by X-ray analysis. [e]Performed at 50 °C.

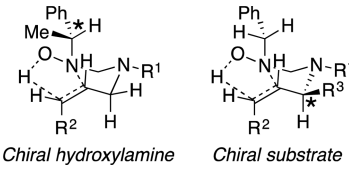
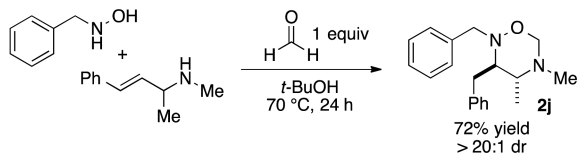


Figure 1. Rationale for stereoinduction: proposed transition state models for diastereoselective Cope-type hydroaminations.

(>20:1, entry 1). The overall reaction was very tolerant to steric hindrance α to the amine, with little effect on the reactivity (entries 5−8). Of note is the chemoselectivity observed with the diene substrate (entry 3) and the compatibility with heterocyclic substituents (entries 6−7). Higher yields could be obtained with *N*-methyl as opposed to the *N*-benzyl substrates. This is likely due to steric hindrance affecting the initial addition onto the formaldehyde-derived nitrone as well as steric destabilization present in the tether and transition state model (interaction between R^1 and R^3; see Figure 1). A limitation of this catalytic approach was substitution on the alkene; however, this could be overcome by using stoichiometric amounts of formaldehyde (eq 1).[11]



(1)

Such cyclic derivatives were also produced by Knight[10b] and converted into other diamine motifs.[10c] In our hands, hydrolysis of **2j** was challenging; an improved procedure to

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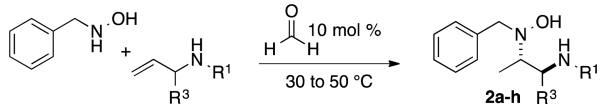
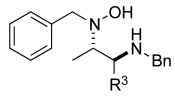
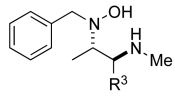
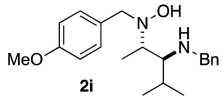
Table 3. Diastereoselective Hydroamination of Chiral Allylic Amines[a]



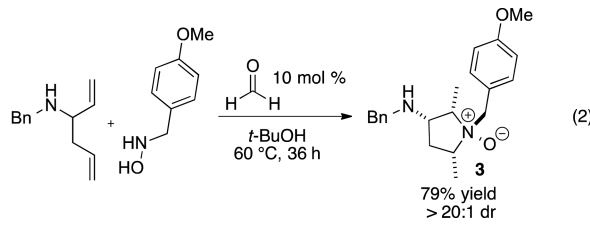
entry	product	yield (%)[b]	dr[c]
			
1	R^3 = Me (**2a**)	92	>20:1
2	R^3 = $(CH_2)_2CH_3$ (**2b**)	72	>20:1
3	R^3 = CH=CHPh (*E*, **2c**)	71	>20:1
			
4	R^3 = Ph (**2d**)	80	>20:1
5	R^3 = (CH_2)OTBS (**2e**)	70	>20:1
6	R^3 = 2-furyl (**2f**)	86	>20:1
7	R^3 = 3-pyridyl (**2g**)	81	>20:1
8	R^3 = *i*-Pr (**2h**)	76	>20:1
9[d]	 **2i**	65	>20:1

[a]Conditions: see Table 2. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Performed at 50 °C.

convert such cyclic derivatives to the parent amino-hydroxylamine was developed using $NH_2OH{\cdot}HCl$ (see Supporting Information).

The selectivity for these diastereoselective transformations originates from the rigid cis-bicyclic 5,5-transition state structure for the concerted hydroamination event, presented in the models below (Figure 1). In both models the benzylic substituent on the hydroxylamine is in a pseudoaxial orientation, with its C−H bond positioned to avoid destabilizing syn-pentane interactions with the tether (i.e., C−H is eclipsed with C−NR^1). For reactions of chiral hydroxylamines, the large substituent on the stereocenter (R_L = Ph) is oriented opposite to the forming C−N bond, to minimize steric interactions between the pseudoaxial substituent (R_M = Me) and the incoming alkene. In the model proposed for chiral allylic amines, the R^3 substituent is adopting a pseudoequatorial position. This orients the tethered hydroxylamine so that C−N bond formation occurs opposite to this R^3 substituent.

We were also interested in probing the efficiency of this catalytic directed reaction procedure.[12] Toward this, we performed a double hydroamination cascade with *N*-benzylhexa-1,5-dien-3-amine under our standard conditions (eq 2). We had previously achieved this cascade using a hydrogen-bonding approach, which yielded the product in 62% yield over 7 days at 80 °C (in the absence of solvent).[13] Utilizing formaldehyde as a catalyst the sequence worked in solution, at a lower temperature, and with a significantly shortened reaction time. The pyrrolidine *N*-oxide **3** was synthesized with excellent

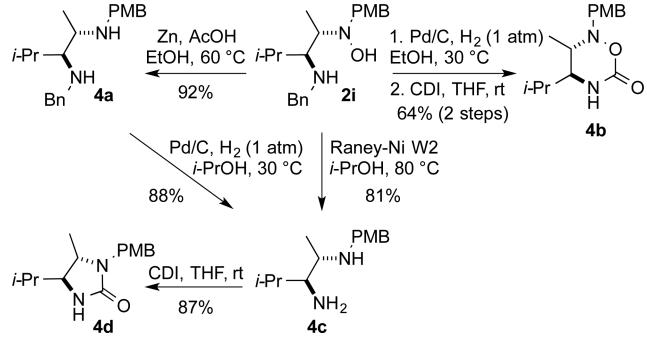


(2)

diastereocontrol (>20:1) and displayed a similar stereochemical outcome to the reaction directed via hydrogen bonding.

As the prevalence and utility of 1,2 diamines continue to grow in pharmaceutical targets and chiral ligands, the ability to achieve diastereocontrolled hydroaminations is significant.[14] Consequently, the products obtained were derivatized into diverse useful structures (Scheme 2). To this end, differentially

Scheme 2. Diamine Motifs: Derivatization Reactions



protected diamine precursor **2i** was used, it was prepared on gram scale (Table 3, entry 9 was performed on a 10 mmol scale to afford 2.36 g of **2i**). The N−O bond could be cleaved easily under mild conditions to yield diamine **4a**. This diamine could be selectively debenzylated to afford diamine **4c**. Diamine **4c** was then converted into imidazolidinone **4d** upon reaction with 1,1′-carbonyldiimidazole (CDI). Alternatively, these diamine motifs could also be cyclized with CDI to yield six-membered heterocycles,[6] which could also be performed after a selective debenzylation in the presence of the hydroxylamine and PMB groups (**4b**).

In conclusion we have developed an efficient approach to 1,2-diamine motifs via highly diastereoselective intermolecular Cope-type hydroaminations of allylamines using hydroxylamines. Using formaldehyde as an efficient tethering organocatalyst, this reaction can proceed with high diastereoselectivity using either chiral allylic amines or chiral hydroxylamines. These results demonstrate that high diastereocontrol can be achieved using tethering catalysis and, more broadly, illustrate the synthetic efficiency that can be achieved by catalysts operating *only* via temporary intramolecularity. Expansion of the scope of this directed hydroamination methodology and applications of aldehyde catalysis to other transformations are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02675.

Complete experimental procedures, characterization, and NMR spectra (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: andre.beauchemin@uottawa.ca.

Author Contributions

§C.R.H. and M.J.M. contributed equally.

Notes

The authors declare no competing financial interest.

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(8) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571. In this mechanistic work, we showed that formaldehyde is an efficient precatalyst. Paraformaldehyde was used as a source of anhydrous formaldehyde (six examples, 5−10 mol %). However, an induction period was observed, likely due to the need for depolymerization to occur. One example showed that using aqueous formaldehyde (37 wt % in H_2O; CH_2O present as its hydrate) could prevent this induction period. However, the presence of water as a possible source of catalyst inhibition was not addressed (see refs 10b, 11 for a related system with a high inhibition).

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(11) For Knight's work using a CH_2O/BnNHOH-derived nitrone, preformed or formed in situ from BnNHOH·HCl, K_2CO_3 and aq. $CH_2(OH)_2$, see ref 10b. No experimental procedure could be found to allow direct comparison with this in situ work. However, collectively our results suggest that the conditions presented herein result in significantly improved hydroamination reactivity compared to the in situ conditions.

(12) (a) For a review of substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) For a review on removable or catalytic directing groups, see: Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

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