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Catalysis through Temporary Intramolecularity: Mechanistic Investigations on Aldehyde-Catalyzed Cope-type Hydroamination Lead to the Discovery of a More Efficient Tethering Catalyst

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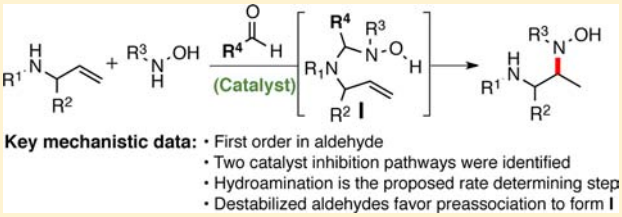
Supporting Information

ABSTRACT: Mechanistic investigations on the aldehyde-catalyzed intermolecular hydroamination of allylic amines using *N*-alkylhydroxylamines are presented. Under the reaction conditions, the presence of a specific aldehyde catalyst allows formation of a mixed aminal intermediate, which permits intramolecular Cope-type hydroamination. The reaction was determined to be first-order in both the aldehyde catalyst (α-benzyloxyacetaldehyde) and the allylic amine. However, the reaction displays an inverse order behavior in benzylhydroxylamine, which reveals a significant off-cycle pathway and highlights the importance of an aldehyde catalyst that promotes a reversible aminal formation. Kinetic isotope effect experiments suggest that hydroamination is the rate-limiting step of this catalytic cycle. Overall, these results enabled the elaboration of a more accurate catalytic cycle and led to the development of a more efficient catalytic system for alkene hydroamination. The use of 5−10 mol % of paraformaldehyde proved more effective than the use of 20 mol % of α-benzyloxyacetaldehyde, leading to high yields of intermolecular hydroamination products within 24 h at 30 °C.



INTRODUCTION

Catalysis of intermolecular reactions is necessary to perform a variety of chemical transformations with high efficiency and control. Bifunctional catalysts and enzymes are particularly effective, as they execute this by combining the ability to perform substrate activation while favoring substrate preassociation. In many respects, the synthetic catalysts developed so far attempt to emulate the remarkable efficiency of enzymes in catalyzing intermolecular reactions (with rate accelerations as high as 10^{17}).[1] To achieve such high activity and control, enzymes preorganize reagents and consequently induce a "temporary intramolecularity" that minimizes the entropic penalty associated with intermolecular reactions. It is generally accepted that rate accelerations of 10^4−10^8 for 1 M reactants can be obtained for room temperature reactions involving such temporary intramolecularity.[2] From this perspective, it is not surprising that synthetic chemists have developed multiple transformations building on preassociation[3,4] and that several families of bifunctional catalysts have emerged.[5] In contrast, the catalysis of chemical transformations *only* through temporary intramolecularity or by building high effective concentrations of reagents has received less attention from the synthetic community.[6] Indeed, simple catalysts operating only through this pathway are rare, perform relatively simple synthetic transformations, and highly efficient examples of enantioselective catalysis have not been reported.

A limited number of examples of catalysis induced only through temporary intramolecularity have been reported using carbonyl catalysts.[6,7] This type of catalysis was developed mainly for hydrolysis reactions, and the original work of Commeyras et al. on the hydrolysis of α-aminoamides using formaldehyde is an illustrative example (Figure 1).[8] In this reaction, the amine moiety of an α-aminoamide reacts with formaldehyde to transiently generate a hemiaminal. The alcohol portion of this hemiaminal then undergoes an intramolecular addition onto the amide moiety. Hydrolysis of the resulting intermediate regenerates the formaldehyde catalyst and yields the corresponding amino acid. Several related reactions building on temporary intramolecularity were developed: CO_2 and aldehyde promoted ester hydrolysis,[9,10] ketone mediated α-thioamide hydrolysis,[11] and ketone and aldehyde catalyzed nitrile hydration.[12] However, common to all these hydrolysis reactions is the use of stoichiometric amounts of a carbonyl catalyst, even though turnover should occur according to the proposed mechanism. This highlights the underdevelopment and opportunities associated with tethering catalysis: simple systems achieving high catalytic efficiency (catalyst turnover number and rates) remain to be established. In addition, highly stereoselective variants and the application of this strategy to complex reactions have barely been studied.[13]

Building on these reports and, most importantly, on the work of Knight et al. on the synthesis of cyclic 1,2-diamine motifs from nitrones and allylamines (Figure 1),[14] we recently disclosed that simple aldehydes catalyze intermolecular Cope-type hydroaminations[15,16] *solely* via temporary intramolecular-

Received: April 5, 2012
Published: September 12, 2012

   dx.doi.org/10.1021/ja303320x | J. Am. Chem. Soc. 2012, 134, 16571−16577

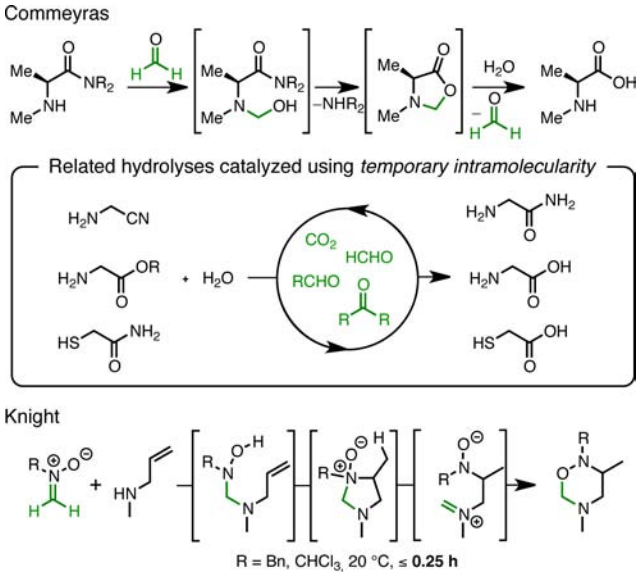


Figure 1. Selected reports of Commeyras and Knight using formaldehyde.

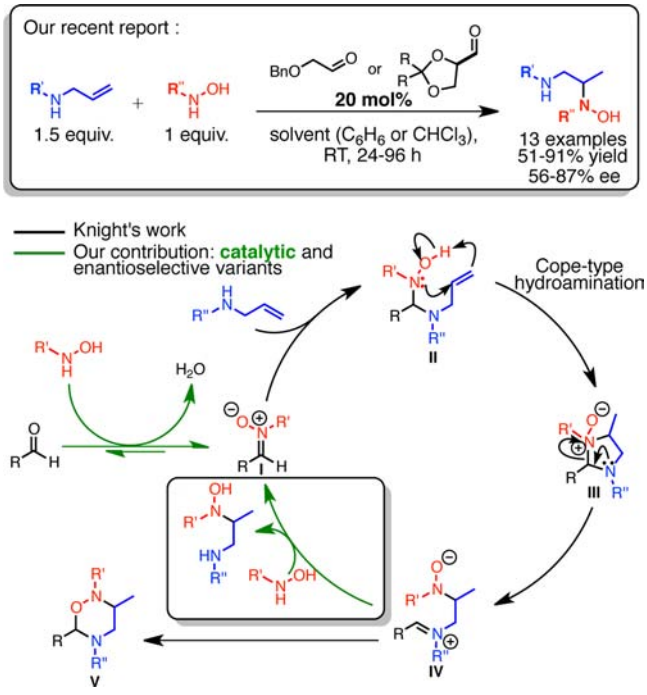


Figure 2. Intermolecular Cope-type hydroamination using aldehydes as tethering catalysts.

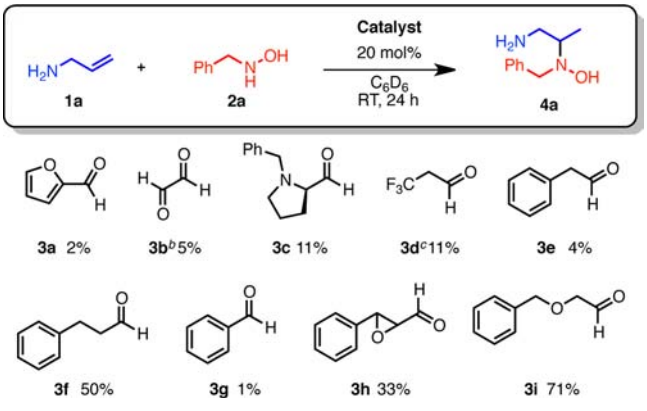
ity. As illustrated in Figure 2, the reaction proceeds via the key in situ formation of a mixed aminal (**II**), which allows for a facile *intramolecular* hydroamination event.[17] As opposed to more traditional tethering strategies,[18] this catalytic method does not require additional synthetic steps for the installation and cleavage of the tether. It also allows room temperature reactivity with a minimal excess of one of the reaction components. Additionally, it enables the formation of enantioenriched molecules through efficient transfer of stereochemical information using a chiral aldehyde catalyst.[19] Given the lack of precedence for such complex catalytic tethering systems (Figure 2) and our desire to achieve higher efficiency and enantioselectivity, we initiated mechanistic studies to probe the catalytic cycle of this transformation. Herein we present a complete picture of this catalytic cycle, including information on the rate-determining step and catalyst inhibition pathways. We also report a system that builds on this information to perform hydroamination reactions with higher catalytic efficiency than previously reported by using only 5 mol % of paraformaldehyde as precatalyst.

RESULTS AND DISCUSSION

Our interest in the development of catalytic tethering reactivity stems from ongoing efforts directed toward intermolecular Cope-type hydroamination reactions of alkenes,[20] which typically require forcing conditions and catalysis to occur. Currently, these reactions show limited applicability: biased alkenes are generally required and highly enantioselective variants are rare. As previously observed,[20b] strained alkenes and vinylarenes (e.g., norbornene and styrene) require heating at elevated temperatures (90 and 140 °C, respectively), and little to no reactivity is detected with unbiased alkenes. Consequently, our efforts were naturally drawn to systems where preassociation or temporary intramolecularity could help to obtain increased reactivity. Indeed, room temperature Cope-type hydroamination is typically efficient in five-membered ring systems.[15] The challenge thus resided in the identification of a practical *catalytic* tethering method.

Our inspiration toward tethering catalysis was drawn from a key precedent from Knight et al. involving the reaction of various nitrones with allylamines.[14] In this system, 1,2-nucleophilic addition of allylic amines triggers a one-pot sequence featuring Cope-type hydroamination, aminal opening, and ring closure (Figures 1 and 2). The products of this sequence were 1,2,5-oxadiazinanes or cyclic derivatives of vicinal diamines. From this well-developed work, we hypothesized that it would be possible, using a substoichiometric amount of an appropriate aldehyde, to achieve catalyst turnover via a transimination step as shown in Figure 2. Encouragingly, extensive screening of carbonyl compounds revealed that α-oxygenated aldehydes were competent catalysts for this transformation (see Table 1 for representative data). Our working hypothesis is that inductively destabilized aldehydes favor thermodynamically the formation of aminals, which likely is an important feature for catalysts operating via temporary intramolecularity.

Table 1. Selected Examples of Aldehydes Tested for Catalytic Activity[a]



[a]Conditions: **1a** (1.5 equiv), **2a** (1 equiv), catalyst (20 mol %), C_6D_6, rt, 24 h. [b]Used as a 40% solution in water. [c]Used as the hydrate.

dx.doi.org/10.1021/ja303320x | J. Am. Chem. Soc. 2012, 134, 16571−16577

Although the prototypical catalytic cycle was based on literature precedents from the work of Knight et al.,[14] the catalyst resting state and potential inhibition pathways were still unknown at this point. Further experiments were thus conducted to identify the rate-determining and kinetically significant steps of this process. To do so, the reaction of *N*-allylbenzylamine **1b** (1.5 equiv) with *N*-benzylhydroxylamine **2a** using α-benzyloxyacetaldehyde **3i** (20 mol %) as catalyst was investigated. The typical reaction conditions employed (1 M in benzene, room temperature) are the result of a thorough optimization previously described.[17a]

At the outset, the order of every component implicated in the reaction was evaluated (Figure 3). It was first determined from the log plots of initial rate versus the initial catalyst concentration that the reaction is approximately first-order in aldehyde (Figure 3a). This is well in agreement with a catalytic cycle where only one molecule of aldehyde is involved prior to or at the rate-determining step. Then, plotting the log of the initial rate of the reaction versus the log of the initial allylbenzylamine concentration also revealed a first order-behavior (Figure 3b). This is again consistent with a single molecule of allylamine being involved before or at the rate-limiting step. Next, the order of *N*-benzylhydroxylamine was probed. Interestingly, a slope of −0.83, indicative of an inverse order, was found for this reaction component (Figure 3c). To gain further insight into the reaction mechanism and explain this result, the title reaction was conducted in a ^{1}H NMR probe using C_6D_6 as solvent (Figure 4). From this experiment, it was

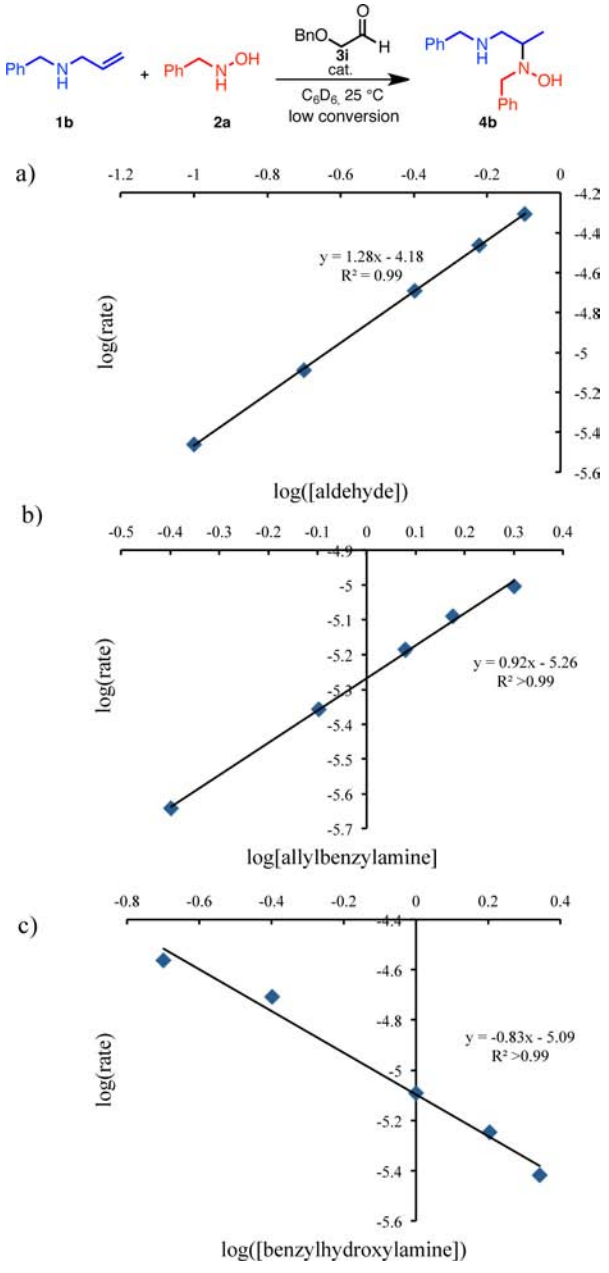


Figure 3. Initial rate dependence on the concentration of the reaction components showing (a) first-order dependence in organocatalyst (**3i**), (b) first-order dependence in allylbenzylamine (**1b**), and (c) inverse-order dependence in benzylhydroxylamine (**2a**).

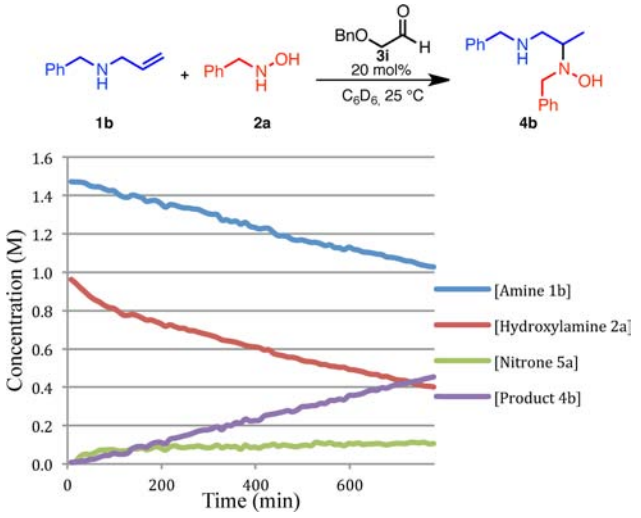


Figure 4. Representative reaction profile over 13 h for a 1 M reaction. Conditions: **1b** (0.75 mmol, 1.5 equiv), **2a** (0.5 mmol, 1 equiv), and **3i** (0.1 mmol, 20 mol %) in C_6D_6 (1 M).

determined that nitrone formation occurs rapidly upon addition of the reagents. The concentration of this intermediate can easily be monitored as the reaction proceeds. It proved to be quite steady while still displaying a very slight increase over time.[21] Of note, the product was formed at a constant rate for the 13 h period monitored (the ^{1}H NMR yield of product formation was 45% after 13 h). This suggests that there is little to no product inhibition under the reaction conditions. This can also be well-rationalized by the fact that the hydroxylamine becomes *N*,*N*-disubstituted as the alkene undergoes hydroamination. Thus, the product cannot interfere with nitrone formation.

Taken together, these results are consistent with initial formation of nitrone **5a** (observed by ^{1}H NMR) followed by the competitive addition of either *N*-benzylhydroxylamine or *N*-allylbenzylamine (Figure 5). The addition of *N*-benzylhydroxylamine affords an unreactive aminal (**6a**).[22] This off-cycle pathway is (fortunately) reversible. On the other hand, the addition of *N*-allylbenzylamine leads to the formation of a key mixed aminal (**7a**) that can undergo the critical Cope-type hydroamination step. Of note, the addition of water to the reaction did not slow down the catalytic process. This rules out the competitive addition of water on the nitrone (or other intermediates) as a potential catalyst deactivation pathway(s).

To get a better picture of the association processes displayed in Figure 5, the equilibrium constants K_A and K_B were

dx.doi.org/10.1021/ja303320x | J. Am. Chem. Soc. 2012, 134, 16571−16577

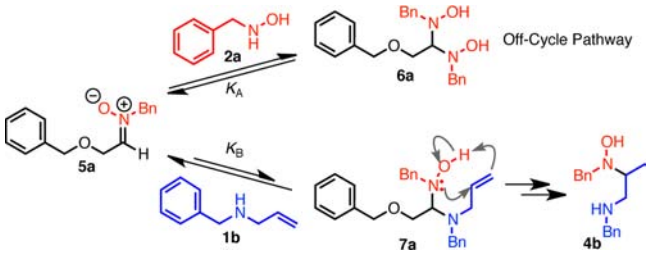
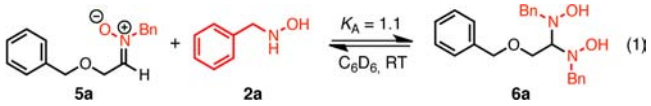
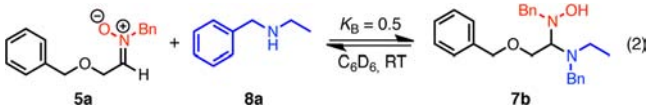


Figure 5. Competing 1,2-addition of **2a** and **1b** on **5a**, which explains the inverse order behavior in **2a**.

measured independently. The value obtained for the reaction of nitrone **5a** with benzylhydroxylamine **2a** forming the symmetrical adduct **6a** is 1.1 (eq 1). This constant suggests that the

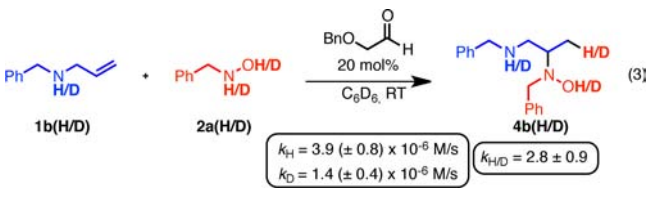


equilibrium is slightly shifted toward the symmetrical adduct **6a** under the initial reaction conditions. It also accounts for a concentration of nitrone a little under 0.1 M during the first hours of the reaction. Experiments to probe the value of the equilibrium constant K_B were also conducted. Since we needed to prevent the Cope-type hydroamination, *N*-benzylethylamine **8a** was used in place of **1b**. A value of 0.5 was obtained for this constant (eq 2). Overall, these values are consistent with the



symmetrical adduct **6a** being the resting state of the catalyst at low conversion and the mixed aminal being a thermodynamically disfavored species.[23]

Deuterium kinetic isotope effect (DKIE) experiments were also conducted to probe the nature of the rate-determining step. All exchangeable protons of both starting materials were replaced by deuterium and the initial rate of the reaction was measured. As shown in eq 3, a primary DKIE of 2.8 ± 0.9 was



obtained for this reaction. If we assume the proton transfer steps to have a low energy barrier, this result suggests that hydroamination is the rate-determining step of this catalytic process.

Toward the turnover-enabling step of the originally proposed catalytic cycle (Figure 2), two competing reactions can occur. The first one, which is desired, is a transimination providing the nitrone catalyst **I** and the hydroamination product (Figures 2 and 7). The second possibility is to generate adduct **V**, which results from a 6-endo-trig addition of the negatively charged oxygen onto the iminium ion in **IV** (Figures 2 and 7, off-cycle straight arrow). The latter gives a 6-membered heterocycle (**V**) that has been extensively described by Knight et al.[14] If the

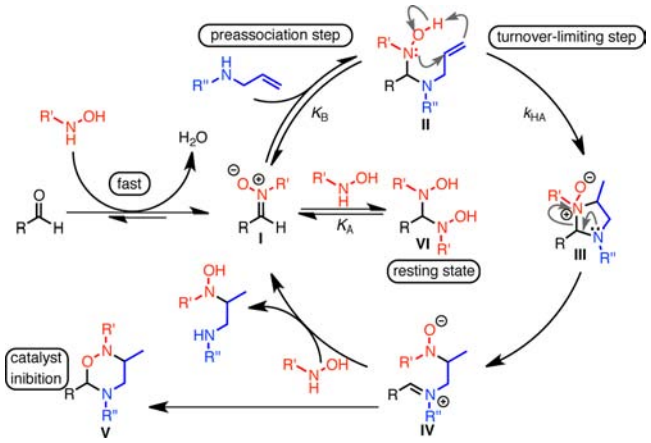
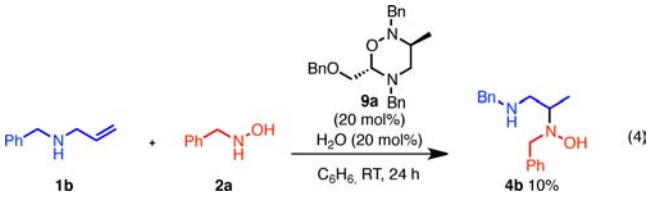


Figure 7. Proposed catalytic cycle.

formation of this cyclized product is irreversible, this might represent an important source of catalyst inhibition. To test this, the cyclic compound **9a** was synthesized according to Knight's procedure and utilized as a precatalyst for our hydroamination reaction (eq 4). Interestingly, only a 10% yield of **4b** was obtained. This observation suggests that this pathway (**IV** → **V**) is hardly reversible and leads to catalyst inhibition.



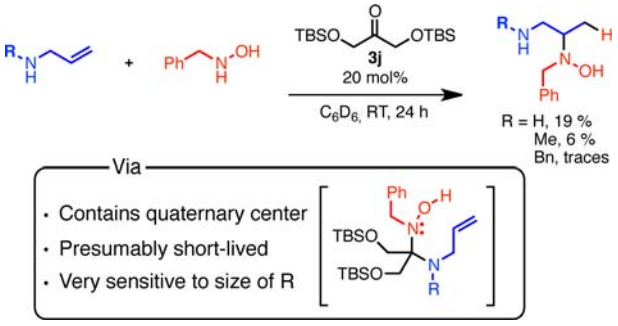
Taking into account the results obtained herein, a more accurate catalytic cycle can now be drawn (Figure 7). The first step is a rapid reaction of the aldehyde precatalyst with benzylhydroxylamine to afford the nitrone catalyst (**I**). From this point, either another molecule of benzylhydroxylamine or the allylamine can effect a 1,2-addition. The reaction of the later yields a mixed aminal (**II**) that can then undergo the proposed rate-determining hydroamination.[24] It is believed that the reason why only a limited number of aldehydes with very specific electronic properties are competent catalysts can be explained as follows. If the aldehyde is not inductively destabilized enough (i.e., most aliphatic aldehydes) or is stabilized (i.e., aromatic or conjugated aldehydes), the nitrone is stable, and consequently, the tetrahedral intermediate is only present in a low concentration. Since the rate of the hydroamination step (rate-determining step) of the reaction is function of the concentration of the mixed aminal **II**, stable nitrones that disfavor the formation of aminals would be poor catalysts. On the other hand, if the aldehyde is too destabilized, it is believed that the aminal could be too stable and thus not easily returned to the nitrone. Since the formation of symmetrical aminal **VI** can compete with the mixed aminal **II**, a situation where the symmetrical aminal is formed and hardly returns to the nitrone could be very detrimental to the reaction. It is thus important to have a nitrone catalyst that favors preassociation while also allowing reversibility between the nitrone and the aminal species. In other words, an ideal catalyst would allow for a high and renewable concentration of mixed aminal **II** via the destabilization of nitrone **I**.[25]

dx.doi.org/10.1021/ja303320x | *J. Am. Chem. Soc.* 2012, 134, 16571−16577

Having a better understanding of the operative catalytic cycle, we decided to reinvestigate the catalyst design in order to increase the rate of the reaction and hopefully broaden its scope. It was initially thought that promoting hydroamination, the proposed rate-limiting step, would lead to increased reactivity. To do so, the possibility of using a ketone catalyst was explored. The rationale was to benefit from a Thorpe-Ingold effect that would favor the difficult cyclization: this is well-known for intramolecular hydroaminations[16] and for Cope-type hydroaminations in particular.[15]

However, intensive screening of electron-deficient ketones revealed that only poor reactivity could be achieved. The best results obtained were with the inductively destabilized ketone **3j**. In contrast to the results obtained with aldehyde **3i**, the ketone precatalysts seemed to be considerably more sensitive to steric factors. Hydroamination of a primary allylamine with benzylhydroxylamine using ketone **3j** provided a ^{1}H NMR yield of 21% over 24 h. The use of methylallylamine (6%) and benzylallylamine (trace) gave much lower yields (Scheme 1).

Scheme 1. Importance of Steric Factors with a Ketone Precatalyst[a]



[a]Conditions: allylamine (1.5 equiv), **2a** (1 equiv), **3j** (20 mol %), C_6D_6, rt, 24 h.

This data suggests that the added steric hindrance present in the mixed aminal (increasing with R = H < Me < Bn) leads to an unfavorable preassociation equilibrium (**I** ⇆ **II**) and that this negative effect is more important than the probable acceleration of the Cope-type hydroamination step (**II** ⇆ **III**). As such, this observation is related to the concept of tether strain recently discussed by Krenske et al. in related systems.[26] In addition, the increased stability of ketonitrones relative to aldonitrones should also result in a disfavored preassociation equilibrium.

Taking these results into account, we aimed at improving the reaction rate by using a more destabilized nitrone, to provide a more favorable preassociation equilibrium for the mixed aminal intermediate. Initial attempts with paraformaldehyde in C_6H_6 and $CHCl_3$ (i.e., original reaction conditions) resulted in low conversion. However, polar solvents proved superior, and the use of either *t*-BuOH or DMSO led to high yields of the desired hydroamination products, with slightly better results using *t*-BuOH (see the Supporting Information for optimization data). In order to compare the performance of α-benzyloxyacetaldehyde (**3i**) and formaldehyde (**3k**), the reaction rates of both catalytic systems were determined in DMSO-d_6. Interestingly, the rate at low conversion is lower with paraformaldehyde than with aldehyde **3i**, but it becomes ca. 3 times faster after an induction period (Figure 8). This is presumably due to the slow depolymerization of the paraformaldehyde precatalyst employed in this reaction.

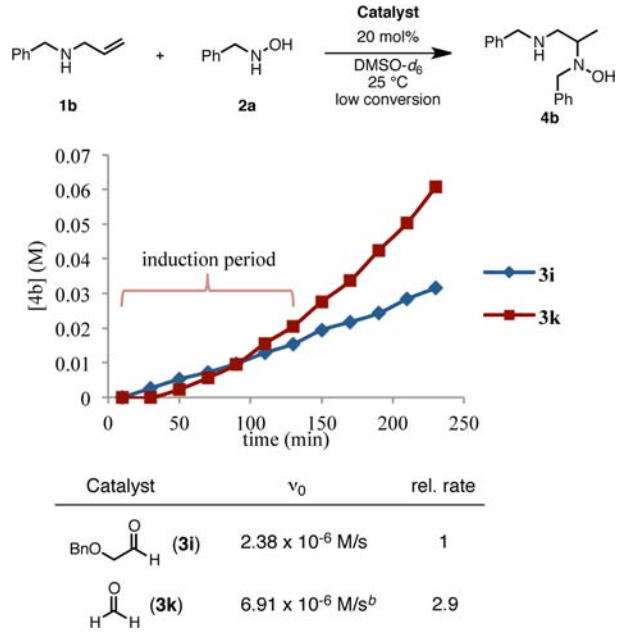
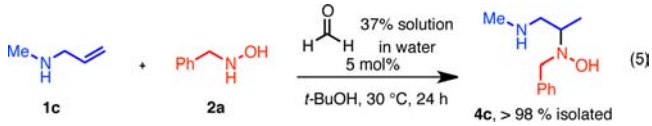


Figure 8. Initial rate comparison in DMSO-d_6 using **1b** (1.5 equiv), **2a** (1 equiv), catalyst **3i** or **3k** (20 mol %), and DMSO-d_6 (1 M), at 25 °C. [b] Value obtained after induction period.

Encouraged by this result, we next sought to determine if this improved reactivity would translate into improved catalytic activity. Gratifyingly, it was found that the catalyst loading in "formaldehyde" could be reduced to 5 mol % while still displaying increased yields compared to reactions using 20 mol % of α-benzyloxyacetaldehyde (**3j**). As shown in Table 2, isolated yields for alkene hydroamination using diverse secondary allylamines are significantly higher. *N*-Methyl, *N*-allyl, and *N*-benzyl allylamines provided quantitative, 92%, and 85% yields, respectively (entries 1–3). Using several other starting materials also gave yield increases compared to the first-generation conditions, albeit using 10 mol % of catalyst (entries 4–6). These results not only make for a more efficient alkene hydroamination method, but also for a more practical approach to vicinal diamines given that paraformaldehyde is inexpensive and readily available.

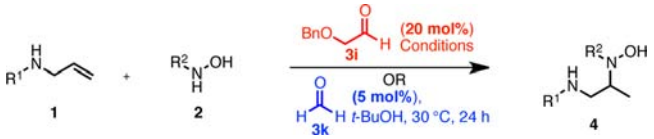
Building on these results under anhydrous (but initially heterogeneous) conditions, we explored the use of a concentrated aqueous solution of formaldehyde (formalin, in which formaldehyde is present as a hydrate). Gratifyingly, a similar result was observed using this convenient precatalyst (eq 5).

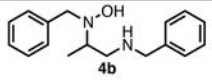
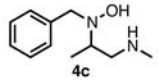
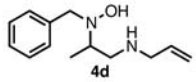
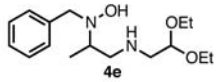
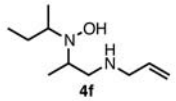
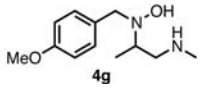


This result again highlights that high catalytic efficiency is achievable with tethering catalysis. The early development of an efficient tethering organocatalytic system operating at 5 mol % despite the presence of two different catalyst inhibition pathways suggests that this concept will be applicable to other reactions. Efforts along this path and the development of a highly enantioselective variant of this tethered hydroamination reactivity are ongoing and will be reported in due course.

dx.doi.org/10.1021/ja303320x | J. Am. Chem. Soc. 2012, 134, 16571–16577

Table 2. Comparative Reaction Scope for the Formaldehyde-Catalyzed Cope-type Hydroamination[a]



Entry	Product	Conditions using **3i**	Yield using **3i**	Yield using **3k**
1	 **4b**	C_6H_6, RT, 24 h	75%	85%
2	 **4c**	C_6H_6, RT, 24 h	72%	>98%
3	 **4d**	C_6H_6, RT, 24 h	69%	92%
4	 **4e**	$CHCl_3$, 60°C, 96 h	56%	66%[b]
5	 **4f**	$CHCl_3$, RT, 24 h	61%	74%[b]
6	 **4g**	$CHCl_3$, RT, 24 h	51%	80%[b]

[a]Conditions: **3i** catalyzed (red), allylamine (1.5 equiv), hydroxylamine (1 equiv), **3i** (20 mol %), C_6H_6 or $CHCl_3$ (1 M), 24–96 h; **3k** catalyzed (blue), allylamine (2 equiv), hydroxylamine (1 equiv), **3k** (5 mol %), *t*-BuOH (1 M), 30 °C, 24 h. [b]Using 10 mol % **3k**.

CONCLUSION

In conclusion, the reaction mechanism of the recently developed aldehyde-catalyzed intermolecular Cope-type hydroaminations was investigated. Key observations that should help the development of tethering catalysis through temporary intramolecularity were made. As expected, the reaction was determined to be approximately first-order in both the aldehyde catalyst (α-benzyloxyacetaldehyde) and the allylic amine. However, the reaction displays an inverse order behavior in benzylhydroxylamine, which reveals a significant off-cycle pathway, leading to an unproductive symmetrical tether. This highlights the importance of an aldehyde precatalyst that ensures reversible aminal formation. Kinetic isotope effect experiments (k_H/k_D = 2.8 ± 0.9) suggest that hydroamination is the rate-limiting step of this catalytic cycle. Overall, the complete mechanistic picture reveals that aldehyde **3i** is a particularly effective precatalyst since its reduced stability and higher kinetic reactivity inherently lead to a more efficient preassociation to access the productive mixed aminal tether. Given that the formation of symmetrical tethers is also possible, reversibility is required for efficient catalysis to occur. Finally, the results obtained enabled the elaboration of a more accurate catalytic cycle and the development of a more efficient catalytic system for alkene hydroamination. Indeed, the use of 5–10 mol % of paraformaldehyde, a destabilized aldehyde known to hydrate or polymerize readily, proved more effective than the use of 20 mol % of α-benzyloxyacetaldehyde, leading to high yields of intermolecular hydroamination products within 24 h at 30 °C in *t*-BuOH.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was initiated through support of an Enantioselective Synthesis Grant [sponsored by the Canadian Society for Chemistry, AstraZeneca Canada, Boehringer Ingelheim (Canada) Ltd. and Merck Frosst Canada] and the NSERC collaborative R & D program. Support from the University of Ottawa, the Canadian Foundation for Innovation, the Ontario Ministry of Research and Innovation (Ontario Research Fund and Early Researcher Award to A.M.B.), NSERC (Discovery Grant and Discovery Accelerator Supplement to A.M.B.) and AstraZeneca are also gratefully acknowledged. Acknowledgment is also made to the donors of The American Chemical Society Petroleum Research Fund for support of related research efforts. N.G. thanks NSERC for a CGS D scholarship. M.J.M. thanks Boehringer Ingelheim (Canada) Ltd for a collaborative graduate scholarship. We also thank Marc Pesant for stimulating discussions. We also thank Prof. Derek Pratt (University of Ottawa) and the reviewers for insightful comments and suggestions.

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(24) The kinetic equation for the proposed catalytic cycle can be expressed as follows:

$$\text{rate} = \frac{k_{HA}K_B[\mathbf{1}][\mathbf{3}]}{1 + K_B[\mathbf{1}] + K_A[\mathbf{2}]}$$

See the Supporting Information for more details.
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