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A Catalytic Tethering Strategy: Simple Aldehydes Catalyze Intermolecular Alkene Hydroaminations

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Supporting Information

ABSTRACT: Herein we describe a catalytic tethering strategy in which simple aldehyde precatalysts enable, through temporary intramolecularity, room-temperature intermolecular hydroamination reactivity and the synthesis of vicinal diamines. The catalyst allows the formation of a mixed aminal from an allylic amine and a hydroxylamine, resulting in a facile intramolecular hydroamination event. The promising enantioselectivities obtained with a chiral aldehyde also highlight the potential of this catalytic tethering approach in asymmetric catalysis and demonstrate that efficient enantioinduction relying *only* on temporary intramolecularity is possible.

Catalysis of intermolecular reactions is at the basis of chemical reactivity. Bifunctional catalysts performing both substrate activation and substrate preassociation—thus offsetting the negative reaction entropy—are particularly effective in achieving high catalytic activities for intermolecular reactions. In addition, the preorganization that results from substrate preassociation usually leads to increased control in reactions where multiple products can be formed (regio-, chemo-, or stereoselectivity).[1] Recently, several strategies to incorporate a "preassociation domain" on catalysts or ligands have been reported, thus allowing increased efficiency through temporary intramolecularity.[2] However, most catalysis still operate by performing the activation of one or both substrates. In contrast, the catalysis of intermolecular reactions *only* through temporary intramolecularity has received less attention from the synthetic community.[2a,3] Indeed, simple catalysts operating only through this pathway are rare and achieve relatively simple synthetic transformations,[4] and efficient examples of enantioselective catalysis have not been reported. In contrast, the inherent increased reactivity and control associated with temporary intramolecularity has typically been used in *stepwise* approaches involving the formation of "temporary" tethers.[5] Despite being applicable to a wide variety of chemical transformations, such tethering strategies are unfortunately not catalytic and generally involve two or three additional steps required for tether assembly and cleavage. Catalytic variants of this reactivity are critically needed since they would allow tethered reactivity to be possible in one step and would avoid the inherent inefficiency and byproduct formation that are associated with stepwise approaches. Herein we show that simple activated aldehydes display catalytic tethering activity and demonstrate that such organocatalysis can lead to the formation of enantioenriched molecules through efficient transfer of stereochemical information.

Aldehydes offer an opportunity to develop a catalytic tethering reactivity because of their propensity to form acetals or aminals

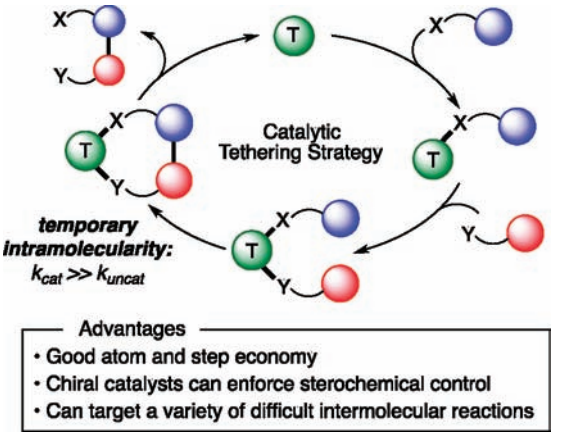
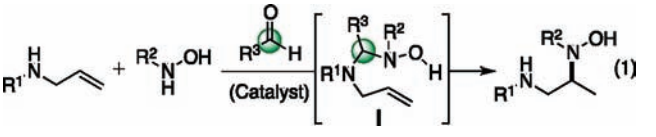


Figure 1. Prototypical catalytic tethering strategy: activation only through temporary intramolecularity.

reversibly from alcohols or amines under mild conditions. However, the necessity of favoring substrate preassociation and formation of the mixed tether (over unproductive homodimers) along with the issue of catalyst turnover have been serious obstacles to overcome for the development of a prototypical catalytic system (Figure 1). In our efforts to develop metal-free Cope-type hydroaminations,[6,7] we had noted the stark difference between the excellent intramolecular reactivity in five-membered-ring systems[7] and the forcing conditions required for limited intermolecular reactivity. Thus, we speculated that notoriously difficult intermolecular alkene hydroaminations could be achieved provided that a mixed aminal such as **I** (eq 1), and thus temporary intramolecularity, could be accessed reversibly in the presence of a tethering catalyst. Herein we report that aldehyde-based organocatalysts form a temporary tether between hydroxylamines and allylic amines in situ, thus enabling room-temperature directed intermolecular metal-free hydroaminations (eq 1). We also demonstrate the potential of this approach in asymmetric catalysis, showing that a readily available α-chiral aldehyde catalyst leads to the synthesis of enantioenriched vicinal diamines with high stereocontrol.



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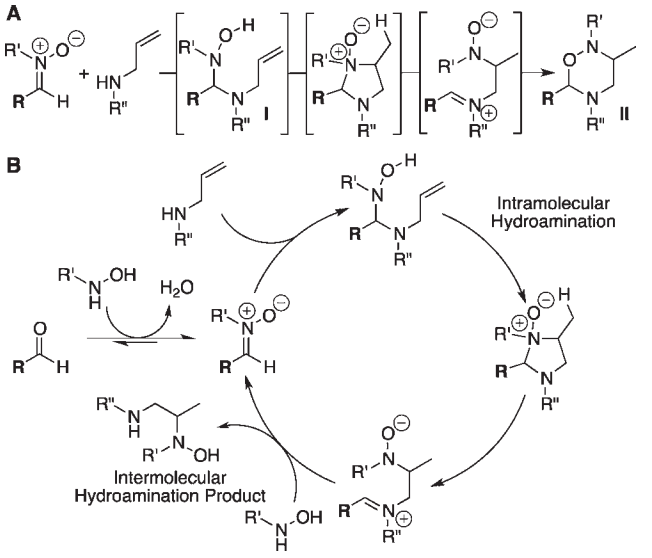


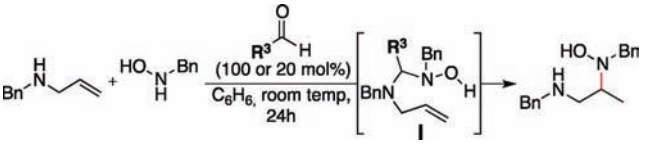
Figure 2. (A) A stoichiometric system leading to hydroamination products through a transient hydroxylamine (Knight and co-workers, ref 11). (B) Proposed catalytic cycle for a catalytic variant in which an aldehyde is used as the tethering precatalyst (this work).

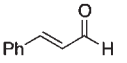
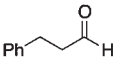
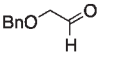
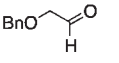
Intermolecular alkene hydroamination stands out as a simple and desirable reaction for which no general solution currently exists. While progress has been achieved using transition-metal catalysts to overcome the high activation energy associated with the addition of an N−H bond across electron-rich alkenes,[8] reactions of unbiased alkenes typically require catalysis at high temperatures and have limited synthetic applicability. Enantioselective variants are also severely underdeveloped despite the industrial importance of chiral amines.[9] Furthermore, a consequence of the near-thermoneutral profile of the hydroamination reaction and its negative entropy is that ideally the temperature should be as low as possible to maximize the yield and minimize reversibility.[10] Surprisingly, directed or tethered intermolecular reactions are rare in the hydroamination literature.

To address this issue, we sought to validate the catalytic tethering strategy described above to achieve intermolecular Cope-type hydroaminations of allylic amines (eq 1). This reaction required the formation of a mixed aminal intermediate (**I**) with selective tethering of the hydroxylamine through the nitrogen atom (since an O-linkage would prevent a further Cope-type hydroamination step). In this context, the work of Knight and co-workers[11] on the reaction of nitrones with allylic amines provided strong support for the formation of a transient hydroxylamine displaying the desired hydroamination reactivity (Figure 2A). In this system, nitrones are used as reagents and become incorporated into the product through an aminal formation/hydroamination/ring-opening/ring-closing sequence. Indirectly, this work also suggested that a catalytic version (Figure 2B) would be possible provided that the formation of a cyclic intermediate such as **II** could be avoided (or be reversible) and that an aldehyde precatalyst possessing the desired ability to promote the formation of the mixed aminal and allow catalyst turnover could be identified.

Our work began with an extensive screening of aldehydes and ketones that could potentially act as tethering organocatalysts [see Table S1 in the Supporting Information (SI)].[12] Representative reactivity and optimization data are presented in Table 1. In a departure from this work, optimal reactivity was observed for

Table 1. Representative Reactivity and Optimization Data[a]



Entry	Aldehyde	Quantity	NMR Yield (%)[b]
1	none	—	0
2		100 mol%	1
3		100 mol%	41
4		100 mol%	0
5		100 mol%	22
6		100 mol%	94
7		20 mol%	12
8		**20 mol%**	**77**

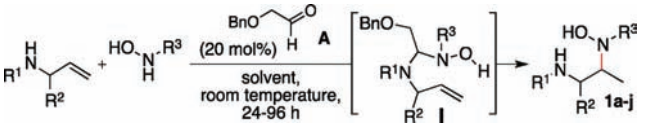
[a] Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), aldehyde (20 mol %), and C_6H_6 (1 mL) were charged into a vial and stirred at room temperature for 24 h. [b] Determined using 1,4-dimethoxybenzene as an internal standard.

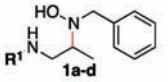
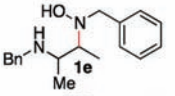
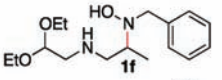
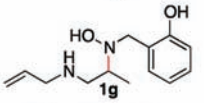
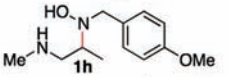
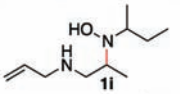
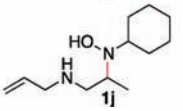
aldehydes bearing electron-withdrawing substituents (Table 1, entries 6 and 8). Our working hypothesis is that inductively destabilized aldehydes favor the formation of aminal **I** kinetically and thermodynamically, thus helping to offset the negative reaction entropy associated with formation of this mixed aminal intermediate. We were delighted to see that catalytic turnover is indeed possible with aldehydes containing an α-heteroatom, with α-benzyloxyacetaldehyde (**A**) being optimal (entries 6 and 8). Further optimization of the conditions revealed that the reaction can be carried out at room temperature with 20 mol % catalyst and that both benzene and chloroform are competent solvents (see Tables S2−S4).

With the optimized reaction conditions in hand, we probed the reaction scope, and the results are presented in Table 2. The organocatalytic reaction is compatible with allylamine (entry 1) as well as *N*-substituted allylamines (entries 2−12). Both allyl and benzyl substituents are tolerated, allowing the synthesis of orthogonally protected vicinal diamines. Hydroxylamines bearing benzylic (entries 1−10) and aliphatic (entries 11−12) substituents are also suitable substrates. Tolerance of the steric hindrance associated with *N*-cyclohexylhydroxylamine (entry 12) is also noteworthy. However, attempts to use this tethering catalyst with disubstituted allylic amines and homoallylic amines led to minimal product formation. Typically, related intramolecular hydroaminations proceed efficiently but require heating at temperatures in the 60−100 °C range.[7,11b] Preliminary data suggested that *irreversible* formation of the cyclic 1,2,5-oxadiazinane **II** (see Figure 2A) results in catalyst inhibition and limited substrate scope with catalyst **A**. Efforts to expand the scope of this transformation are ongoing.

One of the hallmarks of successful organocatalytic activation modes is that access to enantioenriched products is possible

Table 2. Aldehyde-Catalyzed Intermolecular Cope-Type Hydroamination[a]

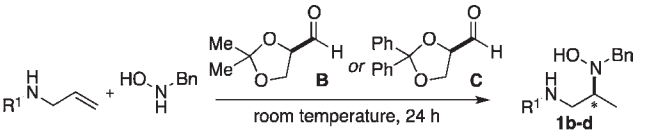


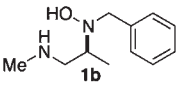
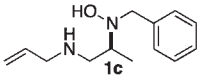
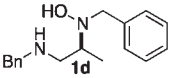
Entry	Solvent	Product	Yield (%)[b]
		 1a-d	
1	$CHCl_3$	R^1 = H (**1a**)	83
2	C_6H_6	R^1 = Me (**1b**)	72
3	C_6H_6	R^1 = allyl (**1c**)	69
4	C_6H_6	R^1 = Bn (**1d**)	75
5	C_6H_6	 1e	61[c,d]
6	$CHCl_3$	 1f	56[d]
7	C_6H_6	 1g	61
8	$CHCl_3$	 1h	51
9	$CHCl_3$	 1i	61[e]
10	$CHCl_3$	 1j	57

[a] Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), catalyst **A** (20 mol %), and solvent (1 mL) were charged into a vial and stirred at room temperature for 24 h [except for entries 5 (48 h), 6 (96 h), 7 (46 h), and 10 (29 h)]. [b] Isolated yields. [c] 1:1 mixture of diastereoisomers. [d] At 60 °C.

through asymmetric catalysis.[13] Encouraged by the success of this catalytic tethering strategy and the importance of the chiral 1,2-diamine motif,[14] we sought to validate this approach in the context of enantioselective catalysis.[15] Gratifyingly, encouraging enantiomeric excess (ee) was observed in the reactions of several secondary allylic amines with *N*-benzylhydroxylamine using commercially available (*R*)-glyceraldehyde acetonide (**B**) as the catalyst (Table 3, entries 1−3). Higher yields were also obtained using this catalyst rather than **A** (Table 2, entries 2−4 vs Table 3). Optimization efforts were pursued with the related, more easily handled catalyst **C** (see the SI), and improved enantioselectivity was observed for the formation of **1d** (87% ee; entry 4). Importantly, the enantioselectivities obtained for **1c** and **1d** (75 and 87% ee; entries 3 and 4) validate this tethering approach as an effective strategy in asymmetric catalysis. To the best of our knowledge, this enantioselectivity is the highest obtained for intermolecular hydroaminations of unactivated alkenes by any method, including metal-catalyzed reactions.[16,17] The observed

Table 3. Asymmetric Catalysis Using (*R*)-Glyceraldehyde Ketals as Chiral Catalysts[a]



Entry	Product	Catalyst	Yield[b]	ee (%)[c]
1	 1b	**B**	91	47
2	 1c	**B**	81	78
3	 1d	**B**	93	75
4	"	**C**	91	87

[a] Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), catalyst (20 mol %), and C_6H_6 (1 mL) were charged into a vial and stirred at room temperature for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis (see the SI).

sense of induction is consistent with formation of the temporary stereocenter present in the tether via a Felkin−Anh-controlled addition of the allylamine to the chiral nitrone[18] followed by efficient transposition of chirality[19] through the rigid bicyclic transition state associated with Cope-type hydroaminations.[7] Efforts to identify a highly enantioselective catalyst(s) and expand the substrate scope are ongoing and will be reported in due course.

Our proposed catalytic cycle (Figure 2B) first involves the condensation of the hydroxylamine onto the aldehyde to form a nitrone (this nitrone was observed by ^{1}H NMR spectroscopy). Attack on this nitrone by the allylamine leads to an aminal intermediate that undergoes a facile intramolecular Cope-type hydroamination. The resulting charged intermediate favors aminal cleavage to yield an iminium ion. Finally, condensation of a second molecule of hydroxylamine completes the catalytic cycle and releases the product, which is the result of a formal intermolecular hydroamination process. Current experiments are directed at probing this mechanistic scenario, preventing catalyst inhibition (via irreversible formation of intermediate **II**), and determining the rate-limiting step to allow subsequent improvement of this catalytic system.

In conclusion, we have reported the validation of a catalytic tethering strategy to achieve challenging intermolecular Cope-type hydroaminations under mild and metal-free conditions. This new paradigm in organocatalysis is also applicable in asymmetric synthesis, and this work highlights the fact that simple molecules such as chiral α-oxygenated aldehydes are capable of efficiently inducing asymmetry *only* through temporary intramolecularity. Therefore, we expect this advance will prompt the investigation and development of a broad range of transformations using this concept.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization, catalyst identification and optimization

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data, assignment of absolute configuration, and NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

[+]These authors contributed equally.

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