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Enantioselective Thiourea-Catalyzed Intramolecular Cope-Type Hydroamination

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Supporting Information

ABSTRACT: Catalysis of Cope-type rearrangements of bis-homoallylic hydroxylamines is demonstrated using chiral thiourea derivatives. This formal intramolecular hydroamination reaction provides access to highly enantioenriched α-substituted pyrrolidine products and represents a complementary approach to metal-catalyzed methods.

Enantioselective intramolecular olefin hydroamination affords a direct and atom-economical synthetic approach to chiral nitrogen heterocycles with useful properties as biologically active compounds,[1] small-molecule catalysts,[2] and ligands.[3] Significant advances in metal-catalyzed asymmetric intramolecular hydroaminations have relied mostly on highly air- and moisture-sensitive lanthanide, group 4 metal (Zr, Ti), or highly electropositive main-group metal (Mg, Li) complexes.[4] Late transition metal-catalyzed hydroamination[4s,t] and carboamination[4a,5] reactions have been identified that hold promise for broader functional group tolerance and concomitant substrate generality.[6,7]

The retro-Cope elimination reaction (Figure 1) represents a mechanistically distinct alternative to metal-catalyzed processes for alkene hydroamination. In this type of transformation, a hydroxylamine undergoes reaction with an olefin in a pericyclic pathway involving concerted C−H and C−N bond formation

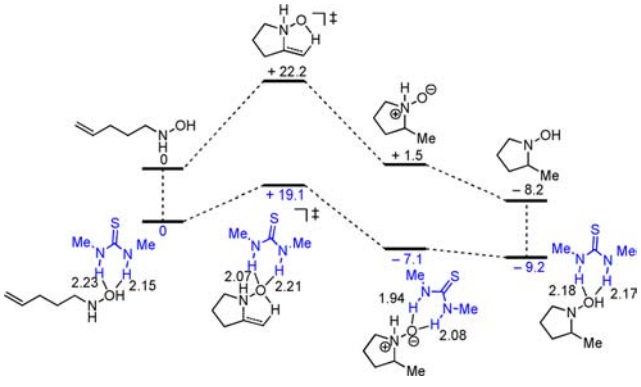


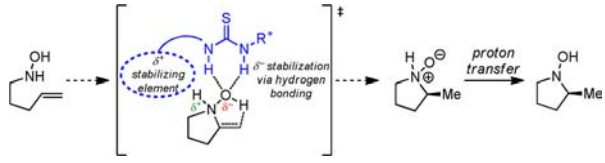
Figure 1. Calculated electronic energies for the optimized structures of the substrate, transition state, *N*-oxide intermediate, and product for both an uncatalyzed (black, top) and an *N*,*N*′-dimethylthiourea-catalyzed (blue, bottom) Cope hydroamination reaction (B3LYP/6-311+G(d,p) level of DFT). Relative energies are in kcal/mol and key hydrogen bonding distances are shown in angstroms.

(Figure 1).[8,9] Protic solvents have been shown to accelerate the Cope-type hydroamination,[10] and computational studies have identified specific stabilizing H-bonding interactions in the polar cyclization transition structure to account for this effect.[11]

We considered whether ureas and thioureas,[12] which have demonstrated utility as enantioselective dual hydrogen-bond donor catalysts, could facilitate the Cope-type hydroamination in a similar manner.[13] In order to evaluate this hypothesis, we analyzed the effect of a simple thiourea on the reaction coordinate for the Cope reaction using DFT methods (Figure 1). This analysis predicts that the thiourea lowers the activation barrier for the cyclization by 3.1 kcal/mol, thereby supporting the hypothesis that this family of H-bond donors could serve as viable catalysts for the hydroamination reaction. We report here the development of chiral thiourea derivatives bearing electron rich aromatic components that catalyze highly enantioselective Cope-type hydroaminations, providing access to enantioenriched α-substituted pyrrolidine products.

The principle we applied to the design of chiral catalysts for the Cope hydroamination is outlined in Scheme 1. In prior

Scheme 1. Design Strategy for Enantioselective Cope-Type Hydroamination Catalyst



work on enantioselective catalytic Claisen rearrangements,[14] the combined effect of hydrogen-bonding and secondary stabilization in the dipolar transition structure was shown to underlie the observed rate acceleration and asymmetric induction.[15] We reasoned that the polar character of the Cope-type hydroamination transition structure might render it susceptible to analogous cooperative, attractive, non-covalent interactions with the appropriate polyfunctional catalyst framework.

The cyclization of hydroxylamine **1a** was evaluated in the presence of a variety of thiourea catalysts bearing polarizable and conformationally constrained aromatic components (Table 1). While catalysts **3a** and **3b** (Table 1, entries 2 and 3) provided modest acceleration over the background, uncatalyzed reaction, catalysts containing electron-rich π-systems, such as

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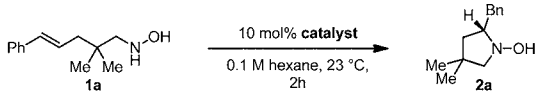
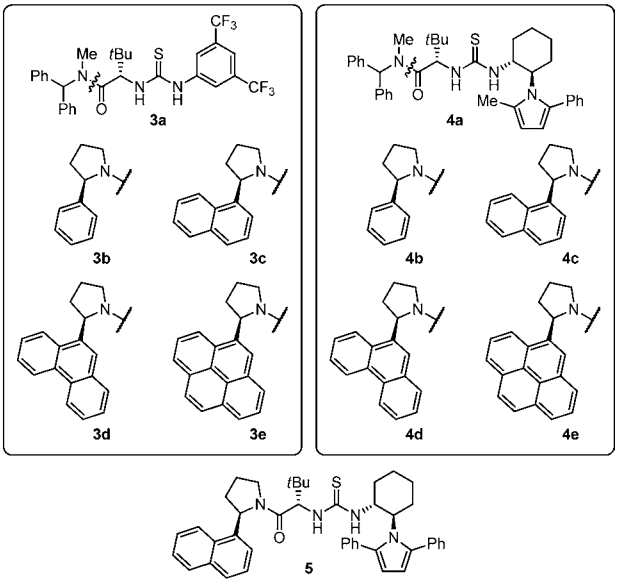
Table 1. Catalyst Evaluation[a]



entry	catalyst	yield (%)[b]	ee (%)[c]
1	none	8	--
2	**3a**	43	9
3	*ent*-**3b**	45	–14
4	**3c**	58	40
5	**3d**	67	85
6	**3e**	74	87
7	**4a**	77	76
8	**4b**	85	86
9	*ent*-**4c**	82	–89
10	**4d**	60	81
11	**4e**	64	85
12	**5**	83	91

[a]Hydroxylamine **1a** was generated *in situ* from the corresponding trifluoroacetate salt by addition of aqueous potassium carbonate. Reactions were performed on a 0.046-0.049 mmol scale, and were quenched by the addition of *p*-NO_2 benzoyl chloride. [b]Yields of the *O*-benzoylated products were determined by ^{1}H NMR analysis using mesitylene as an internal standard. [c]Determined by HPLC analysis using commercial chiral columns.

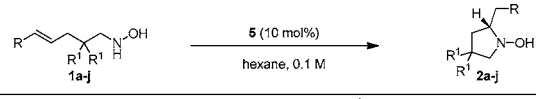


extended arenes or arylpyrroles, led to more significant rate enhancements. For catalysts **3b**–**3e** (Table 1, entries 3–6), an increase in yield and enantioselectivity was observed as the expanse of the α-aryl group of the pyrrolidine was increased. Comparable correlations between arene expanse and rate and enantioselectivity have been observed previously for this class of catalysts (**3c**–**3e**) in the context of polyene cyclizations and episulfonium ion ring-openings.[16] In these systems, stabilizing cation–π interactions between the catalyst arene and the cationic transition state were identified.

Catalysts bearing arylpyrrole components capable of similar interactions[15] were also found to be effective and highly enantioselective catalysts for the model transformation (Table 1, compare entries 2 and 7). For catalysts containing both a pyrrole and an α-arylpyrrolidine moiety, the level of enantioinduction was relatively insensitive to the size of the aryl group on the pyrrolidine portion of the catalyst (Table 1, entries 8–11). These results suggest that catalyst–transition state interactions with the arylpyrrole are stronger than those with the arylpyrrolidine for this class of catalysts. After extensive optimization of these structural motifs, thiourea **5** was identified as the optimal catalyst for the hydroamination.[17]

With the optimal catalyst identified, the substrate scope of the hydroamination reaction was evaluated. Several 4-alkenyl-1-hydroxylamines bearing electronically diverse (*E*)-styryl groups underwent cyclization in the presence of thiourea **5** in good yields and moderate to excellent enantioselectivities (Table 2, entries 1–10). *Ortho*, *meta*, and *para* substitution on the arene were all well tolerated (Table 2, entries 3, 6 and 7), as were halogen- and oxygen-containing functionality (Table 2, entries 3 and 5). Substrates with geminal disubstitution at the 2-position reacted more rapidly and with higher enantioselectivity than substrates lacking such groups (Table 2, entries 1, 8, and 9), presumably as a result of a favorable Thorpe–Ingold effect in the cyclization reaction.[18] Terminal olefin substrate **1j** also underwent cyclization to the desired pyrrolidine product, albeit with slightly lower enantioselectivity than the corresponding styrenyl analogues (Table 2, entries 11 and 12). The catalytic

Table 2. Scope of Enantioselective Hydroamination[a]



entry	R	R^1	product	time (h)	temp (°C)	yield(%)[b]	ee(%)[c]
1	C_6H_5	Me	**2a**	12	3	83	94
2[d]	C_6H_5	Me	**2a**	72	3	79	92
3	*p*-ClC_6H_4	Me	**2b**	5	3	87	95
4	*p*-$(Me)C_6H_4$	Me	**2c**	36	3	84	87
5	*p*-$(OMe)C_6H_4$	Me	**2d**	96	3	96	91
6	*o*-ClC_6H_4	Me	**2e**	5	3	91	92
7	*m*-ClC_6H_4	Me	**2f**	5	3	87	94
8	C_6H_5	-$CH_2(CH_2)_3CH_2$-	**2g**	5	3	82	96
9	C_6H_5	H	**2h**	72	30	68	81
10	*p*-ClC_6H_4	H	**2i**	36	30	93	83
11	H	Me	**2j**	2	3	86	78
12[e]	H	Me	**2j**	2	3	91	85

[a]Reactions were performed on a 0.18-0.25 mmol scale, and were quenched by the addition of *p*-NO_2 benzoyl chloride. For entries 1-3, 6-8, and 11-12 the hydroxylamine was generated *in situ* from the corresponding trifluoroacetate salt by addition of aqueous potassium carbonate. [b]Isolated yields of *O*-benzoylated products after purification on silica gel. [c]Determined by HPLC analysis of *O*-benzoylated products using commercial chiral columns. [d]2 mol% of **5** was used. [e]10 mol% of **3e** was used as the catalyst.

efficiency of the system is also notable, as the catalyst loading could be decreased from 10 to 2 mol% with only slight diminution of enantioselectivity (Table 2, entry 2).[19]

In conclusion, we have developed a highly enantioselective thiourea-catalyzed Cope-type hydroamination that provides access to a variety of pyrrolidine products under mild reaction conditions. Thiourea catalysts capable of stabilizing the dipolar transition structure in the pericyclic reaction via multiple non-covalent interactions were found to be most effective for catalysis and enantioinduction. Elucidation of the specific catalyst–substrate interactions at play is the focus of ongoing study, and will be applied to future catalyst design strategies.

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■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization data for products and all isolated intermediates. 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.

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(17) See Supporting Information for complete catalyst optimization.

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(19) In order to prevent racemic cyclization of any unreacted hydroxylamine during workup, the catalytic reactions were quenched by the addition of *p*-nitrobenzoyl chloride. The resultant *O*-benzoylated products can be reduced to the corresponding pyrrolidine in good yield and without erosion of enantiomeric excess. See Supporting Information for further details.