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FULL PAPER

Cu-Catalyzed Cope-Type Hydroamination of Non-activated Olefins toward Cyclic Nitrones: Scope, Mechanism and Enantioselective Process Development

Mengru Zhang,[a]†Shuang Liu,[a]†Hexin Li,[a]Yajing Guo,[a] Na Li,[a]Meihui Guan,[a] Haroon Mehfooz,[a] Jinbo Zhao*[a] and Qian Zhang*[a,b]

Abstract: Catalytic synthesis of cyclic nitrones, an important type of functional molecules for both synthetic chemistry and related fields, remains underdeveloped. Herein we report the Cu-catalyzed Cope-type hydroamination of oximes with pendant non-activated olefins enables facile access to a series of 5- and 6-membered cyclic nitrones under mild conditions. Heterocycle-tethered oximes were incorporated to the Cope-type hydroamination for the first time. High enantioselectivity was realized for carbon-tethered γ,δ-vinyl oximes to afford enantioenriched five-membered nitrones. Preliminary mechanistic studies indicate a mononuclear catalytic species and a unified catalytic pathway over a large temperature range.

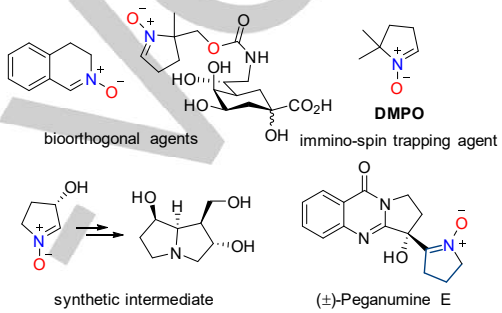

Figure 1. Selected Nitrone-based Functional Molecules, Therapeutic Agents, Synthetic Intermediates and Natural Products.

Introduction

Cyclic nitrone and their immediate derivatives have received increasing attention for their occurrence in natural products,[1] and their role as key intermediates for the preparation of *N*-heterocycles,[2,3]therapeutic immuno-spin-trapping reagents,[4,5] liquid crystal materials, and paramagnetic modification agents, et. al. (Figure 1). A striking contrast to their multifaceted application is the limited number and diversity of these compounds available owing to the paucity of catalytic strategies for their preparation. Accessing chiral cyclic nitrones mainly hinges on non-catalytic diastereoselective transformations from electrophile-induced annulation processes, *via* either substrate control[6] or reagent control.[7] A recent advance used chiral pool strategy with natural carbohydrate derived chiral backbone as template for substrate control.[8]Catalytic asymmetric transformations represent a highly efficient, cost-effective and versatile solution to chiral nitrone synthesis, but relevant protocols are rare.[9-12] Highly enantioselective catalytic synthesis of chiral cyclic nitrones remains highly underdeveloped.

Cope-type hydroamination has gained increasing attention over the past decades as a unique alternative to the traditional hydroamination paradigm.[13,14]Variants with sp^3-hybridized N-nucleophiles, such as hydroxyl amine, hydrazine, *et. al.*, has received significant attention and was systematically investigated in the past two decades, both experimentally[15-22] and theoretically.[23,24]These efforts culminated in highly enantioselective versions to be developed by the Beauchemin[22]and Jacobson[25] groups with organocatalysts, demonstrating the feasiblity of catalytic strategies for this traditionally thermal proess. On the other hand, since the seminal reports of Bishop[26]and Grigg[27], Cope-type hydroaminations of sp^2-hybridized N- nucleophiles remain highly underdeveloped,[28-32] likely due to their attenuated reactivity. Furthermore, the charge-separated property of the products of these sp^2-hybridized N-nucleophiles (such as nitrone for the reaction of oxime) indicates further thermodynamic unfavourability, exacerbating the situation for the development of effective catalytic protocols. In this context, a notable recent advance by Chiba *et. al.* employed inorganic base to facilitate the annulation of γ, δ-vinyl oxime toward formation of 5-membered cyclic nitrones.[30] Under these conditions, oximes bearing tethered styrene-type activated olefins were shown to be highly yielding, while those bearing terminal, non-activated alkene moieties were much less reactive even under forcing conditions (Scheme 1, *a*).To date, general applicable catalytic strategies for efficient Cope-type hydroamination of sp^2-hybridized N-sources remains lacking.

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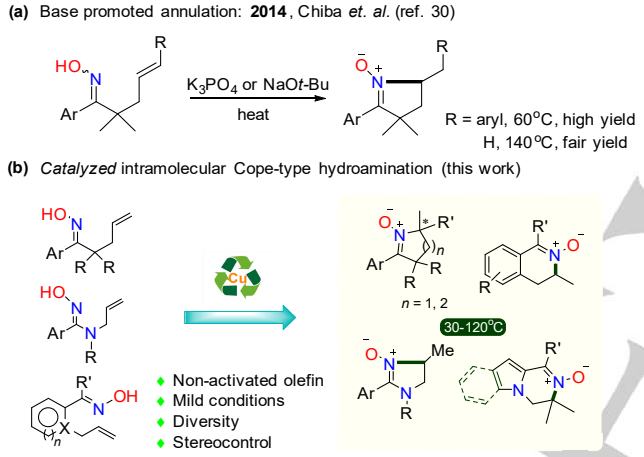
We recently reported the Cu^{I}-catalyzed Cope-type hydroamination of oxime with the highly strained cyclopropene proceeds with high efficiency,[12] demonstrating that π-activation by transition metal is a feasible catalytic strategy. Despite of this advance, the reaction of non-activated olefins is more challenging due to thermodynamic unfavourability. We envisioned that the catalyst-controlled cyclization of the readily available alkenyl oximes may provide highly efficient synthesis of cyclic nitrones that can be rendered asymmetric, provided that a viable catalytic activation of the non-activated olefins can be realized. Herein we show that with the appropriate choice of supporting ligands, a Cu^{I}-based catalytic system can catalyze vinyl oximes tethered by an array of scaffolds toward the construction of various 5- and 6-membered cyclic nitrones with high level of conversion. This catalytic protocol displays unparalleled substrate profile and offers highly enantioselective conditions for the synthesis of carbon-tethered 5-membered cyclic nitrones under mild conditions (Scheme 1, *b*).



Scheme 1. Cope-type Hydroamination of Oxime: Base-Promoted Reaction (a) and a Cu-Catalyzed Variant (b, this work).

Results and Discussion

We set out to examine the reactivity of readily available γ,δ-alkenyl oxime **1a** to probe the feasibility of activating non-activated olefin in an intramolecular setting. Remarkably, treatment of **1a** with catalytic CuCl/dppbz and 30 mol% NaO*t*-Bu in toluene led to efficient cyclization with a high conversion and moderate yield even at room temperature (entry 1, Table 1)! Notably, for these substrates the base-promoted conditions only provided moderate yields at 140°C.[31] Control experiments with copper salt or ligand alone led to no conversion (entries 2-3), indicative of dramatic ligand accelerated catalysis (LAC).[33] The reactions promoted by more electron-rich ligands gave higher conversion and yields, with IMes retrieving the highest 98% conversion and 87% yield (entries 4-7, Table 1). With this ligand, Cu(OAc)$_2$ demonstrates superior reactivity (entries 8-11). Upon elevation of temperature, Cu(OAc)$_2$/IMes catalyzed reaction reached full conversion at 60°C or above, and gave excellent yields of **4a** (entries 12-13).

Table 1. Optimization of Cu-Catalyzed Annulation of γ-Alkenyl Oxime 1a.[a]

Entry[a]	Cat.	Ligand	Temp./°C	Conv.	Yield[b]
1	CuCl	Dppbz (**L1**)	25	80%	55%
2	CuCl	--	25	0	0
3	--	Dppbz (**L1**)	25	0	0
4	CuCl	rac-BINAP (**L2**)	25	< 5%	trace
5	CuCl	PCy$_3$ (**L3**)	25	>99%	69%
6	CuCl	dcype (**L4**)	25	99%	85%
7	CuCl	IMes (**L5**)	25	98%	87%
8	CuTC	**L5**	25	<5 %	trace
9	Cu(OTf)$_2$	**L5**	25	< 5%	trace
10	CuBr$_2$	**L5**	25	< 5%	trace
11	Cu(OAc)$_2$	**L5**	25	97%	90%
12	Cu(OAc)$_2$	**L5**	60	>99%	88%
13	Cu(OAc)$_2$	**L5**	80	>99%	>99%

[a] Reactions were performed on 0.20 mmol scale. [b] NMR Yields versus an internal standard of CH_2Br_2.

Under the optimized condition (entry 13, Table 1) a variety of germinal dimethyl substituted carbon-tethered γ-alkenyl oximes delivered the expected 5-membered cyclic nitrones uneventfully in high yields (Scheme 2). The reactivity is insensitive to the electronic properties of substituents, and**4b**-**4j** were all delivered in excellent yields (83-99%). The reaction can also be uneventfully scaled up to gram scale, as a 10 mmol (2.37 g) scale reaction of oxime **1d** catalyzed by 2 mol% CuCl and3 mol% IMes at 80°C efficiently deliveredthe product **4d** in 80% yield (1.90 g).Furthermore, naphthyl (**4k**, **4l**) and thienyl (**4m**) substrates gave nearly quantitative yields. Alkyl substitution of the olefin at the terminal carbon led to compromised reactivity, as the substrate bearing a *cis*-internal olefin required higher temperature (120°C) to react, albeit still delivered the expected product **4n** in a good yield of 67%. Similarly, a substrate bearing a ring-fused *cis*-1,2-olefin also delivered the product **4o** in a good yield of 69%. In contrast, substrate bearing a phenyl substitution at this position retrieved a high yield of 87% (**4p**). In this case, activation by coordination is not as dramatic as for the mono-substituted terminal alkene, and base-promoted cyclization may account for part of the reactivity. To our delight, alkyl substitution at the internal olefinic carbon seems to exert less significant impact, as

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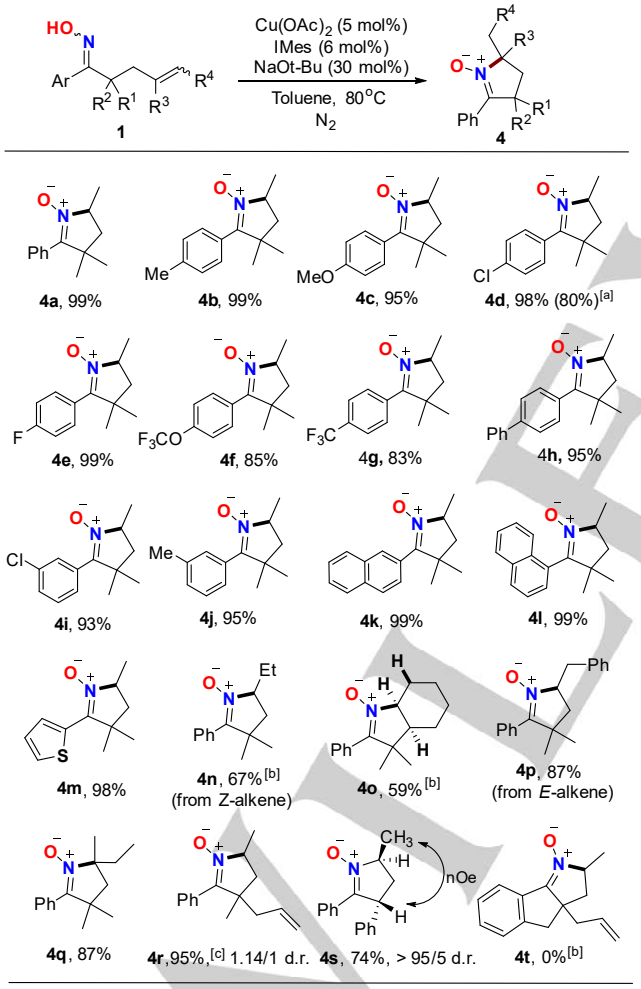
4q, which bears a tertiary α-carbon, was produced in a high 87% yield at 80°C.

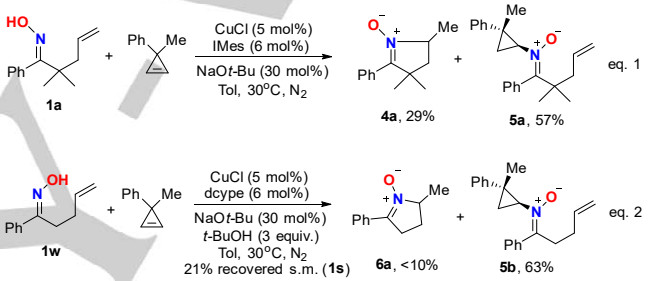
We then examined the effects of tether on the reactivity. While not surprisingly a substrate bearing sterically highly similar R^3 and R^4 (R^3 = Me, R^4 = allyl) afforded product **4r** in a high yield but low diastereocontrol, the oxime bearing an α-phenyl substituent afforded the product **4s** in 74% yield and > 95/5 d.r., whose *trans* configuration is supported by NOESY ananlysis, showing the strong 1,3-diastereocontrol exerted by the α-phenyl group. 1-Indanone derived substrate failed to deliver the expected product **4t**even at 120°C, indicating that for effective coordination activation, some degree of conformational flexibility is required.

Furthermore, substrates without germinal dimethyl substitution α -to the oxime moiety were also viable under the catalyzed conditions but resulted in lower conversions. As such, compound **5a** could only be obtained in 55% conversion and 52% yield catalyzed by $Cu(OAc)_2$/dppbz at 70°C for 24h in the presence of 3 equiv. of *t*-BuOH as additive (entry 1, Table 2).



Scheme 2. Scope of Thorpe-Ingold type carbon-tethered γ -Alkenyl Oximes.Conditions: oxime (0.20 mmol), $Cu(OAc)_2$ (5 mol%), IMes(6 mol%), NaO*t*-Bu (30 mol%), toluene [0.1M], 80°C, N_2. [a] Yield of 10 mmol scale reaction. [b] Performed at 120°C. [c] Performed at 30°C with dppbz as ligand.

We believe the lower conversion may arise from the unfavorable thermodynamics for non-activated olefins compared to the highly strained cyclopropene,[34] and/or the likely strong product inhibition, as indicated by the highly efficiency of Cu^I-catalyzed 1,3-dipolar cycloadditions of nitrones.[35,36] To probe the favorability of this intramolecular version vs intermolecular reaction with the strained cyclopropene, as well as the relative favorability of Thorpe-Ingold effect on the reactivity of intramolecular cyclization, we performed the following competing experiments (Scheme 2). Competitionbetween**1a**and cyclopropene showed clear preference in favor of intermolecular process, although as expected, the intramolecular process still contributed to an appreciable degree (29% yield of **4a**, eq. 1, Scheme3). In contrast, the intramolecular cyclization of substrate **1s** which lacks germinal dimethyl substitution was much more sluggish in the presence of cyclopropene (eq. 2, Scheme 3). These results highlight the challenge for the effective catalysis of non-activated olefins, even in intramolecular settings, especially for the substrates that lack germinal dimethyl substitution.



Scheme 3. Competition experiments.

Accordingly, we briefly re-optimized the conditions for these substrates. As can be seen from Table 2, the conversion for**6a**can be improved to 80% (yield was also 80%) with electron-rich bidentate alkyl phosphine ligand dcype**L4** (entry 2). To further improve the conversion, we surmised that addition of additives that can bind to Cu salts can facilitate the catalyst's ligand exchange process to liberate it from product-bound form to re-enter the catalytic cycle. Indeed, some olefin and alkyne additives were found to have moderate effects on the conversion. Of note, *trans*-stilbene also showed improvement of the conversion to 90%, and gave the highest yield among the additives evaluated (entry 5). The effect of diphenyl acetylene was almost as effective as *trans*-stilbene, with the conversion being >95% (entry 7). A higher loading (10 equiv.) of diphenyl acetylene did not retard the catalytic reaction but showed less obvious improvement to the yield (entry 8). Thus, the condition of entry 7 in Table 2was adopted in the subsequent scope studies.

This condition can be applied to a variety of substituted oximes bearing aryls and heteroaryls of distinct electronic characters, which all proceeded with high conversion and yields (Scheme 4).[37]Substitution at *ortho*-position is also nicely accommodated (**6j**, 75%). Similar to that observed above, the reaction of substrate bearing a methyl substitution at the internal carbon of the olefin moiety is equally facile (**6n**, 87% yield), while

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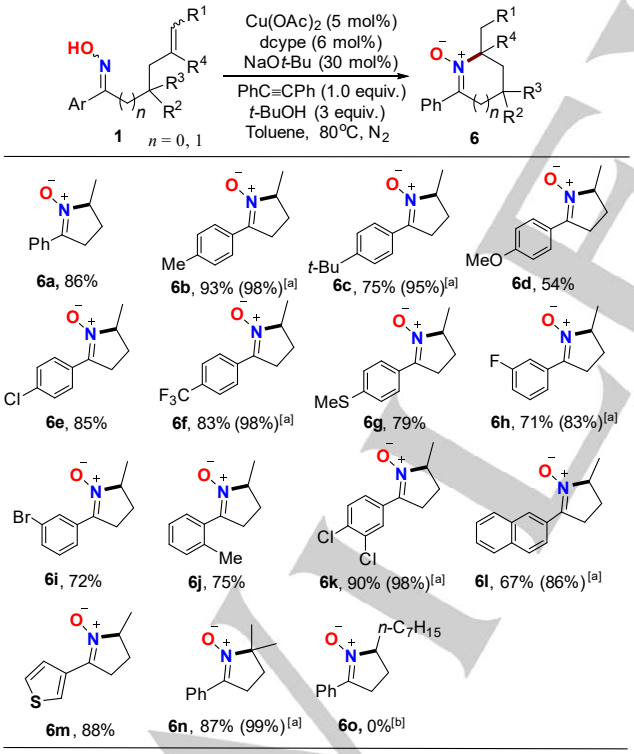
Table 2. Ligand and Additive Effect on Cu-Catalyzed Annulation of γ-Alkenyl Oxime**1s**.

Entry[a]	Ligand	Additive (equiv.)	Conv./%[a]	Yield/%[b]
1	Dppbz (**L1**)	--	55	52
2	dcype (**L4**)	--	80	80
3	IMes (**L5**)	--	74	52
4	P(3,5-di-CF_3-C_6H_3)$_3$ (**L6**)	--	< 5%	0
5	dcype (**L4**)	*trans*-stilbene (1)	90	88
6	dcype (**L4**)	4-F-styrene (1)	75	74
7	dcype (**L4**)	PhC≡CPh (1)	>95	86
8	dcype (**L4**)	PhC≡CPh (10)	>95	82

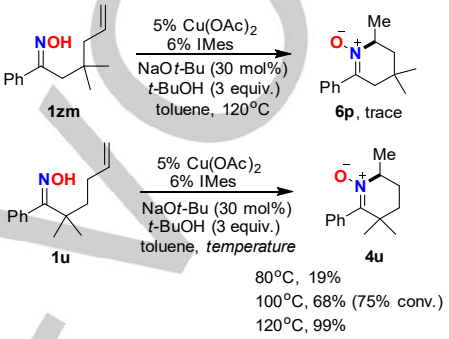
[a] Determined by ^{1}H NMR of crude reaction mixture. [b] Isolated yields.



Scheme 4. Scope of non-Thorpe-Ingold type carbon-tethered γ -Alkenyl Oximes.[a] Conversions were reported in parentheses where incomplete conversion was observed. [b] Performed at 120°C.

substitution at the terminal carbon led to no reaction even at elevated temperature of 120°C (**6o**, 0%).

We also examined the reactivity of δ,ε-alkenyl oxime under $Cu(OAc)_2$/IMes catalysis, but found that one-carbon homologated six-membered cyclic nitrones **6p**could not be cyclized with this protocol even at 120°C. In contrast, the product **4u**, which contains geminal dimethyl substitution α to the oxime, could be obtained with 99% yield at this temperature (Scheme 5), highlighting the significance of conformational effect.



Scheme 5. Reactivity of δ,ε-alkenyl oximes.

The scope of the current transformation also encompasses *N*-tethered substrates, such as *N*-hydroxy-*N'*-allyl arylarboximidamides **2** to access imidazoline-*N*-oxides **7** (Scheme 5). To our delight, these compounds demonstrate superior reactivities compared to carbon-tethered γ,δ-alkenyl oximes, i.e., the reaction of **2a** catalyzed by CuCl/dppbz afforded the expected product **7a** in 89% yield with > 95% conversion at 50°C. An examination of the *N*-substituent indicated that *N*-*t*-butyl derivative afforded cyclization product **7c** in a high yield of 97%. Under the above conditions, a series of *N*-*tert*-butyl substrates were efficiently transformed to the products, in typically > 95% conversion and high yields, including various substituted aryl (**7d-i**) and naphthyl (**7j**) bearing vinyl oximes, demonstrating insensitivity to electronic perturbation caused by substituents on the aryl group. The mild reaction conditions also enable successful cyclization to construct tertiary C-N bond, as demonstrated by **7k**. Notably, our recent studies showed that these compounds show different selectivity in Pd(0)-catalyzed annulation, in favor of *O*-annulation.[38]

Furthermore, ring fused *N*-tethered vinyl oximes can also be efficiently promoted to cyclize under the identical mild conditions as for the *N*-hydroxy-*N'*-allyl arylcarboximidamides (Scheme 6). Hence, as representative examples, benzene-fused and pyrrolyl/indolyl substituted oximes bearing various substituents uneventfully delivered the tricyclic nitrones **8a-c** and **9a-g** in good to high yields. Notably, the reactivity of oximes with disubstituted olefins also gave the expected products in good yields as well (**9b** and **9g**). Functionalities such as iodine can be nicely tolerated, allowing for further elaboration. Here, it is worthwhile to note the marked differential reactivities of carbon-tethered δ ,ε-alkenyl

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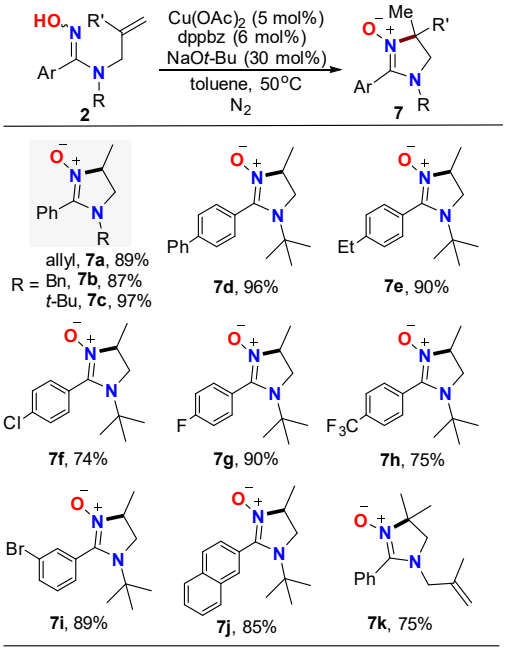
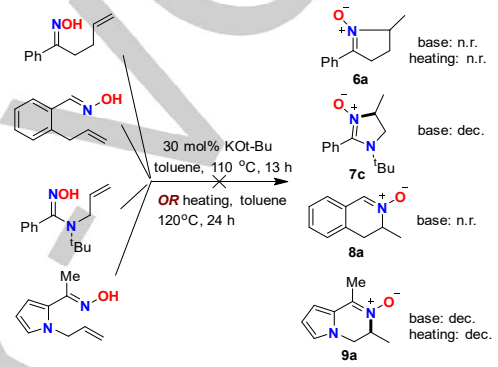


Scheme 5. Scope of *N*-hydroxy-*N*'-allyl arylarboximidamides for the synthesis of imidazole *N*-oxides.

Scheme 6. Scope of Benzene- and *N*-heterocycle Fused δ -alkenyl Oximes.[a] Performed at 70°C.

oxime (0% for **6p** even at 120°C) with that of the arene- and heteroarene fused alkenyl oxime (high yield of **7**-**9** at 50°C). We hypothesize that conformational effects may play a pivotal role for the catalytic reactivity.

To demonstrate the role of the catalytic system, cyclization of representative oximes under base-promoted or simple heating conditions were performed. These reactions only led to no conversion or decomposition of starting materials (Scheme 6), showing the essential role of catalysts.



Scheme 7. Control experiments.

Table 3. Catalytic Highly Enantioselective Synthesis of Cyclic Nitrones Enabled by Chiral Ligands.Optimization of Cu-Catalyzed Annulation of γ-Alkenyl Oxime**1a**.[a]

Entry	Catalyst	Ligand	Solvent	Additive	Yield/%[b]	e.r.[c]
1	CuCl	**L6**	Toluene	--	69	65:35

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2	CuCl	**L7**	Toluene	--	93	64:36
3	CuCl	**L8**	Toluene	--	79	75:25
4	CuCl	**L9**	Toluene	--	78	87:13
5	CuCl	**L10**	Toluene	--	> 99	70:30
6	CuBr	**L9**	Toluene	--	27	86:14
7	CuI	**L9**	Toluene	--	trace	--
8	$Cu(OAc)_2$	**L9**	Toluene	--	82	87:13
9	$Cu(OTf)_2$	**L9**	Toluene	--	75	81:19
10	$Cu(OAc)_2$	**L9**	THF	--	96	73:27
11	$Cu(OAc)_2$	**L9**	Et_2O	--	97	82:18
12	$Cu(OAc)_2$	**L9**	MTBE	--	46	86:14
13	$Cu(OAc)_2$	**L9**	Dioxane	--	93	73:27
14	$Cu(OAc)_2$	**L9**	CyH	--	32	95:5
15	$Cu(OAc)_2$	**L9**	CyH	--	68	90:10
16	$Cu(OAc)_2$	**L9**	CyH	*t*-BuOH (1 equiv.)	81 (89)[d]	92:8
17	$Cu(OAc)_2$	**L9**	CyH	*t*-BuOH (2 equiv.)	83 (93) [d]	91:9
18	$Cu(OAc)_2$	**L9**	CyH	*t*-BuOH (3 equiv.)	85 (94) [d]	92:8

[a] Conditions: oxime (0.20 mmol), Cu (0.01 mmol, 5 mol%), **L** (0.012 mmol, 6 mol%), NaO*t*-Bu, additive (if applicable), solvent (2 mL), 10°C, 24 h.[b] Isolated yields. [c] Enantioselectivities were determined by HPLC on a chiral stationary phase. [d] Values in parentheses are conversion of the reaction based on recovered starting material.

The effect of asymmetric induction with chiral ligands was subsequently investigated with the model reaction of **1a** following the establishment of the substrate scope and the factors controlling the reactivity (Table 3). Evaluation of ligand structure revealed DuPhos and BPE types ligands to be promising, with (*R*,*R*)-Ph-BPE **L9** giving (+)-**4a** in 87:13 e.r. (entry 4, Table 3). The pre-catalysts were also important for the conversion and enantiocontrol, among which $Cu(OAc)_2$ was found to be more competent in both reactivity and enantioselection (entries 5-9). A remarkable effect on the enantioselectivity was also noted: ethereal solvents tend to give higher conversion with lower enantioselectivities, while non-polar cyclohexane (CyH) delivered the product with high enantiocontrol (95:5 e.r.) but a low conversion of 32% (entry 14). Alcoholic additives were then added to improve the conversion in CyH (entries 16-18). To our delight, with 3 equiv. of *t*-BuOH the reaction can reach 94% conversion, retrieving product (+)-**4a**in 85% yield and 92:8 e.r. (entry 18).

Under these optimized conditions, a plethora of carbon tethered alkenyl oximes undergo ligand-prompted Cu-catalyzed cyclization to afford the corresponding chiral 5-membered cyclic nitrones with high enantiomeric ratios (Scheme 8). Tolerated functionalities include various halides, fluorine, methylthio group, *et. al.* Notably, the reaction of oximes displaying α,α-dimethyl substitution can reach high conversion at 10 °C, a temperature under which substrates without the dimethyl substituents were more reluctant to cyclize. These latter substrates can undergo efficient cyclization at 50°C to deliver the products **6** in good conversions and high level of enantiocontrol.[39]Generally, the enantioselectivity remained high irrespective of the electronic properties of the substituents on the aryl groups. Furthermore, the enantioselective conditions are efficient for the establishment of tertiary center by activating olefins bearing alkyl substitution at the internal olefinic carbon (**4p**). However, the enantiocontrol for other types of substrates, such as aza-, benzo- and heterocycle-fused substrates remains low with a variety of commonly used ligand scaffolds. Further studies are warranted and are currently underway.

We subsequently performed some preliminary studies to gain mechanistic insights of the reaction. Upon monitoring the enantioselectivity of the cyclization product vs the enantioselectivity of the catalyst, a linearrelationship between the enantiomeric excess of the catalyst andthat of the product was observed (Figure 3, left). The lack of non-linear effect suggests that neithercatalyst aggregation nor dimer formation is present.[40] In addition, Eyring plot of the enantioselectivities of reactions performed within a large temperature range (–20 ~ 80 °C) displayed good linearity (Figure 3, right), suggesting of a unified mechanism operates over this large temperature range,[41] and that no appreciable competing background reaction is present, as

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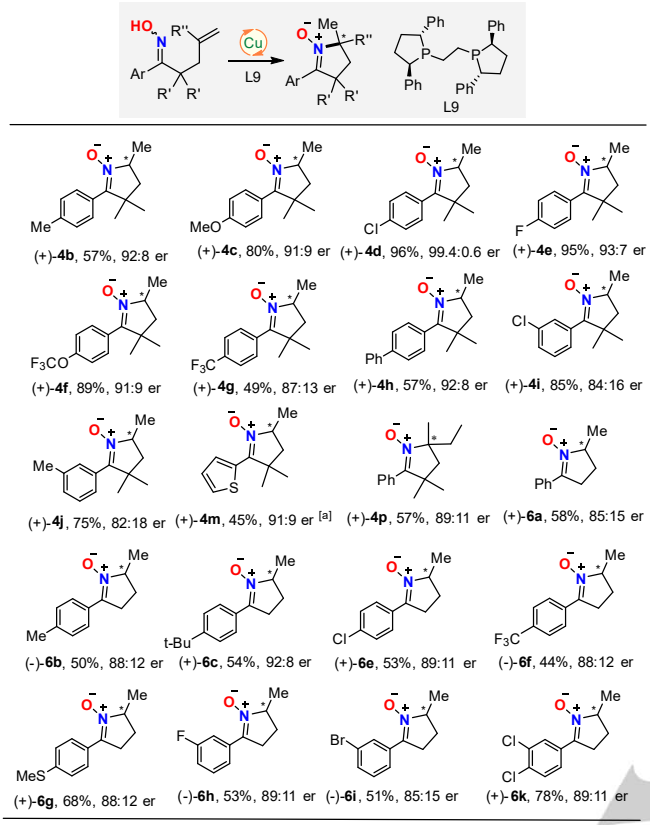

Scheme 8. Substrate Scope of the Enantioselective Intramolecular Cope-type Hydroamination of Alkenyl oximes **1**. Conditions: oxime **1** (0.20 mmol), Cu (5 mol%), **L9** (0.012 mmol, 6 mol%), NaO*t*-Bu (0.06 mmol, 30 mol%), *t*-BuOH (0.60 mmol, 3 equiv.), CyH (2 mL), N_2.For **4**, the reactions were performed with $Cu(OAc)_2$ at 10°C; for **6**, the reactions were performed with CuCl at 30°C for 12 h, then 50°C, 12 h. [a] **L8** was used as ligand.

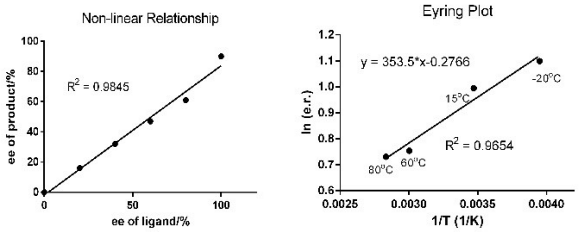

Figure 3. Mechanistic studies. Non-linear effect (left) and Eyring plot (right) of the reaction of **1a**catalyzed by CuCl/(*R*, *R*)-Ph-BPE to form (+)-**4a** at various temperatures in toluene.

observed experimentally.From the Eyring plot, differential activation parameters ($\Delta\Delta H^{\neq} = -0.70$ kcal/mol; $\Delta\Delta S^{\neq} = -0.55$ cal/mol· K) can be facily extracted.This relatively small differential activation enthalpy and especially smalldifferntial activation entropy indicate that the enthalpy term plays a more dominant role in the the stereodiscrimination process.[42]The appreciable solvent effect on the enantiocontrol likely arises from the formation of solvent clusters that affected the enthalpy-entropy control of the enantioselective process.[43]

A mechanistic hypothesis was proposed (Figure 4) based on our previous work and the experimental evidence gained herein. First, the reaction of oxime (as exemplified with **1s**), base and copper catalyst CuL*X affords adduct **A**, with subsequent association of the olefin to form π-complex **B**. Ligand promoted inner-sphere *metalla*-retro-Cope cyclization to forge the key C–N bond, leading to alkyl copper species **C**. Protonation of the latter either with *t*-BuOH or with the substrate oxime can deliver the final product **6a** and regenerate catalyst for the next cycle. Unlike the reaction of cyclopropene, herein, especially for the carbon-tethered substrates which lacks germinal di-substitution, the addition of alkyne as additive is necessitated to possibly accelerate the catalyst's ligand exchange process to liberate it from the product-bound species **D** to re-enter the next cycle.

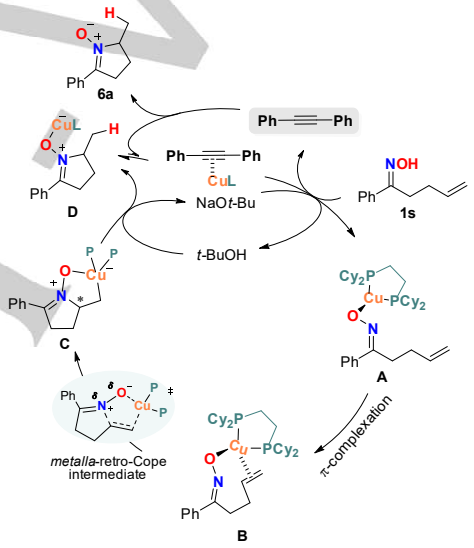

Figure 4. A plausible mechanism.

Conclusions

In conclusion, a Cu^{I}-based catalytic system is proven effective for intramolecular Cope-type hydroamination of oxime with non-activated olefins, enabling efficient access to a variety of 5- and 6-membered cyclic nitrones that are otherwise challenging to attain or intangible. For the first time, aza- and heterocycle fused vinyl oximes were incorporated into the reactivity domain of Cope-type hydroamination, expanding the diversity and accessibility of cyclic nitrones. Moreover, high enantioselectivities were also achieved for carbon-tethered 5-membered nitrones, representing the first example of high enantioselective catalytic cyclic nitrones synthesis from alkenyl oximes. Mechanistic studies suggest a mononuclear catalytic species and a unified catalytic pathway over a large temperature range. Further studies are underway in our laboratory to expand this strategy to other types of substrates.

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Mengru Zhang,Shuang Liu,Hexin Li, Yajing Guo, Na Li, Meihui Guan, Haroon Mehfooz, Jinbo Zhao and Qian Zhang**

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Cu-Catalyzed Cope-Type Hydroamination of Non-activated Olefins toward Cyclic Nitrones:Scope, Mechanism and Enantioselective Process Development

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