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Chemo-, Regio-, and Enantioselective Synthesis of Allylic Nitrones *via* Rhodium-Catalyzed Addition of Oximes to Allenes

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Abstract: *The first chemo-, regio-, and enantioselective rhodium-catalyzed addition of oximes to allenes is reported. Using Rh(I) /Josiphos catalyst system under mild conditions, the construction of allylic C–N bonds instead of C–O bonds were achieved. This method permits the atom-economic synthesis of branched allylic nitrones in good to quantitative yields and excellent enantioselectivities.*

Chiral nitrones are useful building blocks that can undergo a variety of reactions and play an important role in the history of cycloaddition reaction.[1-3] The most important reaction is the 1,3-dipolar cycloaddition (1,3-DC), which was used for the preparation of numerous synthetic targets and a diverse array of heterocyclic compounds.[4-8] Oximes are also attractive synthetic reagents and have been widely used in both metal-free and metal-involved chemistry since they are both nitrogen and oxygen nucleophiles.[9] Due to their potential applications, we became interested in the development of a feasible strategy employing oximes as selective nitrogen nucleophiles for the addition to allenes to furnish chiral allylic nitrones as versatile organic building blocks.[10]

Over the past years, the metal-catalyzed enantioselective reactions of oximes mostly provided access to oxime ethers rather than *N*-functionalized nitrones.[11-18] To the best of our knowledge, rhodium-catalyzed asymmetric hydroamination of oximes to allenes has not been investigated. In 2005, Takemoto *et al.* reported a palladium-catalyzed allylic substitution of oximes, which depending on the reaction medium provided access to either *N*- or *O*- allylation products. (Scheme 1, upper part).[19] Based on our previous results on rhodium-catalyzed addition of pronucleophiles to allenes[20] and alkynes,[10] we speculated that the addition of a hydroxylamines to allenes in the presence of an appropriate rhodium catalyst and acidic cocatalyst might give access towards synthetically valuable branched allylic nitrones .

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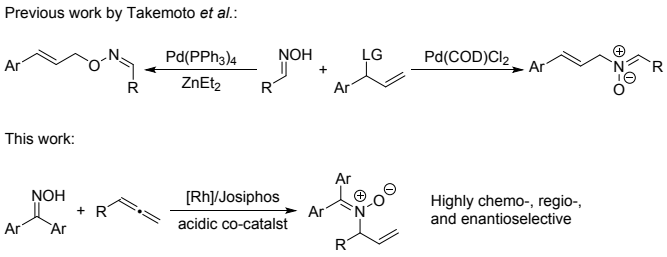
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

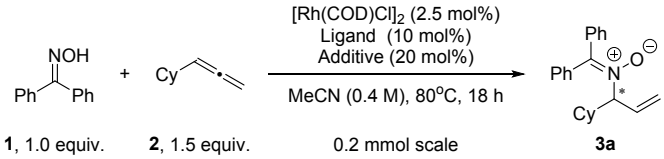
Herein, we reported the first enantioselective intermolecular hydroamination of oximes to allenes using a rhodium catalyst, producing versatile branched allylic nitrones (Scheme 1, lower part).

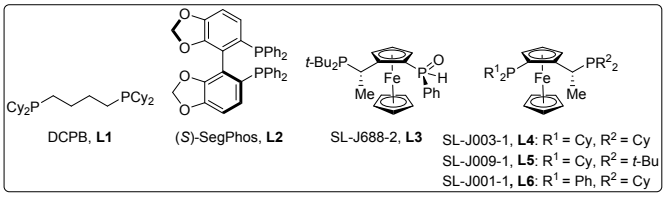


Scheme 1. Transition metal catalyzed addition of oximes

The initial reactions were conducted with benzophenone oxime **1a** (1.0 equiv.) and cyclohexylallene **2** (1.5 equiv.) as model substrates (Table 1). In the presence of $[Rh(COD)Cl]_2$ (2.5 mol%) and racemic ligand DCPB (**L1**, 10 mol%) in nitromethane at 80°C, the desired product **3a** was obtained in 87% yield by employing benzoic acid (entry 2, 20 mol%) as a Brønsted acid cocatalyst. The effect of the acid cocatalyst on reaction efficiency was enormous (compare entries 1 and 2). Inspired by these results, various chiral bidentate diphosphine ligands with different backbones were tested in this model reaction containing Brønsted acid cocatalyst. While many standard privileged chiral ligands led to poor results, a promising enantioselectivity was obtained by employing the chiral ferrocene based ligand **L4** (entries 5 and 6). After screening all the parameters of the reaction conditions, we were pleased to find out that *p*-methoxybenzoic acid as additive gave the desired allylic nitrone **3a** in 96% yield with a remarkable 92% *ee* (entry 6).

Table 1. Ligand screening and optimization of reaction conditions



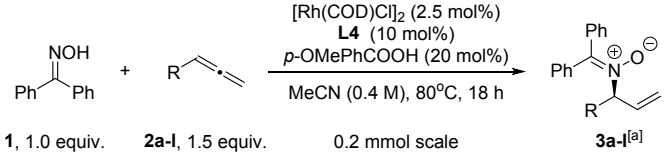


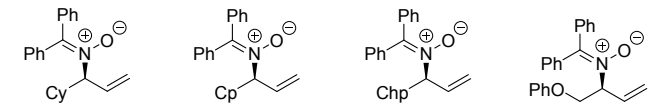
Entry	Ligand	Additive	Yield[a]	*ee*[b]
1	**L1**	-	9	rac
2	**L1**	PhCOOH	87	rac
3	**L2**	PhCOOH	43	36
4	**L3**	PhCOOH	8	78
5	**L4**	PhCOOH	96	82
6	**L4**	*p*-OMeC$_6$H$_4$COOH	96	92
7	**L5**	PhCOOH	35	28
8	**L6**	PhCOOH	8	10

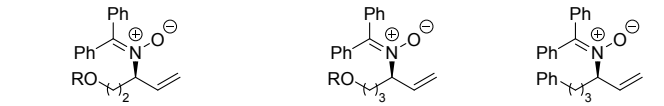
[a] Isolated yield of the branched product **3a**. [b] The enantiomeric excess of **3a** was determined by chiral HPLC.

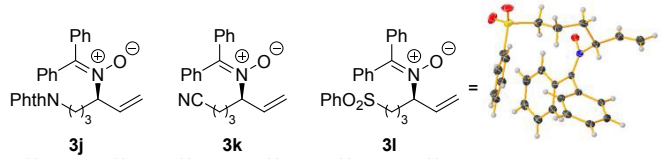
With the optimid conditions in hand, we first explored the scope of terminal allenes, which were readily prepared in one or two steps from either commercial or known starting materials (Table 2).[21]

Table 2. Scope of the rhodium-catalyzed coupling of benzophenone oxime with allenes[a]







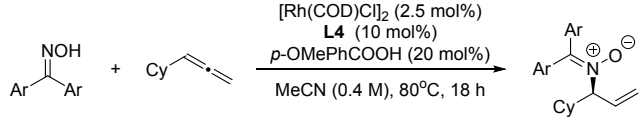


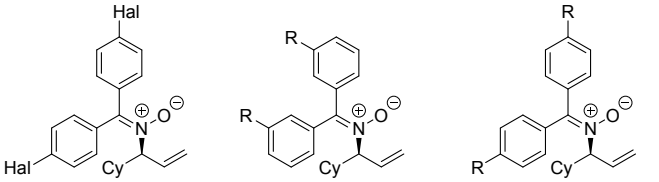
[a] Isolated yield and the *ee* value was determined by chiral HPLC.
[b] 4 mmol scale reaction was carried out.

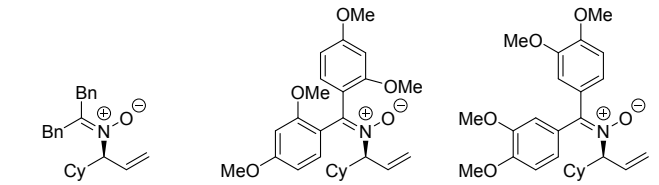
The allenes with a cycloalkyl substituent containing five, six, and seven membered rings were suitable substrates (**3a–c**). Also, protected alcohols were tolerated in the reaction (**3d–h**). Allenes bearing various functional groups, such as phenyl (**2i**), phthalimide (**2j**), nitrile (**2k**), and thioethers (2**l**), reacted smoothly with good to excellent yields and enantioselectivities. At this point, the assignment of the absolute configuration was accomplished by an X-ray crystallographic analysis of **3l**. Furthermore, branched allylic nitrone **3a** was synthesized under scope conditions on gram scale in 94% yield and 92% *ee*, which indicated the practicality of this method.

Next, we moved on to expand the scope with respect to oxime derivatives, which can be easily obtained by a simple condensation of ketones with hydroxylamine (Table 3).[22] As the electronegativity of the halogen in *para*-position decreases, a significant increase in yield from 75% to 99% was observed while maintaining high enantioselectivity (**3m–o**). Further exploration of electronic effects showed that electron-withdrawing and electron-donating groups in either *meta* or *para* positions are well compatible with the reaction conditions (**3p–t**). Even di-substituted benzophenone oximes effectively furnished the corresponding products as well (**3u** and **3v**).

Table 3. Scope of the rhodium-catalyzed coupling of cyclohexylallene with aryl oximes[a]

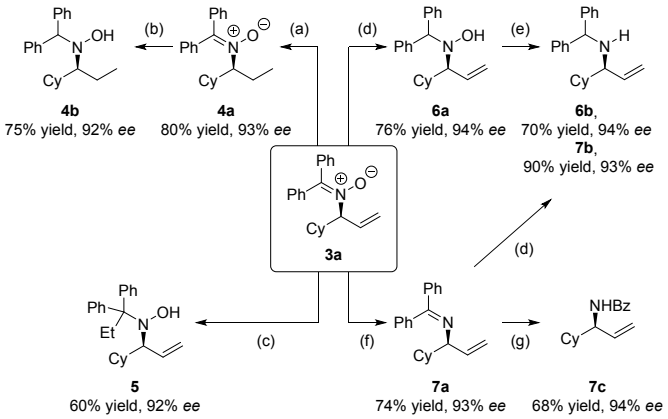






[a] Isolated yield and the *ee* value was determined by chiral HPLC.

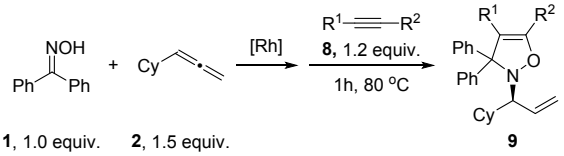
To explore the potential utility of this methodology for synthesis, chiral allylic nitrone **3a** was subjected to various transformations (Scheme 2). Hydrogenation of **3a** gave the nitrone **4a** in 4 h, whereas a prolonged reaction time (overnight) afforded the hydroxylamine **4b** by further addition of hydrogen across the nitrone moiety. Addition of ethyl magnesium chloride in the presence of 10 mol% $ZnCl_2$ allowed the 1,2-addition product **5**. Nitrone **3a** could be chemoselectively reduced to hydroxylamine **6a** with sodium cyanoborohydride. Alternatively, deoxygenation led to the imine **7a**. Both **6a** and **7a** could be further reduced chemoselectively to the corresponding secondary amines **6b** and **7b**, respectively. Moreover, imine **7a** can be hydrolysed to the corresponding primary amine and protected as the corresponding benzoate **7c**.

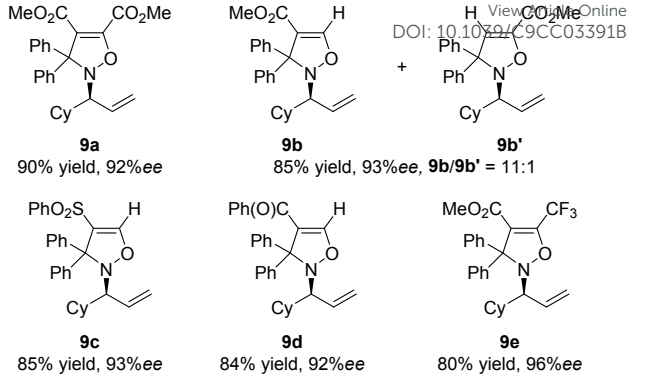


Scheme 2. Synthetic transformations of chiral allylic nitrones: (a) Pd/C (10 mol%), H_2 (1 atm), PhMe, r.t., 4 h. (b) Pd/C (10 mol%), H_2 (1 atm), PhMe, r.t., overnight. (c) EtMgCl (1.3 equiv.), $ZnCl_2$ (10 mol%), THF, r.t., 2 h. (d) $NaBH_3CN$ (1 equiv.), 2N HCl (2 equiv.), MeOH, 0 °C, 20 min. (e) Zn (5 equiv.), 2N HCl, reflux, 1 h. (f) $TiCl_4$ (7 equiv.), $LiAlH_4$ (5 equiv.), NEt_3 (45 equiv.), THF, 30 min. (g) 2N HCl, Et_2O, r.t., overnight; then NEt_3 (4 equiv.), benzoyl chloride (1.5 equiv.), DCM, r.t., overnight.

Inspired by these synthetic possibilities, the one-pot synthesis of rhodium-catalyzed hydroamination of oximes towards allylic nitrones, followed by 1,3-dipolar cycloaddition reaction, was conducted (Table 4). The reaction proceeded smoothly employing alkyne **8** containing electron withdrawing group to furnish isoxazoline **9** in good yield and excellent enantiomeric excess (**9a**-e).

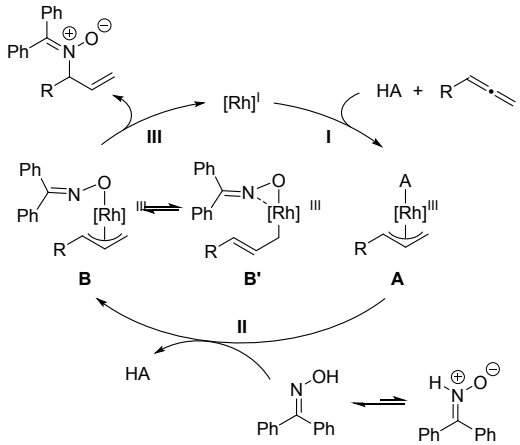
Table 4. Scope of one-pot synthesis *via* 1,3-dipolar cycloaddition reaction.[a]





[a] Scope conditions. [b] The *ee* values were determined by chiral HPLC. [c] The regioselectivity was determined by ^1H NMR analysis of the crude reaction mixture.

On the basis of these experiments and our previous investigations on allene chemistry,[10, 23-25] the reaction mechanism can be proposed as depicted in Scheme 3. Oxidative addition of benzoic acid to Rh(I) and hydrometalation of allene forms Rh(III) π-allyl complex **A** (step **I**). Then, exchange with benzophenone oxime, which is in equilibrium with its nitrone tautomer,[26-29] leads to an equilibrium of π- and σ-allyl complexes **B** and **B'** (step **II**). Finally, reductive elimination of **B** and **B'**, which presumably undergoes an intramolecular attack of the lone-pair of the adjacent nitrogen, leads to the branched allylic nitrone product along with regeneration of the rhodium catalyst (step **III**).



Scheme 3. Proposed catalytic cycle for the Rh-catalyzed addition of benzophenone oxime to allene.

To conclude, we have developed the first chemo-, regio-, and enantioselective coupling of benzophenone oximes with allenes *via* a rhodium/Josiphos catalyst system to afford branched allylic nitrones in good to excellent yields and excellent enantioselectivities. The protocol was found to be applicable to a broad range of substituted benzophenone oximes and functionalized allenes. A subsequent 1,3-dipolar cycloaddition could generate *N*-allylated chiral isoxazoles, demonstrating the potential for *N*-allylated chiral heterocycles. Further mechanistic studies and exploration of the synthetic

potential of *N*-allylated chiral nitrones are being pursued in our laboratory.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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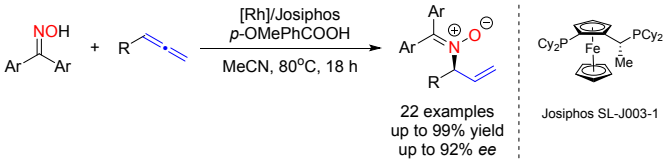
Scheme for Table of Contents



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