Enantioselective Synthesis of Cyclic Nitrones by Chemoselective Intramolecular Allylic Alkylation of Oximes

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Abstract: The enantio- and chemoselective iridium-catalyzed *N*-allylation of oximes is described for the first time. Intramolecular kinetic resolution provides access to cyclic nitrones and enantioenriched aliphatic allylic alcohols. Salient features of this transformation are its ability to employ *E/Z*-isomeric mixtures of oxime starting materials convergently and high functional group tolerance. The implementation of *N*-allylation/1,3-dipolar cycloaddition reaction sequences furnish tricyclic isoxazolidines in highly enantio- and diastereoselective fashion. The synthetic utility of the approach is demonstrated by the efficient, formal synthesis of the marine natural product (+)-halichlorine.

Nitrones are valuable intermediates for the synthesis of nitrogen containing pharmaceuticals,[1] complex natural products,[2] functional materials,[3] and bioconjugates.[4] They can function as electrophiles,[5,6] as directing groups in C–H fuctionalizations,[7] and as dipoles in 1,3-dipolar cycloadditions.[8] The latter stand out as particularly important tools for synthetic chemists as they enable concomitant formation of C–C and C–O bonds, heterocy-cle syntheses, and approaches to β-lactams.[9] In particular, intramolecular 1,3-dipolar cycloadditions forge multiple rings in a single step and have found widespread utility in complex target synthesis.[10]

Racemic, cyclic nitrones are featured as key intermediates in numerous, classic syntheses of fused rings and/or spirocycles.[11] Some of the most famous examples include syntheses of cocaine and a variety of poison dart frog toxins.[12] The discovery of synthetically useful, asymmetric, catalytic approaches to optically active, cyclic nitrones stands to significantly impact the development of new synthetic strategies in complex target synthesis. Herein, we report the enantioselective synthesis of 5-, 6- and 7-membered cyclic nitrones by enantioselective *N*-allylation of hydroxy oximes under dual catalyst control involving iridium(I) and Brønsted acids (Scheme 1A). Implementation of this strategy in tandem *N*-allylation/dipolar cycloaddition sequences furnished oxazatriquinanes in a highly stereo-controlled fashion, which is showcased in the formal synthesis of (+)-halichlorine, an inhibitor of vascular cell adhesion protein 1.[13]

There have been a number of key developments in asymmetric catalysis for the preparation of acyclic, optically active nitrones from oximes via intermolecular olefin hydroamination by the groups of Zhang,[14] Kobayashi,[15] and Breit.[16] Yet, to date, only one example of catalytic, enantioselective synthesis of cyclic nitrones has appeared in the literature (Scheme 1B). In 2019, Zhang reported the intramolecular hydroamination of olefins using a copper/bisphosphine catalyst.[17] The method prescribes the use of oximes derived from γ,δ-unsaturated aryl ketones and furnishes exclusively 5-membered nitrones. Optimal results were reported with substrates that incorporate aryl ketoximes with gem-dimethyl substitution at Cα (R1 = Me).
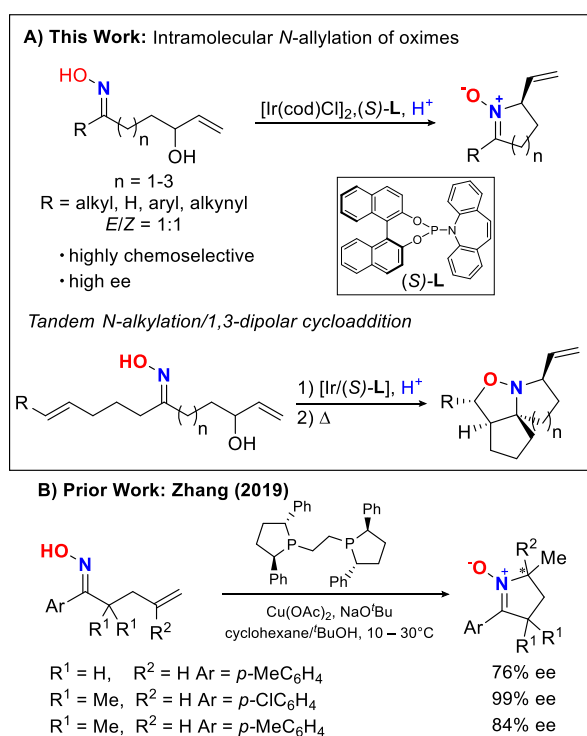
Scheme 1. Chemodivergent, enantioselective Ir-catalyzed synthesis of cyclic nitrones and intramolecular hydroamination by Zhang.

Based on our long-standing interest in iridium-catalyzed allylic substitution reactions,[18,19] we sought to investigate chiral catalysts derived from [Ir(cod)Cl]₂ and phosphoramidite-olefin ligands for the enantioselective synthesis of cyclic nitrones. In contrast to olefin hydroamination reactions, the use of secondary allylic alcohols for the N-functionalization of oximes introduces several complications (Scheme 2). In the most general process, the starting material employed is a mixture of 4 stereoisomers
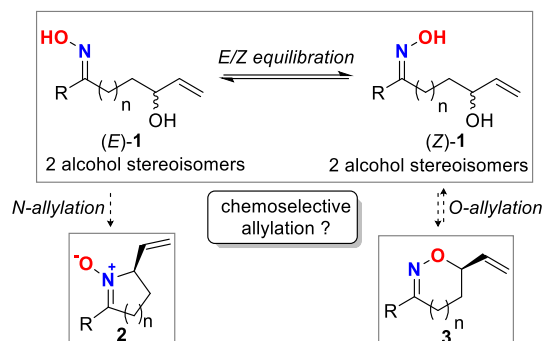

Scheme 2. Intramolecular enantio- and chemoselective allylation of oximes.

because the substrate allylic alcohols are racemic and include oxime geometric isomers. At the outset of our investigations, the compatibility of chiral iridium catalysts when confronted with this mixture was uncertain, because both olefins and oximes may be ligands for iridium.[20] Additionally, as oximes are ambident nucleophiles,[21] it was not clear whether oxime geometry or product ring size might favor undesired O-alkylation.[22,23] In the ideal process, a Curtin-Hammett scenario[24,25] would allow both diastereomers of the oxime starting material to converge into a single cyclic nitrone product.

We commenced our studies with allylic alcohol **1a** (Scheme 2, R = H, n = 2) obtained as a 1:1 mixture of E/Z-oxime isomers. Initial screening experiments (see Supporting Information) using [Ir(cod)Cl]₂ (3 mol%), (S)-**L** (12 mol%), and Zn(OTf)₂ as a Lewis acidic promoter furnished cyclic nitrone **2a** as the sole product in 31% yield an 97% ee. Interestingly, oxime **1a** was recovered with an enantiomeric purity of 58% ee, indicating that kinetic resolution is operative. Further experimentation revealed efficient kinetic resolution of allylic alcohol **1a** with dichloroacetic acid as a promoter, furnishing cyclic nitrone **2a** in 98% ee, along with recovered starting material **1a** in 94% ee. By contrast, employing stronger Brønsted acids such as trifluoroacetic acid led to higher conversion accompanied by a significant decrease in enantiomeric purity (58 % yield, 78% ee). Notably, these reactions proceeded with complete chemoselectivity for the N-allylated nitrone product

With optimized conditions for the chemo- and enantioselective synthesis of cyclic nitrones, we focused on exploring substrate scope (Scheme 3). Ketoxime **1b** (R = Me, R' = H, n = 2), was readily converted to cyclic nitrone **2b** with excellent enantio- and chemoselectivity (98% ee, N/O >20:1). E/Z-mixtures of ketoximes (E/Z = 1:1 to 1.5:1) bearing longer and bulkier aliphatic sidechains
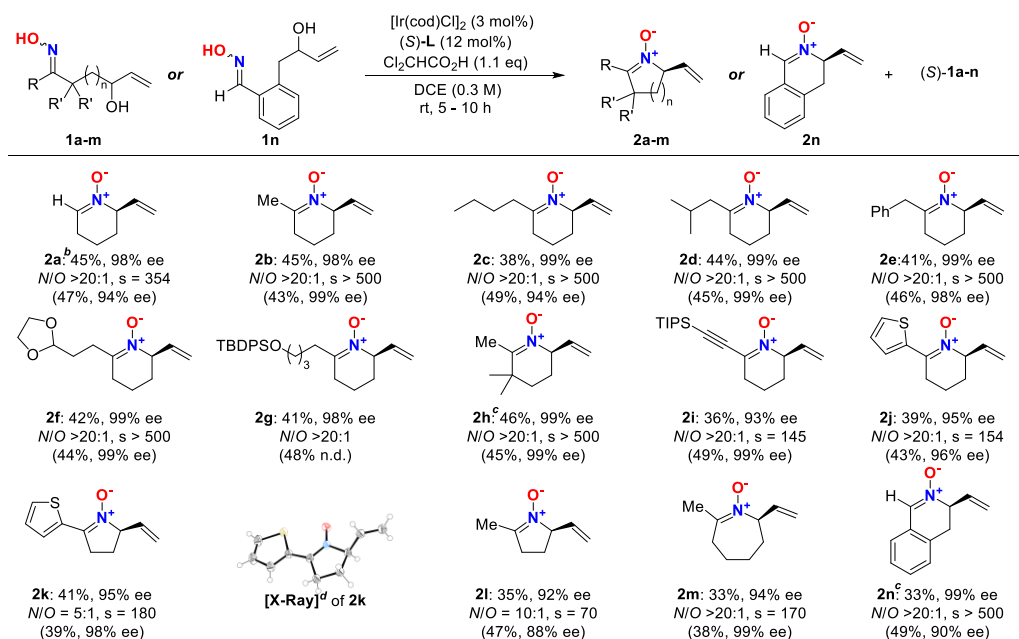
Scheme 3. [a]Reactions on 0.3 mmol scale. Numbers in parentheses refer to recovered starting material. Yields of isolated products. ee determined by HPLC, SFC or GC analysis on a chiral stationary phase. Ratio N- vs. O-alkylation (N/O) determined by ¹H NMR analysis of the unpurified reaction mixtures. Selectivity factors (s) were calculated by Kagan's method[26] [b]Yields determined by ¹H NMR spectroscopy with 1,4-dinitrobenzene as internal standard. [c]Reaction run at 0 °C. [d]Thermal ellipsoids at 50% probability level.

also furnished the expected products (**2c** and **2d**). In addition, we could establish that different functional groups were well tolerated, leading to products incorporating benzyl-substitution (**2e**), acetals (**2f**) and silyl ethers (**2g**) in 41-46% yields (max = 50%), 98-99% ee, and >20:1 *N*-/*O*- chemoselectivity. Furthermore, *gem*-dimethyl substituted nitrone (**2h**) was accessed in 46% yield and 99% ee. Alkynyl nitrone **2i** was prepared in 93% ee, and nitrones **2j-l** were synthesized in 95% ee, 95% ee, and 92% ee, respectively. Interestingly, for the preparation of 5-mebered nitrone **2k**, ^{1}H-NMR analysis of unpurified products revealed a 5:1 ratio of *N/O*-allylation products, marking the first time we observe *O*-cyclization. Interestingly, in addition to 5- and 6-membered ring nitrones, 7-membered azepane-derived nitrone **2m** was accessed in 94% ee, without any formation of the oxazocane. Finally, cyclization of aromatic aldoxime **1n** furnished dihydroisoquinoline *N*-oxide **2n** in 99% ee and with complete chemoselectivity for *N*-alkylation. Notably, this kinetic resolution is highly efficient with selectivity factors s > 50 for all substrates.[26]

Subsequent experimentation was aimed at preparing tricyclic ring systems *via* iridium-catalyzed enantioselective oxime *N*-allylation followed by intramolecular 1,3-dipolar cycloaddition. Grigg,[27] Stockman,[12b,28] and Coldham[29] have reported a series of cascade reactions of racemic nitrone intermediates, which are accessed by aza-Michael addition or *N*-alkylation of oximes and undergo intramolecular 1,3-dipolar cycloaddition with olefins.[30] Although these reactions proceed with excellent diastereocontrol, catalytic enantioselective versions have remained elusive. Therefore, we prepared oxime **1o** and subjected the mixture of four stereoisomers to the optimized reaction protocol, whereupon cycloadduct **4** was isolated in 43% yield and 94% ee, as a single diastereomer (Scheme 3). Reductive cleavage of the N-O bond gave spirocyclic amino alcohol **5** in 91% yield. X-ray crystallographic analysis of **5·HCl** allowed unambiguous assignment of the absolute configuration. Similarly, reaction of **1p** afforded oxazatriquinane **6** as a single product in 90% ee. To
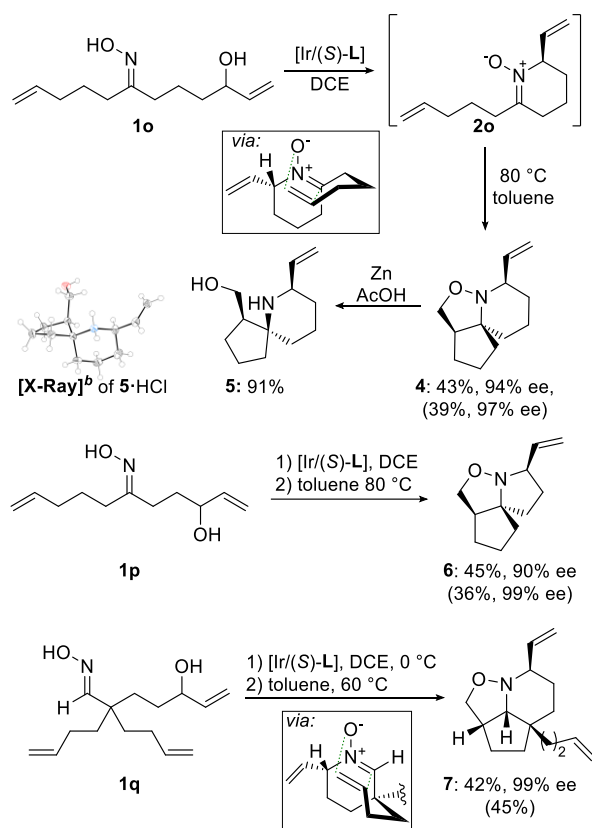

Scheme 4. Tandem *N*-alkylation/1,3-dipolar cycloaddition reactions. For experimental details, see Table 2 and Supporting Information. Numbers in parentheses refer to recovered starting materials. All cycloadduct were formed in >20:1 d.r. Reagents and conditions: Cycloadditions carried out in degassed toluene (0.025 M). (a) Zn, H₂O/AcOH (2:1), 60 °C. [b]Thermal ellipsoids displayed at 50% probability, chloride counterions were omitted for clarity.

showcase the versatility of the method to access various ring scaffolds, we investigated the cyclization/dipolar cycloaddition sequence of oxime **1q**. Gratifyingly, tricyclic isoxazolidine **7** was obtained as a single stereoisomer in 99% ee.

To highlight the synthetic utility of the enantioselective tandem *N*-allylation/cycloaddition reaction, we targeted the formal synthesis of (+)-halichlorine (**8**). (+)-Halichlorine was isolated from the marine sponge *Halichondria okadai* and possesses an intriguing spirocyclic core structure. It was shown to have interesting biological activities such as inhibition of the vascular cell adhesion molecule VCAM-1, which is of relevance in the treatment of inflammatory diseases and in anti-cancer research.[13]

Racemic isoxazolidine **9** was prepared by the Stockman group[28c] to intercept a synthetic route towards halichlorine (*via* lactam **10**) previously reported by Clive and co-workers.[31] In pursuit of alcohol **9**, we identified oxime **13** as a suitable starting material for the iridium-catalyzed key step. The synthesis commenced with Grignard addition of **12** to racemic lactone **11**.[32] Slow addition of **12** to a solution of lactone **11** at –78 °C followed by warming to –30 °C allowed selective mono-addition of the organometallic reagent. After treatment with hydroxylamine hydrochloride, oxime **13** was isolated in 73% yield over two steps. Iridium-catalyzed chemoselective *N*-alkylation and thermal 1,3-dipolar cycloaddition cleanly afforded tricyclic isoxazolidine **14**
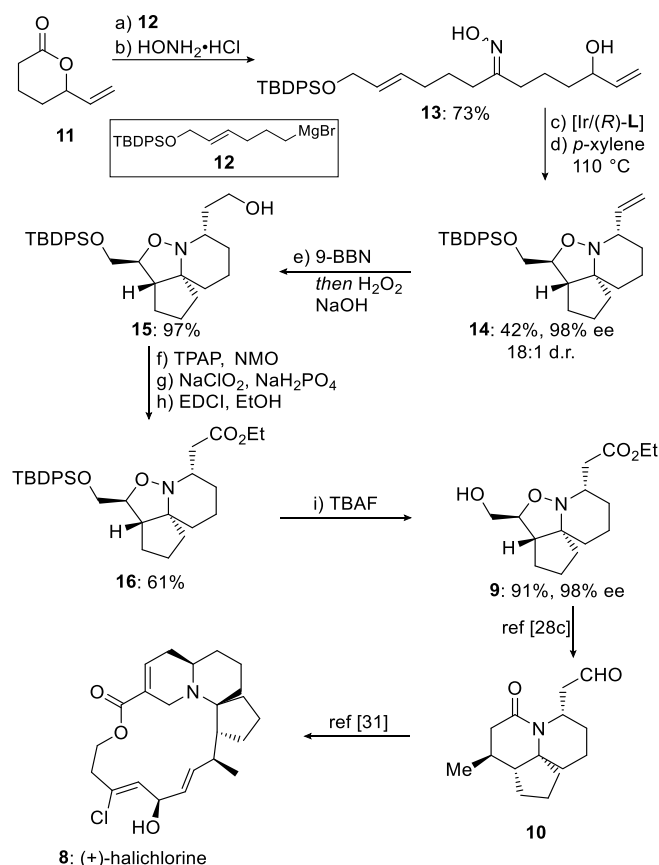
Scheme 5. Formal synthesis of (+)-halichlorine. Reagents and conditions: (a) Grignard reagent **12**, THF, −78 to −30 °C; (b) HONH₂·HCl, pyridine, EtOH; (c) [Ir(cod)Cl]₂ (3 mol%), (R)-**L** (12 mol%), DCE; (d) p-xylene, 110 °C; (e) 9-BBN, THF *then* H₂O₂, aq. NaOH, THF/H₂O (3:1); (f) TPAP, NMO, CH₂Cl₂; (g) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, t-BuOH/H₂O (3:1); (h) EDCI, DMAP, EtOH, CH₂Cl₂; (i) n-Bu₄NF, THF.

bearing four stereogenic centers in 42% yield, 98% ee, and 18:1 d.r. on 2.5 mmol scale. Isoxazolidine **14** was hydroborated and oxidized to the corresponding primary alcohol **15** in nearly quantitative yield using 9-BBN and H₂O₂/NaOH. A sequence involving Ley oxidation, Pinnick oxidation and Steglich esterification provided access to ester **16** as a single diastereomer in 61% overall yield. Finally, cleavage of the silyl ether gave alcohol **9** in 91% yield and completed the formal synthesis of (+)-halichlorine. Gratifyingly, SFC analysis confirmed that isoxazolidine **9** was formed without erosion of optical purity (98% ee).

It is worth noting that most of the oximes employed for nitrone formation are found as a mixture of *E/Z* geometric isomers ranging from 1.5:1 to 1:1. Oximes **1h**, **1n**, and **1q** are exceptions, as expected because of overwhelming steric biases inherent to the structures. To probe this remarkable convergence of *E/Z* isomeric mixtures, control experiments were conducted (Scheme 6). During the preparation of nitrone **2b** under the catalytic, enantioselective conditions described, an aliquot was taken after 6 hours and analyzed by ¹H NMR spectroscopy. Analysis revealed at this point in time a 1:1 ratio of starting material to product as well as a 1:1 mixture of oxime *E/Z*-isomers, and starting material as well as product were then isolated in high enantiomeric purity (Scheme 6A). Additionally, for benzylic nitrone **2e** all four stereoisomers of reisolated starting material (S)-**1e** (*E/Z* = 1:1) were separated in one run on chiral HPLC, allowing confirmation that both oxime diastereomers had identical enantiomeric purities (98% ee, Scheme 6B). Collectively, these data suggest that *E* and *Z* oxime isomers interconvert rapidly under the reaction conditions, thus enabling highly efficient kinetic resolution of the allylic alcohols under Curtin-Hammet regimes.
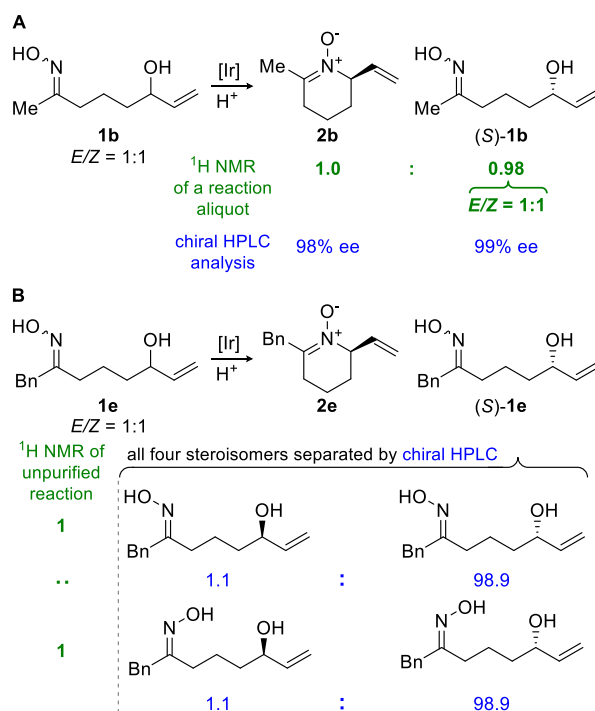
Scheme 6. Control experiments on oxime *E/Z*-isomers.

In summary, we have developed the highly enantio- and chemoselective iridium-catalyzed kinetic resolution of allylic alcohols *via* *N*-allylation of oximes. The catalytic method provides convenient access to optically active cyclic nitrones. The approach employs readily available mixtures of oximes (*E/Z*) and allylic alcohols (*R* and *S*). We document for the first time entry into enantioselective tandem nitrone formation/1,3-dipolar cycloaddition cascades which are highly relevant for the asymmetric synthesis of complex molecules, as demonstrated by the efficient formal synthesis of the marine natural product (+)-halichlorine. More broadly, the approach provides avenues for incorporating catalytic enantioselective process in cascading reactions that furnish complex structures in optically active form.

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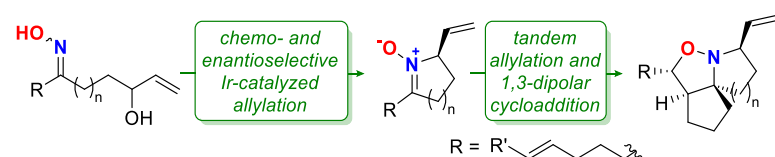
The iridium-catalyzed intramolecular chemo- and enantioselective *N*-allylation of oximes is reported. The method employs *E*/*Z*-mixtures of oximes and furnishes cyclic nitrones with high enantioselectivity. Tandem *N*-allylation/dipolar cycloaddition sequences provide access to enantioenriched tricyclic isoxazolidines and enable the formal synthesis of the marine natural product Halichlorine.