Enantioselective Synthesis of Cyclic Nitrones and Oxime Ethers by Chemoselective Allylic Alkylation of Oximes

Tobias Sandmeier, Erick M. Carreira*

ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

ABSTRACT: The enantio- and chemoselective iridium-catalyzed *N*- and *O*-allylation of oximes is described for the first time. Kinetic resolution in an intramolecular setting provides access to cyclic nitrones, oxime ethers and enantioenriched aliphatic allylic alcohols. Salient features of this transformation are its ability to employ *E*/*Z*-isomeric mixtures of oxime starting materials convergently, high functional group tolerance, and divergent *N*- or *O*-allylation by choice of the reaction conditions. The implementation of *N*-allylation/1,3-dipolar cycloaddition reaction cascades furnish tricyclic oxazolines in highly enantio- and diastereoselective fashion. Expansion of this approach to the selective allylation of hydrazones allows enantioselective preparation of azomethine imines. The synthetic utility of the approach is demonstrated by the efficient, formal syntheses of glycoprotein GP IIb-IIIa receptor antagonist (–)-roxifiban and marine natural product (+)-halichlorine.

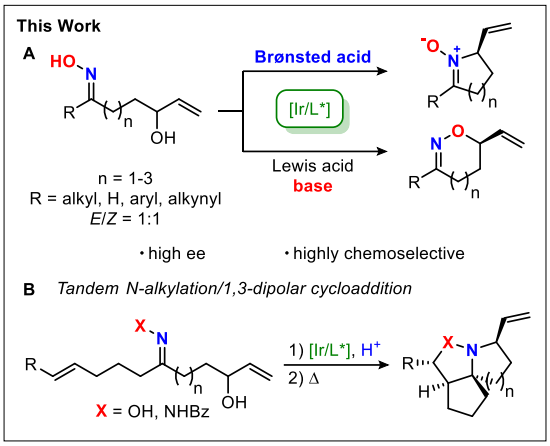
Introduction

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 a particularly important tools for synthetic chemists as they enable concomitant formation of C–C and C–O bonds, heterocycle 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 evolution of strategic considerations in complex 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). Interestingly, in the presence of Lewis acids and base under otherwise identical conditions the same iridium catalyst furnished cyclic oxime ether products, resulting from enantioselective *O*-allylation. We applied the latter to the formal synthesis of DuPont's (–)-roxifiban, a glycoprotein receptor antagonist.[13] Implementation of the former in tandem *N*-allylation/dipolar cycloaddition sequence furnished oxazatriquinanes in a highly stereo-controlled fashion (Scheme 1B), which is showcased in the formal synthesis of (+)-halichlorine, an inhibitor of vascular cell adhesion protein 1.[14]

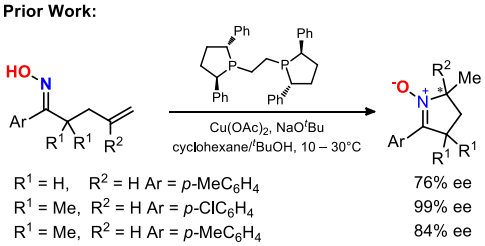
There have been a number of key developments in asymmetric catalysis for the preparation of acyclic, optically active nitrones from oximes *via* intermolecular olefin hydroamination. Zhang has reported copper/bisphosphine- catalyzed diastereo- and enantioselective hydroamination of cyclopropenes using oximes as nucleophiles, furnishing *N*-cyclopropyl substituted nitrones.[15] Kobayashi has described enantioselective conjugate addition of aldoximes to various Michael acceptors using a chiral Lewis acid combined with single-walled carbon nanotubes and a surfactant in aqueous media.[16] Breit documented the rhodium-catalyzed chemo- and enantioselective hydroamination of symmetrical diaryl or dibenzyl oximes to allenes, providing access to *N*-allylated nitrones.[17] By contrast, there is a paucity of catalytic, enantioselective approaches to cyclic nitrones.

Scheme 1. Chemodivergent, Enantioselective Synthesis of Cyclic Nitrones and Oxime Ethers.



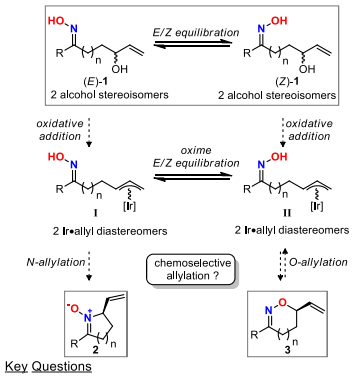
To date, only one example of catalytic, enantioselective synthesis of cyclic nitrones has appeared in the literature (Chart 1). In 2019, Zhang reported the intramolecular hydroamination of olefins using a copper/bisphosphine catalyst.[18] The method prescribes the use of oximes derived from γ,δ-unsaturated aryl ketones and furnishes 5-membered nitrones. Optimal results were reported with substrates that incorporate aryl ketoximes with *gem*-dimethyl substitution at Cα (R1 = Me).

Chart 1. Intramolecular hydroamination



Based on our long-standing interest in iridium-catalyzed allylic substitution reactions,[19,20] 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 because the substrate allylic alcohols are racemic and include oxime geometric isomers (Scheme 2). 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.[21] Additionally, as oximes are ambident nucleophiles,[22] it was not clear whether *O* versus *N*-cyclization would be simply determined by oxime geometry (**I** ⟶ **2** and **II** ⟶ **3**) or alternatively by product ring size (e.g., in Scheme 2: **2** versus **3**).[23,24] In the ideal process, a Curtin-Hammet scenario[25,26] would allow both diastereomers of the oxime starting material to converge into a single cyclic nitrone or cyclic oxime ether products. Finally, if *O*-allylation leading to **3** is reversible, an additional competing pathway could operate that interconverts *O*- and *N*-cyclization products.[20f]

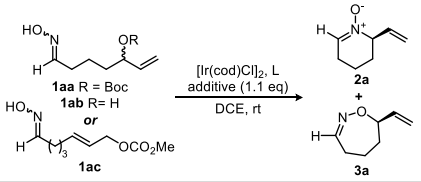
Scheme 2. Intramolecular Enantio- and Chemoselective Allylation of Oximes.



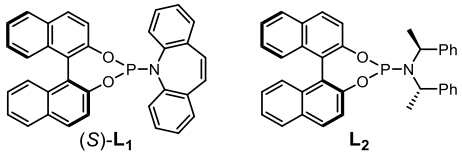
Results and Discussion

Reaction Development. We commenced our studies with allylic carbonate **1aa** obtained as a 1:1 mixture of *E*/*Z*-oxime isomers (Table 1). Initial screening experiments (see Supporting Information) revealed efficient kinetic resolution of allylic carbonate **1aa** with dichloroacetic acid as a promoter, furnishing cyclic nitrone **2a** in 98% ee (entry 1). Notably, this reaction proceeded with complete chemoselectivity for the *N*-allylated nitrone product. In order to streamline substrate synthesis and in the interest of atom-economy, we next examined free allylic alcohols **1ab**

Table 1. Selected Optimization of Conditions[a]



entry	**1**	L	additive	product yield (ee)	ratio **2a**/**3a**	recovered **1** (ee)
1	**1aa**	L_1	Cl_2HCCO_2H	44% (98%)	99:1	49% (93%)
2	**1ab**	L_1	$Zn(OTf)_2$	31% (97%)	99:1	58% (41%)
3	**1ab**	L_1	F_3CCO_2H	58% (78%)	99:1	29% (89%)
4	**1ab**	L_1	Cl_2HCCO_2H	45% (98%)	99:1	47% (94%)
5	**1ac**	L_2	Cs_2CO_3	71% (61%)	1:99	-
6	**1ab**	L_1	$Zn(OTf)_2$ Cs_2CO_3	33% (90%)	1:99	60% (38%)
7	**1ab**	L_1	$Sc(OTf)_3$ Cs_2CO_3	47% (96%)	1:99	46% (93%)



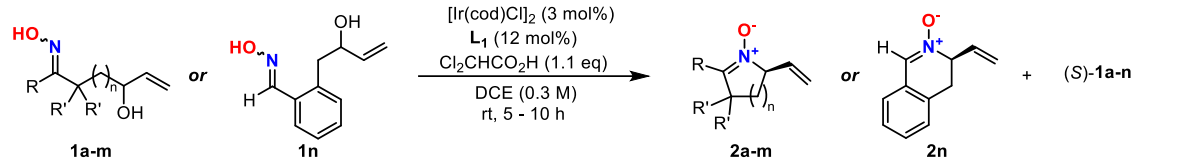
[a]Reactions run on 0.15 mmol scale, yields were determined by ^{1}H NMR analysis of the unpurified reaction mixtures with 1,4-dinitrobenzene as an internal standard, ee was determined using supercritical fluid chromatography (SFC) or HPLC.

as substrates. Lewis acids ($Zn(OTf)_2$, entry 2) and strong Brønsted acids (TFA, entry 3) combined with **1ab** resulted in excellent chemoselectivity for *N*-allylation but only modest enantiomeric purity of either reisolated **(*S*)-1ab** or nitrone **2a**. The use of dichloroacetic acid enabled highly chemo- and enantioselective kinetic resolution of **1ab**, giving nitrone **2a** and allylic alcohol (*S*)-**1ab** in 98 and >94% ee, respectively, as well as good yields (entry 4).

Over the course of the optimization studies, we also examined ligand $\mathbf{L_2}$ in the reaction, which is usually used in iridium-catalyzed allylation reactions with activated electrophiles derived from the corresponding primary alcohols.[27] Intriguingly, when linear carbonate **1ac** was utilized in combination with Cs_2CO_3 and iridium(I) $\mathbf{L_2}$ complex, *O*-alkylated oxazepane product **3a** was obtained exclusively (71% yield, 61% ee, entry 5).[28] We next employed secondary allylic alcohol **1ab** together with $\mathbf{L_1}$, Cs_2CO_3. and $Zn(OTf)_2$ (entry 6). Under these conditions exclusive formation of **3a** was again observed, albeit with low yield. This result nicely demonstrates that the use of the same catalyst, starting material, and solvent can furnish either **2a** or **3a** selectively by excluding or adding Cs_2CO_3. Further screening of reaction conditions (see Supporting Information) led to the identification of $Sc(OTf)_3$ as the ideal promoter for the formation of cyclic oxime **3a** from highly chemoselective *O*-allylation of **1ab** *via* kinetic resolution (47% yield, 96% ee, entry 7).

Substrate scope. With optimized conditions for the chemo- and enantioselective synthesis of cyclic nitrones, we focused on exploring substrate scope (Table 2). 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 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.

Table 2. Substrate Scope of the Intramolecular *N*-Allylation of Oximes[a]



1a-m | 1n | 2a-m | 2n

2a:[b] 45%, 98% ee
N/*O* >20:1
(47%, 94% ee)

2b: 45%, 98% ee
N/*O* >20:1
(43%, 99% ee)

2c: 38%, 99% ee
N/*O* >20:1
(49%, 94% ee)

2d: 44%, 99% ee
N/*O* >20:1
(45%, 99% ee)

2e:41%, 99% ee
N/*O* >20:1
(46%, 98% ee)

2f: 42%, 99% ee
N/*O* >20:1
(44%, 99% ee)

2g: 41%, 98% ee
N/*O* >20:1
(48% n.d.)

2h:[c] 46%, 99% ee
N/*O* >20:1
(45%, 99% ee)

2i: 36%, 93% ee
N/*O* >20:1
(49%, 99% ee)

2j: 39%, 95% ee
N/*O* >20:1
(43%, 96% ee)

2k: 41%, 95% ee
N/*O* = 5:1
(39%, 98% ee)

[X-Ray][d] of **2k**

2l: 35%, 92% ee
N/*O* = 10:1
(47%, 88% ee)

2m: 33%, 94% ee
N/*O* >20:1
(38%, 99% ee)

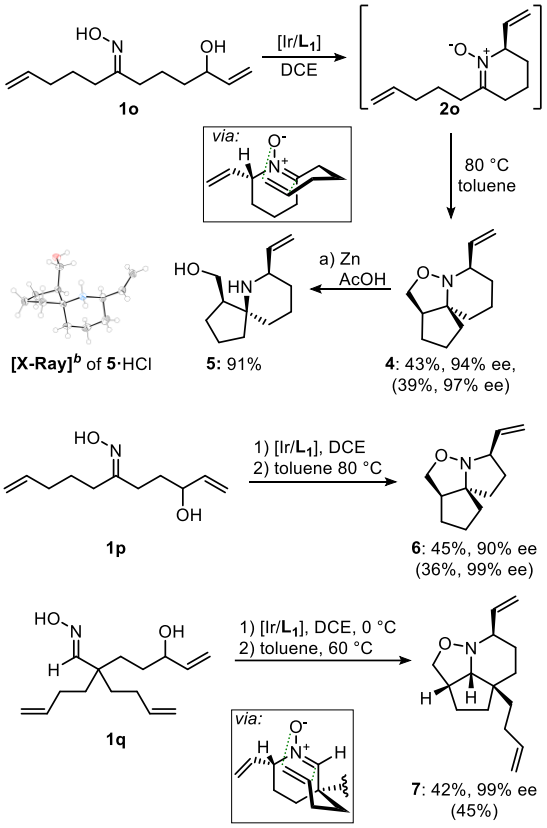
2n:[c] 33%, 99% ee
N/*O* >20:1
(49%, 90% ee)

[a]Reactions run on 0.3 mmol scale. Numbers in parentheses refer to recovered starting material **1**. Yields refer to isolated products after flash column chromatography. Enantiomeric excess values (ee) were determined by HPLC, SFC or GC analysis on a chiral stationary phase. The ratio of *N*- vs. *O*-alkylation (*N*/*O*) was determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]Yields determined using ^{1}H NMR spectroscopy with 1,4-dinitrobenzene as an internal standard. [c]Reaction run at 0 °C. [d]Thermal ellipsoids displayed at 50% probability level.

Interestingly, for the reaction of substrate **1k**, ^{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 under Brønsted acidic conditions. Notably, 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.[29]

Subsequent experimentation was aimed at preparing tricyclic ring systems *via* iridium-catalyzed enantioselective oxime *N*-allylation followed by intramolecular 1,3-dipolar cycloaddition. Grigg,[30] Stockman,[12c,31] and Coldham[32] 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.[33] Although these reactions proceed with excellent diastereocontrol, catalytic enantioselective versions have remained elusive, and to the best of our knowledge are lacking precedence. 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 showcase the versatility of the method to access various ring scaffolds, we investigated the cyclization/dipolar cycloaddition sequence of oxime **1q**. Gratifyingly, tricyclic oxazolidine **7** was obtained as a single stereoisomer in 99% ee.

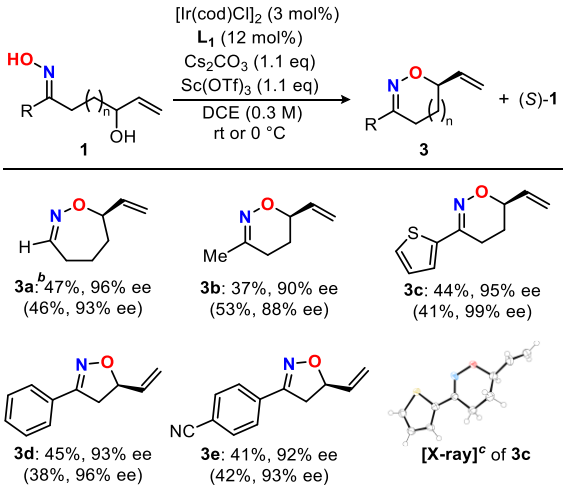
Scheme 3. Tandem *N*-alkylation/1,3-Dipolar Cycloaddition Reactions[a]



[a]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, H_2O/AcOH (2:1), 60 °C. [b]Thermal ellipsoids displayed at 50% probability level. The chloride counterions were omitted for clarity.

Having established substrate scope for the iridium-catalyzed *N*-allylation of oximes, we next focused on chemoselective *O*-allylation reactions, which furnishes cyclic oxime ethers, a common structural motive in pharmaceuticals and crop protection agents (Table 3).[34] The optimized protocol for this transformation includes the combination of Lewis acid and Cs_2CO_2. It allowed facile preparation of six membered dihydrooxazine **3b** with complete *O*-selectivity. Similarly, 2-thienyl dihydroxazine **3c** was accessed in 44% yield and 95% ee as a crystalline solid suitable for X-ray crystallographic analysis. Enantiopure allylic alcohol (*S*)-**1m** was reisolated in 41% yield. In addition to seven-membered oxazepane (**3a**) and six-membered oxazine (**3b** and **3c**) scaffolds, we examined the formation of five-membered isoxazolines. The optimized protocol for *O*-allylation furnished **3d** in 45% yield and 93% ee. Analogously, isoxazoline **3e**, was accessed in good yield and high enantiomeric purity (41% yield, 92% ee).

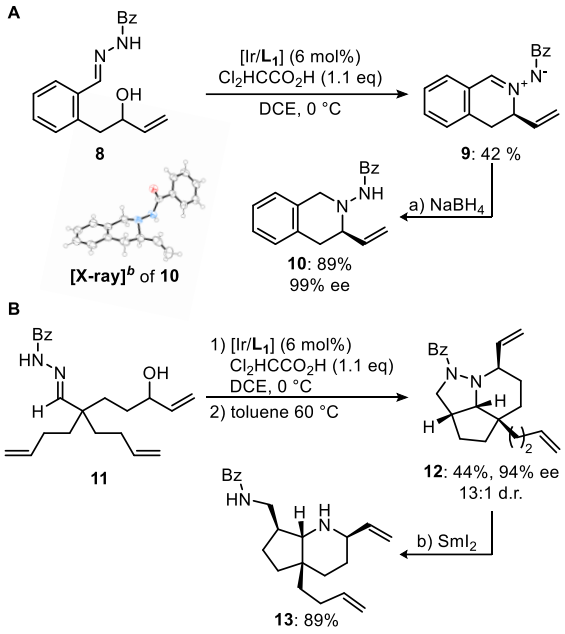
Table 3. Substrate Scope of the Intramolecular *O*-Allylation of Oximes[a]



[a]Reactions run on 0.3 mmol scale. Numbers in parentheses refer to recovered starting material **1**. Yields refer to isolated products after flash column chromatography. Enantiomeric excess values (ee) were determined by HPLC, SFC or GC analysis on a chiral stationary phase. [b]See table 1, entry 7 for conditions. [c]Thermal ellipsoids displayed at 50% probability level.

Azomethine Imines. To further expand the synthetic utility of the approach, we investigated the enantioselective synthesis of additional 1,3-dipoles, such as azomethine imines generated by enantio- and chemoselective *N*-allylation under iridium catalysis (Scheme 4).[35] Accordingly, treatment of hydrazone **8** with Cl_2CHCO_2H and the iridium complex derived from $\mathbf{L_1}$ afforded a compound that was tentatively assigned as azomethine imine **9**. Subsequent reduction with $NaBH_4$ and recrystallization from CH_2Cl_2 afforded X-ray quality crystals of hydrazide **10**, which allowed confirmation of its structure and absolute configuration. Encouraged by this finding, we wondered whether hydrazones would participate in sequences involving *N*-allylation/dipolar cycloaddition. To this end, hydrazone **11** was prepared and subjected to the reaction conditions at 0 °C followed by heating to effect cycloaddition. This protocol provided tricyclic hydrazide **12** in 44% yield, 94% ee and 13:1 d.r. SmI_2-mediated cleavage of the *N*–*N* bond afforded diamine **13**, bearing a quaternary stereocenter (2-steps). These experiments clearly showcase that the strategy to build up optically active heterocycles via asymmetric *N*-allylation and cycloaddition can be expanded to additional 1,3-dipoles and thus paves the way for further developments.

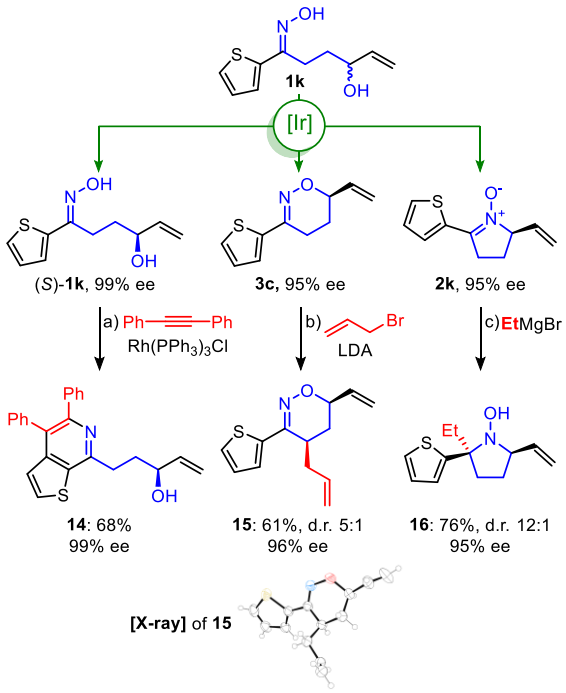
Scheme 4. Enantioselective Synthesis of Azomethine Imines[a]



[a]Reactions run on 0.3 mmol scale. Yields refer to isolated products after flash column chromatography. Reagents and conditions: (a) $NaBH_4$, MeOH. (b) SmI_2, THF/MeOH (4:1). [b]Thermal ellipsoids displayed at 50% probability level.

Synthetic Applications. To highlight the synthetic utility of this chemodivergent kinetic resolution process that gives rise to optically active nitrones, cyclic oxime ethers, and aliphatic allylic alcohols we examined the preparation of diverse optically active building blocks. To this end γ-hydroxy thienyl oxime **1k** was chosen as a starting point (Scheme 5). Rhodium-catalyzed, oxime directed C–H activation of enantioenriched (*S*)-**1k** furnished thienopyridine **14**, a promising motif in drug discovery,[36] without erosion of optical purity. Lithiation of dihydrooxazine **3c** and subsequent trapping with allyl bromide allowed the selective installation of an additional stereocenter (**15**),[37] showcasing the applicability of the method for the synthesis of highly substituted heterocycles. Having employed several nitrones as chiral 1,3-dipoles in diastereoselective cycloadditions (Scheme 3), we investigated their use as an electrophile in 1,2-additions. Therefore, **2k** was treated with EtMgBr at –78 °C to afford trisubstituted pyrrolidine **16** in 95% ee and 12:1 dr. These experiments highlight that starting from a single racemic compound (**1k**), a series of structurally diverse enantioenriched products can be accessed rapidly.

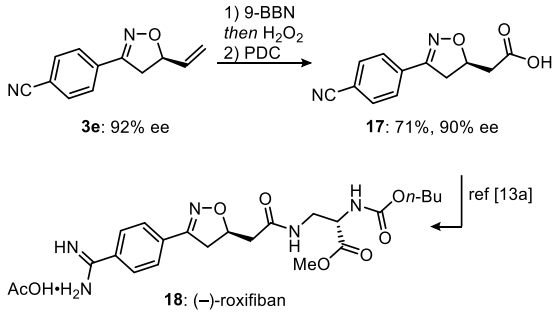
Scheme 5. Functionalization of Products Derived from Oxime 1k[a]



[a]Reagents and conditions: (a) $Rh(PPh_3)_3Cl$ (3 mol%), diphenylacetylene, toluene, 120°C; (b) LDA, TMEDA, *then* allyl bromide, THF, –78 °C to rt; (c) EtMgBr, THF, –78 °C to rt. LDA = lithium diisopropylamide.

We next investigated the approach in the context of target-oriented synthesis. Initially we focused on the formal synthesis of (–)-roxifiban (**18**), a glycoprotein GP IIb-IIIa receptor antagonist investigated in clinical trials by DuPont for the treatment of various cardiovascular ailments including platelet adhesion (Scheme 6).[13,38] Enantioenriched isoxazoline **3e** was hydroborated and oxidized to the corresponding primary alcohol using 9-BBN and H_2O_2. Further oxidation with pyridinium dichromate (PDC) in anhydrous DMF cleanly afforded carboxylic acid **17** in 71% yield over two steps. Compound **17** has been used previously by Olson and co-workers in their synthesis of (–)-roxifiban thus completing the formal synthesis of **18**.[13]

Scheme 6. Formal Synthesis of Roxifiban[a]



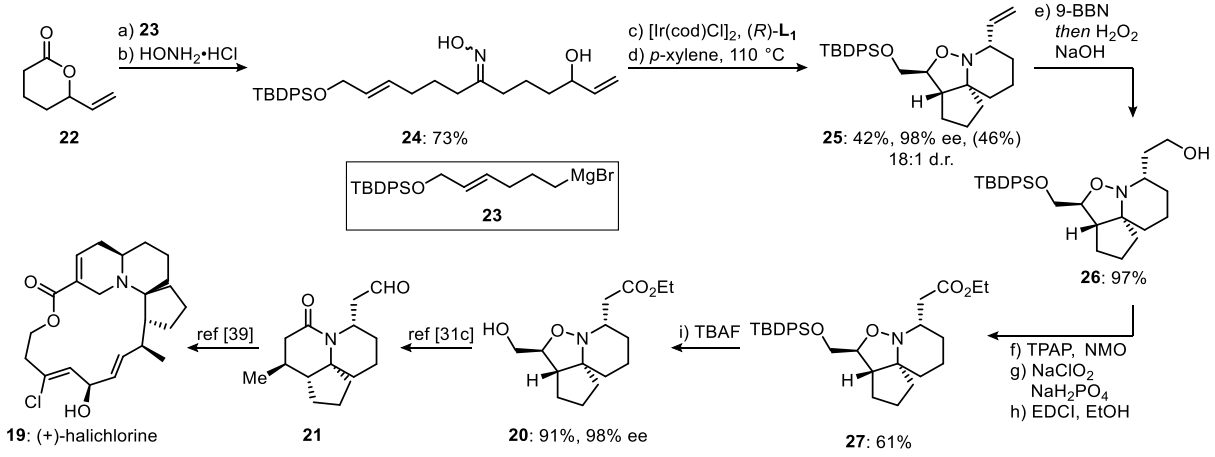
[a]Reagents and conditions: (a) 9-BBN, THF *then* H_2O_2, aq. NaOH, THF/H_2O (3:1); (b) PDC, DMF.

The second synthetic endeavor was centered around the enantioselective tandem *N*-allylation/cycloaddition reaction established in Scheme 3. We identified (+)-halichlorine (**19**) as a suitable target to demonstrate the synthetic efficiency of the method to access the intriguing spirocyclic core structures (Scheme 7). (+)-Halichlorine was isolated from the marine sponge *Halichondria okadai* and was shown to possess interesting biological activities such as inhibition of the vascular cell adhesion molecule VCAM-1, which is of interest in the treatment of inflammatory diseases and in anti-cancer research.[14]

Racemic isoxazolidine **20** was prepared by the Stockman group[31c] to intercept a synthetic route towards halichlorine (*via* lactam **21**) previously reported by Clive and co-workers.[39] In pursuit of alcohol **20**, we identified oxime **24** as a suitable starting material for the iridium catalyzed key step. The synthesis commenced with Grignard addition of **23** to racemic lactone **22**.[40] Slow addition of **23** to a solution of lactone **22** at –78 °C followed by warming to –30 °C allowed selective mono-addition of the organometallic reagent. After treatment with hydroxylamine hydrochloride, oxime **24** was isolated in 73% yield over two steps. Iridium-catalyzed chemoselective *N*-alkylation and thermal 1,3-dipolar cycloaddition cleanly afforded tricyclic isoxazolidine **25** bearing four stereogenic centers in 42% yield, 98% ee, and 18:1 d.r. on 2.5 mmol scale. Isoxazolidine **25** was hydroborated and oxidized to the corresponding primary alcohol **26** in nearly quantitative yield using 9-BBN and H_2O_2/NaOH. A sequence involving Ley oxidation, Pinnick oxidation and Steglich esterification provided access to ester **27** as a single diastereomer in 61% overall yield. Finally, cleavage of the silyl ether

gave alcohol **20** in 91% yield and completed the formal synthesis of (+)-halichlorine. Gratifyingly, SFC analysis confirmed that isoxazolidine **20** was formed without erosion of optical purity (98% ee).

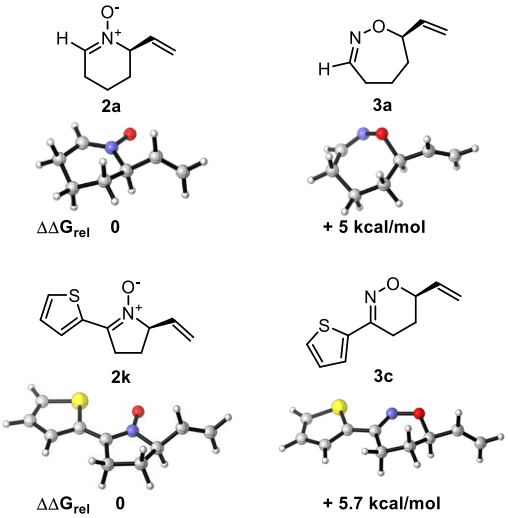
Scheme 7. Formal Synthesis of (+)-Halichlorine[a]



[a] Reagents and conditions: (a) Grignard reagent **23**, THF, –78 to –30 °C; (b) hydroxylamine hydrochloride, pyridine, EtOH; (c) $[Ir(cod)Cl]_2$ (3 mol%), (*R*)-$\mathbf{L_1}$ (12 mol%), DCE, number in parentheses refers to recovered starting material; (d) *p*-xylene, 110 °C; (e) 9-BBN, THF *then* H_2O_2, aq. NaOH, THF/H_2O (3:1); (f) tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO), CH_2Cl_2; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (3:1); (h) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), DMAP, EtOH, CH_2Cl_2; (i) *n*-Bu_4NF (TBAF), THF.

Control Experiments. Over the course of this study we became interested in the origin of the remarkable chemoselectivity observed for both *N*- and *O*-alkylation reactions. In particular, we wondered if the formation the cyclic nitrones or oxime ethers is governed by a thermodynamic bias and whether the size of the newly formed ring factors into this. The relative energies of two pairs of constitutionally isomeric nitrones and oxime ethers were calculated (**2a**/**3a** and **2k**/**3c**, Scheme 8). Interestingly, density functional theory calculations at the B3PW91/6-311++G(d,p) level of theory revealed the nitrone products to be thermodynamically favored over the oxime ethers by $\Delta\Delta G^0$= 5.0 kcalmol^{-1} and $\Delta\Delta G^0$= 5.7 kcalmol^{-1}, respectively, regardless of ring size.[41,42] Notably, the calculated optimized geometry of 2-thienyl nitrone **2k** was consistent with the conformation observed by X-ray crystallography (Table 2).

Scheme 8. Calculated Optimized Structures and Relative Energies[a]

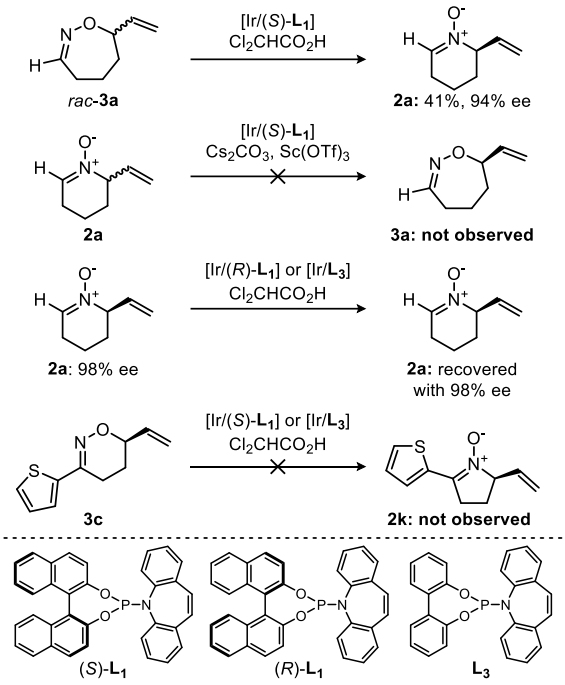


[a]Values calculated using DFT at the B3PW91/6-311++G(d,p) level of theory, see supporting information for details.

To probe whether the chemoselective formation of nitrone **2a** may occur *via* thermodynamic equilibration from **3a**, we conducted a series of control experiments (Scheme 9). Subjecting racemic oxime ether **3a** to the optimized reaction conditions for *N*-allylation afforded the corresponding nitrone **2a**. This result demonstrates that C–O bond cleavage occurs for **3a** in the presence of the iridium catalyst under acidic conditions. Control experiments indicated that both Cl_2CHCO_2H and [Ir/(*S*)-$\mathbf{L_1}$] were necessary for conversion of **3a** to give **2a**. Next, we investigated whether nitrone **2a** undergoes reversible C-N bond cleavage. Subjecting **2a** to the conditions optimized for *O*-alkylation did not afford any detectable formation of oxime ether **3a**. Treating **2a** with Cl_2CHCO_2H

and the iridium catalysts derived from either (*R*)-**L$_1$**, the enantiomeric ligand, or achiral **L$_3$** did not lead to any erosion of optical purity, even after prolonged reaction times (48 hrs). Collectively, these experiments indicate that C-N bond cleavage does not occur under basic nor acidic conditions. We postulate that while *O*-alkylated product **3a** may be formed under acidic conditions as the kinetic product, it can undergo C-O bond cleavage to afford thermodynamically favored nitrone **2a**. The formation of oxime ether **3a** under basic conditions is kinetically favored, as a consequence of deprotonation of the oxime-OH (pKa of benzophenone oxime in water ~ 11).[43] However, our observations with **2a**/**3a** were not generalizable, as subjecting six membered oxime ether **3c** to Cl_2CHCO_2H/[Ir] did not lead to formation of nitrone **2m**.

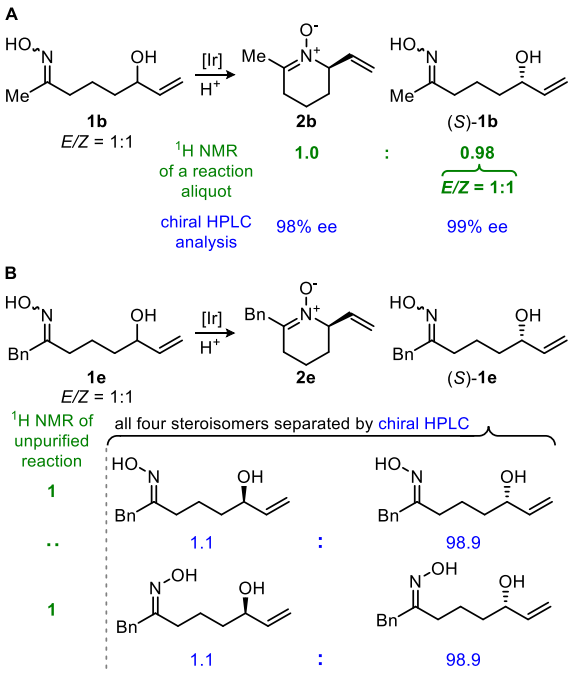
Scheme 9. Control experiments on *N*/*O*-alkylation [a]



[a]Reactions were set up according to general procedures, see Tables 2 and 3.

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. Moreover, during the preparation of nitrone **2b** under the catalytic, enantioselective conditions described, an aliquot was taken after 6 hours and analyzed by ^{1}H 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 each were then isolated in high enantiomeric purity (Scheme 10A). 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 10B). 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.[25]

Scheme 10. Control experiments on oxime *E*/*Z*-isomers



Conclusions

In summary, we have developed the highly enantio- and chemoselective iridium-catalyzed kinetic resolution of allylic alcohols *via* either *N*- or *O*-allylation of oximes even when these starting materials are mixtures of E/Z geometric isomers. The catalytic method provides for the first time convenient access to optically active cyclic nitrones and oxime ethers. 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. We have also shown that enantio- and chemoselective *N*-allylation can be expanded to the synthesis of optically active azomethine imines. Altogether, this methodology provides access to a diverse set of enantioenriched building blocks amenable to numerous further synthetic transformation and target-oriented synthesis. More broadly, the approach provides avenues for incorporating catalytic enantioselective process in cascading reactions that furnish complex structures in optically active form.

Corresponding Author

*E-mail: erickm.carreira@org.chem.ethz.ch

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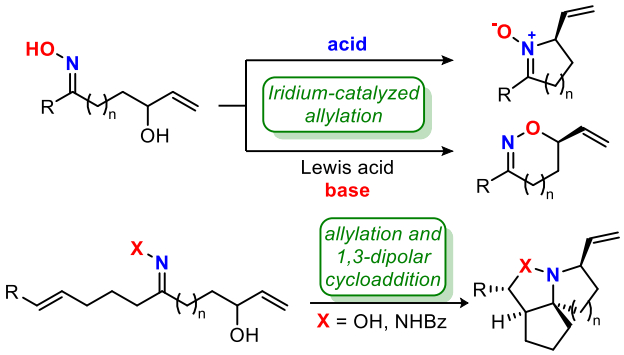

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