OL Organic Letters

pubs.acs.org/OrgLett Letter

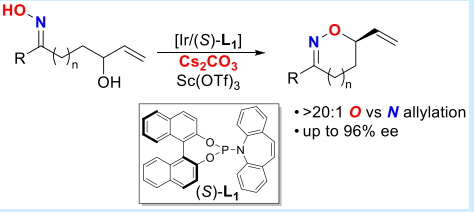
Enantio- and Chemoselective Intramolecular Iridium-Catalyzed *O*-Allylation of Oximes

Tobias Sandmeier and Erick M. Carreira*

Cite This: *Org. Lett.* 2021, 23, 2643–2647 Read Online

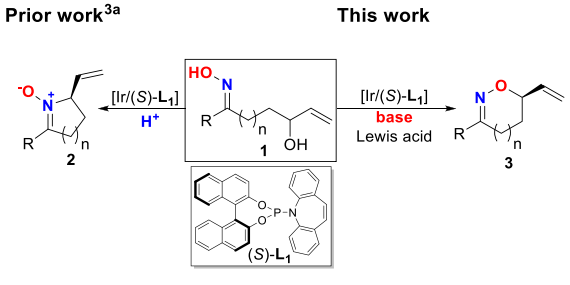
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A method for the enantio- and chemoselective iridium-catalyzed *O*-allylation of oximes is described. Kinetic resolution in an intramolecular setting provides enantioenriched oxime ethers and aliphatic allylic alcohols. The synthetic potential of the products generated with this method is showcased by their elaboration into a series of heterocyclic compounds and the formal synthesis of glycoprotein GP IIb-IIIa receptor antagonist (−)-roxifiban. Preliminary mechanistic experiments and computational data shed light on the remarkable chemoselectivity of the reaction.



Transition-metal-catalyzed allylic substitution has emerged as a powerful tool for the enantioselective formation of carbon−carbon and carbon−heteroatom bonds.[1] Iridium-catalyzed reactions in particular have proven useful for the asymmetric synthesis of chiral building blocks due to a strong preference for branched allylation products.[2] In this area, we recently reported the iridium and Brønsted acid-catalyzed enantio- and chemoselective intramolecular *N*-allylation of oximes (Scheme 1).[3] The method provides five-, six-, and seven-membered cyclic nitrones **2** via the kinetic resolution of secondary allylic alcohols and proceeds with a remarkable selectivity for *N*-allylation. *O*-Allylated cyclic oxime ethers, which are important structural motifs in drug discovery and crop protection,[4] were only observed as minor side products. However, procedures that enable chemodivergent *O*-allylation would stand to significantly improve the synthetic utility of enantioselective oxime allylation. Herein, we report the iridium-catalyzed chemoselective intramolecular *O*-allylation of oximes. Preliminary mechanistic studies were conducted to investigate this remarkable inversion of chemoselectivity.

Scheme 1. Iridium-Catalyzed Intramolecular Allylation of Oximes



Cyclic oxime ethers, particularly five-membered isoxazolines, have been highlighted as privileged structural motifs in pharmaceuticals and pesticides.[4] However, methodologies for the enantioselective synthesis of cyclic oxime ethers relying on transition-metal-catalyzed allylic substitution remain undeveloped.[5−7] The groups of Du[8] and Takemoto[9] have reported enantioselective intermolecular *O*-allylation reactions to access acyclic oxime ethers using palladium and iridium catalysts, respectively. In 2019, You and co-workers documented a single example of the intramolecular iridium-catalyzed *O*-allylation of an oxime, which furnished a seven-membered 1,2,5-oxadiazepane product.[10] Yet, a general enantioselective method that provides access to cyclic oxime ethers of various ring sizes remains elusive.

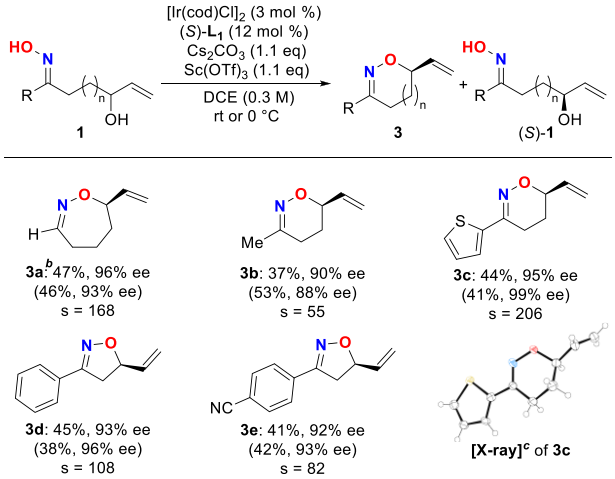
At the onset of the methodological studies described herein, we envisioned that the chemo- and enantioselective *O*-allylation of oximes in an intramolecular setting could provide a convenient approach for preparing cyclic oxime ethers of various ring sizes. In our previous report,[3a] the chiral catalyst derived from $[Ir(cod)Cl]_2$ and the phosphoramidite-olefin ligand (*S*)-**L$_1$** were combined with a Brønsted acid, cleanly converting oxime **1a** (Scheme 1, R = H and n = 2) to the corresponding six-membered nitrone **2a** with complete chemoselectivity for *N*-allylation. Thus, a series of experiments aimed at identifying optimal conditions for selective *O*-allylation were conducted (see the Supporting Information). Gratifyingly, we found that in the presence of a base (Cs_2CO_3) and a Lewis acid ($Sc(OTf)_3$), the same iridium(I) catalyst ([Ir/(*S*)-**L$_1$**]) effected the conversion of the hydroxy oxime **1a** to the seven-membered oxime ether **3a** via kinetic resolution

Received: February 16, 2021
Published: March 22, 2021

https://doi.org/10.1021/acs.orglett.1c00559
Org. Lett. 2021, 23, 2643−2647

(47% yield, theoretical yield of 50%, 96% ee, Table 1). Under these conditions, the allylic alcohol **1a** was recovered in a 46%

Table 1. Substrate Scope of the Intramolecular *O*-Allylation of Oximes[a]



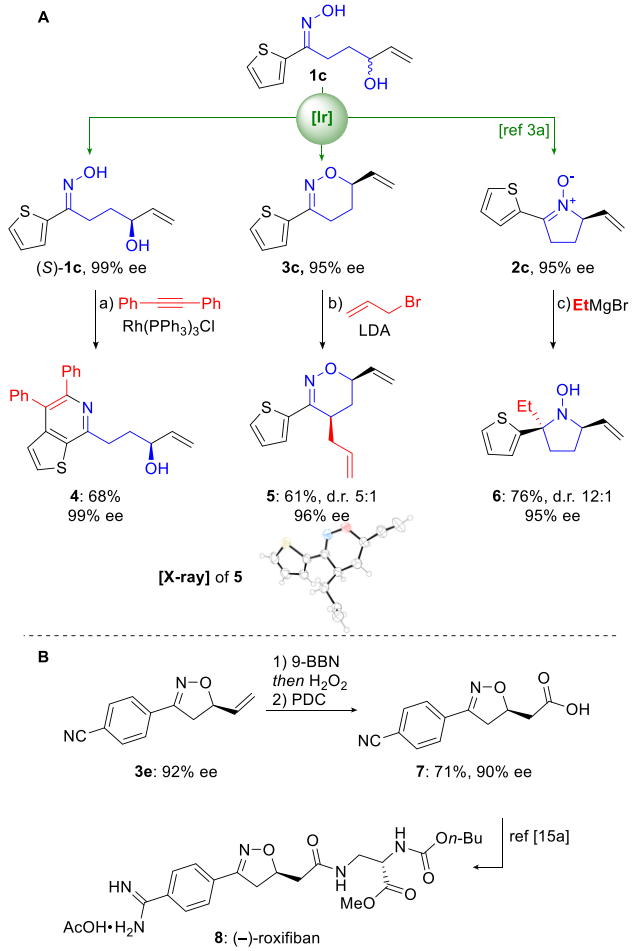
[a]Reactions were run on a 0.3 mmol scale. Numbers in parentheses refer to the amount of the recovered starting material **1**. Yields refer to isolated products after flash column chromatography. Enantiomeric excess values (ee) were determined by HPLC, SFC, or GC analysis on a chiral stationary phase. Selectivity factors (*s*) were calculated using Kagan's method.[11] [b]The reaction was run at rt. [c]Thermal ellipsoids are displayed at the 50% probability level.

yield and 93% ee. Notably, *N*-allylated nitrone **2a** was not detected when using Brønsted basic reaction conditions.

Having established the conditions for the iridium-catalyzed chemoselective *O*-allylation of oximes, we next focused on the substrate scope (Table 1). The optimized reaction protocol allowed the facile preparation of six-membered dihydroxazine **3b** with complete *O*-selectivity. Similarly, 2-thienyl dihydroxazine **3c** was accessed in a 44% yield and 95% ee as a crystalline solid suitable for X-ray crystallographic analysis. The enantiopure allylic alcohol (*S*)-**1c** (R = 2-thienyl and n = 1) was reisolated in a 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 the *O*-allylation furnished **3d** in a 45% yield and 93% ee. Analogously, isoxazoline **3e** was accessed in a good yield and high enantiomeric purity (41% yield and 92% ee). Notably, the kinetic resolution described is highly efficient, with a calculated selectivity factors $s > 50$ for all substrates.[11]

Next, we aimed to highlight the synthetic utility of the established protocols for the chemodivergent kinetic resolution of oximes that give rise to optically active cyclic oxime ethers, nitrones,[3a] and aliphatic allylic alcohols. To this end, γ-hydroxy thienyl oxime **1c** was chosen as a starting point for the preparation of diverse enantioenriched building blocks (Scheme 2A). The rhodium-catalyzed and oxime-directed C−H activation[12] of enantioenriched (*S*)-**1c** furnished thienopyridine **4**, a promising motif in drug discovery,[13] without any erosion of the optical purity. The lithiation of dihydrooxazine **3c** and subsequent trapping with allyl bromide allowed the selective installation of an additional stereocenter (**5**),[14] showcasing the applicability of the method for the synthesis of highly substituted heterocycles. Next, nitrone **2c**

Scheme 2. Functionalization of Products Derived from Oxime 1c[a]



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

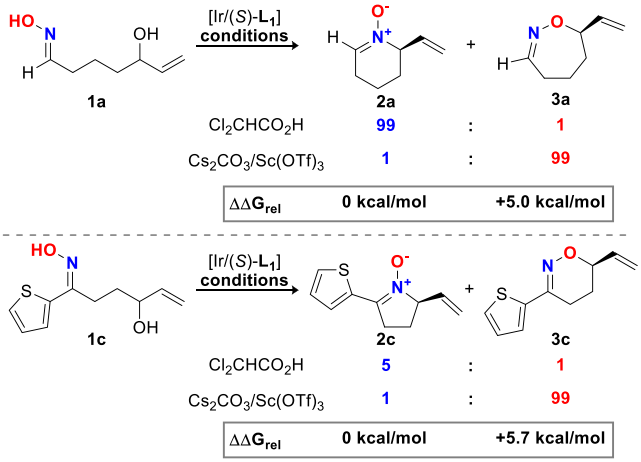
was treated with EtMgBr at −78 °C to afford trisubstituted pyrrolidine **6** in a 95% ee and 12:1 dr. These experiments showcase that a series of structurally diverse enantioenriched products can be rapidly accessed starting from a single racemic compound (**1c**).

In addition, we sought to showcase the method in the context of target-oriented synthesis (Scheme 2B). We aimed for the formal synthesis of (−)-roxifiban (**8**), a glycoprotein GP IIb-IIIa receptor antagonist investigated in clinical trials by DuPont for the treatment of various cardiovascular ailments, including platelet adhesion.[15] Enantioenriched isoxazoline **3e** was hydroborated and oxidized to the corresponding primary alcohol using 9-BBN and H_2O_2, respectively. Further oxidation with pyridinium dichromate (PDC) in anhydrous DMF cleanly afforded the carboxylic acid **7** in a 71% yield over two steps. Compound **7** was used previously by Olson and co-workers in their synthesis of (−)-roxifiban, thus completing the formal synthesis of **8**.[15a]

Over the course of this study we became interested in the origin of the remarkable chemoselectivity observed for both *N*- and *O*-alkylation reactions (Scheme 3). In particular, we wondered if the formation the cyclic nitrones or oxime ethers is governed by a thermodynamic bias and whether the size of

https://doi.org/10.1021/acs.orglett.1c00559
Org. Lett. 2021, 23, 2643−2647

Scheme 3. Chemodivergent Allylation and Calculated Relative Energies[a]

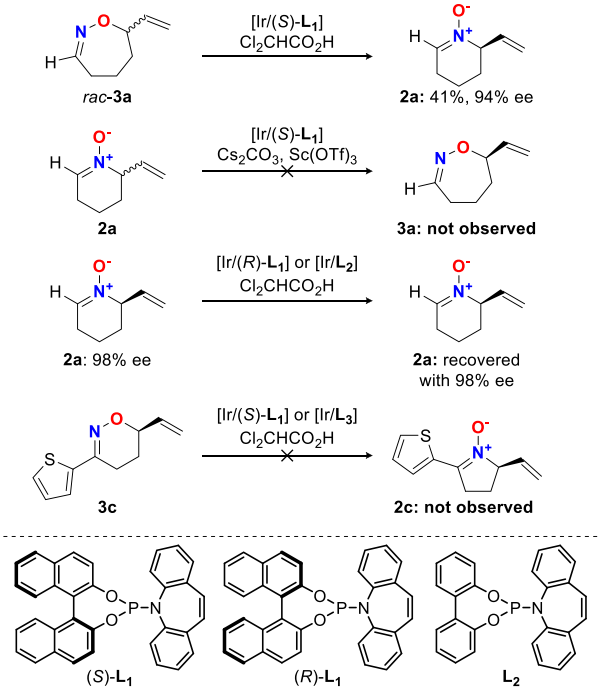


[a]$\Delta\Delta G_{rel}$ values were calculated using DFT at the B3PW91/6-311++G(d,p) level of theory, see the Supporting Information for details.

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 **2c**/**3c**, Scheme 3). Interestingly, density functional theory calculations at the B3PW91/6-311++G(d,p) level of theory revealed that the nitrone products were thermodynamically favored over the oxime ethers by $\Delta\Delta G^0$ = 5.0 kcal mol^{-1} and $\Delta\Delta G^0$ = 5.7 kcal mol^{-1}, respectively, regardless of ring size.[16,17]

To probe whether the chemoselective formation of nitrone **2a** may occur via a thermodynamic equilibration from **3a**, we conducted a series of control experiments (Scheme 4). 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*)-**L**$_1$] were necessary for the conversion of **3a** to **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**$_2$ did not lead to any erosion of optical purity even after prolonged reaction times (48 h). Collectively, these experiments indicate that C−N bond cleavage occurs under neither under basic nor acidic conditions. We postulate that while the *O*-alkylated product **3a** may be formed under acidic conditions as the kinetic product, it can undergo C−O bond cleavage to afford the 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 bond (the pK_a of benzophenone oxime in water is ∼11).[18] However, our observations with **2a** and **3a** were not generalizable, as subjecting the six-membered oxime ether **3c** to Cl_2CHCO_2H/[Ir] did not lead to the formation of nitrone **2c**. Hence, the six-membered oxime ether **3c** cannot undergo thermodynamic equilibration, which explains the lower chemoselectivity observed in the formation of nitrone **2c** despite a strong thermodynamic bias for *N*-allylation.

Scheme 4. Control Experiments on *N*- or *O*-Alkylation[a]



[a]Reactions were set up according to general procedures; see Table 1 and the Supporting Information.

In conclusion, we have developed conditions for the highly enantio- and chemoselective intramolecular *O*-allylation of oximes. The method furnishes cyclic five-, six-, and seven-memberd oxime ethers in a high enantiomeric purity. Combined with our earlier report on the chemoselective *N*-allylation of oximes, we have established conditions for the chemodivergent synthesis of cyclic oxime ethers and nitrones from the same oxime starting materials. Experimental and computational data suggest that for some substrates the *N*-allylation occurs via thermodynamic equilibration, whereas *O*-allylation proceeds under kinetic control. The synthetic utility of the method was shown by the functionalization of the cyclization products to give a diverse set of chiral building blocks and the enantioselective formal synthesis of glycoprotein GP IIb-IIIa receptor antagonist (−)-roxifiban.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00559.

General methods, experimental procedures, and spectral data (PDF)

Accession Codes

CCDC 1995673 and 2001544 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://doi.org/10.1021/acs.orglett.1c00559
Org. Lett. 2021, 23, 2643−2647

AUTHOR INFORMATION

Corresponding Author

Erick M. Carreira − *Eidgenössische Technische Hochschule (ETH) Zürich, 8093 Zürich, Switzerland;* orcid.org/0000-0003-1472-490X; Email: erickm.carreira@org.chem.ethz.ch

Author

Tobias Sandmeier − *Eidgenössische Technische Hochschule (ETH) Zürich, 8093 Zürich, Switzerland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00559

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the ETH Zürich and the Swiss National Science Foundation (200020_172516) for financial support. Simon L. Rössler (ETH Zürich) is thanked for carrying out the DFT calculations. We also thank Dr. N. Trapp (ETH Zürich) and M. Solar (ETH Zürich) for X-ray crystallographic analyses.

REFERENCES

(1) For general reviews on metal-catalyzed allylic substitution, see: (a) Halpern, J.; Trost, B. M. Asymmetric Catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5347. (b) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921. (c) Oliver, S.; Evans, P. A. Transition-Metal-Catalyzed Allylic Substitution Reactions: Stereoselective Construction of α- and β-Substituted Carbonyl Compounds. *Synthesis* **2013**, *45*, 3179. (d) Trost, B. M.; Van Vranken, D. L. Asymmetric Ligands for Transition-Metal-Catalyzed Reactions: 2-Diphenylphosphinobenzoyl Derivatives of C2-Symmetric Diols and Diamines. *Angew. Chem., Int. Ed. Engl.* **1992**, *31* (2), 228−230. For selected examples using Pd, Mo, and Rh, see: (e) Trost, B. M.; Lautens, M. Molybdenum Catalysts for Allylic Alkylation. *J. Am. Chem. Soc.* **1982**, *104*, 5543−5545. (f) Turnbull, B. W. H.; Evans, P. A. Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2015**, *137*, 6156. (g) Butt, N. A.; Zhang, W. Transition Metal-Catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929.

(2) (a) Stanley, L. M.; Hartwig, J. F. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461. (b) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969. (c) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite, Olefin) Ligands. *Acc. Chem. Res.* **2019**, *52*, 2657.

(3) (a) Sandmeier, T.; Carreira, E. M. Enantioselective Synthesis of Cyclic Nitrones by Chemoselective Intramolecular Allylic Alkylation of Oximes. *Angew. Chem., Int. Ed.* **2021**, DOI: 10.1002/anie.202100150. (b) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. Iridium-Catalyzed Synthesis of Primary Allylic Amines from Allylic Alcohols: Sulfamic Acid as Ammonia Equivalent. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. For relevant reactions using *O*- and *N*-nucleophiles, see: (c) Roggen, M.; Carreira, E. M. Enantioselective Allylic Etherification: Selective Coupling of Two Unactivated Alcohols. *Angew. Chem., Int. Ed.* **2011**, *50*, 5568. (d) Lafrance, M.; Roggen, M.; Carreira, E. M. Direct, Enantioselective Iridium-Catalyzed Allylic Amination of Racemic Allylic Alcohols. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470. (e) Hamilton, J. Y.; Rössler, S. L.; Carreira, E. M. Enantio- and Diastereoselective Spiroketalization Catalyzed by Chiral Iridium Complex. *J. Am. Chem. Soc.* **2017**, *139*, 8082. (f) Sandmeier, T.; Goetzke, F. W.; Krautwald, S.; Carreira, E. M. Iridium-Catalyzed Enantioselective Allylic Substitution with Aqueous Solutions of Nucleophiles. *J. Am. Chem. Soc.* **2019**, *141*, 12212.

(4) For general reviews, see: (a) Sukhorukov, A. Y.; Ioffe, S. L. Chemistry of Six-Membered Cyclic Oxime Ethers. Application in the Synthesis of Bioactive Compounds. *Chem. Rev.* **2011**, *111*, 5004. (b) Agrawal, N.; Mishra, P. The Synthetic and Therapeutic Expedition of Isoxazole and its Analogs. *Med. Chem. Res.* **2018**, *27*, 1309. (c) Kaur, K.; Kumar, V.; Sharma, A. K.; Gupta, G. K. Isoxazoline containing natural products as anticancer agents: A review. *Eur. J. Med. Chem.* **2014**, *77*, 121. (d) Lamberth, C. Oxazole and Isoxazole Chemistry in Crop Protection. *J. Heterocycl. Chem.* **2018**, *55*, 2035. (e) Mirjafary, Z.; Abdoli, M.; Saeidian, H.; Kakanejadifard, A.; Farnia, S. M. F. Review on the Synthesis of Acyclic and Cyclic Oxime Ethers. *RSC Adv.* **2016**, *6*, 17740.

(5) For reports on the synthesis of cyclic oxime ethers via Pd-catalyzed carboetherification, see: (a) Li, N.; Sun, B.; Liu, S.; Zhao, J.; Zhang, Q. Highly Enantioselective Construction of Dihydrooxazines via Pd-Catalyzed Asymmetric Carboetherification. *Org. Lett.* **2020**, *22*, 190. (b) Wang, L.; Zhang, K.; Wang, Y.; Li, W.; Chen, M.; Zhang, J. Enantioselective Synthesis of Isoxazolines Enabled by Palladium-Catalyzed Carboetherification of Alkenyl Oximes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4421.

(6) For reports on the enantioselective iodocyclization and fluorocyclization of oximes, see: (a) Suresh, R.; Simlandy, A. K.; Mukherjee, S. A Catalytic Enantioselective Iodocyclization Route to Dihydrooxazines. *Org. Lett.* **2018**, *20*, 1300. (b) Tripathi, C. B.; Mukherjee, S. Catalytic Enantioselective 1,4-Iodofunctionalizations of Conjugated Dienes. *Org. Lett.* **2015**, *17*, 4424. (c) Tripathi, C. B.; Mukherjee, S. Catalytic Enantioselective Iodoetherification of Oximes. *Angew. Chem., Int. Ed.* **2013**, *52*, 8450. (d) Rouno, T.; Niwa, T.; Nishibashi, K.; Yamamoto, N.; Egami, H.; Hamashima, Y. Enantioselective 5-exo-Fluorocyclization of Ene-Oximes. *Molecules* **2019**, *24*, 3464. For reports employing other electrophiles, see: (e) Li, X.-T.; Gu, Q.-S.; Dong, X.-Y.; Meng, X.; Liu, X.-Y. A Copper Catalyst with a Cinchona-Alkaloid-Based Sulfonamide Ligand for Asymmetric Radical Oxytrifluoromethylation of Alkenyl Oximes. *Angew. Chem., Int. Ed.* **2018**, *57*, 7668. (f) Li, X.-T.; Lv, L.; Wang, T.; Gu, Q.-S.; Xu, G.-X.; Li, Z.-L.; Ye, L.; Zhang, X.; Cheng, G.-J.; Liu, X.-Y. Diastereo- and Enantioselective Catalytic Radical Oxysulfonylation of Alkenes in β,γ-Unsaturated Ketoximes. *Chem.* **2020**, *6*, 1692.

(7) For approaches based on 1,3-dipolar cycloadditions, see: (a) Bartlett, S. L.; Sohtome, Y.; Hashizume, D.; White, P. S.; Sawamura, M.; Johnson, J. S.; Sodeoka, M. Catalytic Enantioselective [3 + 2] Cycloaddition of α-Keto Ester Enolates and Nitrile Oxides. *J. Am. Chem. Soc.* **2017**, *139*, 8661. (b) Suga, H.; Hashimoto, Y.; Toda, Y.; Fukushima, K.; Esaki, H.; Kikuchi, A. Amine-Urea-Mediated Asymmetric Cycloadditions between Nitrile Oxides and o-Hydroxystyrenes by Dual Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 11936. (c) Lian, X.; Guo, S.; Wang, G.; Lin, L.; Liu, X.; Feng, X. Asymmetric Synthesis of Spiro[isoxazolin-3,3′-oxindoles] via the Catalytic 1,3-Dipolar Cycloaddition Reaction of Nitrile Oxides. *J. Org. Chem.* **2014**, *79*, 7703. (d) Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides Catalyzed by Chiral Binaphthyldiimine-Ni(II) Complexes. *J. Org. Chem.* **2009**, *74*, 1099. (e) Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kundig, E. P. Chiral Ruthenium Lewis Acid-Catalyzed Nitrile Oxide Cycloadditions. *Tetrahedron* **2007**, *63*, 8413. (f) Shimizu, M.; Ukaji, Y.; Inomata, K. Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides to an Achiral Allyl Alcohol Utilizing Diisopropyl Tartrate as a Chiral Auxiliary. *Chem. Lett.* **1996**, *25*, 455.

(8) Cao, Z.; Liu, Z.; Liu, Y.; Du, H. Pd-Catalyzed Asymmetric Allylic Etherizations with Oximes by Chiral Alkene-Phosphine Ligands. *J. Org. Chem.* **2011**, *76*, 6401.

(9) (a) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. Utility of the Iridium Complex of the Pybox Ligand in Regio- and

Enantioselective Allylic Substitution. *Org. Lett.* **2004**, *6*, 4631. (b) Miyabe, H.; Matsumura, A.; Yoshida, K.; Takemoto, Y. Synthesis of chiral oxime ethers based on regio- and enantioselective allylic substitution catalyzed by iridium-pybox complex. *Tetrahedron* **2009**, *65*, 4464.

(10) Wang, Y.; Zhang, W.-Y.; You, S.-L. Ketones and Aldehydes as *O*-Nucleophiles in Iridium-Catalyzed Intramolecular Asymmetric Allylic Substitution Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 2228.

(11) *s*-Factors were calculated as described by Kagan and co-workers: Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249. See the Supporting Information for details.

(12) Parthasarathy, K.; Cheng, C.-H. Easy access to isoquinolines and tetrahydroquinolines from ketoximes and alkynes via rhodium-catalyzed C-H bond activation. *J. Org. Chem.* **2009**, *74*, 9359.

(13) (a) Zhu, G. D.; Arendsen, D. L.; Gunawardana, I. W.; Boyd, S. A.; Stewart, A. O.; Fry, D. G.; Cool, B. L.; Kifle, L.; Schaefer, V.; Meuth, J.; Marsh, K. C.; Kempf-Grote, A. J.; Kilgannon, P.; Gallatin, W. M.; Okasinski, G. F. Selective Inhibition of ICAM-1 and E-Selectin Expression in Human Endothelial Cells. 2. Aryl Modifications of 4-(Aryloxy)thieno[2,3-*c*]pyridines with Fine-Tuning at C-2 Carbamides. *J. Med. Chem.* **2001**, *44*, 3469. (b) Kawakubo, H.; Okazaki, K.; Nagatani, T.; Takao, K.; Hasimoto, S.; Sugihara, T. Potent anticonflict activity and lessening of memory impairment with a series of novel [1]benzothieno[2,3-*c*]pyridines and 1,2,3,4-tetrahydro[1]-benzothieno[2,3-*c*]pyridines. *J. Med. Chem.* **1990**, *33*, 3110.

(14) For literature precedence, including a model of the stereochemical outcome, see: Reißig, H. U.; Hippeli, C. Lithiated 5,6-Dihydro-4H-1,2-oxazines: Synthesis, Highly Diastereoselective Reactions with Electrophiles, and Subsequent Transformations. *Chem. Ber.* **1991**, *124*, 115.

(15) (a) Xue, C.-B.; Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Batt, D. G.; Cain, G. A.; Sworin, M.; Rockwell, A. L.; Roderick, J. J.; Wang, S.; Orwat, M. J.; Frietze, W. E.; Bostrom, L. L.; Liu, J.; Higley, C. A.; Rankin, F. W.; Tobin, A. E.; Emmett, G.; Lalka, G. K.; Sze, J. Y.; Di Meo, S. V.; Mousa, S. A.; Thoolen, M. J.; Racanelli, A. L.; Hausner, E. A.; Reilly, T. M.; DeGrado, W. F.; Wexler, R. R.; Olson, R. E. Discovery of an Orally Active Series of Isoxazoline Glycoprotein IIb/IIIa Antagonists. *J. Med. Chem.* **1997**, *40*, 2064. (b) Serebruany, V. L.; Malinin, A. I.; O'Connor, C. M.; Gurbel, P. A. Effects of Roxifiban on Platelet Aggregation and Major Receptor Expression in Patients with Coronary Artery Disease for the Roxifiban Oral Compound Kinetics Evaluation Trial-I (ROCKET-I Platelet Substudy). *Am. Heart J.* **2003**, *146*, 91. For the pharmacological activity of roxifiban, see: (c) Murphy, J.; Wright, R. S.; Gussak, I.; Williams, B.; Daly, R. N.; Cain, V. A.; Pieniaszek, H. J.; Sy, S. K. B.; Ebling, W.; Simonson, K.; Wilcox, R. A.; Kopecky, S. L. The Use of Roxifiban (DMP754), a Novel Oral Platelet Glycoprotein IIb/IIIa Receptor Inhibitor, in Patients with Stable Coronary Artery Disease. *Am. J. Cardiovasc. Drugs* **2003**, *3*, 101. (d) Mousa, S. A.; Bozarth, J. M.; Naik, U. P.; Slee, A. Platelet GPIIb/IIIa binding characteristics of small molecule RGD mimetic: distinct binding profile for Roxifiban. *Br. J. Pharmacol.* **2001**, *133*, 331.

(16) See the Supporting Information for details.

(17) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980**, *72*, 650. (b) McLean, A. D.; Chandler, G. S. Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, Z = 11−18. *J. Chem. Phys.* **1980**, *72*, 5639. DFT calculations were done with the Gaussian software package: (c) Firsch, J. M.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 09*, rev. D.01; Gaussian, Inc.: Wallingford, CT, 2016.

(18) Roca-López, D.; Darù, A.; Tejero, T.; Merino, P. Revisiting Oxime-Nitrone Tautomerism. Evidence of Nitrone Tautomer Participation in Oxime Nucleophilic Addition Reactions. *RSC Adv.* **2016**, *6*, 22161.

https://doi.org/10.1021/acs.orglett.1c00559
Org. Lett. 2021, 23, 2643−2647