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

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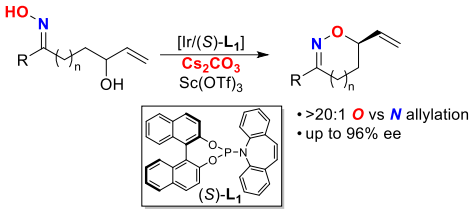
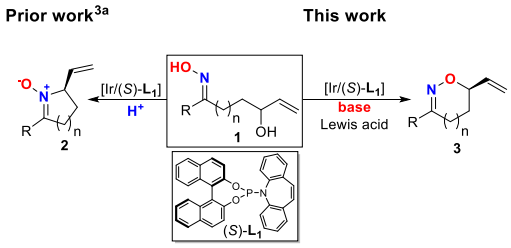


ABSTRACT: A method for the enantio- and chemoselective iridium-catalyzed *O*-allylation of oximes is described. Kinetic resolution in an intramolecular setting provides enantioenriched oxime ethers and aliphatic allylic alcohols. The synthetic potential of the products generated with this method is showcased 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 reactions have emerged as powerful tools for enantioselective carbon-carbon and carbon-heteroatom bond formation.[1] In particular, iridium-catalyzed reactions have proven useful for the asymmetric synthesis of chiral building blocks due to a strong preference for branched allylation products.[2] We have recently documented the iridium and Brønsted acid-catalyzed enantio- and chemoselective intramolecular *N*-allylation of oximes (Scheme 1).[3] The method provides 5-, 6-, and 7-membered cyclic nitrones **2** *via* kinetic resolution of secondary allylic alcohols and proceeds with remarkable selectivity for *N*-allylation with the *O*-allylation adducts merely as minor side products. Because *O*-allylated cyclic oxime ethers are important structural subunits in drug discovery and crop protection,[4] procedures for their enantioselective synthesis are warranted. Herein, we report the iridium-catalyzed, chemoselective, intramolecular *O*-allylation of oximes. Preliminary mechanistic studies were conducted to investigate this remarkable switch in chemoselectivity.

Cyclic oxime ethers, in particular 5-membered isoxazolines, have been highlighted as privileged structural motives in pharmaceuticals and pesticides.[4] However, methodology for the enantioselective synthesis of cyclic oxime ethers relying on transition metal-catalyzed allylic substitution remain undeveloped.[5,6,7] The groups of Du[8] and Takemoto[9] have reported enantioselective intermolecular *O*-allylation reactions to access acyclic oxime ethers using palladium or iridium catalysts, respectively. In 2019, You and co-workers documented a single example of intramolecular iridium-catalyzed *O*-allylation of an oxime furnishing a 7-membered 1,2,5-oxadiazepane product.[10] Yet, a general enantioselective method that provides access to cyclic oximes ethers of various ring sizes remains elusive.

Scheme 1. Iridium-Catalyzed Intramolecular Allylation of Oximes

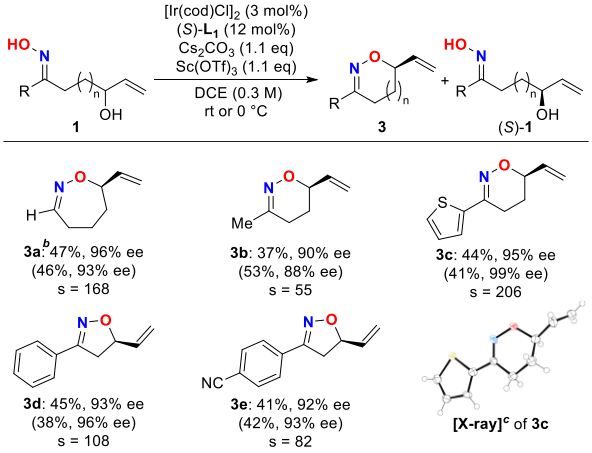


At the onset of the methodological studies described herein, we envisioned that chemo- and enantioselective *O*-allylation of oximes in an intramolecular setting could provide convenient approaches for the preparation of cyclic oxime ethers of various ring sizes. In our previous report,[3a] the chiral catalyst derived from $[Ir(cod)Cl]_2$ and phosphoramidite-olefin ligand (*S*)-**L₁** combined with Brønsted acid cleanly converted oxime **1a** (Scheme 1, R = H, n = 2) to the corresponding 6-membered nitrone **2a** with complete chemoselectivity for *N*-allylation. Thus, a series of experiments aimed at identifying conditions for selective *O*-allylation were conducted (see supporting information). Gratifyingly, we found that in the presence of base

(Cs_2CO_3) and a Lewis acid ($Sc(OTf)_3$), the same iridium(I) catalyst ([Ir/(*S*)-**L₁**]) effected the conversion of hydroxy oxime **1a** to 7-membered oxime ether **3a** *via* kinetic resolution (47% yield, theoretical yield: 50%, 96% ee, Table 1). Notably, *N*-allylated nitrone **2a** was not detected using these reaction conditions.

Having established optimal parameters for iridium-catalyzed, chemoselective *O*-allylation of oximes, we next focused on the substrate scope (Table 1). The optimized reaction protocol allowed facile preparation of 6-membered dihydroxazine **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*)-**1c** (R = 2-thienyl, n =1) was reisolated in 41% yield. In addition to 7-membered oxazepane (**3a**) and 6-membered oxazine (**3b** and **3c**) scaffolds, we examined the formation of 5-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). Notably, the kinetic resolution described is highly efficient with calculated selectivity factors s > 50 for all substrates.[11]

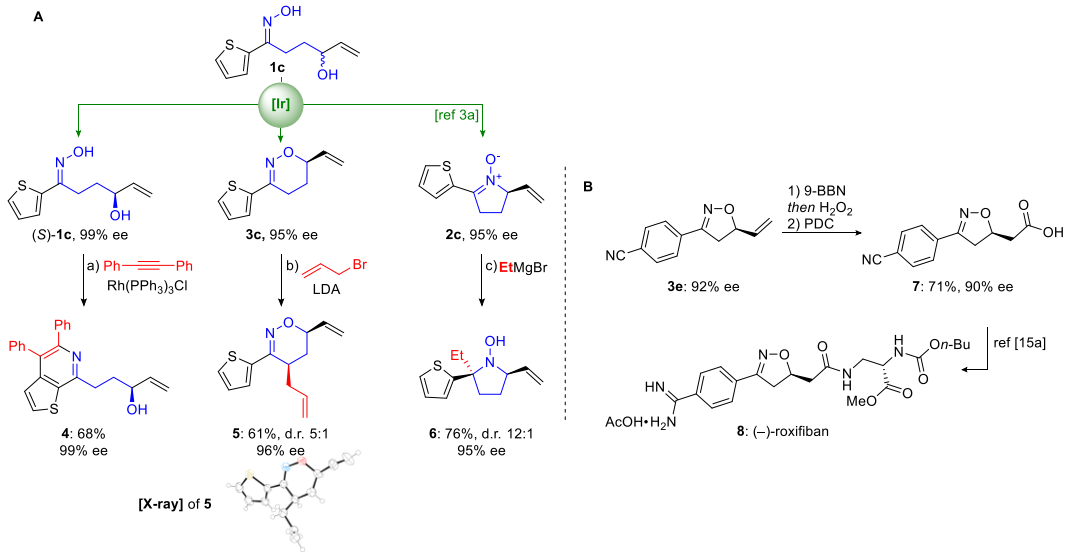
Table 1. Substrate Scope of the Intramolecular *O*-Allylation of Oximes[a]



[a]Reactions conducted 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. Selectivity factors (s) calculated using Kagan's method.[11] [b] reaction run at rt. [c]Thermal ellipsoids displayed at 50% probability level.

Next, we aimed to highlight the synthetic utility of the established protocol for chemodivergent kinetic resolution of oximes that would 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 3A).

Scheme 3. Functionalization of Products Derived from Oxime 1c[a]



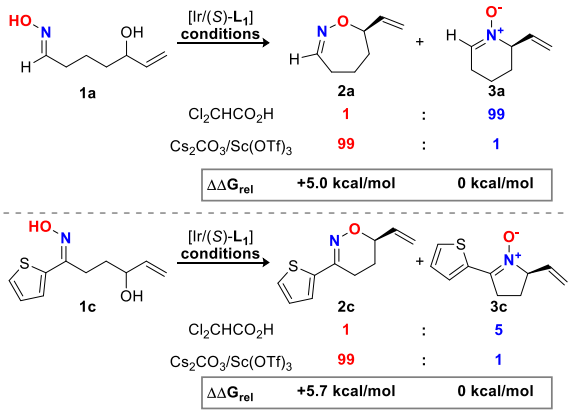
[a]Reactions conducted on 0.3 mmol scale. Yields refer to isolated products after flash column chromatography. Reagents and conditions: (a) $NaBH_4$, MeOH. (b) SmI_2, THF/MeOH (4:1). [b]Thermal ellipsoids displayed at 50% probability level.

Rhodium-catalyzed, oxime directed C–H activation[12] of enantioenriched (*S*)-**1c** furnished thienopyridine **4**, a promising motif in drug discovery,[13] without erosion of optical purity. 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** was treated with EtMgBr at –78 °C to afford trisubstituted pyrrolidine **6** in 95% ee and 12:1 dr. These experiments showcase that starting from a single racemic compound (**1c**), a series of structurally diverse enantioenriched products can be accessed rapidly.

In addition, we sought to showcase the method in the context of target-oriented synthesis (Scheme 3B). We aimed at 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 (Scheme 3B).[15] 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 **7** in 71% yield over two steps. Compound **7** has been 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 4). In particular, we wondered if the formation the cyclic nitrones or oxime ethers is governed by thermodynamic biases 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 **2c**/**3c**, Scheme 4). 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 as shown in Scheme 4.[16,17]

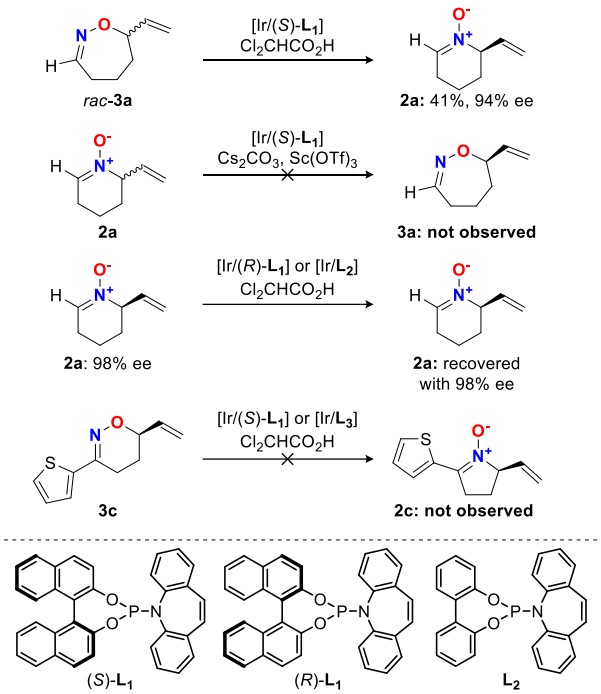
Scheme 4. Chemodivergent Allylation and Calculated Relative Energies[a]



[a]$\Delta\Delta G_{rel}$ 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* equilibration from **3a**, we conducted a series of control experiments (Scheme 5). 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*)-**L₁**] 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*)-**L₁**, the enantiomeric ligand, or achiral **L₂** 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).[19] 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 **2c**. Hence, 6-membered oxime ether **3c** does not undergo equilibration which explains the lower chemoselectivity observed in the formation of nitrone **2c** despite a strong thermodynamic bias for *N*-allylation

Scheme 5. Control experiments on *N/O*-alkylation[a]



[a]Reactions were set up according to general procedures, see Table1 and supporting information.

In conclusion, we have developed conditions for the highly enantio- and chemoselective intramolecular *O*-allylation of oximes. The method furnishes cyclic 5-, 6-, and 7-membered oxime ethers in high enantiomeric purity. Combined with our earlier report on chemoselective *N*-allylation of oximes, we have established conditions chemodivergent synthesis of cyclic oxime ethers and nitrones from the same oxime starting materials. Experimental and computational data suggest that for some substrates *N*-allylation occurs via equilibration whereas *O*-allylation proceeds under kinetic control. The synthetic utility of the method was shown by functionalization of the cyclization products to give a diverse set of chiral building blocks and the entioselective formal synthesis of glycoprotein GP IIb-IIIa receptor antagonist (−)-roxifiban.

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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. For selected examples using Pd, Mo, and Rh, see: (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.* **1992**, *31*, 229. (e) Trost, B. M.; Lautens, M Molybdenum Catalysts for Allylic Alkylation. J. Am. Chem. Soc. **1982**, *104*, 5543. (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.

(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.; Zhen, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855. (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. For relevant reactions using *O*- and *N*-nucleophiles, see: (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. (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 theSynthesis 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.; Farina, 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.; 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 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) Ruono, T.; Niwa, T. Nishibashi, 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.(f) 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) Barlett, 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.; Bernadinelli, G.; Kündig, 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. Supporing Information of 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**, *75*, 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 for the stereochemical outcome, see: Reissing, H. U.; Hippeli, C. *Chem. Ber.* **1991**, *124*, 115.

(15) (a) Xue, C.-B.; Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Batt, D. G.; G. A.; Cain; 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. For the pharmacological activity of roxifiban, see: (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. (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 OralPlatelet 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.* **2009**, *133*, 331.

(16) See Supporting Information for details.

(17) (a) R. 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) MacLean, 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. (c) DFT calculations were done with the Gaussian software package: Firsch, J. M. et al. Gaussian 09, revision D.01, Gaussian, Inc., Wallingford CT, **2013**.

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