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Highly Enantioselective Construction of Dihydrooxazines via Pd-Catalyzed Asymmetric Carboetherification

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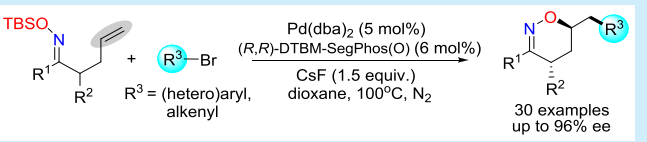
Supporting Information

ABSTRACT: A straightforward synthesis of highly enantioenriched 5,6-dihydro-4*H*-1,2-oxazines is realized by Pd-catalyzed asymmetric carboetherification of *γ*,*δ*-alkenyl oximes with (hetero)aryl and alkenyl halides in the presence of a commercially available bisphosphine ligand. The enantioenriched products can be facilely converted to functionalized alcohols with high fidelity of chiral transfer.



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The partially saturated six-membered cyclic oxime ether (SCOE), 5,6-dihydro-4*H*-1,2-oxazine, is displayed in bioactive natural products (Figure 1) and serves as versatile

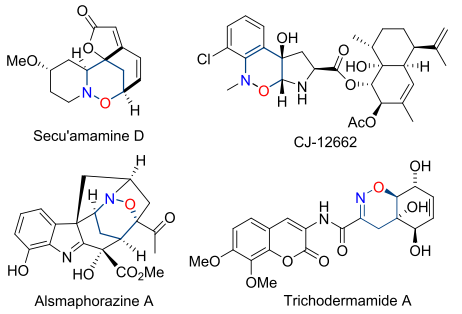
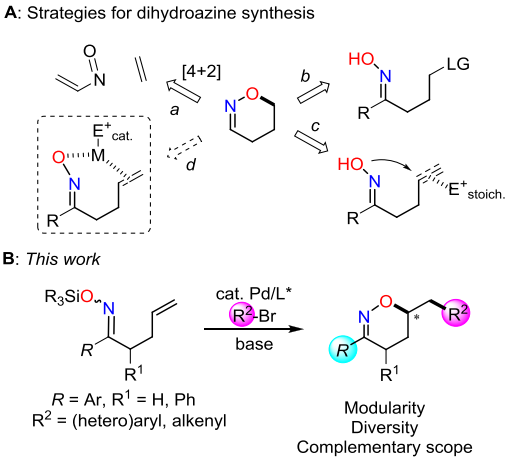


Figure 1. Selected 1,2-oxazine-containing bioactive natural products.

synthetic intermediates that can be trivially manipulated to key building blocks, such as 1,4-amino alcohols, various *N*- and *O*-containing heterocycles, etc.[1] Despite its high synthetic versatility, however, this ring system has received much less attention compared to its five membered congener, isooxazoline.[2] Traditional synthetic approaches to this scaffold mainly involve noncatalytic processes, such as hetero-Diels−Alder reaction of *in situ* generated reactive *α*-nitrosoalkene,[3] intramolecular S_N2 reaction,[4] electrophile-induced cyclization of alkenyl oxime,[5] among others (Scheme 1A, a−c). In contrast, catalytic asymmetric syntheses of this scaffold are highly underdeveloped.[6] Most recently, Mukherjee et al. reported a highly enantioselective organocatalytic iodocyclization approach en route to chiral 5,6-dihydro-4*H*-1,2-oxazines,[7] as an extension to the strategy's success in asymmetric isoxazoline synthesis.[8] Despite this advance, high enantiocontrol was only realized for construction of specialized structural units, i.e., tertiary benzylic C−O moieties. In addition, the diversity of electrophile is restricted. Furthermore, the few

Scheme 1. Strategies for the Synthesis of 5,6-Dihydro-4*H*-1,2-oxazine Framework



enantioselective catalytic methods applicable to isoxazoline syntheses[9] are not amenable to dihydrooxazines. To access chiral dihydrooxazines with complementary structural characteristics and broader diversity, there still remains a significant methodological gap. Thus, alternative approaches for the asymmetric synthesis of this scaffold would be highly valuable.

Pd-catalyzed heterocyclization reactions represent a highly enabling strategy for heterocycle synthesis.[10] In this context, olefin carboetherification has become a powerful tool for the synthesis of various *O*-heterocycles during the past two decades.[10b,11] The first example of Pd-catalyzed carboetherification was reported in 2004 by Wolf and co-workers.[12] A breakthrough in enantioselective catalysis was realized by Wolf in 2015 on the cyclization of alkenols to chiral tetrahydrofur-

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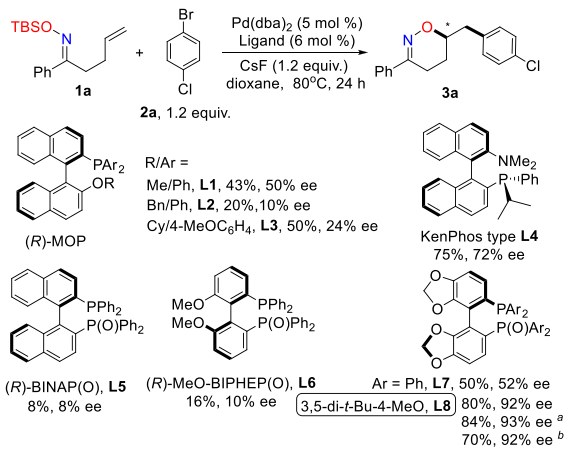
an.[13] The Tang[14] and Mazet[15] groups subsequently developed asymmetric synthesis of chiral 1,4-benzodioxanes and 2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran, respectively. These scarce yet elegant examples underscore the versatility and prospect of asymmetric carboetherification in constructing important *O*-heterocycles. On the other hand, readily available alkenyl oximes have long been harnessed to access cyclic chiral nitrone/oxime ethers via substrate-controlled diastereoselective synthesis, while catalyst-controlled bond formation processes (e.g., Scheme 1A, d, M = catalyst) are expected to hold promise for asymmetric synthesis of the important cyclic nitrones and/or oxime ethers. To this end, we commenced on investigating the Pd-catalyzed asymmetric cyclization/coupling of *γ,δ*-alkenyl oxime with organohalides for the synthesis of enantioenriched cyclic oxime ethers, with the aim to develop highly enantioselective protocols for this important scaffold. Herein we disclose that such a reaction can be realized with a commercial bisphosphine ligand, which enables rapid construction of various highly enantioenriched 5,6-dihydro-4*H*-1,2-oxazines (Scheme 1B).

We started by examining the enantioselective coupling cyclization of 4-chlorobromobenzene with *γ,δ*-alkenyloxime. However, we observed sluggish reactivity with a variety of bases (Table S1). Instead, in the presence of a fluoride base, the corresponding silyl ether **1a** in dioxane at 80 °C turned out to be more productive with some prototype commercial monophosphine ligands, among which (*R*)-MeO-MOP retrieved product **3a** in a moderate enantioselection of 50% ee (**L1**, Scheme 2). Increasing the steric hindrance of the

Scheme 2. Survey of Chiral Ligands

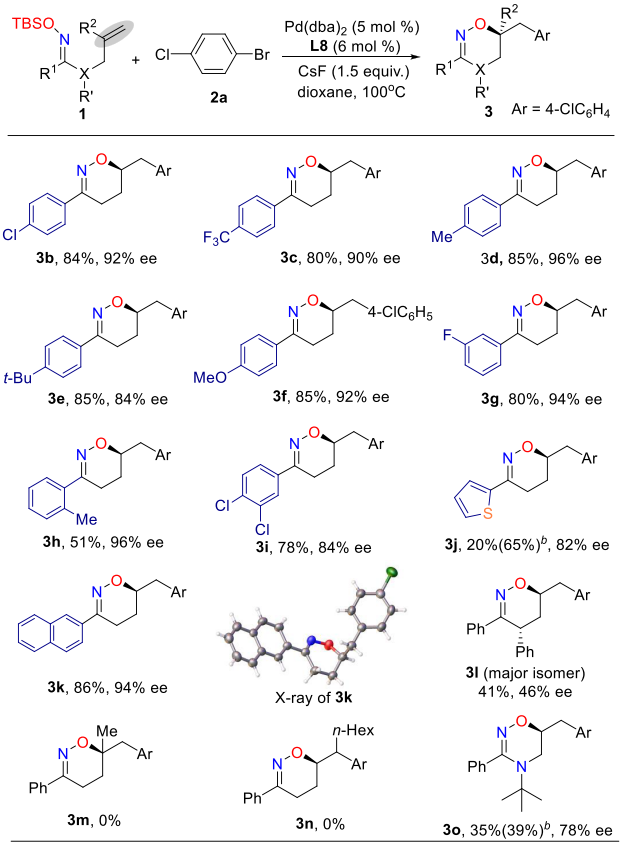


[a]1.5 equiv of **2a** and CsF, 100 °C. [b]5 mmol scale with *in situ* generated ligand from oxidation of (*R, R*)-DTBM-SegPhos (6 mol %) with $Pd(OAc)_2$ (5 mol %) and H_2O (40 mol %).

ethereal moiety led to a decrease of enantiocontrol, as BnO-MOP (**L2**) was much less selective. However, the obvious deviation from this trend by the ligand bearing a more bulkyl *O*-cyclohexyl moiety (**L3**, 24% ee) suggests that steric and/or electronic perturbation on the P-aryl may have a significant beneficiary effect. In line with this hypothesis, a KenPhos analogue **L4**, developed for the atroposelective Catellani-type biaryl cross-coupling,[16] was found to be more selective (72% ee), showing the high significance of P-substituents. Inspired by Mazet's report on the efficiency of monophosphines derived from partial oxidation of commercial bisphosphine ligands in the related reaction of 2-bromophenol with dihydrofurans,[15] we interrogated the effect of several ligand scaffolds (**L5**–**L7**).[17] Notably, while (*R*)-BINAP(O) and (*R*)-BIPHEP(O) were both sluggish in reactivity and selectivity, (*R*)-Segphos-(O) showed a highly promising 50% ee. To our delight, combining the favorable structural features of SegPhos with more sterically hindered P-aryls resulted in higher selectivity, as (*R*)-DTBM-SegPhos(O) (**L8**) delivered the product **3a** in 81% conversion, 80% yield, and 92% ee. Further increasing the loading of halide and base, as well as elevating the temperature to 100 °C, eventually led to 93% conversion, 84% isolated yield, and 93% ee. According to Mazet's report, *in situ* oxidation of the bisphosphine could be realized using $Pd(OAc)_2$ in the presence of 40 mol % H_2O.[15] By following this condition, we found that a 5 mmol scale reaction uneventfully delivered product **3a** in good yield with no erosion of enantiocontrol (1.002 g, 70%, 92% ee).

Under the optimized conditions the scope of this transformation was examined (Table 1). First, we examined the

Table 1. Scope of *γ,δ*-Vinyl Oximes[a]



[a]Reaction conditions: alkenyl oxime ether (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv), $Pd(dba)_2$ (5 mol %), (*R*)-DTBM-SegPhos(O) **L8** (6 mol %), CsF (0.30 mmol, 1.5 equiv), dioxane (2 mL), 100 °C. [b]brsm yield.

substitution effects on the aryl of alkenyl oxime silyl ether **1**. Various 4-substituents with distinct electronic properties were found to have negligible effects on the reactivity or enantioselectivity (**3b**–**3f**). Besides, 3- and 2-substitution was also compatible. Albeit *ortho*-substitution led to a significantly diminished yield, the enantiocontrol was exceptional (**3h**). 3,4-Disubstitution (**3i**), electron-rich 2-thienyl (**3j**), and 2-naphthyl (**3k**) were also accommodated. The absolute

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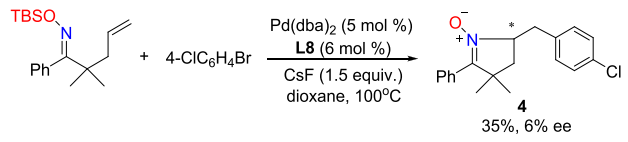
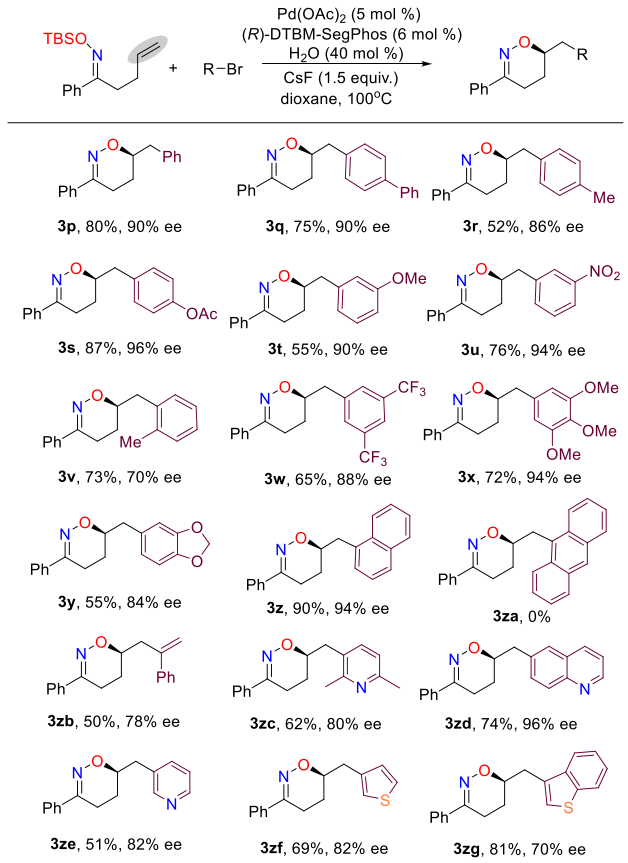
configuration of the products was unambiguously determined by X-ray diffraction studies of **3k**. A racemic α-phenyl substituted substrate could also react, and the major diasteromer **3l** was obtained in 41% yield and a fair 46% ee, indicating that the enantiodifferentiation of the chiral ligand **L8** was counteracted by a bulkyl α-substituent of the substrate due to intrinsic 1,3-asymmetric induction.[18] α,α-Dimethyl substitution led to the corresponding nitrone product **4** in merely 6% ee (Scheme 3), which requires further optimization for the enantioselective process.[19] Furthermore, the diazine product **3o** could also be delivered with good enantioselectivity, although the reactivity is somewhat lower.

Scheme 3. Pd-Catalyzed Cyclization of α,α-Disubstituted γ,δ-Alkenyl Oxime Silyl Ether



Variation of the bromide under the conditions of *in situ* generated ligand (Table 2) also showed the high versatility of this process, as reaction of a panel of aryl bromides with distinct electronic properties were also found insensitive to electronic perturbation (**3p**–**3u**). *Ortho*-, *meta*-, and multi-substituted aryl (**3v**–**3y**), naphthyl (**3z**), and alkenyl (**3zb**) substrates were all uneventfully accommodated. Electronically distinct heterocyclic substrates were also applicable (*N*-heterocycles **3zc**–**3ze**; *S*-heterocycles **3zf** and **3zg**). These results highlight the modularity of this process in the incorporation of various C(sp^2)-moieties onto the dihydrooxazine scaffold.

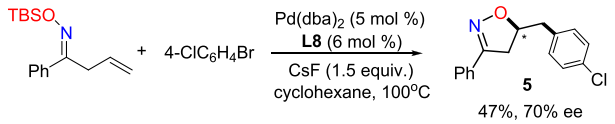
Table 2. Scope of Organohalide[a]



[a]Reaction conditions: alkenyl oxime ether (0.20 mmol), aryl halide (0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), (*R*)-DTBM-SegPhos (0.012 mmol, 6 mol %), H_2O (0.08 mmol, 1.5 μL, 40 mol %), CsF (0.30 mmol, 1.5 equiv), dioxane (2 mL), 100 °C.

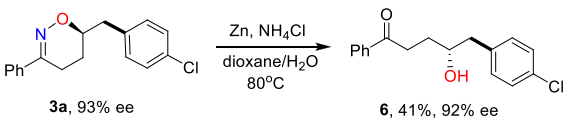
For the construction of analogous five-membered cyclic oxime ether, isoxazolines, the same ligand attained promising enantioselectivity, as use of (*R*)-DTBM-SegPhos(O) delivered isoxazoline **5** in a good 70% ee (Scheme 4). Notably, a number of other ligands demonstrating appreciable enantiocontrol for the synthesis of dihydrozaines turned out to be ineffective (Table S3). Further optimization will be required for these substrates.

Scheme 4. Pd-Catalyzed Asymmetric Carboetherification of β,γ-Alkenyl Oxime



Due to the ready availability of the oxime derivatives from their parent ketones, and the ease of N–O cleavage, the current protocol can offer a unique ketone "δ,γ-carbooxygenation". Thus, the products of this study can be efficiently used for the synthesis of various enantioenriched functionalized alcohols upon reductive cleavage of the N–O bond. As such, **3a** can be converted to γ-hydroxyl ketone **6** in a reasonable yield with enantiomeric fidelity (Scheme 5).

Scheme 5. Synthetic Elaboration



In conclusion, we have developed a straightforward approach for the highly enantioselective synthesis of 6-membered N,O-heterocycles 5,6-dihydro-4*H*-1,2-oxazine by Pd-catalyzed asymmetric carboetherification of ω-vinyl oximes directed by a commercially available phosphine ligand. The products can be facilely converted to enantioenriched γ-hydroxyketones and β-amino alcohol derivatives. Further studies to improve the enantioselection for isoxazolines are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04123.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1935678 contains 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 Cam-

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Notes

The authors declare no competing financial interest.

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