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# Site-Selective Nitrene Transfer to Conjugated Olefins Directed by Oxazoline Peptide Ligands

Golo Storch, Naudin van den Heuvel, and Scott J. Miller\*

Department of Chemistry, Yale University, New Haven, CT 06520-8107, USA  
E-mail: scott.miller@yale.edu

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**Abstract.** Site-selective nitrene transfer to di- and polyene substrates has been achieved using designed peptide-embedded bioxazoline ligands capable of binding copper. In model 1,3-diene substrates, the olefinic position proximal to a directing group was selectively functionalized. Additional studies indicate that this selectivity stems from non-covalent substrate-catalyst interactions. The peptide-mediated nitrene transfer was also applied to polyene natural product retinol and selective proximal functionalization allowed access to a *cis*-pyrroline modified retinoid.

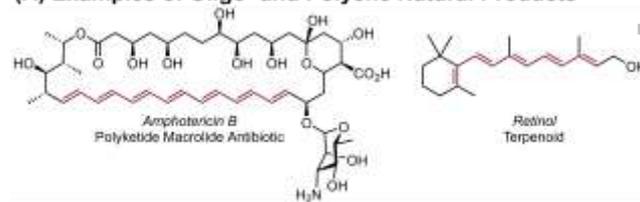
**Keywords:** peptide ligands • site-selectivity • polyene natural products • nitrene transfer • aziridination

Chemo- and site-selective functionalization of complex molecules *via* incorporation of nitrogen is a valuable tool for diversifying biologically active natural products.<sup>[1]</sup> In this context, nitrene transfer to olefins—resulting in aziridination<sup>[2]</sup>—can potentially be applied to a large variety of natural products since carbon-carbon double bonds are a prevalent structural feature. However, selective olefin modification is challenging as a result of their non-polar properties. On the other hand, selective nitrene transfer to polyene natural products<sup>[3]</sup> (see Figure 1A for examples) would offer access to derivatives with potentially altered biological activity<sup>[4]</sup> and additionally the vinylaziridine products would allow for a variety of follow-up chemistry.<sup>[5]</sup> In most reports on diene aziridination, site-selectivity, if observed at all, has been a result of inherent selectivity.<sup>[6]</sup> The first studies on catalyst-control in diene functionalization were reported by Pérez and coworkers using silver complexes of homoscorpionate ligands (Tp<sup>\*,Br</sup>) which allowed for directing nitrene transfer to the closer olefinic position, presumably as a result of catalyst interactions with the OH-group (Figure 1B, I).<sup>[7]</sup> In a related study, Schreiner and coworkers successfully designed a Rh<sup>II</sup>-catalyst for aziridination of the central olefinic position in a farnesol derivative,

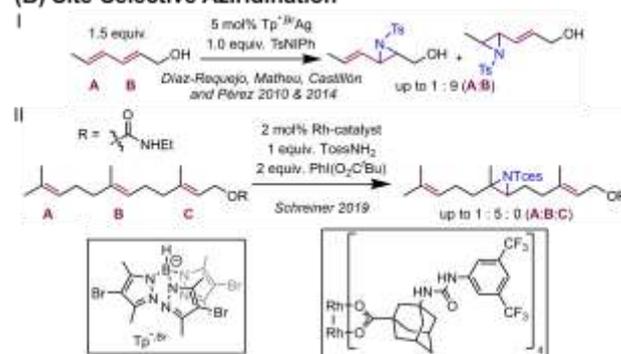
mediated through hydrogen bonding (Figure 1B, II).<sup>[8]</sup>

On the basis of precedents for reactions catalyzed by peptidyl-copper complexes,<sup>[9,10]</sup> the use of amides as directing groups in aziridinations,<sup>[11]</sup> and for bis(oxazoline) ligands influencing the course of site-selective reactions,<sup>[12]</sup> we wondered whether short peptide sequences could be designed that would act as ligands for transition metals and thereby allow for achieving site-selective nitrene transfer as a function of non-covalent substrate-catalyst interactions. With the aim of subsequent application in oligo- and polyene natural product functionalization, we were especially interested in conjugated olefin substrates (Figure 1C).

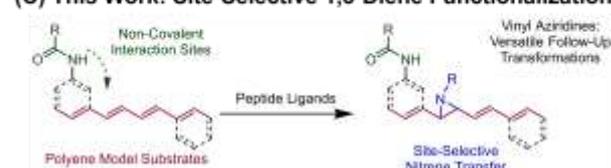
## (A) Examples of Oligo- and Polyene Natural Products



## (B) Site-Selective Aziridination



## (C) This Work: Site-Selective 1,3-Diene Functionalization

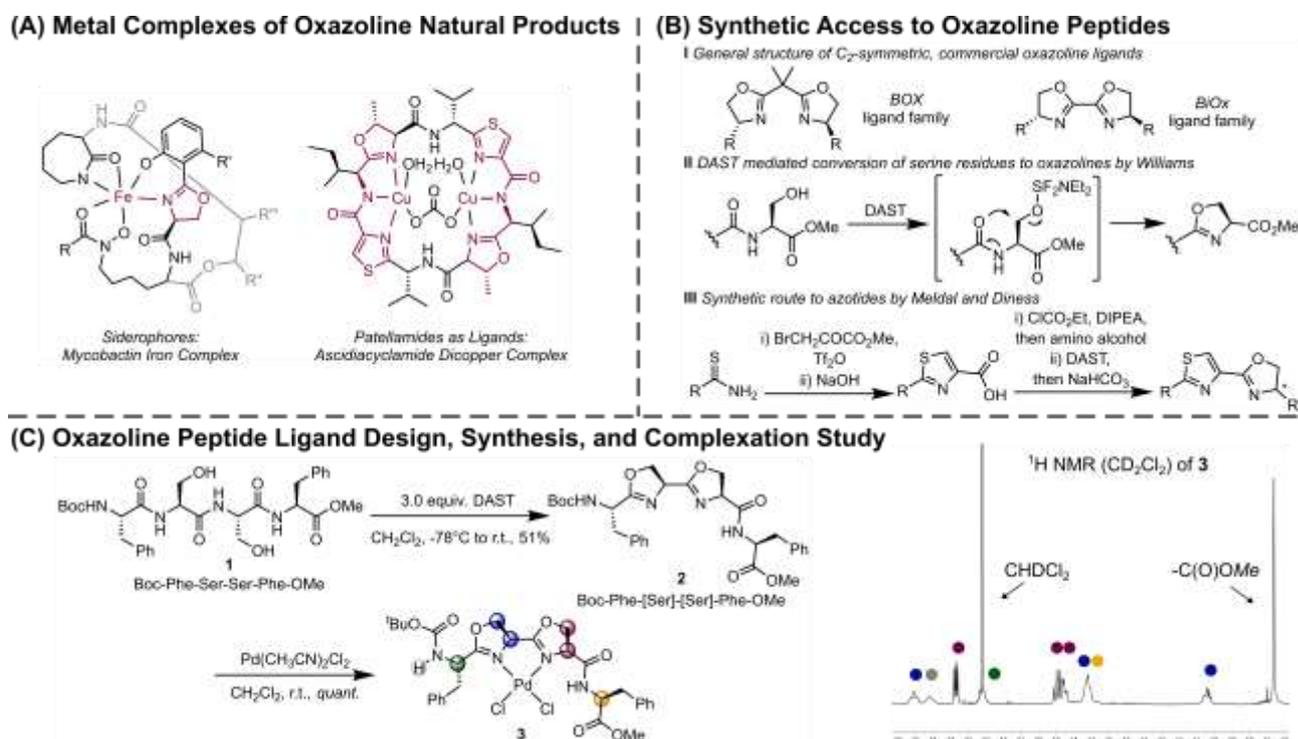


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**Figure 1.** Polyene natural products and site-selective aziridination strategies. TcesNH<sub>2</sub>: 2,2,2-Trichloroethoxysulfonamide.

Oxazolines were also chosen as promising metal coordinating residues due to the analogy to bisoxazolines and related L<sub>2</sub>-type ligands<sup>[13]</sup> that are highly effective ligands in copper-catalyzed aziridinations. Furthermore, as a common structural feature in peptide-based natural products, oxazolines can be embedded in peptides *via* cyclodehydration of serine residues—a post-translational modification that results in alternation of hydrogen bonding networks and rigidification of peptide structure.<sup>[14]</sup> Naturally occurring oxazoline-containing peptides have been found to bind transition metals in peptide siderophores,<sup>[15]</sup> westiellamides, and patellamides (Figure 2A).<sup>[16]</sup> However, to the best of our knowledge, no catalytic activity for these naturally occurring complexes has been reported so far. The

enzymatic mechanism of cyclodehydration is initiated *via* nucleophilic attack of the serine OH-group,<sup>[16b]</sup> while synthetic strategies include the *aza*-Wittig reaction,<sup>[17]</sup> and (di-ethylamino)sulfur trifluoride (DAST) mediated dehydration (Figure 2B).<sup>[18]</sup> Related to the recently reported and elegant approach of Meldal and Diness,<sup>[19]</sup> we hypothesized that double cyclodehydration of a Ser-Ser sequence would lead to bidentate oxazoline (BiOx) ligands (Figure 2B). Indeed, treatment of linear peptide **1** with DAST resulted in clean formation of bioxazoline **2** (Figure 2C). Complexation of **2** to Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub>—square planar d<sup>8</sup> configuration analogous to Cu<sup>III</sup> nitrene species—was studied in order to probe for transition metal binding, and clean formation of one single species was observed *via* NMR spectroscopy, presumably the *N,N*-chelate **3** (Figure 2C, see SI for details). These results allowed for preparation of designed bioxazolines embedded in peptide structures.



**Figure 2.** Examples of metal complexes of naturally occurring oxazolines and synthesis of oxazoline peptide ligands. DAST: (diethylamino)sulfur trifluoride.

We began our catalytic studies with unsymmetrical 1,4-diarylbuta-1,3-dienes as model substrates since we expected these compounds to share similarities with polyene natural products in terms of reactivity, while being easier to handle and less prone to *cis/trans* isomerization. Also, they have previously been investigated in terms of their analogy to retinoids.<sup>[20]</sup> Non-covalent interaction sites were installed in the aryl *meta*-position, since *para*-functionalization was anticipated to be too remote while *ortho*-modified substrates showed high intrinsic selectivity as a result of electronic perturbation of the

diene unit. We focused on studying amide interaction sites, and isovaleryl amide substrate **4**, unlike similar compounds, showed excellent solubility properties and was therefore chosen for screening. However, initial studies were hindered by the high reactivity of the vinylaziridine products, which made their isolation challenging. We considered this an opportunity to develop a clean one-pot reaction sequence for the functionalization of dienes. Using parent 1,4-diphenyl-1,3-butadiene we were able to identify and isolate the vinyl aziridine products and found that a palladium-catalyzed hydrogenation with

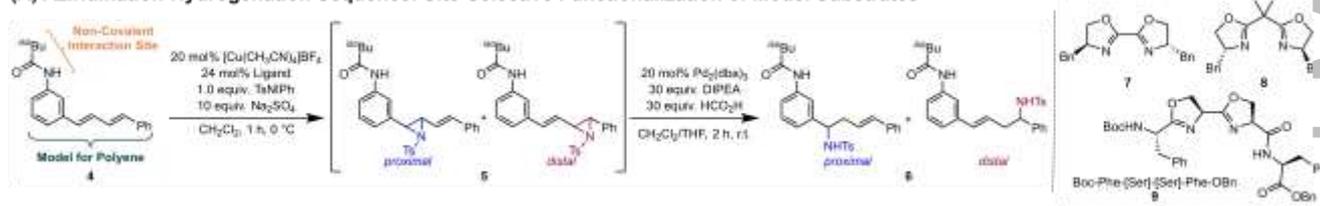
formic acid<sup>[21]</sup> resulted in highly selective cleavage of the allylic C-N bond while leaving the olefinic double bond intact (Figure 3A, see SI for details). In a control experiment we observed that 2,5-dimethyl-1-tosyl-3-pyrrolidine is not converted to the homoallylic amine under analogous reaction conditions (see SI for details) and, therefore, the involvement of pyrroline species stemming from formal [4+1] addition of the nitrene may be less likely. Interestingly, this one-pot reaction sequence to homoallylic amines complements methods for site-selective hydroamination of dienes.<sup>[22]</sup>

In order to assess intrinsic selectivity with bidentate oxazoline ligands, we initially used bioxazoline **7** as a truncated mimic of our oxazoline peptide ligands.<sup>[23]</sup> Almost equal amounts of *proximal* and *distal* products were formed (Figure 3B, entry 1). A quick screen of commercial ligands revealed that isopropylidene bisoxazolines performed slightly better but still only with low site-selectivity (Figure 3B, entry 3). Our study of peptide ligands began with optimizing the geometry of the chelating binding site through a screen of serine epimers (Figure 3B, entry 4-6) that revealed superior performance of homochiral ligands both in terms of yield and site-selectivity compared to other epimers and also commercial ligands. Investigation of a large variety of *C*- and *N*-terminal modified peptide ligands showed optimal results in cases with aromatic amino acid side chains (Figure 3B, entry 7-12), which led to

the identification of the Boc-Phe-[Ser]-[Ser]-NH-CHPh<sub>2</sub> sequence that resulted in good yield and selectivity greater than 1 : 5, favouring proximal functionalization. Notably, high levels of selectivity were maintained concomitant with only a slight decrease in yield at lowered catalyst loading (Figure 3B, entry 13).<sup>[24]</sup> Direct comparison of experiments in CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN (Figure 3B, entry 1,2 & 7,8) revealed that site-selectivity in the peptide ligand catalyses is fully depleted when using a polar organic solvent capable of interfering with defined non-covalent substrate-catalyst interactions.

In order to gain more detailed insights into the origins of the site-selectivity enhancement, we expanded our study to similar meta-substituted 1,4-diaryl-1,3-butadiene substrates. We were especially curious whether indications for a hydrogen bond between the substrate amide NH and the catalyst could be found. In this context, we studied trifluoroacetamide **10** in direct comparison to the *N*-methylated analogue **11** (Figure 4, A). Bn-BiOx, again, resulted in an unselective reaction with **10**, and screening (see SI for details) of our peptide oxazoline library led to the identification of a sequence—Boc-Phe-[Ser]-[Ser]-3,3-Dpa-OBn—with significantly improved site-selectivity (Figure 4B, Entry 1-2). Intriguingly, none of this selectivity enhancement was observed in the case of *N*-methylated substrate **11**, which even showed a slight inherent selectivity towards the *distal* product (Figure 4B, Entry 3-4).

#### (A) Aziridination-Hydrogenation Sequence: Site-Selective Functionalization of Model Substrates



#### (B) Screening of Commercial and Peptide Oxazoline Ligands

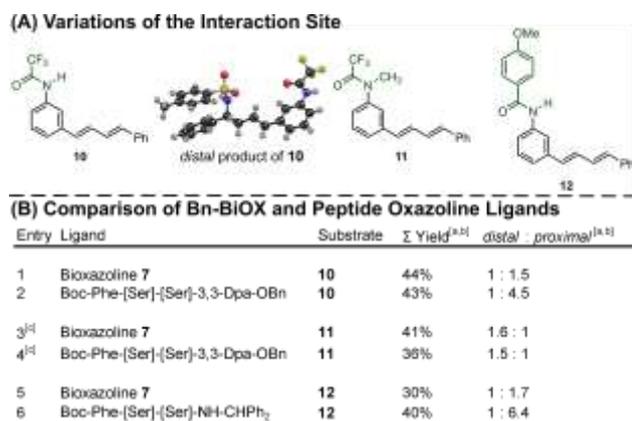
Entry	Ligand	Σ Yield <sup>[a,b]</sup>	distal : proximal <sup>[a,b]</sup>	Entry	Ligand	Σ Yield <sup>[a,b]</sup>	distal : proximal <sup>[a,b]</sup>
1	Bioxazoline <b>7</b>	42%	1 : 1.3	7	Boc-Phe-[Ser]-[Ser]-Phe-OMe	69%	1 : 4.3
2 <sup>[c]</sup>	Bioxazoline <b>7</b>	36%	1 : 1.2	8 <sup>[c]</sup>	Boc-Phe-[Ser]-[Ser]-Phe-OMe	58%	1 : 1.5
3	Bisoxazoline <b>8</b>	56%	1 : 2.3	9	Boc-Phe-[Ser]-[Ser]-1-Nal-OBn	65%	1 : 3.8
4	Boc-Phe-[Ser]-[Ser]-Phe-OBn	70%	1 : 3.7	10	Boc-3,3-Dpa-[Ser]-[Ser]-Phe-OBn	66%	1 : 4.5
5	Boc-Phe-[Ser]-[ <sup>D</sup> Ser]-Phe-OBn	65%	1 : 2.6	11	Boc-Phe-[Ser]-[Ser]-3,3-Dpa-OBn	69%	1 : 4.2
6	Boc-Phe-[ <sup>L</sup> Ser]-[Ser]-Phe-OBn	68%	1 : 3.0	12	Boc-Phe-[Ser]-[Ser]-NH-CHPh <sub>2</sub>	71%	1 : 5.2
				13 <sup>[d]</sup>	Boc-Phe-[Ser]-[Ser]-NH-CHPh <sub>2</sub>	61%	1 : 5.2

**Figure 3.** Investigation of unsymmetrical 1,4-diarylbuta-1,3-dienes as polyene model substrates in an aziridination-hydrogenation sequence. [a]: Average of two catalysis trials. [b]: Determined by NMR versus trimethyl trimesic acid internal standard. [c]: CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> (4:1) instead of CH<sub>2</sub>Cl<sub>2</sub> as solvent. [d]: 10 mol% copper catalyst.

This observation supports involvement of the NH group in hydrogen bonding interaction between substrate and catalyst. Additionally, we studied **12** bearing an electron-rich 4-methoxybenzoyl group that could potentially engage in secondary  $\pi$ -stacking interactions. Ligand Boc-Phe-[Ser]-[Ser]-NH-CHPh<sub>2</sub> (see SI for all data points) resulted in a significant site-selectivity increase to 1 : 6.4 favouring the proximal product, which corresponds to almost fourfold intrinsic selectivity (Figure 4B, Entries 5-6).

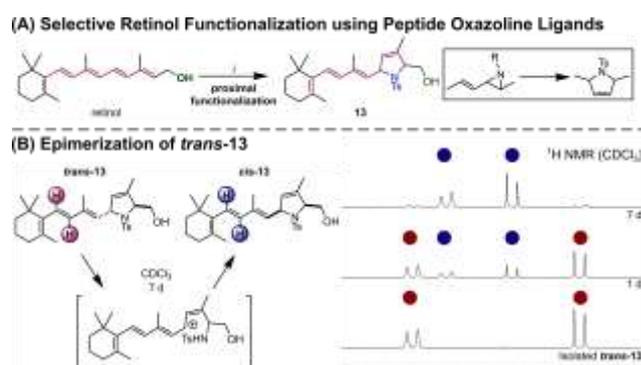
On the basis of these results, we turned our attention towards an application of peptide oxazolines to the site-selective functionalization of the polyene natural product retinol, as postulated in Figure 1A. Interest in derivatives of the latter mainly stems from activity in dermatology and cancer treatment. In this context, synthetic derivatives offer the possibility to increase stability towards *cis/trans* isomerism as well as selectivity enhancement for certain types of receptors.<sup>[25]</sup> Also, retinol contains a primary alcohol

functionality that we hypothesized could act as non-covalent directing group with the peptide ligands. Following the general reaction scheme (Figure 5A), we aimed for functionalization of the proximal, polar site. Using UPLC-MS analysis, the reaction using Bn-BOX **8** was found to result in multiple species each exhibiting MS characteristics consistent with reaction of retinol with the nitrene source (see SI for details). However, using Boc-Phe-[Ser]-[Ser]-Phe-OMe, formation of all but two products was suppressed, which were identified as *cis*-**13** and *trans*-**13** (in almost equal amounts), two diastereomers of *proximal* functionalization. Most probably this overall [4+1] cycloaddition occurs *via* ring expansion of an initially formed vinyl aziridine intermediate (Figure 5A, top right).<sup>[26,27]</sup>



**Figure 4.** Study of non-covalent substrate-catalyst interactions as origin for the increased site-selectivity. The distal functionalization product of **10** in the solid state<sup>[28]</sup> is depicted. [a] Results are the average of two catalytic trials. [b] 10 mol% catalyst loading, yields and site-selectivity determined *via* UPLC-MS versus trimethyl trimesic acid internal standard. [c] 20 mol% catalyst loading, yields and site-selectivity determined *via* NMR versus trimethyl trimesic acid internal standard. Dpa: 3,3-Diphenylalanine.

In order to probe for hydrogen bonding interactions, we also studied CH<sub>3</sub>CN as a polar solvent, which fully inhibited the Bn-BOX-mediated reaction while the peptide variant still showed formation of **13**, albeit with significantly reduced yield and selectivity (see SI for details). Intriguingly, the isolated pyrroline retinoid *trans*-**13** underwent reversible ring-opening in CDCl<sub>3</sub> solution resulting in complete, clean epimerization to *cis*-**13** over the course of several



days (Figure 5B).

**Figure 5.** Site-selective functionalization of retinol. (i) 1.0 equiv. retinol, 1.0 equiv. TsNIPh, 24 mol% ligand, 20 mol% [Cu(CH<sub>3</sub>CN)<sub>4</sub>]BF<sub>4</sub>, 10 equiv. Na<sub>2</sub>SO<sub>4</sub>, 33 mM in CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to r.t., overnight, 50%.

In contrast, isolated *cis*-**13** remained unchanged under analogous conditions and the increased thermodynamic stability of *cis*-**13** has been confirmed by DFT studies on a model pyrroline (see SI for details). This product epimerization implies that the peptide-catalyzed version of this reaction overall results in exclusive formation of *cis*-**13** in 50% yield (NMR versus internal standard) without using either retinol or TsNIPh in excess.

In this study, peptide embedded oxazolines were designed and applied as ligands for site-selective nitrene transfer reactions with model dienes and—at the proof-of-concept level—the polyene natural product retinol. Additional studies strongly point towards non-covalent interactions between substrate and catalyst being the origin of highly increased selectivity for reactive sites close to directing groups capable of hydrogen-bonding. The successful selective functionalization of retinol *via* clean formation of stable pyrroline products opens up a variety of possible applications of this catalytic system, for example nitrene transfer to polyene antibiotics. Furthermore, this new class of bidentate oxazoline ligands could be useful in a variety of different catalytic transformations, with their C<sub>1</sub>-symmetry allowing for diverse tuning in the context of addressing challenges in stereo- and site-selective transformations.

## Experimental Section

The *Supporting Information* contains experimental details for substrate synthesis, characterization of all catalysts and products, copies of NMR spectra, additional data regarding the analysis of catalytic experiments and assignments, as well as details on DFT investigations.

### General procedure for the DAST mediated cyclodehydration

The serine peptide (1.0 equiv.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (anhydrous, 0.1 M) and the solution was cooled to -78 °C. DAST (3.0 equiv.) was added and the reaction mixture was stirred for 1 h at -78 °C and then slowly warmed to r.t. in the cooling bath over additional 3 h (excess dry ice was removed). The homogeneous, clear solution was then cooled down to -78 °C again, K<sub>2</sub>CO<sub>3</sub> (anhydrous, 6.0 equiv.) was added, and stirring was continued for 1 h. Subsequently, the reaction mixture was poured into NaHCO<sub>3</sub> solution (aqueous, saturated, fivefold amount w.r.t. CH<sub>2</sub>Cl<sub>2</sub>) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (fourfold amount w.r.t. reaction solvent). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified *via* automated reversed phase chromatography (load in CH<sub>3</sub>CN; C18 silica; CH<sub>3</sub>CN/water; 1 CV: 30%, 10 CV: 30–100%, 1 CV: 100%; product containing fractions were combined,

extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure). The pure product was precipitated from  $\text{Et}_2\text{O}/\text{pentane}$ , dried *in vacuo* overnight, and stored in a glove box to prevent decomposition.

### General procedure for the aziridination-hydrogenation sequence

A Schlenk flask loaded with  $\text{Na}_2\text{SO}_4$  (anhydrous, 0.50 mmol, 10 equiv.) was heated with a heat gun and conditioned with  $\text{N}_2$  while cooling down to room temperature. Ligand (12  $\mu\text{mol}$ , 24 mol%) and  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$  (10.0  $\mu\text{mol}$ , 20 mol%) were added, and the flask was evacuated and backfilled with  $\text{N}_2$ . Then,  $\text{CH}_2\text{Cl}_2$  (anhydrous, 2.0 mL, 25 mM w.r.t. nitrene source) was added and the catalyst solution was stirred at room temperature for 1 h. Subsequently, diene substrate (75.0  $\mu\text{mol}$ , 1.5 equiv.) was added and the solution was cooled to 0 °C (ice bath) followed by addition of TsNIPh (50.0  $\mu\text{mol}$ , 1.0 equiv.). The reaction was stirred at 0 °C for 1 h. While still in the cooling bath, the reaction mixture was diluted with THF (anhydrous, 2.0 mL), and DIPEA (anhydrous, 1.50 mmol, 30 equiv.),  $\text{Pd}_2(\text{dba})_3$  (10.0  $\mu\text{mol}$ , 20 mol%), and formic acid (1.50 mmol, 30 equiv.) were added. The ice bath was removed and the reaction mixture was stirred at room temperature for 2 h. Then, it was passed through a plug of silica (Pasteur pipette, 5 cm, rinsed with 5 CV hexanes/EtOAc (50:50)) and concentrated under reduced pressure. The crude products were purified *via* automated normal phase chromatography (silica;  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ; 1 CV: 0%, 12 CV: 0–15%; all fractions containing product—as determined by UPLC–MS analysis—were collected). Then, 350  $\mu\text{L}$  internal standard solution (trimethyl trimesic acid in deacidified  $\text{CDCl}_3$ , 47.7 mM, 16.7  $\mu\text{mol}$ , 0.33 equiv.) was added, the sample was diluted with  $\text{CDCl}_3$ , and analyzed *via* NMR spectroscopy (10 s relaxation time).

### Site-Selective Retinol Functionalization

A Schlenk flask loaded with  $\text{Na}_2\text{SO}_4$  (anhydrous, 1.00 mmol, 10 equiv.) was heated with a hot air gun and conditioned with  $\text{N}_2$  while cooling down to room temperature. Ligand (12  $\mu\text{mol}$ , 12 mol%) and  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4$  (10.0  $\mu\text{mol}$ , 10 mol%) were added, and the flask was evacuated and backfilled with  $\text{N}_2$ . Then,  $\text{CH}_2\text{Cl}_2$  (anhydrous, 3.0 mL, 33 mM w.r.t. nitrene source) was added and the catalyst solution was stirred at room temperature for 1 h. Subsequently, diene substrate (100  $\mu\text{mol}$ , 1.0 equiv.) was added and the solution was cooled to 0 °C (ice bath) followed by addition of TsNIPh (100  $\mu\text{mol}$ , 1.0 equiv.). The reaction mixture was let warm up in the cooling bath overnight. Subsequently, it was passed through a plug of silica (Pasteur pipette, 5 cm, rinsed with 5 CV hexanes/EtOAc (50:50)). See Figure SI-21 for UPLC-MS analysis. Then, 700  $\mu\text{L}$  internal standard solution (trimethyl trimesic acid in deacidified  $\text{CDCl}_3$ , 47.7 mM, 33.3  $\mu\text{mol}$ , 0.33 equiv.) were added and the yield was determined *via* NMR spectroscopy (10 s relaxation time).

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- [28] CCDC-1943272 contains the supplementary crystallographic data and it can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

## COMMUNICATION

## Site-Selective Nitrene Transfer to Conjugated Olefins Mediated by Oxazoline Peptide Ligands

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