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Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes for polycyclic heterocycles with four chiral stereogenic centers

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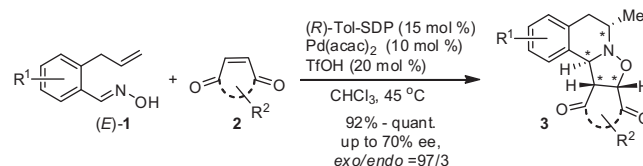
ABSTRACT

Diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes were established using a Pd(II)–(*R*)-Tol-SDP complex and triflic acid. The present process gave polycyclic heterocycles with four chiral stereogenic centers in almost quantitative yields and high stereoselectivities (up to 70% ee, *exo/endo* = 97/3).

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The development of a facile construction of polycyclic heterocycles is a subject of intensive research because of their potential use in medicinal chemistry.^{1,2} Among them, domino cyclization has become a powerful strategy for the formation of two or more rings in a single operation. In the domino cyclization, multiple chiral centers can often be formed with high stereoselectivities.² Nitrones derived from the reaction of oximes and alkenes are widely used 1,3-dipoles that endure cycloadditions with alkenes affording versatile isoxazolidine derivatives.³ In 1994, Grigg et al. developed Pd(II)-catalyzed cyclization/cycloaddition cascade reaction of alkenyl oximes, effectively furnishing isoxazolidines with multiple stereocenters.⁴ Despite the potential of this transformation, no enantioselective domino cyclization process has been reported.⁵ Herein, we present the first enantioselective protocol of a cyclization/cycloaddition sequence of alkenyl oxime (*E*)-**1** with enedione **2** catalyzed by a Pd(II)–(*R*)-Tol-SDP complex and triflic acid (TfOH) (Scheme 1).

With the aim of developing a diastereoselective and enantioselective cyclization/cycloaddition sequence, the reaction of alkenyl oxime (*E*)-**1a** and *N*-methyl maleimide (**2a**) as prototypical substrates was attempted (Table 1).⁴ Although a chiral complex derived from PdCl₂(MeCN)₂ with (*S*)-BINAP was used, no desired cyclic product **3a** was obtained. ESI-MS studies of the reaction

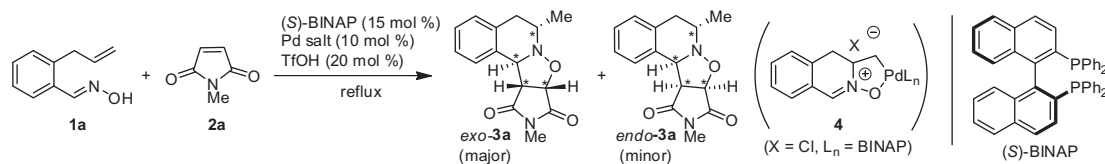


Scheme 1. Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reaction of alkenyl oxime **1** and enedione **2**.

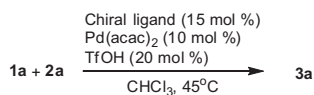
indicated the formation of intermediate **4**.^{4,6} To promote the protonolysis of the Pd–C bond in **4** that lead to the domino process, various Brønsted acids as proton sources were employed. Among the acids tested (HClO₄, HCl_{aq}, *p*-Tol-SO₃H, CF₃CO₂H, *o*-NO₂-C₆H₄-CO₂H, HCO₂H, and AcOH), the addition of TfOH was found to promote the domino process effectively, resulting in the formation of **3a** with 70% yields in the ratio of *exo/endo*-**3a** to 93/7; the *exo*-cycloadduct **3a** was obtained as a major product in 37% enantiomeric excess (ee) (entry 2). Encouraged by these results, we further studied the effects of other reaction conditions such as solvents, Pd salts, a ratio of substrates, and temperature. The use of CHCl₃ as a reaction solvent resulted in the formation of **3a** with 46% ee (entry 4). Chiral Pd complexes prepared from Pd(acac)₂ with (*S*)-BINAP were found to give **3a** in higher enantioselectivity (55% ee, entry 7) than those prepared from other Pd salts. The optimal result (quant, *exo/endo* = 93/7, 56% ee) with

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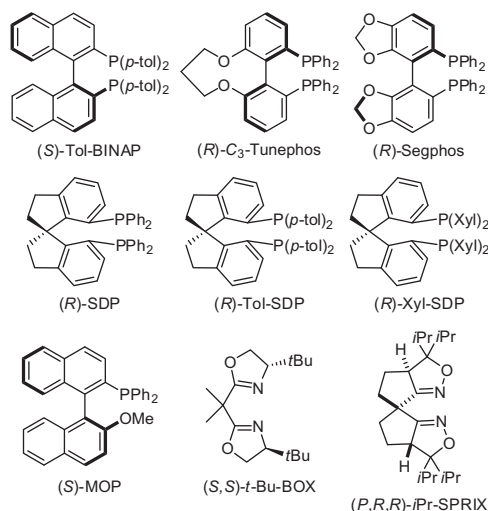
E-mail address: taki@sanken.osaka-u.ac.jp (S. Takizawa).

Table 1
Screening of reaction conditions^a

Entry	Pd salt	Ratio (1a : 2a)	Solvent	Time (h)	Total yields of 3a (%) ^a	Ratio of <i>exo/endo-3a</i> ^b	ee of <i>exo-3a</i> (%) ^b
1	PdCl ₂ (MeCN) ₂	1:1	CH ₂ Cl ₂	24	Trace ^c	—	—
2	PdCl ₂ (MeCN) ₂	1:1	CH ₂ Cl ₂	12	70	93/7	37
3	PdCl ₂ (MeCN) ₂	1:1	THF	6	64	91/9	37
4	PdCl ₂ (MeCN) ₂	1:1	CHCl ₃	6	60	92/8	46
5	PdCl ₂ (PhCN) ₂	1:1	CHCl ₃	6	79	90/10	47
6	PdCl ₂ (COD)	1:1	CHCl ₃	6	85	91/9	46
7	Pd(acac) ₂	1:1	CHCl ₃	6	67	91/9	55
8	Pd(acac) ₂	1:2	CHCl ₃	6	36	92/8	41
9	Pd(acac) ₂	2:1	CHCl ₃	6	83	91/9	46
10 ^d	Pd(acac) ₂	2:1	CHCl ₃	10	Quant	93/7	56

^a Isolated yield.^b Determined by HPLC.^c In the absence of TfOH.^d At 45 °C.**Table 2**
Screening of chiral ligands^a

Entry	Chiral ligand	Time (h)	Total yields of 3a (%) ^a	Ratio of <i>exo/endo-3a</i> (%) ^b	ee of <i>exo-3a</i> (%) ^b
1	(S)-Tol-BINAP	10	94	92:8	46
2	(R)-C ₃ -Tunephos	15	43	92:8	–55 ^c
3	(R)-Segphos	15	Quant	92:8	–58 ^c
4	(R)-SDP	8	72	92:8	62
5	(R)-Tol-SDP	8	Quant	94:6	70
6	(R)-Xyl-SDP	8	Quant	90:10	48
7	(S)-MOP	15	78	93:7	0
8	(S,S)- <i>t</i> -Bu-BOX	12	78	93:7	0
9	(P,R,R)- <i>i</i> -Pr-SPRIX	12	92	90:10	4

^a Isolated yield.^b determined by HPLC.^c Opposite enantiomer was obtained.

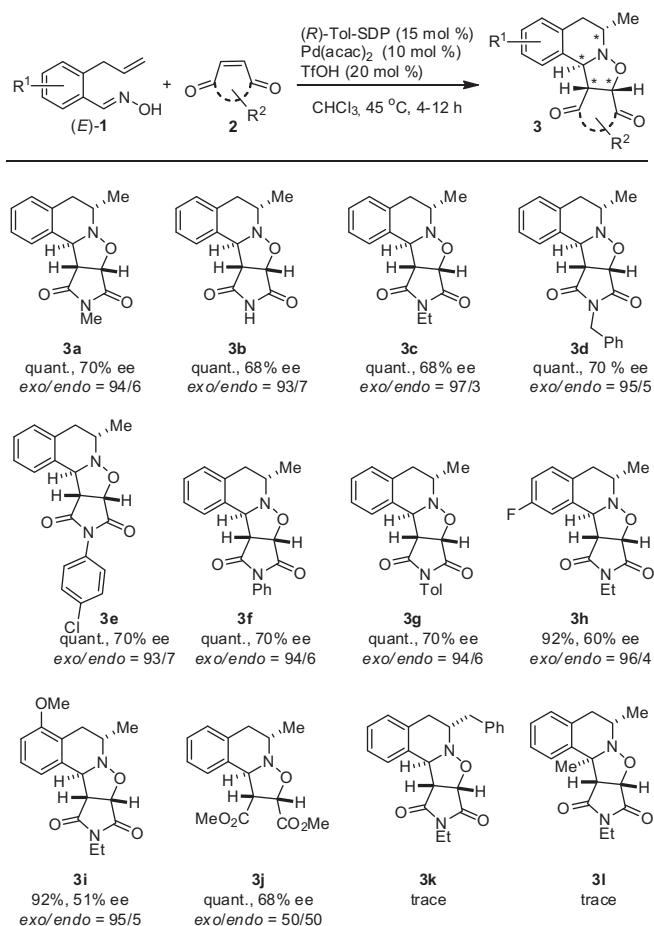
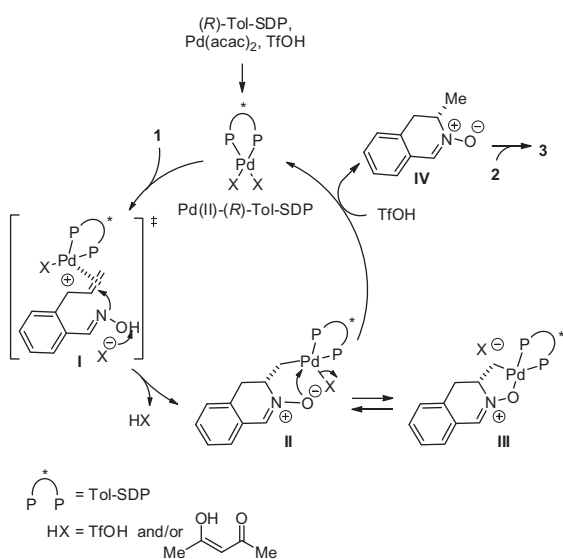
Scheme 2. Substrate scope.¹¹

Figure 1. Plausible reaction mechanism.

Pd(II)–(S)–BINAP was obtained when the reaction of **1a** with **2a** in a ratio of 2 to 1 was performed in CHCl₃ at 45 °C (entry 10).

Next, we focused on searching for an appropriate chiral ligand to construct isoxazolidine **3a** with high optical purity (Table 2). The catalysts derived from Pd(acac)₂ with (S)–Tol–BINAP, (R)–C₃–

Tunephos, or (R)–Segphos were virtually ineffective in improving the stereoselectivity (entries 1–3). Because a larger bite angle of the chiral ligand is suggested to increase the ee value of domino product **3a**,⁷ we shifted our attention to utilizing a chiral spiro-type ligand having a wide bite angle. A spiro-type ligand would provide a geometrically distinct and more rigid chiral pocket than its BINOL-derived counterpart.⁸ As expected, the Pd(acac)₂/(R)–SDP system was found to be efficient in affording good enantioselectivity (62% ee, entry 4). An ee of 70% was achieved with the Pd(acac)₂/(R)–Tol–SDP catalyst (entry 5). The use of (R)–Xyl–SDP possessing bulky substituents on the phosphine region resulted in diminished enantioselectivity (entry 6). Pd(II) complexes of other chiral monodentate phosphine ligands, (S)–MOP, and chiral bidentate nitrogen ligands, such as (S,S)–*t*-BuBOX or (P,R,R)–*i*-Pr–SPRIX,^{8a,9} failed to induce enantioselectivity (entries 7–9). The relatively weakly coordinated ligands might be replaced by the substrate, allowing the background reaction to afford the racemic product.^{8d} In fact, after the addition of (E)–**1a** to the chiral Pd(II) complex derived from SPRIX, only the dissociated free ligand signals were observed in the ¹H NMR spectra.

The scope and limitations of this protocol were then studied by employing the optimized reaction conditions (Pd(acac)₂/(R)–Tol–SDP, 45 °C, CHCl₃) to the enantioselective domino cyclization (Scheme 2). The reaction of alkenyl oxime (E)–**1a** and maleimides **2** bearing various substituents on the nitrogen atom afforded the corresponding tetracycles **3a–3g** with four chiral stereogenic centers in quantitative yields with good stereoselectivities (68–70% ee, exo/endo = 93/7–97/3). Alkenyl oximes (E)–**1h** and (E)–**1i** bearing an electron-withdrawing or electron-donating substituent on the aromatic rings also afforded domino products **3h** and **3i** in excellent yields with moderate enantioselectivities. When using (E)–**1a** and dimethyl maleate for the domino reaction, the corresponding *exo*- and *endo*-cycloadduct **3j** in a ratio of 1:1 were obtained in 68% ees, respectively. No desired product was formed when using **1k**, having a phenyl substituent at the terminal olefin moiety, and ketoxime **1l**,¹⁰ presumably because of the bulky substituents preventing catalyst activation.

A plausible reaction mechanism for the Pd(II)–catalyzed enantioselective domino cyclization/cycloaddition reactions is shown in Figure 1. The initial coordination of the chiral Pd(II)–(R)–Tol–SDP complex with alkenyl oxime **1** led to transition state **I**. The subsequent nucleopalladation of **I** afforded the cyclic intermediate **II** and **III**, thus controlling the enantioselectivity. The protonation of generated Pd(II) intermediate **II** (or **III**) made the releasing catalyst, together with the formation of nitrene **IV**. Finally, 1,3-dipolar cycloaddition of **IV** with **2** gave domino product **3**.

In summary, we have developed a domino cyclization/cycloaddition of alkenyl oximes catalyzed by the chiral Pd(II) complex and TfOH. The use of the (R)–Tol–SDP ligand led to the formation of polycyclic heterocycles having four chiral stereogenic centers in almost quantitative yields with high stereoselectivities. A fine-tuning of the spiro catalysts, investigation into the detailed reaction mechanism, scope, as well as its application to the enantioselective synthesis of biologically active compounds are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.05.070>.

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- Yields of isolated **3**. The ee and ratio of *exo/endo*-**3** were determined by HPLC. Determination of absolute configuration of **3** is in progress.