# Palladium(II)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to 3-Alkenoyl-1,3-oxazolidin-2-ones

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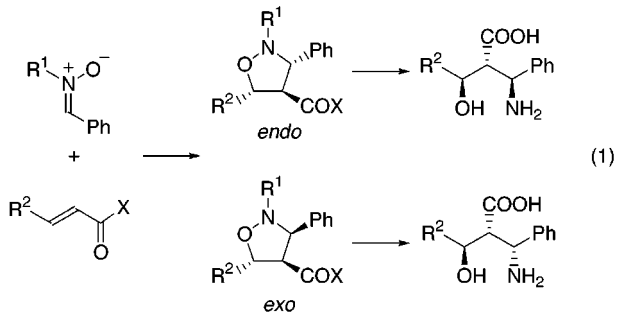
Chiral phosphinepalladium(II)-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated carboxylic acid derivatives has been investigated. In the presence of a catalytic amount of [Pd(NCMe)$_2$\{(*S*)-tolbinap\}](BF$_4$)$_2$ [TolBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl], the reaction of 3-alkenoyl-1,3-oxazolidin-2-ones as dipolarophiles and N-substituted *N*-benzylidenenitrones has been successfully performed to give isoxazolidine derivatives in high yields with high enantioselectivities. For example, 3-((2,5-dimethyl-3-phenylisoxazolidin-4-yl)carbonyl)-1,3-oxazolidin-2-one was obtained from the reaction of *N*-benzylidenemethylamine *N*-oxide and 3-crotonoyl-1,3-oxazolidin-2-one in 89% yield with 60% endo selectivity and 91% ee of the endo isomer. The cycloaddition of *N*-benzylidenebenzylamine *N*-oxide and 3-crotonoyl-1,3-oxazolidin-2-one afforded 3-((2-benzyl-5-methyl-3-phenylisoxazolidin-4-yl)carbonyl)-1,3-oxazolidin-2-one in 94% yield with 93% endo selectivity and 89% ee of the endo isomer. Remarkably, the endo/exo selectivity of the products depended on the N-substituent group of the nitrones. These selectivities were explained using molecular modeling.

## Introduction

Optically active heterocyclic compounds are not only useful in themselves but are also widely employable intermediates for preparing chiral acyclic compounds.[1] In particular, isoxazolidines can be converted to γ-amino alcohols, which are precursors to biologically active compounds such as alkaloids and β-lactam antibiotics[2] (eq 1).




These heterocycles traditionally are prepared from the 1,3-dipolar cycloaddition of nitrones to olefins.[2] Over the past few years, the use of chiral olefins[3] and nitrones[4] has provided for the asymmetric synthesis of isoxazolidine.[5] However, only a few catalytic asymmetric 1,3-dipolar cycloadditions have been reported so far.[5a] Since 1994, very good asymmetric induction has been achieved by Jørgensen,[6] Scheeren,[7] and Inomata[8] using chiral Lewis acids as catalysts under stringently anhydrous conditions. Recently, Jørgensen and Kobayashi reported the same reaction catalyzed by chiral magnesium(II)[9] or ytterbium(III)[10] complexes as stable catalysts in moisture; however, the enantioselectivity depended on the amount of water or the structure of the nitrone. In contrast, late transition metal complexes[11] such as palladium or ru-

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**Table 1. Asymmetric 1,3-Dipolar Cycloaddition of 1a to 2a Catalyzed by Transition Metal−BINAP Complexes[a]**

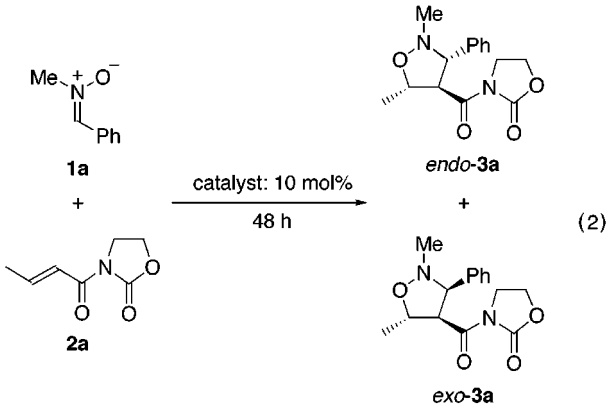
| entry | catalyst | solvent | temp | yield, %[b] | endo/exo[c] | % ee of *endo*-**3a**[d] | % ee of *exo*-**3a**[d] |
|---|---|---|---|---|---|---|---|
| 1 | none | $CHCl_3$ | reflux | 17 | 8:92 | | |
| 2 | **4** | $CHCl_3$ | reflux | 78 | 5:95 | 5 | 4 |
| 3 | **5** | $CHCl_3$ | reflux | 61 | 45:55 | 91 | 25 |
| 4 | **5** | $CH_2Cl_2$ | rt | 9 | 10:90 | 12 | 5 |
| 5 | **5** | $CH_2Cl_2$ | reflux | 34 | 23:77 | 79 | 9 |
| 6 | **5** | $C_6H_6$ | reflux | 50 | 40:60 | 71 | 31 |
| 7 | **5** | $CH_3CN$ | rt | 13 | 7:93 | 3 | 1 |
| 8 | **5** | $CH_3CN$ | reflux | 27 | 26:74 | 1 | 11 |
| 9 | **6** | $CH_2Cl_2$ | reflux | 24 | 11:89 | 23 | 1 |
| 10 | **6** | $C_6H_6$ | reflux | 80 | 10:90 | 1 | 13 |
| 11 | **7** | $CHCl_3$ | reflux | 63 | 47:53 | 91 | 24 |
| 12 | **7** | $C_6H_6$ | reflux | 90 | 27:73 | 66 | 7 |
| 13 | **7** | $CH_3CN$ | reflux | 48 | 15:85 | 15 | 1 |

[a] Reaction conditions: nitrone **1a** (1.0 mmol), olefin **2a** (1.0 mmol), and catalyst (0.1 mmol) were dissolved in a solvent (10 mL), and then the resulting mixture was stirred for 48 h. [b] Based on olefin **2a**. [c] Determined by $^1$H NMR spectroscopy of the reaction mixture. [d] Determined by chiral HPLC using Daicel Chiralcel OJ-R.

thenium can be used even in the presence of water. Herein, we wish to describe the asymmetric 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated carbonyl compounds catalyzed by palladium(II) complexes coordinated with chiral phosphine ligands. A preliminary account of this work has appeared.[12]

## Results and Discussion

**Catalysts and Reaction Conditions.** The late transition metal-catalyzed 1,3-dipolar cycloaddition of *N*-benzylidenemethylamine *N*-oxide (**1a**) and 3-crotonoyl-1,3-oxazolidin-2-one (**2a**) was first investigated because this bidentate olefinic substrate is often used for highly selective asymmetric reactions such as the Diels−Alder reaction[13] (eq 2, Table 1).




The 1,3-dipolar cycloaddition of the nitrone **1a** and the olefin **2a** without catalyst gave the isoxazolidine **3a** with exo selectivity in only 17% yield (Table 1, entry 1). When the complex **4** was used as a catalyst, **3a** was obtained in 78% yield with exo selectivity but without enantioselectivities of both isomers (Table 1, entry 2). Next, the palladium(II) complex **5** was prepared by the reaction of **4** and $AgBF_4$ in an organic solvent, and then the nitrone **1a** and the olefin **2a** were added to the catalyst solution. When chloroform was used as a solvent, **3a** was obtained in 61% yield and the enantioselectivity of *endo*-**3a** drastically increased to 91% ee (Table 1, entry 3). This reaction did not proceed efficiently using $CH_2Cl_2$ as a solvent at room temperature (Table 1, entry 4). However, at reflux, the yield of **3a** was increased with higher endo selectivity and with 79% enantiomeric excess of the endo isomer than at room temperature (Table 1, entry 5). In refluxing benzene, the enantioselectivity of the endo isomer decreased slightly compared to the reaction in chloroform (Table 1, entry 6). In acetonitrile, neither the yield nor the enantioselectivity was favored at either room temperature or under reflux.

**Table 2. Ligand Effect on Palladium(II)-Catalyzed 1,3-Dipolar Cycloaddition of Nitrone 1a and 3-Crotonoyl-1,3-oxazolidine-2-one (2a)[a]**

| entry | ligand | yield, %[b] | endo/exo[c] | % ee of *endo*-**3a**[d] | % ee of *exo*-**3a**[d] |
|---|---|---|---|---|---|
| 1 | **8** | 61 | 27:73 | 9 | 1 |
| 2 | **9** | 59 | 12:88 | 50 | 34 |
| 3 | **10** | 61 | 45:55 | 91 | 25 |
| 4 | **11** | 88 | 57:43 | 89 | 60 |
| 5 | **12** | 65 | 62:38 | 25 | 72 |
| 6 | **13** | 76 | 50:50 | 71 | 48 |

[a] Reaction conditions: nitrone **1a** (1.0 mmol), olefin **2a** (1.0 mmol), $AgBF_4$ (0.2 mmol), and $PdCl_2$(ligand) (0.1 mmol) were dissolved in $CHCl_3$ (10 mL), and then the resulting mixture was stirred for 48 h under reflux. [b] Based on olefin **2a**. [c] Determined by $^1$H NMR spectroscopy of the reaction mixture. [d] Determined by chiral HPLC using Daicel Chiralcel OJ-R.

In the presence of the ruthenium(II) complex **6,** which was efficient for the asymmetric hydrogenation of olefins,[14] the reaction proceeded with exo selectivity, but the enantioselectivities of the products were poor (Table 1, entries 9 and 10).

On the basis of the above results, cationic (*S*)-BINAP-palladium(II) complex **7**, which can be easily prepared by the method in eq 3 and has two acetonitriles as labile ligands, was selected as a catalyst for the asymmetric 1,3-dipolar cycloaddition of **1a** and **2a** (Table 1, entries 11−13). Previously, a chiral phosphinepalladium(II)−nitrile complex such as **7** has been used for the synthesis of chiral alternating α-olefin−carbon monoxide copolymers.[15] Significantly, complex **7** is stable in air and shows excellent solubility in a variety of solvents with the exception of diethyl ether and hexane. Therefore, the catalyst can be conveniently recovered simply by precipitation from the reaction mixture by adding hexane or diethyl ether. When this reaction was performed in chloroform as solvent at refluxing temperature, **3a** was obtained in 63% yield and the enantiomeric excess of *endo*-**3a** was 91% ee, the same as when the catalyst **5** prepared in situ was used (Table 1, entry 11).

Interestingly, the enantioselectivity of the exo product is considerably smaller compared to the enantioselectivity

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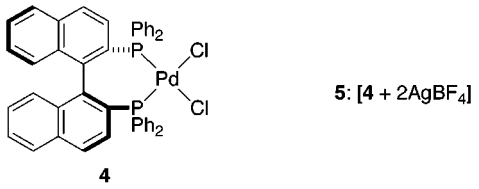
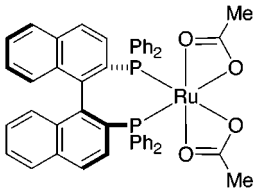
of the endo product in most cases. Thermal reaction of nitrone **1a** and **2a** proceeds with exo selectivity. Consequently, endo product was mainly formed from the catalytic reaction by palladium, while exo product was produced by both thermal and catalytic reactions. That could be the reason for the difference between both isomers in enantioselectivities, though it cannot be excluded that the enantioselectivities of the catalytic reactions giving both isomers are basically different.




**4** **5**: [**4** + 2AgBF$_4$]

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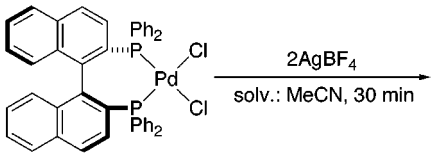


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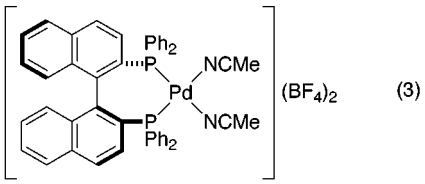
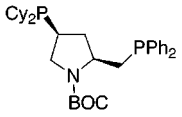



(3)

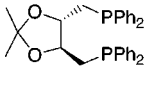
**7**

**Ligand Effect.** Using chloroform as an optimal solvent, to improve the stereoselectivity and the enantioselectivity, the influence of the bidentated chiral-phosphine ligand on this reaction was studied (Table 2). When BCPM (**8**) and (+)-DIOP (**9**) were used instead of (*S*)-BINAP, the product yields were moderate and the enantioselectivities were not satisfactory (Table 2, entries 1 and 2). Employing (*S*)-TolBINAP (**11**) as a ligand

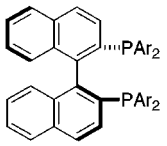
Ligand




**8**: BCPM




**9**: (+)-DIOP




**10**: Ar = Ph : (*S*)-BINAP
**11**: Ar = *p*-Tol : (*S*)-TolBINAP
**12**: Ar = *p*-ClPh : (*S*)-ClBINAP
**13**: Ar = *p*-MeOPh : (*S*)-MeOBINAP

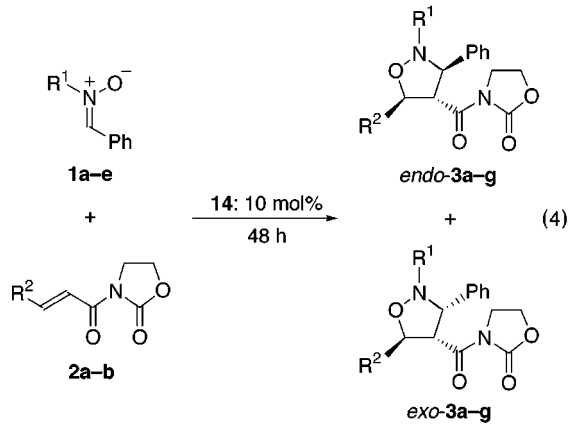
**Table 3. Asymmetric 1,3-Dipolar Cycloaddition of Various Nitrones 1 and Olefins 2 Catalyzed by Palladium(II) Complex 14**[a]

| entry | nitrone | olefin | product | yield, %[b] | endo/exo[c] | % ee of endo product[d] | % ee of exo product[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 89 | 60:40 | 91 | 34 |
| 2 | **1b** | **2a** | **3b** | 94 | 93:7 | 89 | 93 |
| 3[e] | **1c** | **2a** | **3c** | 94 | 28:72 | 54 | 48 |
| 4 | **1d** | **2a** | **3d** | trace | | | |
| 5 | **1e** | **2a** | **3e** | trace | | | |
| 6 | **1a** | **2b** | **3f** | trace | | | |
| 7 | **1b** | **2b** | **3g** | *f* | | | |

[a] Reaction conditions: nitrone **1** (1.2 mmol), olefin **2** (1.0 mmol), and **14** (0.1 mmol) were dissolved in $CHCl_3$ (10 mL), and then the resulting mixture was stirred for 48 h under reflux. [b] Based on olefin **2**. [c] Determined by $^1$H NMR spectroscopy of the reaction mixture. [d] Determined by chiral HPLC using Daicel Chiralcel OJ-R or Daicel Chiralcel OD-H (see Experimental Section). [e] This reaction was performed in $CH_2Cl_2$ (10 mL), and then the resulting mixture was stirred for 48 h under reflux. [f] No reaction.

increased both the yield (88%) and the endo selectivity of **3a**, in which reaction the enantiomeric excess of the endo isomer was 89% and that of the exo isomer was improved to 60% ee (entry 4). Other BINAP derivatives were used as a ligand, but the stereo- and enantioselectivities of the products were not improved (Table 2, entries 5 and 6).

**The Reaction of Various Nitrones and 3-Alkenoyl-1,3-oxazolidin-2-ones.** On the basis of these results, cationic (*S*)-TolBINAP-palladium(II) nitrile complex **14** was prepared and used as a catalyst for this asymmetric 1,3-dipolar cycloaddition. The results of the asymmetric 1,3-dipolar cycloaddition of various nitrones **1a**−**e** and olefins **2a**−**b** (eq 4) are presented in Table 3.




(4)

**1a**: $R^1$ = Me **2a**: $R^2$ = Me
**1b**: $R^1$ = Bn **2b**: $R^2$ = Ph
**1c**: $R^1$ = Ph
**1d**: $R^1$ = $^t$Bu
**1e**: $R^1$ = Tr

**3a**: $R^1$ = $R^2$ = Me
**3b**: $R^1$ = Bn, $R^2$ = Me
**3c**: $R^1$ = Ph, $R^2$ = Me
**3d**: $R^1$ = $^t$Bu, $R^2$ = Me
**3e**: $R^1$ = Tr, $R^2$ = Me
**3f**: $R^1$ = Me, $R^2$ = Ph
**3g**: $R^1$ = Bn, $R^2$ = Ph

When the reaction of **1a** and **2a** was catalyzed by preformed **14**, isoxazolidine **3a** was obtained in a higher yield than in the reaction using the catalyst prepared in situ. In the reaction of *N*-benzyl nitrone **1b** and **2a**, the isoxazolidine **3b** was obtained in 94% yield with high endo selectivity and with excellent enantioselectivity for both isomers. The absolute configuration of *endo*-**3b** was

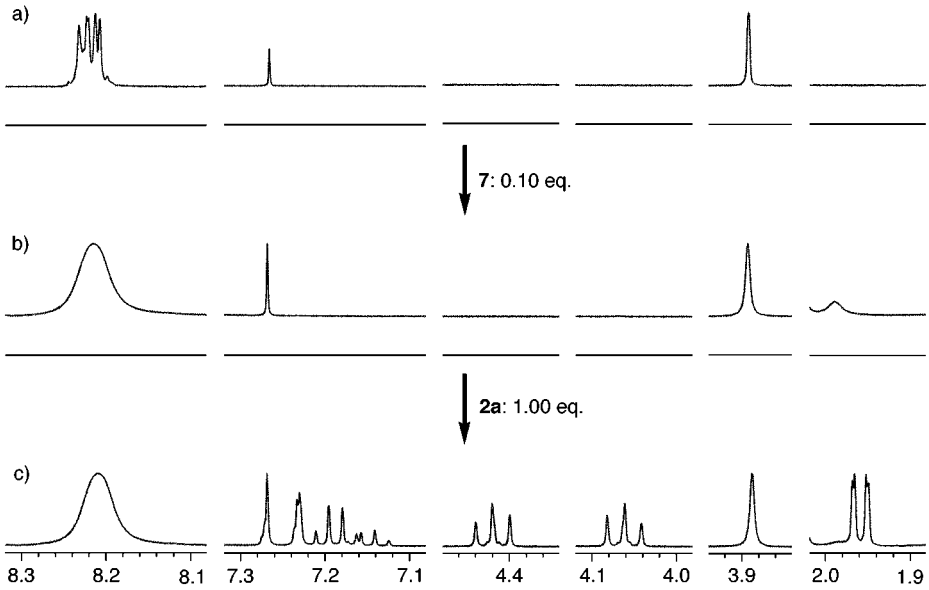
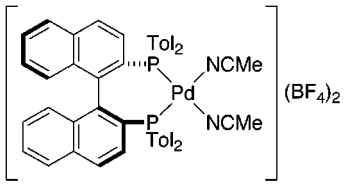



**Figure 1.** $^1$H NMR spectra (400 MHz, $CDCl_3$) of a mixture of nitrone **1a**, palladium(II) complex **7**, and olefin **2a**. (a) The nitrone **1a** (0.05 mmol) was dissolved in 0.5 mL of $CDCl_3$. (b) The complex **7** (0.005 mmol) was added to a mixture in (a). (c) The olefin **2a** (0.05 mmol) was added to a mixture in (b).

determined as 3*R*,4*S*,5*R*.[16] On the other hand, the reaction of *N*-phenyl nitrone **1c** proceeded with high exo




**14**

selectivity and with moderate enantioselectivity for both exo and endo isomers. The absolute configuration of *exo*-**3c** could not be determined, and that of *endo*-**3c** was determined as 3*R*,4*S*,5*R*.[17] Using the larger *N*-*tert*-butyl nitrone **1d** or *N*-trityl nitrone **1e**, only small amounts of the isoxazolidines **3d** and **3e** were obtained. Similarly, the use of 3-cinnamoyl-1,3-oxazolidin-2-one (**2b**) resulted in only trace amounts of cycloaddition product.

**Reaction Mechanism.** For mechanistic considerations, two series of $^1$H NMR analyses were presented in Figures 1 and 2. In Figure 1, aromatic and methine protons (8.18−8.26 ppm) of nitrone **1a** became broader in the presence of 10 mol % catalyst **7** (b) than in the absence of complex (a). This broadening indicates that some interaction occurred between the nitrone **1a** and the complex. Addition of olefin **2a** to the above mixture of **1a** and **7** in $CDCl_3$ did not make any change in their signals. Next, to a solution of olefin **2a** was added the complex in three portions, and then the nitrone **1a** was added to this mixture successively. The results are listed in Figure 2. All proton signals of the olefin **2a** became broad by adding complex (Figure 2a−d). These broadenings also indicate that the olefinic substrate interacted quickly with the complex. Interestingly, by addition of nitrone **1a** to the above mixture broad signals of the olefin became sharp, like the signals of the olefin alone. These observations show that both substrates can coordinate to the palladium center and the nitrone **1a** coordinates to the complex **7** more strongly than the olefin **2a**. That is to say, most of the palladium species could be formulated as **A** at room temperature. At room temperature, the palladium complex showed virtually no catalytic activity as mentioned above (Figure 3). If elevated temperature accelerates the transformation between **A** and **B**, **B** therefore must react with nitrone more smoothly than the free olefin. For obtaining some evidence for this prediction, an $^1$H NMR study at elevated temperature was attempted. But all signals including TMS became broadened at 40−60 °C. The structure **B** cannot be confirmed by any experimental way, but there are several examples in which Lewis acids are thought to activate olefins such as **2a** through bidentate coordination in 1,3-dipolar cycloaddition reactions.[9a,18]

**Origin of Stereo- and Enantioselectivity.** The endo adduct **3b** was selectively obtained in the reaction of *N*-benzyl nitrone **1b** and **2a**. On the other hand, *exo*-**3c** was the major product from **1c**. Such differences in selectivity could be explained by the steric effect in the transition state between the intermediate **B** and the two nitrones (Figures 4−6). From the model the *Si* face of the olefin's α-carbon in **B** is not covered by any atoms or groups in **B**, while the *Re* face of the olefin's α-carbon in **B** is partially shaded by the aryl substituent on phosphorus atom of TolBINAP. That is to say, the *Si* face of the coordinated olefin's α-carbon is less sterically hindered (top view) than the *Re* face (bottom view). For *N*-benzyl nitrone **1b**, endo approach to the *Si* face of olefin's α-carbon in **B** seems to be the most favored, and the exo approach to the *Si* face creates some steric repulsion between the aryl moiety on phosphorus atom

(16) The optical rotation of (+)-*endo*-**3b** was reported as $[\alpha]_D = +5.5$ (51% ee), and the absolute configuration of the isoxazolidine ring of (+)-*endo*-**3b** was assigned as 3*S*,4*R*,5*S* in the literature (see ref 6c).

(17) The optical rotation of (−)-*endo*-**3c** was reported as $[\alpha]_D = -13.1$ (75% ee), and the absolute configuration of the isoxazolidine ring of (−)-*endo*-**3c** was assigned as 3*S*,4*R*,5*S* in the literature (see ref 9a).

(18) Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889−7892.

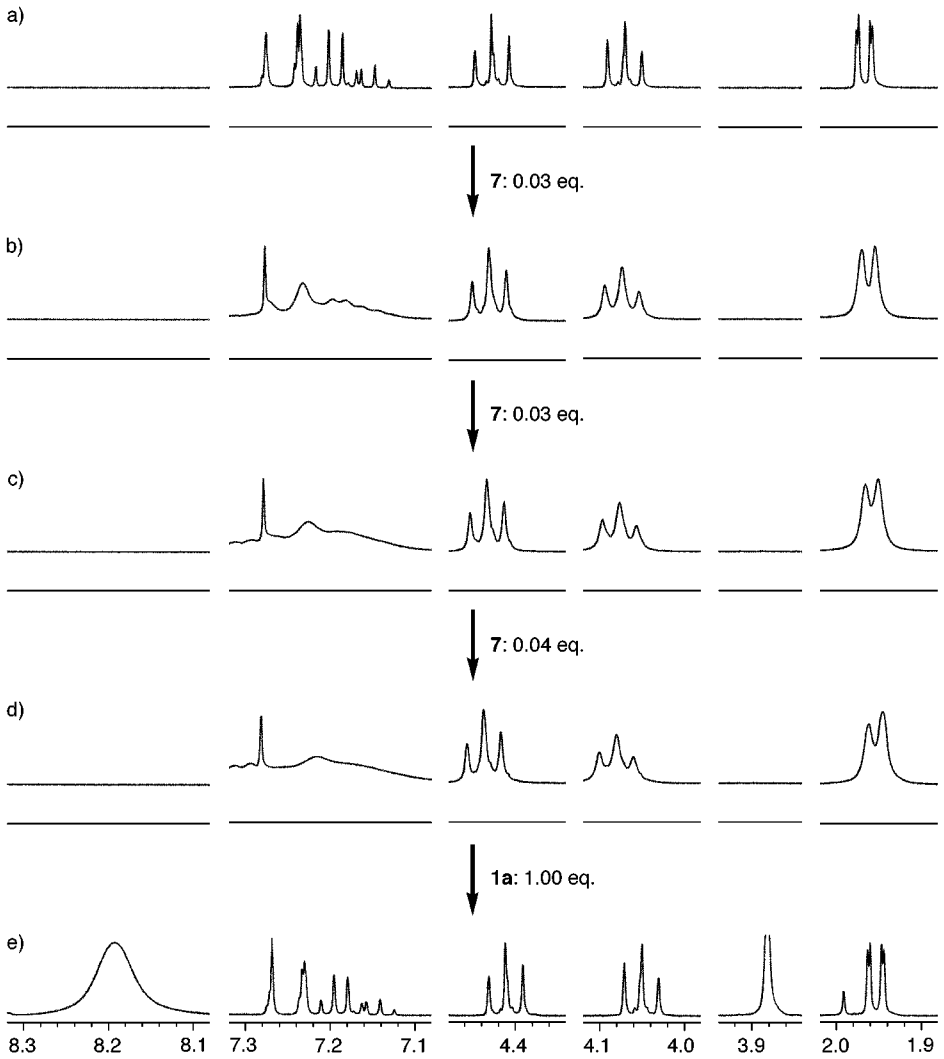



**Figure 2.** $^1$H NMR spectra (400 MHz, $CDCl_3$) of a mixture of olefin **2a**, palladium(II) complex **7**, and nitrone **1a**. (a) The olefin **2a** (0.05 mmol) was dissolved in 0.5 mL of $CDCl_3$. (b) The complex **7** (0.0015 mmol) was added to a mixture in (a). (c) The complex **7** (0.0015 mmol) was further added to a mixture in (b). (d) The complex **7** (0.0020 mmol) was further added to a mixture in (c). (e) The nitrone **1a** (0.05 mmol) was added to a mixture in (d).

and the benzyl group on nitrone (dotted atoms in Figure 5). Meanwhile, the phenyl substituent of *N*-phenyl nitrone **1c** prevents the endo contact on the *Si* face of the olefin's α-carbon in **B** (dotted atoms in Figure 6). Consequently, the exo attack for the *Si* face of the olefin's α-carbon in **B** is thought to be the most preferential.

## Conclusion

In conclusion, the 1,3-dipolar cycloaddition of nitrone **1** to olefin **2** was catalyzed by a cationic TolBINAP-palladium(II) complex **14** resulting in moderate to excellent yields and good enantioselectivities for the resulting isoxazolidine derivatives. To the best of our knowledge, this is the first example of a late transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition. Further investigation of this catalytic system is currently in progress.

## Experimental Section

**General Methods.** The $^1$H and $^{31}$P NMR spectra were recorded at 400 and 160 MHz, respectively. Chemical shifts for NMR are reported in ppm downfield from TMS as an internal standard for $^1$H and 85% $H_3PO_4$ as an external standard for $^{31}$P. Melting points were not corrected. Solvents were dried using standard procedures[19] and distilled under Ar. Nitrones **1a**,[20] **1b**,[21] **1c**,[22] and **1d**[23] and 3-alkenoyl-1,3-oxazolidin-2-ones **2a**[24] and **2b**[24] were prepared according to the procedures in published literature. Nitrone **1e** was used as supplied without further purification.

**Preparation of (*S*)-TolBINAP-Palladium(II) Nitrile Complex 14.** Silver tetrafluoroborate (1.23 g, 6.3 mmol) under argon atmosphere was added to a solution of (*S*)-TolBINAP-palladium dichloride[25] (2.56 g, 3 mmol) in acetonitrile (60 mL). The solution was stirred at room temperature. After being stirred for 30 min, the resulting mixture was filtered and concentrated to ca. 5 mL, and then the solution was slowly

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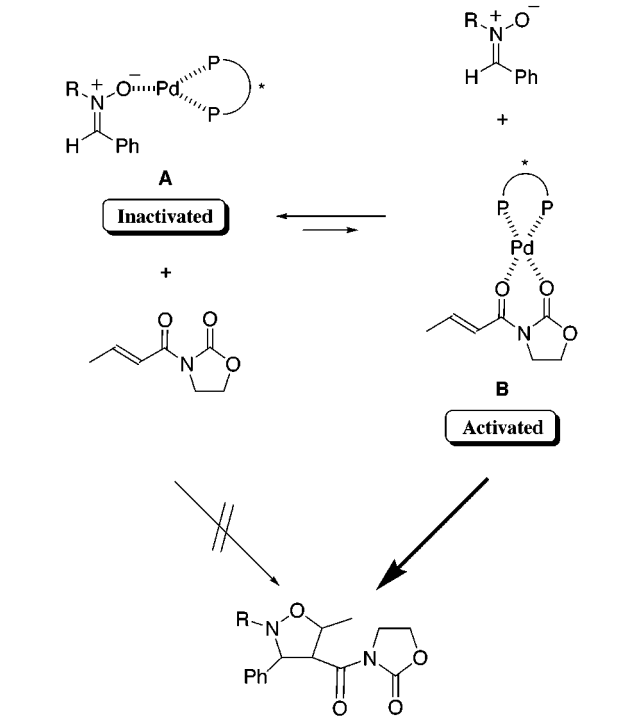


**Figure 3.** Plausible mechanism.

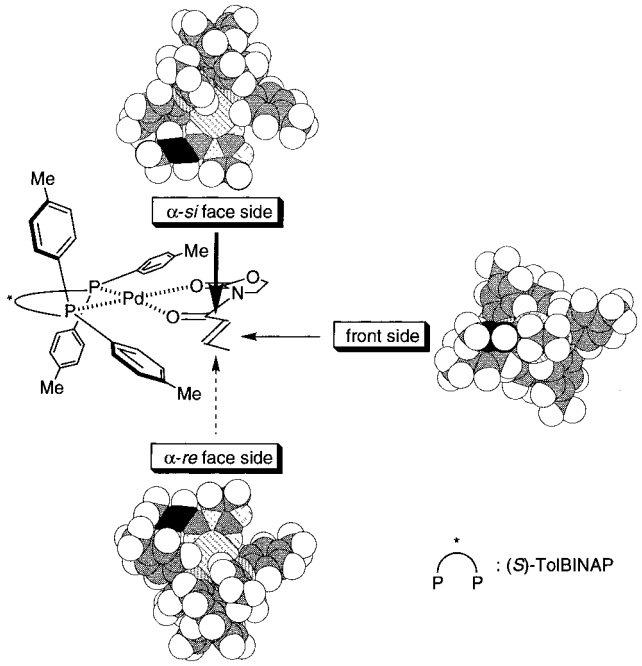


**Figure 4.** Space-filling model of (*S*)-TolBINAP-Pd(II)-**2a** complex (olefinic carbons as dark areas).

added into ether (50 mL). The light yellow precipitate was filtered and dried in vacuo. The obtained yellow solid was identified as **4** by NMR and used directly as a catalyst: yield of **14** 2.30 g (63%); mp 123.0 °C dec; $^1$H NMR ($CDCl_3$) $\delta$ 2.05 (s, 6H), 2.41 (s, 6H), 3.25 (br, 6H), 6.70 (d, $J$ = 8.4 Hz, 4H), 7.17−7.73 (m, 24H); $^{31}$P NMR ($CDCl_3$) $\delta$ 32.52 (s).

**General Procedure for Palladium(II)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrones 1 with Olefins 2**. In a 50 mL three-necked reaction vessel equipped with a condenser and a magnetic stirring bar were placed **1** (1.2 mmol), **2** (1.0 mmol), and **4** (104 mg, 0.1 mmol) under argon atmosphere. To this was added $CHCl_3$ (10 mL) by syringe. The resulting mixture was stirred under reflux for 48 h. The yields of the isoxazolidines **3** were determined by $^1$H NMR spectroscopy of the reaction mixture using the ratio of the integral value between the signal of **2a** ($\delta$ 1.97 (dd, $J$ = 6.2, 1.0 Hz, 3H, Me)) and 5-Me of *endo*- and *exo*-**3** (see below). After addition of silica gel (ca. 1 g) to the solution and concentration of the mixture in vacuo, the residue was extracted with diethyl ether (20 mL) by Soxhlet extractor for 6 h. Removal of the solvent followed by silica gel column chromatography gave *endo*-**3** and *exo*-**3**. The results of 1,3-dipolar cycloaddition of **1a**−**c** with **2a** and **2b** are given in Table 3. Spectral and analytical data of **3a**−**c** are listed below.

**3-((2,5-Dimethyl-3-phenylisoxazolidin-4-yl)carbonyl)-1,3-oxazolidin-2-one (3a).**[26] Yield: 89%. *endo*-**3a**: viscous colorless liquid; $[\alpha]^{20}_D$ = +10.0 (*c* 1.0, $CHCl_3$, ee 87%); $^1$H NMR ($CDCl_3$) $\delta$ 1.53 (d, $J$ = 6.0 Hz, 3H, 5-Me), 2.59 (s, 3H, *N*-Me), 3.88−3.99 (m, 2H), 4.10 (d, $J$ = 7.6 Hz, 1H), 4.22−4.34 (m, 3H), 4.54 (dd, $J$ = 4.8, 7.6 Hz, 1H), 7.20−7.33 (m, 5H). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.00; H, 6.26; N, 9.61. *exo*-**3a**: white crystal; mp 125.2−133.5 °C; $[\alpha]^{20}_D$ = −20.0 (*c* 1.0, $CHCl_3$, ee 34%); $^1$H NMR ($CDCl_3$) $\delta$ 1.30 (d, $J$ = 6.0 Hz, 3H, 5-Me), 2.54 (s, 3H, *N*-Me), 2.98−3.04 (m, 1H), 3.50−3.65 (m, 2H), 3.95 (d, $J$ = 10.8 Hz, 1H), 4.03 (dt, $J$ = 4.8, 8.4 Hz, 1H), 4.33 (dd, $J$ = 4.8, 10.8 Hz, 1H), 4.85 (qd, $J$ = 6.0, 8.4 Hz, 1H), 7.21−7.28 (m, 5H). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.88; H, 6.25; N, 9.61. The endo/exo ratio was determined by $^1$H NMR spectroscopy using the integral ratio of each 5-Me protons of **3a** in the reaction mixture. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Daicel Chiralcel OJ-R, mobile phase: methanol/water = 60:40, detector: UV 220 nm, flow rate: 0.5 mL/min, *endo*-**3a**: $t_R$ = 64.4 (minor) and 72.6 min (major), *exo*-**3a**: $t_R$ = 24.0 (major) and 28.5 min (minor)).

**3-((2-Benzyl-5-methyl-3-phenylisoxazolidin-4-yl)carbonyl)-1,3-oxazolidin-2-one (3b)**. Yield: 94%. These products were identified by comparison of their $^1$H NMR signals with those in the literature.[6a] *endo*-(3*R*,4*S*,5*R*)-**3b**: viscous colorless liquid; $[\alpha]^{20}_D$ = −11.0 (*c* 1.0, $CHCl_3$, ee 83%) (lit.[6c] $[\alpha]_D$ = +5.5 (*c* 1.0, $CHCl_3$, ee 51%)). *exo*-**3b**: white crystal; mp 105.0−112.1 °C; $[\alpha]^{20}_D$ = −33.0 (*c* 1.0, $CHCl_3$, ee 89%) (lit.[6a] $[\alpha]_D$ = +15.0 (*c* 1.0, $CHCl_3$, ee 27%)). The endo/exo ratio was determined by $^1$H NMR spectroscopy using the integral ratio of each 5-Me protons (*endo*-**3b**: 1.59 (d, $J$ = 6.0 Hz, 3H), *exo*-**3b**: 1.33 (d, $J$ = 6.0 Hz, 3H)) of **3b** in the reaction mixture. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H; *endo*-**3b**: mobile phase: *n*-hexane/2-propanol = 80:20, detector: UV 220 nm, flow rate: 0.3 mL/min, $t_R$ = 39.6 (3*S*,4*R*,5*S*) and 59.8 min (3*R*,4*S*,5*R*); *exo*-**3b**: mobile phase: *n*-hexane/2-propanol = 85:15, detector: UV 220 nm, flow rate: 0.3 mL/min, $t_R$ = 29.9 (major) and 34.3 min (minor)).

**3-((5-Methyl-2,3-diphenylisoxazolidin-4-yl)carbonyl)-1,3-oxazolidin-2-one (3c)**. Yield: 94%. These products were identified by comparison of their $^1$H NMR signals with those in the literature.[6a] *endo*-(3*R*,4*S*,5*R*)-**3c**: viscous light yellow liquid; $[\alpha]^{20}_D$ = +9.0 (*c* 1.0, $CHCl_3$, ee 54%) (lit.[9a] $[\alpha]_D$ = −13.1 (*c* 1.0, $CHCl_3$, ee 75%)). *exo*-**3c**: viscous light yellow liquid; $[\alpha]^{20}_D$ = −10.0 (*c* 1.0, $CHCl_3$, ee 39%) (lit.[6a] $[\alpha]_D$ = +11.9 (*c* 1.0, $CHCl_3$, ee 60%)). The endo/exo ratio was determined by $^1$H NMR spectroscopy using the integral ratio of each 5-Me proton (*endo*-**3c**: 1.54 (d, $J$ = 6.0 Hz, 3H), *exo*-**3c**: 1.45 (d, $J$ = 6.0 Hz, 3H)) of **3c** in the reaction mixture. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H; *endo*-**3c**: mobile phase: *n*-hexane/2-propanol = 90:10, detector: UV 220 nm, flow rate: 0.3 mL/min, $t_R$ = 98.9 (3*R*,4*S*,5*R*) and 130.7 min (3*S*,4*R*,5*S*); *exo*-**3c**: mobile phase: *n*-hexane/2-propanol = 90:10, detector: UV 254 nm, flow rate: 0.3 mL/min, $t_R$ = 41.7 (major) and 44.1 min (minor)).

(26) Identification of the endo/exo isomers was performed on the basis of their $^1$H NMR spectra by coupling constants as well as NOE analysis (see ref 12).

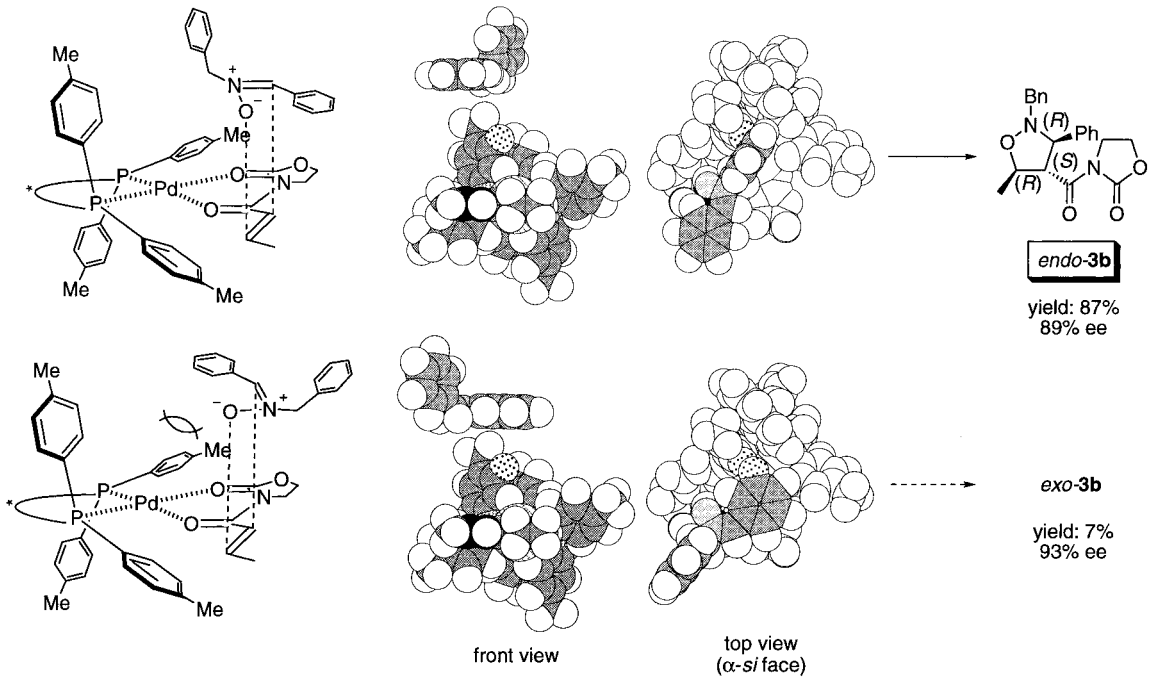


**Figure 5.** Proposed exo and endo approach of nitrone **1b** for intermediate **B**.

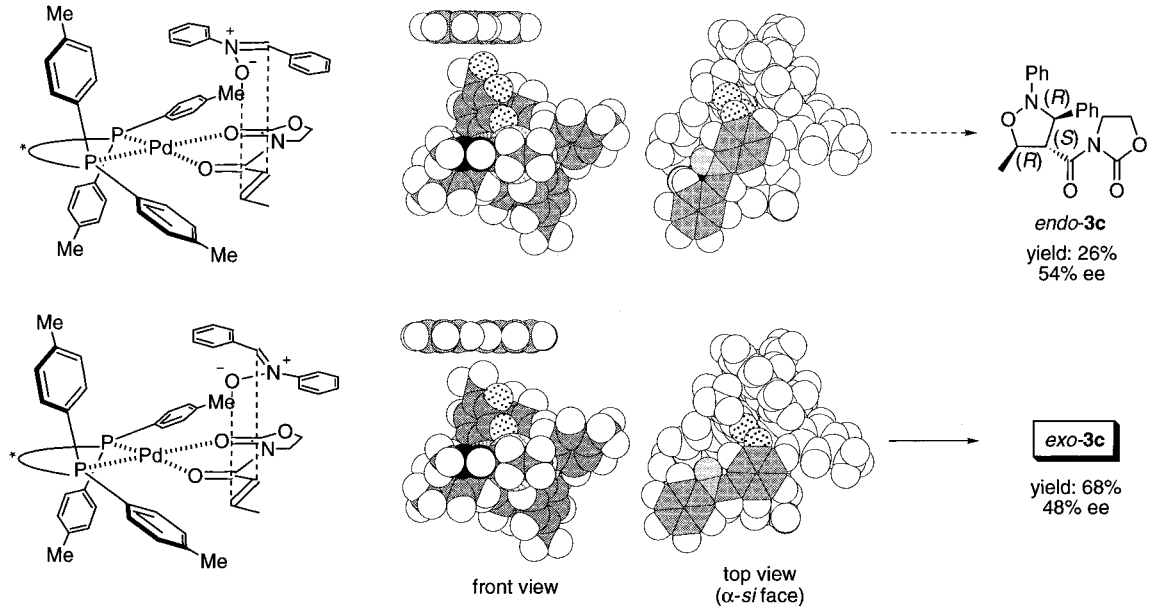


**Figure 6.** Proposed exo and endo approach of nitrone **1c** for intermediate **B**.

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**Supporting Information Available:** HPLC charts of racemates and reaction mixtures and $^1$H NMR and IR spectra of both endo and exo isomers of **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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