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Palladium–Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to Olefins

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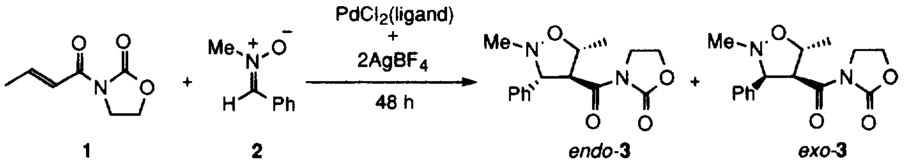
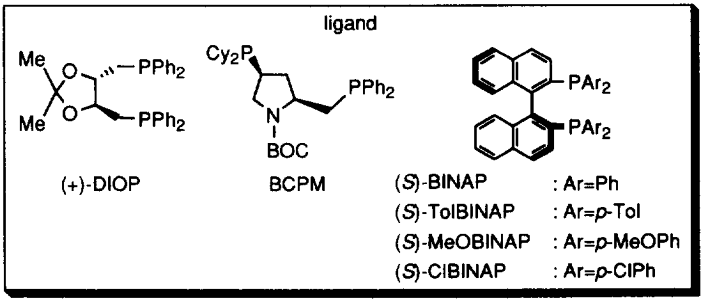
Abstract: *Asymmetric 1,3-dipolar cycloaddition of nitrone 2 to olefin 1 was catalyzed by chiral phosphine–palladium complexes to give isoxazolidine 3 in high yield with high enantioselectivity up to 91% ee.* Copyright © 1996 Elsevier Science Ltd

1,3-Dipolar cycloaddition is a useful method for the synthesis of five-membered heterocyclic compounds.[1] In particular, isoxazolidines, which are obtained by the reaction of nitrones with olefins, can be converted into aminoalcohols, precursors to biologically important alkaloids.[1] Asymmetric 1,3-dipolar cycloadditions could directly give optically active products. Although chiral nitrones or olefins have been utilized for such purpose,[2,3] a few asymmetric 1,3-dipolar cycloaddition reactions by chiral catalysts have been reported so far, in which Lewis acids with chiral ligands were employed as catalysts.[4,5] In these reactions, the catalysts were quite sensitive to a small amount of water. Usually, late transition metal complexes can be used in the presence of water and are handled easily. Here, we wish to describe 1,3-dipolar cycloaddition of 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one (**1**)[6] with *N*-benzylidenemethylamine *N*-oxide (**2**)[7] catalyzed by a Pd(II) complex coordinated by chiral phosphine ligands.[8]





While the 1,3-dipolar cycloaddition without catalyst gave **3** *exo*-selectively in only 17% yield (Table 1, entry 1), a cationic palladium complex was found to accelerate the reaction and showed the best catalytic activity among the complexes used. So, cationic Pd(II) complexes bearing chiral phosphine ligands were selected as catalysts. A dicationic Pd–chiral phosphine complex was prepared by the reaction of $PdCl_2$(ligand) and $AgBF_4$ in a solvent, and then the olefin **1** and the nitrone **2** were added to the solution. Stirring of the resulting mixture for 48 h at appropriate temperature gave the isoxazolidine **3** as a mixture of *endo* and *exo* forms.[9] Typical results are summarized in Table 1. The Pd–BINAP complex did not work efficiently as a catalyst at room temperature (entries 2 and 6). At reflux temperature, better yields, higher *endo*-selectivities, and over 71% enantiomeric excesses (*endo*-isomer) of the products were obtained (entries 3, 4 and 5).[10] The best enantioselectivity (91% *ee*) using the Pd–BINAP catalyst was accomplished in $CHCl_3$ at reflux temperature. When (+)-DIOP and BCPM were used instead of BINAP, yields of the product were moderate but enantioselectivities were not satisfactory (entries 8 and 9). Employing (*S*)-TolBINAP as a ligand increases both yield (88%) and *endo*-selectivity (entry 10), in which enantiomeric excess of the *endo*-isomer was similar (89%) and that of the *exo*-isomer was improved up to 60%, much better than in reactions using BINAP.

Table 1. Asymmetric 1,3-dipolar cycloaddition of **1** to **2** with Pd–chiral phosphine complexes[a]

Entry	Ligand	Solvent	Temp.	Yield: %[b]	*endo*/*exo*[c]	*ee*: %[d] *endo*/*exo*
1	None	$CHCl_3$	reflux	17	8/92	——
2	(*S*)-BINAP	CH_2Cl_2	r.t.	9	10/90	12/5
3	(*S*)-BINAP	CH_2Cl_2	reflux	34	23/77	79/9
4	(*S*)-BINAP	C_6H_6	reflux	50	40/60	71/31
5	(*S*)-BINAP	$CHCl_3$	reflux	61	45/55	91/25
6	(*S*)-BINAP	CH_3CN	r.t.	13	7/93	3/ 1
7	(*S*)-BINAP	CH_3CN	reflux	27	26/74	1/11
8	(+)-DIOP	$CHCl_3$	reflux	59	12/88	50/34
9	BCPM	$CHCl_3$	reflux	61	27/73	9/1
10	(*S*)-TolBINAP	$CHCl_3$	reflux	88	57/43	89/60
11	(*S*)-MeOBINAP	$CHCl_3$	reflux	76	50/50	71/48
12	(*S*)-ClBINAP	$CHCl_3$	reflux	65	62/38	25/72

a) Reaction conditions: olefin **1** (1.0 mmol), nitrone **2** (1.0 mmol), $PdCl_2$(ligand) (0.1 mmol) and $AgBF_4$ (0.2 mmol) were dissolved in a solvent (10 ml), and the resulting mixture was stirred for 48 h.

b) Based on olefin **1**.

c) Determined by ^{1}H-NMR.

d) Determined by HPLC (Daicel Chiralcel OJ-R).

Since the ^{1}H-NMR study[11] indicates that the nitrone **2** coordinates to Pd(II) more strongly than the olefin **1**, most of the Pd species could be formulated as A at room temperature, where the palladium complex showed almost no catalytic activity as mentioned above. If elevated temperature can accelerate transformation between A and B, B apparently reacts with nitrone more smoothly than the non-coordinated olefin, because there are several examples where Lewis acids are thought to activate olefins such as **1** through bidentate coordination in 1,3-dipolar cycloaddition.[4, 12]

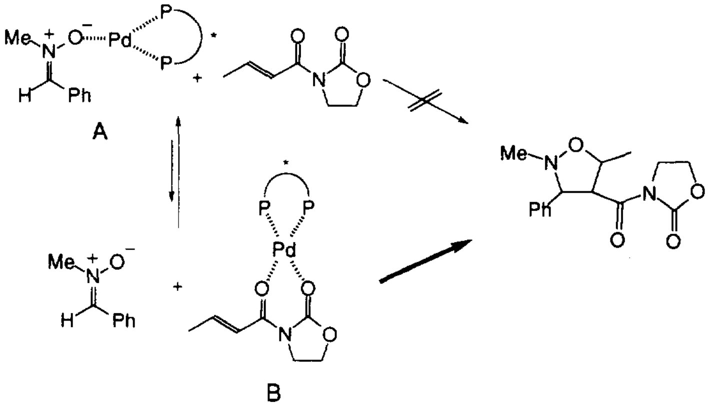


Fig.1

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

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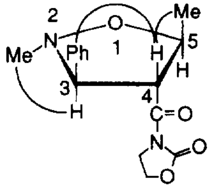
8) For the chiral phosphine ligands used and their abbreviations, see: a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. b) *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden-Penne, J., Ed.; Wiley: New York, 1995.

9) Identification of *endo*/*exo*-isomers was performed on the basis of ^{1}H NMR spectra by coupling constants as well as NOE analysis. a) Coupling constants are shown below: Huisgen, R.; Hauck, H.; Seidl, H.; Burger, M. *Chem. Ber.*, **1969**, *102*, 1117–1128. b) NOESY spectra of both isomers show cross peaks by NOE enhancement described below.

endo-**3**. mp 122.0–123.0 °C (racemic). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.53 (d, J = 6.0 Hz, 3H), 2.59 (s, 3H), 3.88-3.99 (m, 2H), 4.10 (d, J = 7.6Hz, 1H), 4.22-4.34 (m, 3H), 4.54 (dd, J = 4.8, 7.6 Hz, 1H), 7.20-7.33 (m, 5H). IR (KBr): 2900, 1770, 1690, 1380, 1300, 1210, 1110, 755, 700 cm^{-1}.

exo-**3**. mp 137.0–138.0 °C (racemic). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.30 (d, J = 6.0 Hz, 3H), 2.54 (s, 3H), 2.98-3.04 (m, 1H), 3.50-3.65 (m, 2H), 3.95 (d, J = 10.4 Hz, 1H), 4.00-4.06 (m, 1H), 4.33 (dd, J = 8.6, 10.4 Hz, 1H), 4.85 (qd, J = 6.0, 8.6 Hz, 1H), 7.21-7.28 (m, 5H). IR (KBr): 2850, 1765, 1685, 1370, 1280, 1200, 1130, 1085, 1030, 700 cm^{-1}.



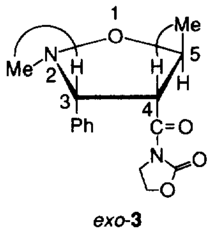
endo-**3**

Coupling constants

$J_{H3,H4}$ = 7.6 Hz
$J_{H4,H5}$ = 4.8 Hz

NOE cross peaks

H4 ⟷ 5-Me
H4 ⟷ 3-Ph
H3 ⟷ 2-Me



exo-**3**

Coupling constants

$J_{H3,H4}$ = 10.4 Hz
$J_{H4,H5}$ = 8.6 Hz

NOE cross peaks

H4 ⟷ 5-Me
H3 ⟷ 2-Me

10) Enantiomeric excesses were determined by HPLC analysis using chiral column (Daicel chiralcel OJ-R, eluent: methanol : water = 3 : 2, detector: UV 220 nm, flow rate: 0.5 ml/min., *endo*-**3**: t_R = 64.4 and 72.6 min., *exo*-**3**: t_R = 24.0 and 28.5 min).

11) To a solution of **1** in CDCl$_3$ was added [Pd((*S*)-BINAP)(MeCN)$_2$](BF$_4$)$_2$ (up to 0.12 eq. to **1**) in three portions. In the course of this addition, all signals of **1** became broad in NMR spectra and then they returned to the original shape after addition of **2** (1.0 eq. to **1**) to the above mixture.

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