Pd-Catalyzed Diastereo- and Enantioselective [3+2]-Cycloaddition Reaction of Vinyl Epoxide with Nitroalkenes

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Abstract: A diastereoselective and enantioselective [3+2]-cycloaddition reaction of vinyl epoxide and nitroalkenes has been developed using Pd/1,1'-ferrocene-*P*,*N*-ligand, providing substituted tetrahydrofurans in high yields and with high diastereo- and enantioselectivities.

Key words: vinyl epoxide, nitroalkene, palladium, asymmetric catalysis, [3+2] cycloaddition

The metal-catalyzed [3+2] cycloaddition reaction of vinyl epoxides,1 aziridines,2 and cyclopropanes bearing electron-withdrawing groups,³ with activated olefins constitutes a powerful approach to construct substituted tetrahydrofurans, pyrrolidines, and cyclopentanes. The use of isocyanates,⁴ carbodiimides,⁵ aldehydes,⁶ and carbon dioxide^{2e} as acceptors was also documented to afford five-membered heterocycles. However, the catalytic asymmetric version of such cycloaddition reaction is very limited.^{3d,6b,c} The asymmetric [3+2] cycloaddition of vinyl oxirane with activated olefins is unknown. Herein, we report our preliminary results of palladium-catalyzed diastereoselective and enantioselective [3+2] cycloaddition of vinyl oxiranes with nitroalkenes. Substituted tetrahydrofurans,⁷ commonly occurring subunits in a broad array of natural products and other biologically active molecules,⁸ bearing three continuous stereocenters were afforded in a diastereo- and enantioselective manner.

Our initial study commenced on the reaction of 1-vinyl-1methyl oxirane (1a) and β -nitrostyrene (2a) in the presence of Pd₂(dba)₃·CHCl₃ and benzylic substituted ligand L1 in THF. Delightfully, 2,3-*trans*-3,4-*cis*-tetrahydrofuran **3a** was obtained as a predominant diastereomer in 70% yield, >20:1 dr, and 31% ee (Scheme 1, equation 1; Table 1, entry 1). The relative configuration of **3a** was assigned by an NOE experiment. The investigation of impact of solvent on the reaction revealed that the reaction in tetrahydrofuran (THF) and dimethoxyethane (DME) provided better enantioselective excess although that in diethyl ether, dioxane, toluene, and methyl *tert*-butyl ether

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(TBME) gave similar results with respect to the yields and the diastereoselectivity (Table 1, entries 1 and 2 vs. 3–6). A remarkable improvement in enantioselectivity was observed using acetonitrile (MeCN) and dichloromethane (CH₂Cl₂) as solvent (Table 1, entries 7 and 8). However, the yield of the product **3a** was very low in these two solvents, which might be attributed to the polymerization of β -nitrostyrene as we observed the formation of precipitate. Using THF–MeCN mixtures as reaction media still afforded **3a** in very low yield (Table 1, entry 9).





^a Conditions: **2a** (0.20 mmol), **1a** (0.40 mmol), Pd₂(dba)₃·CHCl₃ (0.006 mmol), **L1** (0.012 mmol), solvent (1.5 mL), 24 h, 26 °C, under Ar.

^b Isolated yields.

^c Determined by ¹H NMR.

^d Determined by chiral HPLC.

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With THF as solvent, other chiral ligands were screened (Table 2). Ligand (S)-L2⁹ without methyl substituents at the benzylic position provided the product **3a** with opposite absolute configurations in 18% ee, 74% yield, and >20:1 dr (entry 2, Table 2). PHOX (L3) afforded the product **3a** in 58% ee with 30:1 dr and opposite absolute configuration, but the yield was 29% (Table 2, entry 3). The use of FcPHOX (L4) resulted in low yield although the diastereoselectivity was excellent (Table 2, entry 4). Biphosphine ligand such as BINAP was not suitable to the reaction since no reaction occurred (not shown in Table 2). However, ligand L5a,¹⁰ with a ferrocene backbone, afforded the product **3a** in 72% yield, 12:1 dr, and 44% ee

Table 2Ligand Optimization for Pd-Catalyzed Cycloaddition ofVinyl Epoxide 1a with β -Nitrostyrene (2a)^a



^a Conditions: **2a** (0.20 mmol), **1a** (0.40 mmol), Pd₂(dba)₃·CHCl₃ (0.006 mmol), ligand (0.012 mmol), THF (1.5 mL), 24 h, 26 °C, under Ar.

^b Isolated yield.

^c Determined by ¹H NMR.

^d Determined by chiral HPLC.

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(Table 2, entry 5). Since ligand L5a gave the best results in terms of yield and enantioselectivity though with a slightly lower diastereomeric ratio, we synthesized a variety of P,N-ferrocencyl ligands L5b-j bearing a different substituent on the oxazoline ring and aryl group on the P atom.¹¹ Of the ligands L5 with a different substituent on the oxazoline ring, L5b containing the sterically bulky tert-butyl group led to the highest enantioselectivity of 63% (Table 2, entry 6 vs. entries 5, 7, and 8). Then, ligands L5 with a tert-butyl group on the oxazoline ring and a different aryl group on the P atom were examined (Table 2, entries 9-12). The incorporation of an electron-deficient aryl group is not beneficial for the reaction (Table 2, entries 10 and 11). The use of ligand L5g with the 3,5di(trifluoromethyl)phenyl group resulted in the reaction being very sluggish (Table 2, entry 11). Further ligand optimization uncovered that ligand L5h with two methyl groups at the 3,5-position of the phenyl ring afforded the highest enantioselectivity of 71% (Table 2, entry 12).

Table 3 Substrate Scope for Pd-Catalyzed Cyclization of Vinyl Epoxide 1a with Nitroalkenes^{a,12}

		Pd ₂ (dba) ₃ •CHCl ₃ (3 mol%)			
1a	2 2	L5h (6 mol%), THF, r.t.			
Entry	R	Yield (%) ^b	dr ^c	ee (%) ^d	
1	a Ph	69	13:1	71	
2	b 4-MeOC ₆ H_4	47	>10:1	69	
3	c 4-ClC ₆ H ₄	67	9:1	71	
4	\mathbf{d} 4-FC ₆ H ₄	99	10:1	71	
5	e 3-MeOC ₆ H ₄	85	>10:1	72	
6	$f 2-MeOC_6H_4$	53 ^e	>20:1	51	
7	\mathbf{g} 2-BrC ₆ H ₄	74	7:2	4	
8	h 2-F ₃ CC ₆ H ₄	74	7:3	44	
9	i 2-furanyl	77	10:1	71	
10	j <i>n</i> -Pr	75	4:1	64	

^a Conditions: **2** (0.20 mmol), **1a** (0.40 mmol), Pd₂(dba)₃·CHCl₃ (0.006 mmol), **L5h** (0.012 mmol), THF (1.5 mL), 24 h, 26 °C, under Ar. ^b Isolated yields.

^c Determined by ¹H NMR.

^d Determined by chiral HPLC.

^e Reaction time of 4 d; 29% of **2f** recovered.

The substrate scope was investigated under the optimized conditions, and the results are shown in Table 3. Evaluation of a range of aryl-substituted nitroalkenes 2 showed that the incorporation of both electron-withdrawing and electron-donating substituents in *para*-position had little influence on diastereo- and enantioselectivities (Table 3, entries 2–4), although the yield was a little bit lower for

nitroalkene 2b with a methoxy group at the *para*-position of phenyl (Table 3, entry 2). The electron-donating substituent at the meta-position was also well tolerated, maintaining high yield and selectivity (Table 3, entry 5). The cycloaddition worked not so well for aryl nitroalkenes bearing ortho-positioned electron-withdrawing substituents on the phenyl ring (Table 3, entries 7 and 8), affording the products in lower diastereoand enantioselectivities while the selectivities still kept good when o-methoxyphenyl-substituted nitroalkene was the reagent (Table 3, entry 6). The reaction of furanyl derivative also afforded the corresponding 3i in 77% yield, 10:1 dr, and 71% ee (Table 3, entry 9). Notably, the cycloaddition is also applicable to alkyl-substituted nitroalkene, affording a 75% yield of the desired product, albeit with a slightly lower diastereo- and enantioselectivity (Table 3, entry 10).



Scheme 1

The reaction of different vinyl oxiranes was also investigated. 1-Vinyl-oxirane (1b) was subjected to the reaction with β -nitrostyrene (2a) in the presence of Pd₂(dba)₃·CHCl₃ and ligand L1 (Scheme 1, eq. 1). Two isomers of 2,3-*trans*-3,4-*cis*-tetrahydrofuran 3k and 2,3*cis*-3,4-*trans*-tetrahydrofuran 4k were obtained in 39% and 27% yield, respectively. Their relative stereochemistry was determined by NOE experiments. The enantioselectivity of products 3k and 4k was not determined due to their inseparability on HPLC. Further optimization of the reaction conditions could not improve the diastereoselectivity. In the case of vinyl oxiranes 1c and 1d, no cyclization product was observed although both reactants were



Figure 1 ORTEP drawing of compound 5

consumed (Scheme 1, equations 2 and 3). The ¹H NMR of the crude products displayed that polymerization might occur.

The product **3a** was easily converted into compound **5** through reduction and amide formation in 70% yield (Scheme 1, equation 4). X-ray diffraction analysis of compound **5** showed that its absolute configuration is 2R,3S,4R and its relative stereochemistry is 2,3-*trans* and 3,4-*cis* (Figure 1).¹³ Accordingly, the product **3a** has the 2R,3S,4R configuration.

In conclusion, a palladium-catalyzed diastereo- and enantioselective [3+2]-cycloaddition reaction of 2-vinyl-2methyl oxirane and nitroalkenes was developed, affording 2,3-*trans*-3,4-*cis*-trisubstituted tetrahydrofurans in good yields with good diastereo- and enantioselectivities. 1,1'-*P*,*N*-ferrocene ligands are the choice in the reaction. A reversal of enantioselectivity was also observed in this reaction when ligand (*S*)-**L2** with H as the substituent in the benzylic position and ligand (*S*)-**L1** with methyl were used, respectively. Further investigations on the substrate scope as well as the applications of the protocol are in progress.

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- (12) Typical Procedure for the Cycloaddition Reaction of Vinyl Epoxide 1a with Nitroalkenes 2: A Schlenk tube with a magnetic stir bar was charged with Pd₂dba₃·CHCl₃ (6.2 mg, 0.006 mmol), ligand L5h (6.6 mg, 0.012 mmol), and THF (1.5 mL) under an argon atmosphere. The resulting solution was allowed to stir for 30 min before nitroalkene 2a (30 mg, 0.20 mmol) followed by vinyl epoxide 1a (40 µL, 0.40 mmol) were added. The reaction mixture was allowed to stir for about 24 h at r.t. (26 °C) until the reaction was complete (monitored by TLC). The reaction mixture was diluted with CH₂Cl₂ (2 mL) before being passed through a short plug of silica gel to remove the palladium black. After the filtrate was concentrated, the crude product was analyzed by ¹H NMR spectroscopy to determine the diastereomeric ratio, and then the residue was purified by flash chromatography on silica gel (eluent: EtOAc-PE) to afford 32 mg of the product 3a as a light yellow liquid. Analytical Data for 3a: ¹H NMR (300 MHz, CDCl₃): $\delta =$
 - Analytical Data for 3a: ¹H NMR (300 MHz, CDCl₃): $\delta = 1.39$ (s, 3 H), 3.95 (d, J = 8.7 Hz, 1 H), 4.23 (d, J = 8.7 Hz, 1 H), 4.64 (d, J = 6.0 Hz, 1 H), 5.24–5.31 (m, 2 H), 5.62 (d, J = 6.0 Hz, 1 H), 5.88 (dd, J = 11.1, 17.7 Hz, 1 H), 7.33–7.39 (m, 5 H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 23.43$, 50.78, 77.64, 83.39, 100.65, 118.02, 125.31, 128.41, 128.84, 135.65, 138.82. IR (KBr): 2978, 2880, 1552, 1068 cm⁻¹. MS (EI): m/z (%) = 233 (8.88) [M⁺], 171 (100). HRMS (EI): m/z calcd for C₁₃H₁₅NO₃: 233.1052; found: 233.1042. HPLC (Chiraleel OJ-H 0.46 cm × 25 cm, *n*-hexane–*i*-PrOH (65:35); flow rate: 0.7 mL/min, UV: $\lambda = 230$ nm), $t_R = 10.0$ min (minor), 12.6 min (major).
- (13) The crystallographic data are deposited at the Cambridge Crystallographic Data Centre under deposition number CCDC 865918.

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