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Enantioselective Synthesis of Isoxazoline *N*-Oxides via Pd-Catalyzed Asymmetric Allylic Cycloaddition of Nitro-Containing Allylic Carbonates

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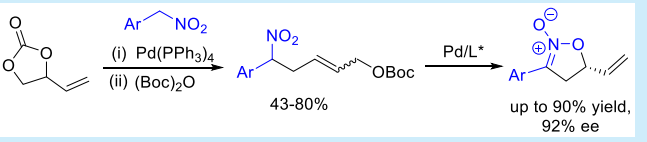
Supporting Information

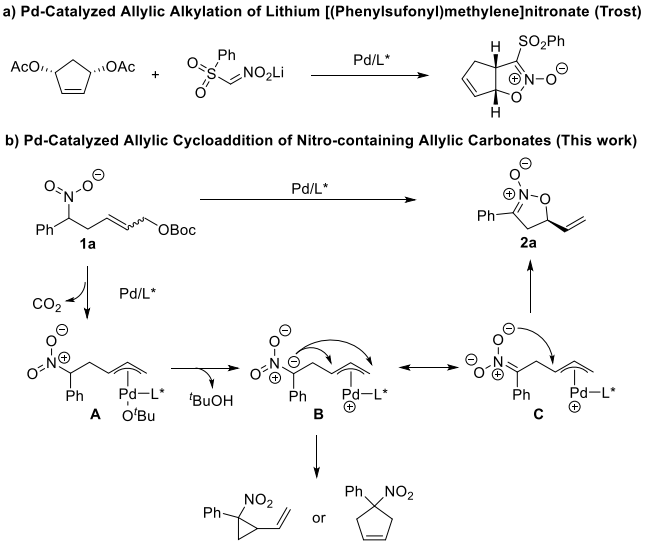
ABSTRACT: A useful method for the enantioselective preparation of isoxazoline *N*-oxides via Pd-catalyzed asymmetric allylic cycloaddition of nitro-containing allylic carbonates has been developed. By using palladium complex in situ generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphoramidite **L2** as a catalyst under mild conditions, the transformation afforded vinylated isoxazoline *N*-oxides in high yields with acceptably high enantioselectivities.



Isoxazoline *N*-oxides are versatile synthetic building blocks for the synthesis of useful organic intermediates, biologically active compounds, and natural products.[1] In this context, various synthetic approaches to this particular framework have been reported.[2] However, the catalytic asymmetric methods for the enantioselective preparation of isoxazoline *N*-oxides have been largely underdeveloped. Only a few examples have been reported based on organocatalytic asymmetric conjugated addition of carbon-nucleophiles with a leaving group to nitroalkene derivatives followed by nucleophilic cyclization.[3] Although this protocol could provide functionalized isoxazoline *N*-oxides with high enantioselectivities, the development of new catalytic asymmetric approaches to this skeleton from available precursors is highly desired.

Pd-catalyzed asymmetric allylic substitution is an important method for the formation of carbon−carbon and carbon−heteroatom bonds.[4] Nitroalkanes as useful carbon-nucleophiles have extensively been applied to the Pd-catalyzed allylic substitution to produce versatile homoallylic nitro-compounds.[5] However, nitroalkanes as *O*-nucleophiles in this transformation remain elusive. There has been only one example reported by Trost in 1992 for Pd-catalyzed allylic alkylation of *cis*-1,4-diacetoxycyclopent-2-ene with lithium [(phenylsufonyl)methylene]nitronate through sequential *C*- and *O*-nucleophilic attacks to afford isoxazoline *N*-oxide (Scheme 1a).[6] Most recently, we[7] and others[8] have developed Pd-catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates (VECs) with various unsaturated electrophiles to construct functionalized heterocycles with high efficiencies. Kleij and co-workers reported Pd-catalyzed allylic substitution of VECs with various nucleophiles to produce linear products with high *E*/*Z*-selective control.[9] On the basis of our continuous efforts to develop efficient methods for the enantioselective construction of valuable heterocycles via Pd-catalyzed allylic cycloaddition, we envisioned that nitro-containing allylic carbonate **1a** would be a useful substrate for the intramolecular allylic cycloaddition to provide isoxazoline *N*-oxide **2a** (Scheme 1b). We hypothesis that the nitro-containing allylic carbonate **1a** could react with palladium complex to afford π-allylpalladium intermediate **A**. The α-proton of nitro-group could be deprotonated by *tert*-butoxide

Scheme 1. Synthetic Strategy for Pd-Catalyzed Asymmetric Allylic Cycloaddition of Nitro-Containing Allylic Carbonates



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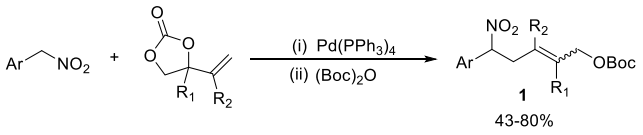
acting as a base to produce zwitterionic π-allylpalladium intermediate **B** and its resonant form of nitronate intermediate **C**. We reasoned that if the oxygen-anion of intermediate **C** attacks as a nucleophile, the subsequent cycloaddition could be feasible to form favored five-membered isoxazoline *N*-oxide **2a**. Nevertheless, if the carbanion of intermediate **B** works as a nucleophile, vinylcyclopropane or cyclopentene would be provided. Herein, we report a palladium-catalyzed asymmetric cycloaddition of nitro-containing allylic carbonates, a useful method that provides isoxazoline *N*-oxides with complete chemo- and regioselectivities and good to high enantioselectivities.

The nitro-containing allylic carbonates were synthesized by allylic substitution of VECs with arylated nitromethanes using $Pd(PPh_3)_4$ as a catalyst as a modified Kleij process,[9e] and followed by Boc-formation (Scheme 2, see Supporting Information for details).

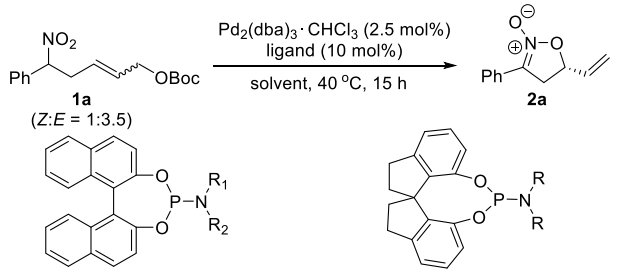
Scheme 2. Synthesis of Nitro-Containing Allylic Carbonates



On the basis of our previous studies,[7] we chose nitro-containing allylic carbonate **1a** (a mixture with *E*:*Z* = 3.5:1) as a standard substrate to examine the cycloaddition reaction with Pd-catalyst bearing different phosphoramidite ligands in THF (Table 1). To our delight, the reactions using phosphoramidites derived from binol[10] gave the desired isoxazoline *N*-oxide **2a** as the only product (entries 1−3), albeit the yields were moderate. The cyclopropane or cyclopentene were not observed in the reaction mixture; only the starting material was recovered. The reaction with ligand **L2** showed the best results to give product **2a** in 53% yield with 80% of enantiomeric excess (ee) (entry 2). The enantioselectivity could be improved by using Zhou's spiro-type phosphoramidite **L6**;[11] however, poor catalytic activity was observed (entry 6). Lower efficiencies were observed while the reaction with BINAP (entry 7) or Trost ligand (entry 8). With phosphoramidite **L2** in hand, the reaction in the different solvents was examined (entries 9−15, for details, see Supporting Information). We found that the reaction was very sensitive for the reaction media. When the reactions were carried out in 1,4-dioxane, the yield and enantioselectivity could be improved (entries 10). The yields were significantly improved when the reaction was performed in the chloride solvents (entries 11−13). The reaction in the chlorobenzene showed best results to afford isoxazoline *N*-oxide **2a** in 89% yield with 89% ee (entry 13). The reactions in methanol or acetonitrile also proceeded smoothly, but poor enantioselectivities were observed (entry 14 and 15).

On the basis of the optimal conditions (Table 1, entry 13), the reaction scope of present process was evaluated. As shown in Scheme 3, a variety of aryl-substituted nitro-containing allylic carbonates **1a**−**1m** (*Z*:*E* = 1:2.4−8.8) bearing different steric and electronic natures could be converted into the corresponding isoxazoline *N*-oxides **2a**−**2m** in high yields with complete chemo- and regioselectivities and good to high enantioselectivities. 1- and 2-naphthyl groups could also be installed to afford **2n** and **2o** in high yield with good enantioselectivities. A heteroaromatic, 3-benzothiophenyl

Table 1. Condition Optimizations[a]



entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	THF	26	46
2	**L2**	THF	53	80
3	**L3**	THF	48	78
4	**L4**	THF	21	9
5	**L5**	THF	11	15
6	**L6**	THF	21	−84
7	(*R*)-BINAP	THF	10	−28
8	Trost ligand	THF	11	−3
9	**L2**	toluene	26	85
10	**L2**	dioxane	70	89
11	**L2**	CH_2Cl_2	85	50
12	**L2**	$ClCH_2CH_2Cl$	95	54
13	**L2**	C_6H_5Cl	89	89
14	**L2**	MeOH	85	31
15	**L2**	CH_3CN	74	33

[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand (10 mol %), **1a** (0.1 mmol), solvent (1.0 mL), 40 °C, 15 h. [b]Isolated yields. [c]Determined by HPLC using a Chiralcel AS-H column. THF = tetrahydrofuran; DME = 1,2-dimethoxyethane; MTBE = methyl *tert*-butyl ether.

isoxazoline *N*-oxide **2p** could also be obtained in 78% yield with 86% ee. Significantly, the reaction of 1-phenylvinyl-substituted allylic carbonate also performed well to furnish the desired isoxazoline *N*-oxide **2q** in 90% yield with 92% ee. However, lower yield and enantioselectivity were observed for the reaction of 1-cyclohexenyl allylic carbonate **1r**. The reaction conditions were less effective for the reaction of the allylic substrates bearing R_1- or R_2-substituents. Although the reactions proceeded smoothly to give corresponding isoxazoline *N*-oxides **2v**−**2w** in good to high yields, poor to moderate enantioselectivities were observed.

The reaction of alkylated nitro-containing allylic carbonate **1x** could not proceed (Scheme 4, eq 1), and the starting material was recovered almost quantitatively. This result implied that a certain degree of acidity of the α-proton of nitro-group is necessary for this transformation. The one-pot sequential reaction of allylic substitution and allylic cycloaddition of allylic bicarbonate **3** with nitromethylbenzene was also investigated (Scheme 4, eq 2). However, under the identical conditions as described in Table 1, the reaction gave a complex mixture including bis-alkylated product **4**, allylic carbonate **1a**, trace amount of cyclized product **2a**, starting material **3**, and some others.

According to the proposed reaction mechanism as shown in Scheme 1, the final cycloaddition should be the stereochemistry-determining step. To acquire the stereochemical outcome of the cycloaddition, density functional theory (DFT)

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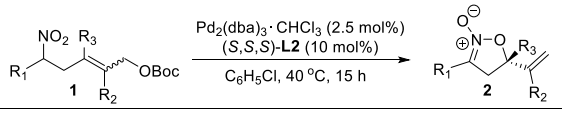
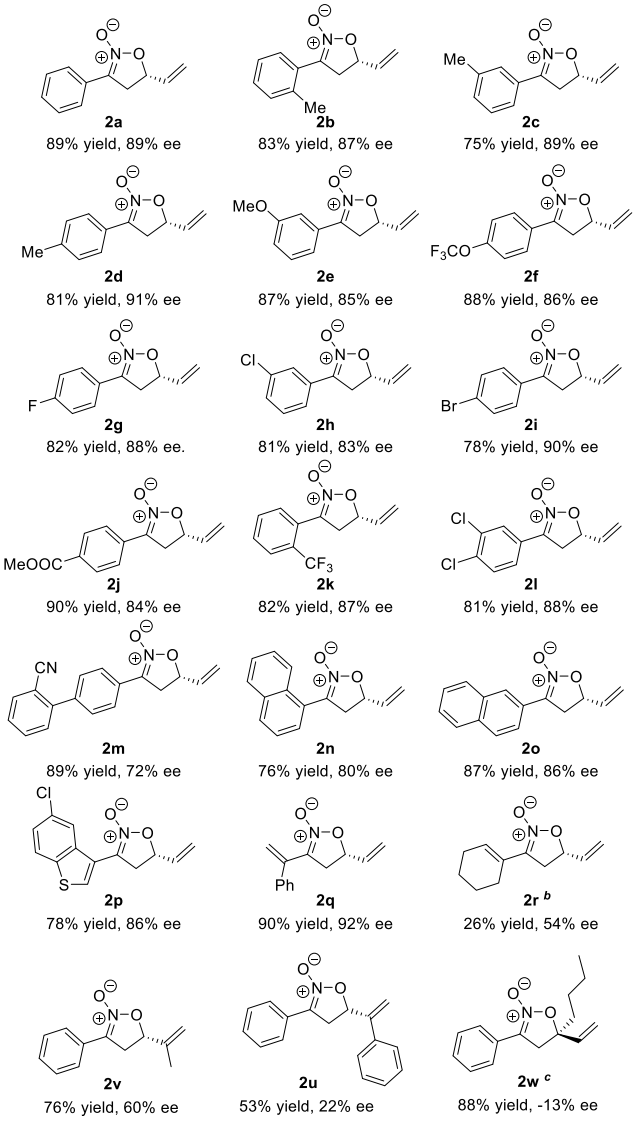
Scheme 3. Pd-Catalyzed Asymmetric Allylic Cycloaddition of Nitro-Containing Allylic Carbonates[a]



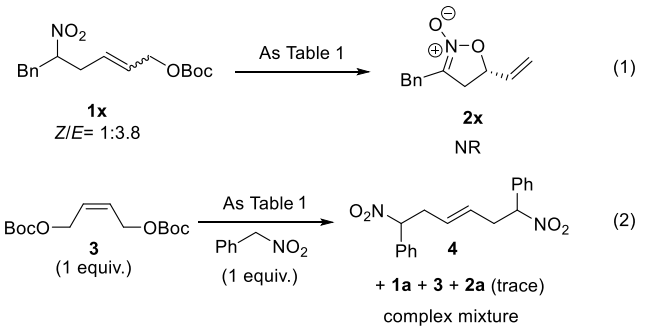
1a; *Z*:*E* = 1:3.5, **1b**; *Z*:*E* = 1:4.3, **1c** *Z*:*E* = 1:2.4, **1d**; *Z*:*E* = 1:4.2, **1e**; *Z*:*E* = 1:3.2, **1f**; *Z*:*E* = 1:8.8, **1g**; *Z*:*E* = 1:2.9, **1h**; *Z*:*E* = 1:2.4, **1i**; *Z*:*E* = 1:4.8, **1j**; *Z*:*E* = 1:3.7, **1k**; *Z*:*E* = 1:3.4, **1l**; *Z*:*E* = 1:2.8, **1m**; *Z*:*E* = 1:3.2, **1n**; *Z*:*E* = 1:5.7, **1o**; *Z*:*E* = 1:7.1, **1p**; only *E* **1q**; only *E*, **1r**; *Z*:*E* = 1:2.7, **1v**; only *Z*, **1u**; only *Z*, **1w**; only *Z*;



[a]Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), (*S*,*S*,*S*)-**L2** (10 mol %), **1a** (0.2 mmol), C_6H_5Cl (2.0 mL), 40 °C, 15 h. The yields are of isolated materials. The enantioselectivities were determined by HPLC using a chiral stationary phase. The absolute configuration of **2v** was confirmed by X-ray crystallography (see Supporting Information). Those of the other products were assigned by analogy. [b]The reaction was carried out in DCE solvent. [c]The reaction was carried out in (*R*)-**L1** and DCE solvent.

calculations were carried out using the three-parameter exchange-correlation hybrid functional B3LYP[12] with D3 dispersion correction[13] for the geometry optimizations of the conceivable four models[14] of π-allylpalladium intermediates **B** with ligand **L2** (see Supporting Information for details). As revealed in Figure 1, the intermediate **B** with *syn* allylic group (*syn* position between nitronate group and C_2-protone of allyl

Scheme 4. Pd-Catalyzed Allylic Cycloaddition of Allylic Carbonate 1x and Intermolecular Cycloaddition of Bicarbonate 3 with Nitromethylbenzene



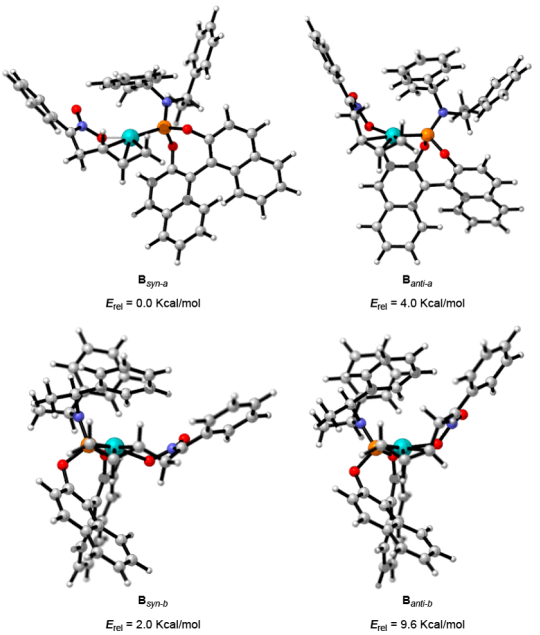


Figure 1. Stereochemical outcome via geometric optimization of plausible allylpalladium intermediates **B**.

group) showed much lower energies than that with *anti* allylic group. The intermediate $\mathbf{B}_{syn\text{-}a}$ revealed lowest relative energy; thus, the reaction afforded product **2a** with (*S*)-configuration as a major enantiomer, which matched with experimental results, through inner-attack of cycloaddition.[15]

The synthetic utility of the allylic cycloaddition reaction was realized by scale-up transformation and the elaboration of the cyclized products (Scheme 5). The cycloaddition of **1a** in 4 mmol scale with 1 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 4 mol % of ligand **L2** proceeded smoothly to afford isoxazoline *N*-oxide **2a** in 83% yield with 89% ee. Hydrogenation of **2a** with Pd/C could isolate hydroxy oxime **5** in 72% yield. When the reaction time was extended to 14 h, the amino alcohol **6** could be obtained in 89% yield, albeit with poor diastereoselectivity observed. Reduction of isoxazoline *N*-oxide **2a** with trimethyl phosphite gave dihydroisoxazole **7** in high yield. The vinyl group of dihydroisoxazole **7** could be oxidized to ester **8** in 61% yield. Reduction of compound **8** with $NaBH_4$ gave 3-phenyl-5-hydoxymethyldihydroisoxazole **9** in 89% yield. The cyclic oxime of **8** could be selectively reduced with $NaBH_4$ in the presence of $NiCl_2$ to afford 3-hydroxy-5-phenylpyrrolidinone **10** in 91% yield with a 1:1.2 diastereomeric ratio.[3d]

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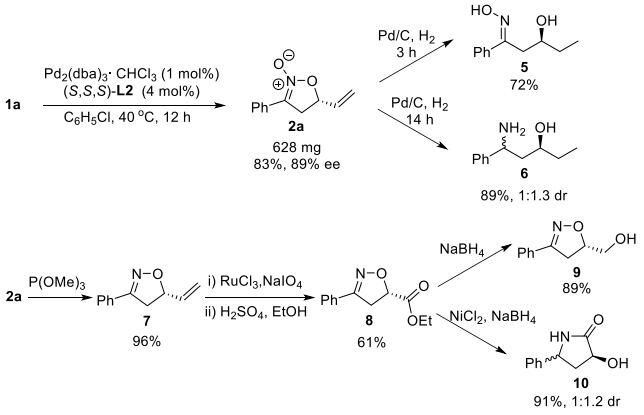
Scheme 5. Scale-up Transformation and the Elaboration of Product 2a



In conclusion, we have presented a useful method for the enantioselective synthesis of isoxazoline *N*-oxides via Pd-catalyzed allylic cycloaddition of nitro-containing allylic carbonates. By using palladium complex in situ generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphoramidite **L2** as a catalyst under mild conditions, the reaction provided vinylated isoxazoline *N*-oxides in high yields with acceptably high enantioselectivities. The stereochemistry of the transformation was rationalized by DFT calculations, and the synthetic utility of the process was realized by the scale-up transformation and the elaboration of the cyclized products. Further studies on extending the chemistry of nitro-containing allylic carbonates are currently underway, and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03443.

Detailed experimental procedures; characterization data of all of the new compounds; copies of HPLC chromatography, ^1H and ^{13}C NMR spectra of the products (PDF)

Accession Codes

CCDC 1947874 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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