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# Palladium-Catalyzed Highly Stereoselective Synthesis of *N*-Aryl-3-arylmethylisoxazolidines via Tandem Arylation of *O*-Homoallylhydroxylamines

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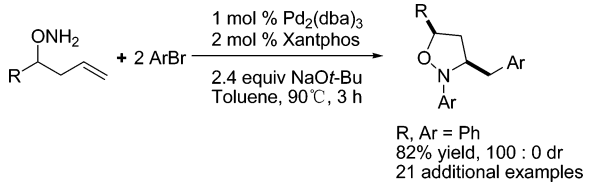

The palladium-catalyzed tandem arylation of *O*-homoallylhydroxylamines with 2 equiv of aryl bromides was examined. With $Pd_2(dba)_3$ (1 mol %) as the catalyst, Xantphos (2 mol %) as the ligand, and NaO*t*-Bu as the base, the reactions of *O*-homoallylhydroxylamines with aryl bromides via sequential *N*-arylation/cyclization/C-arylation in toluene afforded the corresponding *N*-aryl-3-arylmethylisoxazolidines in good yields with excellent diastereoselectivity.

One-pot catalytic processes incorporating two or more different transformations hold great promise for the rapid buildup of molecular complexity and diversity.[1] In recent years great interest has been focused on the development of tandem or sequential reactions that form several different bonds, stereocenters, and rings.[2] Transition metal-catalyzed transformations have played an important role in the development of many of these processes.[3] The palladium-catalyzed intramolecular addition reactions of amines with alkenes,[4] alkynes,[5] and allenes[6] have been intensively studied, since they are often associated with high stereo- and regioselectivities. Furthermore, palladium can usually be used in catalytic amounts, tolerates a wide variety of functional groups, and proceeds under mild reaction conditions. Recently, Krishna Gopal Dongol and Boon Ying Tay[7] reported the Pd-catalyzed cascade reaction of *N*-Boc protected *O*-homoallylhydroxylamines with aryl iodides to afford the corresponding isoxazolidines,[8] contaminated by substantial Heck-type side products with modest diastereoselectivity. Of particular interest to us was that this chemistry could potentially offer a rapid entry to *N*-aryl isoxazolidines which can serve as precursors for $\beta$-amino alcohols[9] and $\beta$-amino acids.[10] Herein, we report on stereocontrolled palladium-catalyzed syntheses of isoxazolidines via tandem arylation of *O*-homoallylhydroxylamines.

It was known that both palladium-catalyzed *N*-arylations of amines and Pd-catalyzed carboamination reactions are very sensitive to catalyst structure and ligand.[4] Therefore, a judicious choice of palladium catalyst, ligand, and base is needed to carry out this domino *N*-arylation[11]/carboamination process of *O*-homoallylhydroxylamine and suppress the formation of the undesired *N,N*-bisarylation[4c] and Heck-type side product.[7] To

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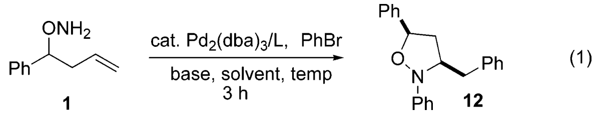
10.1021/jo0625958 CCC: \$37.00

**TABLE 1. Pd-Catalyzed Tandem Reaction Optimization**[a]



| entry | ligand L | base | solvent/temp (°C) | yield[b] |
|---|---|---|---|---|
| 1 | P(*o*-tol)$_3$ | NaO*t*-Bu | toluene/100 | no reaction[c] |
| 2 | P(*o*-tol)$_3$ | KO*t*-Bu | toluene/100 | no reaction[c] |
| 3 | P(*o*-tol)$_3$ | $K_2CO_3$ | toluene/100 | no reaction[c] |
| 4 | P(*o*-tol)$_3$ | $Et_3N$ | toluene/100 | no reaction[c] |
| 5 | P(*o*-tol)$_3$ | $NaHCO_3$ | toluene/100 | no reaction[c] |
| 6[d] | **2** | NaO*t*-Bu | toluene/60 | 25% |
| 7[e] | **3** | NaO*t*-Bu | toluene/60 | trace |
| 8 | dppm | NaO*t*-Bu | toluene/100 | no reaction[c] |
| 9 | dppe | NaO*t*-Bu | toluene/100 | no reaction[c] |
| 10 | dppb | NaO*t*-Bu | toluene/100 | no reaction[c] |
| 11 | dppf | NaO*t*-Bu | toluene/100 | no reaction[c] |
| 12 | Xantphos **4** | NaO*t*-Bu | toluene/90 | 82% |
| 13 | DPE-Phos **5** | NaO*t*-Bu | toluene/90 | complex mixture |
| 14 | BINAP | NaO*t*-Bu | toluene/90 | trace |
| 15 | Xantphos **4** | $Cs_2CO_3$ | toluene/90 | trace |
| 16 | Xantphos **4** | KO*t*-Bu | toluene/90 | 43% |
| 17 | Xantphos **4** | NaO*t*-Bu | $CH_3CN$/reflux | complex mixture |
| 18 | Xantphos **4** | NaO*t*-Bu | dioxane/90 | trace |
| 19 | Xantphos **4** | NaO*t*-Bu | DMF/90 | complex mixture |
| 20 | Xantphos **4** | NaO*t*-Bu | THF/reflux | trace |

[a] Conditions: 1.0 equiv of hydroxylamine, 2.05 equiv of PhBr, 2.4 equiv of base, 1 mol % of $Pd_2(dba)_3$, 2 mol % of ligand, solvent (0.06 M). [b] Yield of isolated product. [c] Complete recovery of starting material. [d] *N*-Phenyl-3-phenyl-*O*-homoallylhydroxylamine and *N*,*N*-diphenyl-3-phenyl-*O*-homoallylhydroxylamine were also isolated from the reaction mixture, in 20% and 40% yield, respectively. [e] *N*-Phenyl-3-phenyl-*O*-homoallylhydroxylamine and *N*,*N*-phenyl-3-phenyl-*O*-homoallylhydroxylamine were isolated from the reaction mixture.

determine the feasibility of the *N*-arylation/carboamination process, we first examined the reaction conditions of *O*-homoallylhydroxylamine (**1**) with 2.05 equiv of bromobenzene and a catalytic amount of $Pd_2(dba)_3$ (1 mol %). Some results from that study are summarized in Table 1. Using a catalyst comprised of $Pd_2(dba)_3$ and P(*o*-tol)$_3$, we examined various bases ($NaHCO_3$, $K_2CO_3$, $Et_3N$, KO*t*-Bu, and NaO*t*-Bu). To our disappointment, no expected isoxazolidine product was obtained while, in all the cases, the starting materials simply remained unchanged (entries 1−5, Table 1). By changing the ligand from P(*o*-tol)$_3$ to the bulky electron-rich phosphane **2**[12] known to be an excellent ligand for *N*-arylation reaction, the desired isoxazolidine product was isolated in 25% yield. The main side product observed in this condition was *N*,*N*-diphenyl-3-phenyl-*O*-(1-phenylbut-3-enyl) hydroxylamine, which was derived from Pd-catalyzed *N*-bisarylation of homoallylhydroxylamine (entry 6, Table 1).

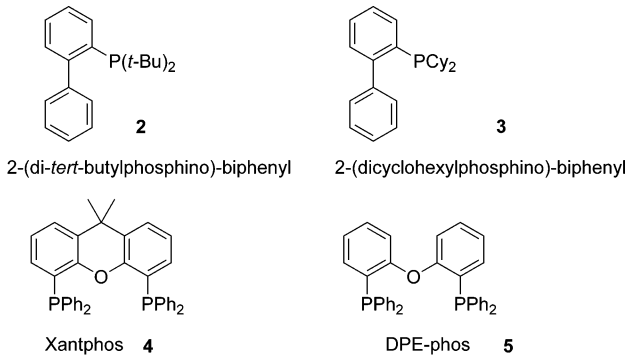
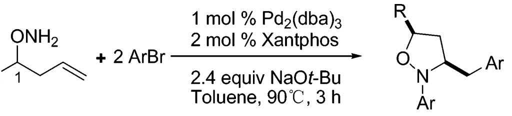


**FIGURE 1.** Phosphorus ligands used in tandem arylation of *O*-homoallylhydroxylamines.

**TABLE 2. Synthesis of *N*-Aryl-3-arylmethylisoxazolidines**[a]



| entry | R | Ar | product | dr[b] | yield[c] (%) |
|---|---|---|---|---|---|
| 1 | Ph, **1** | Ph | **12** | 100:0 | 82 |
| 2[d] | **1** | pyridin-3-yl | **13a** | 100:0 | 45 |
| 3 | **1** | pyridin-2-yl | **14** | 100:0 | 74 |
| 4 | **1** | pyridin-4-yl | **15** | 100:0 | 74 |
| 5 | **1** | 2-thienyl | **16** | | |
| 6 | **1** | *p*-$CH_3$-$C_6H_4$ | **17** | 100:0 | 78 |
| 7 | **1** | *p*-biphenyl | **18** | 100:0 | 86 |
| 8 | **1** | naphthalen-1-yl | **19** | 100:0 | 76 |
| 9 | **1** | *p*-Cl-$C_6H_4$ | **20** | 100:0 | 86 |
| 10 | **1** | *p*-$NO_2$-$C_6H_4$ | **21** | 100:0 | 84 |
| 11 | **1** | *m*-$NO_2$-$C_6H_4$ | **22** | 100:0 | 75 |
| 12 | **1** | *p*-CN-$C_6H_4$ | **23** | 100:0 | 90 |
| 13[e] | **1** | *p*-$CO_2t$Bu-$C_6H_4$ | **24** | 4:1 | 68 |
| 14 | **1** | *p*-(1,3-dioxolan-2-yl)phenyl | **25** | 100:0 | 62 |
| 15[f] | **1** | *p*-$CH_3O$-$C_6H_4$ | **26** | 100:0 | 42 |
| 16 | 2-thienyl, **6** | *p*-$NO_2$-$C_6H_4$ | **27** | 100:0 | 81 |
| 17 | **6** | *p*-$CO_2t$Bu-$C_6H_4$ | **28** | 100:0 | 72 |
| 18 | *p*-$CH_3$-$C_6H_4$, **7** | *p*-$NO_2$-$C_6H_4$ | **29** | 100:0 | 82 |
| 19 | *p*-Cl-$C_6H_4$ , **8** | *p*-$NO_2$-$C_6H_4$ | **30** | 100:0 | 84 |
| 20 | *p*-$CH_3O$-$C_6H_4$, **9** | *p*-$NO_2$-$C_6H_4$ | **31** | 100:0 | 85 |
| 21[g] | (*E*)-styryl, **10** | *p*-$NO_2$-$C_6H_4$ | **32** | 100:0 | 82 |
| 22 | *i*Pr, **11** | *p*-$NO_2$-$C_6H_4$ | **33** | 100:0 | 76 |

[a] Conditions: 1.0 equiv of hydroxylamine, 2.05 equiv of ArBr, 2.4 equiv of NaO*t*-Bu, 1 mol % of $Pd_2(dba)_3$, 2 mol % of Xantphos, toluene (0.06 M), 90 °C. [b] Product ratios refer to the isolated material. [c] Yield of isolated product. [d] 3-(3-Methylene-5-phenylisoxazolidin-2-yl-)pyridine **13b** was also isolated from the reaction mixture in 30% yield. [e] Ratio determined from $^1H$ NMR spectra; the major diastereomer was depicted. [f] The reaction was conducted at 90 °C for 6 h. [g] This material contained ca. 17% of the corresponding (*E*)-1-phenylhexa-2,5-dien-1-hydroxylamine as an inseparable impurity.

To suppress this competitive reaction, we observed another bulky phosphane **3**. Unfortunately this gave poorer product distribution than our previous results (entry 7, Table 1). We then carefully screened various bis(phosphine) ligands (dppm, dppe, dppb, dppf, BINAP, Xantphos **4**, and DPE-phos **5**) which are known to decrease the rate of $\beta$-hydride elimination reaction[13] to suppress the Heck product (entries 8−14, Table 1). We were pleased to find that use of a catalyst comprised of $Pd_2(dba)_3$ and Xantphos (**4**) (Figure 1) in the presence of NaO*t*-Bu (2.4 equiv) provided the desired 2,5-diphenyl-3-benzylisoxazolidine (**12**) in 82% isolated yield (entry 12, Table 1). The stereochemistry of **12** was confirmed to be *cis* by NOESY.[14] NaO*t*-Bu proved to be clearly superior to $Cs_2$-

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(11) *N*-Arylation of *N*-Boc hydroxylamine carbamate has been reported, see ref 7. However, *N*-arylation of primary hydroxylamine has not been reported. For reviews on Pd-catalyzed aminations of aryl halides, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 133. (b) Zapf, A.; Beller, M.; Riermeier, T. H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, p 231.

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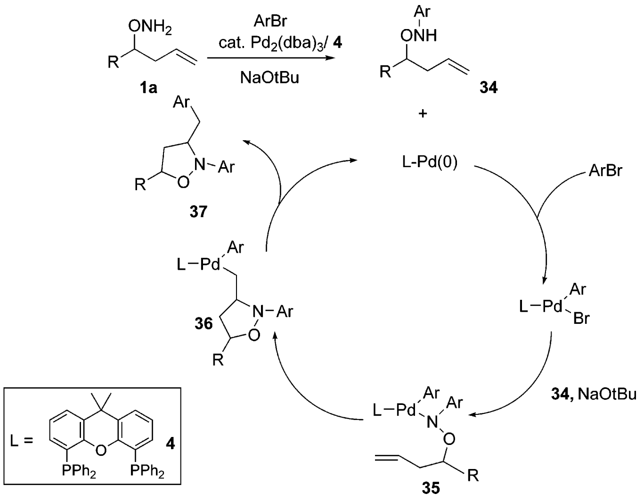
**SCHEME 1. Proposed Catalytic Cycle**



$CO_3$ (entry 12 and 15, Table 1) and to give higher yields than KO*t*-Bu (entry 12 and 16, Table 1). A brief survey of reaction media showed that use of toluene as solvent provided better results than those obtained in THF and 1,4-dioxane (entries 12, 18, and 20, Table 1). However, reactions carried out in polar solvents such as DMF and acetonitrile gave no products (entries 17 and 19, Table 1).

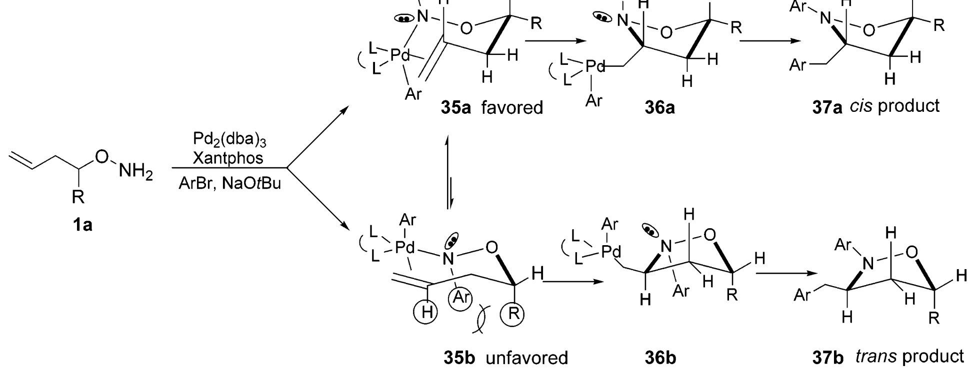
With the optimized reaction condition in hand, we prepared a large range of *N*-aryl-3-arylmethylisoxazolidines (Table 2). As shown in Table 2, this method is effective for the conversion of a variety of 1-substituted-*O*-homoallylhydroxylamines such as aryl (entries 1 to 15, Table 2), heteroaryl (entries 16 and 17, Table 2), alkyl (entry 22, Table 2), and alkenyl (entry 21, Table 2) to *N*-aryl-3-arylmethylisoxazolidine derivatives. A variety of electron neutral and deficient aryl bromides (entries 2−4 and 9−13, Table 2) are effectively transformed under these conditions, several functional groups are tolerated (entries 9−15, Table 2), and the heteroaryl bromides also afforded the corresponding product in good yield. For substrate 3-bromopyridine, the expected isoxazolidine **13a** was obtained in 45% yield along with side product 3-(3-methylene-5-phenylisoxazolidin-2-yl)pyridine **13b** in 30% yield, which derives from domino *N*-arylation/*β*-H elimination (entry 2, Table 2). For the substrates 2-bromopyridine and 4-bromopyridine, only the desired product was observed in high yield (entries 3 and 4, Table 2). However, no expected product was formed for 2-bromothiophene (entry 5, Table 2) and the material was recovered. Electron-rich aryl halides such as 4-bromoanisole (entry 15, Table 2) often resulted in slow reactions and provided only modest yield of the desired product. Overall, aryl bromide bearing an electron-donating or electron-withdrawing substituent at the aryl ring underwent smooth domino arylation, indicating the generality of the above methodology.

The tandem transformations of substrates **1** and **6**−**11**, which bear substituents (aryl, vinyl, and alkyl) at the 1-position, proceeded with high diastereoselectivity. In all cases except for entry 13 (Table 2), a single diastereoisomer was obtained.[8] The stereochemical outcome of these reactions parallels that observed in previously described reactions of *γ*-(*N*-arylamino)alkenes with aryl bromides.[4]

A proposed reaction mechanism of the tandem arylation of *O*-homoallylhydroxylamines to isoxazolidine derivatives is shown in Scheme 1. This transformation presumably occurs through initial *N*-arylation of hydroxylamine **1a** to form intermediate **34** and Pd(0), then oxidative addition of the aryl bromide to Pd(0) followed by reaction of the resulting complex with **34** and base to afford an intermediate [Pd(Ar)(RONAr)] complex **35**. A *syn* insertion of the alkene into the Pd−N in **35** to afford the carboamination intermediate **36**. Complex **36** undergoes C−C bond forming reductive elimination to afford the desired product **37** and Pd(0). The present system can completely suppress the Heck reaction of alkene with aryl bromide and *β*-H elimination of intermediate **36** to afford *N*-aryl-3-arylmethylisoxazolidine derivatives.

The palladium-catalyzed conversion of 1-substituted *O*-homoallylhydroxylamines to *cis*-3,5-disubstituted isoxazolidines (Table 2) proceeds with excellent levels of diastereoselectivity. To explain the stereochemical outcome of these transformations, we suggest that the stereochemistry determining step is the insertion of the alkene into the Pd−N bond of intermediate **35** (Scheme 1).[15] As shown below (Scheme 2), the conversion of a 1-substituted *O*-homoallylhydroxylamine **1a** to a *cis*-3,5-disubstituted isoxazolidine **37a** proceeds via conformer **35a**. In this conformer **35a**, the R substituent is oriented in the pseudoequatorial position to minimize nonbonding interactions with the *N*-aryl group and C-3 hydrogen, moreover, the *N*-aryl group is oriented in the pseudoaxial position to minimize interaction with the aryl group or phosphine ligand bound to the Pd complex. The combination of these two interactions would disfavor reaction through conformer **35b** in which the R group is oriented in the pseudoaxial position. The alkene insertion via **35a** would afford intermediate **36a**, which would provide the observed *cis*-3,5-disubstituted product **37a** upon C−C bond-forming reductive elimination. The origin of the

**SCHEME 2. Proposed Stereochemistry of 3,5-Disubstituted Isoxazolidine Products**



decreased diastereoselectivity observed in the reaction of **1** with *tert*-butyl-4-bromobenzoate is not clear.

In summary, we have successfully developed an efficient protocol for the palladium-catalyzed stereoselective synthesis of *N*-aryl-3-arylmethylisoxazolidines via tandem *N*-arylation/cyclization/*C*-arylation of *O*-homoallylhydroxylamines. The result presented here together with previous research should be of considerable interest of the valuable synthetic building blocks for the construction of biologically active molecules. This finding should also have important implications in the further development of the Pd-catalyzed domino arylation reaction.

## Experimental Section

**General Procedures for the Synthesis of *N*-Aryl-3-arylmethylisoxazolidines.** A flame-dried tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), Xantphos (2 mol %), and NaO*t*-Bu (2.4 equiv). The tube was purged with nitrogen, and toluene (10 mL/mmol hydroxylamine substrate), the hydroxylamine substrate (1.0 equiv), and the aryl bromide (2.05 equiv) were added via syringe. The mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by TLC. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (2 mL), and diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with (2 × 10 mL) ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel (H), eluting with 4−30% ethyl acetate/petroleum ether.

**Product Characterization of Representative Examples: (±)-(*3R,5R*)-3-(4-Chlorobenzyl)-2-(4-chlorophenyl)-5-phenylisoxazolidine (20).** Reaction of 50 mg (0.307 mmol) of 3-phenyl-*O*-homoallylhydroxylamine (**1**) with 1-bromo-4-chlorobenzene (120.2 mg, 0.63 mmol) and NaO*t*-Bu (70.7 mg, 0.74 mmol) following the general procedures afforded 101.4 mg (86%) of the title compound as a light yellow oil. $R_f$ 0.19 (10% EtOAc:petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.42 (m, 5H, Ph), 7.24−7.32 (m, 4H, *p*-Cl-*Ph*), 7.15−7.18 (m, 2H, *p*-Cl-*Ph*), 6.75−6.78 (m, 2H, *p*-Cl-*Ph*), 5.03−5.08 (m, 1H, OCH), 4.03 (m, 1H, NCH), 3.15−3.22 (dd, *J* = 13.5, 8.4 Hz, 1H, Ar$CH_2$), 2.86−2.93 (dd, *J* = 13.5, 5.5 Hz, 1H, Ar$CH_2$), 2.79−2.83 (m, 1H, $CH_2$), 2.12−2.17 (m, 1H, $CH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.4, 138.2, 137.3, 132.5, 131.3, 130.9, 128.9, 128.7, 128.4, 126.6, 126.4, 115.1, 80.0, 69.5, 43.8, 42.1; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{22}H_{19}Cl_2NNaO$ 406.0741, found 406.0744.

**(±)-(*3R,5R*)-3-(4-Cyanobenzyl)-2-(4-cyanophenyl)-5-phenylisoxazolidine (23).** Reaction of 50 mg (0.307 mmol) of 3-phenyl-*O*-homoallylhydroxylamine (**1**) with 4-bromobenzonitrile (114.5 mg, 0.63 mmol) and NaO*t*-Bu (70.7 mg, 0.74 mmol) following the general procedures afforded 100.9 mg (90%) of the title compound as a white solid. $R_f$ 0.24 (20% EtOAc:petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.61−7.64 (d, *J* = 9 Hz, 2H, *p*-CN-*Ph*), 7.34−7.47 (m, 9H, Ar), 6.75−6.78 (d, *J* = 9 Hz, 2H, *p*-CN-*Ph*), 4.97−5.02 (m, 1H, OCH), 4.14−4.18 (m, 1H, NCH), 3.22−3.29 (dd, *J* = 13.5, 9 Hz, 1H, Ar$CH_2$), 3.01−3.07 (dd, *J* = 13.5, 4.8 Hz, 1H, Ar$CH_2$), 2.89−2.93 (m, 1H, $CH_2$), 2.04−2.23 (m, 1H, $CH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 154.5, 143.8, 137.1, 133.3, 132.3, 130.4, 128.7, 128.6, 126.5, 119.2, 118.6, 113.2, 110.7, 103.8, 80.6, 68.0, 43.6, 42.5; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{24}H_{19}N_3NaO$ 388.1420, found 388.1423.

**(±)-(*3R,5R*)-3-(4-Nitrobenzyl)-2-(4-nitrophenyl)-5-(thiophen-2-yl)isoxazolidine (27).** Reaction of 52 mg (0.307 mmol) of 3-(thiophen-2-yl)-*o*-homoallylhydroxylamine (**6**) with 1-bromo-4-nitrobenzene (127.2 mg, 0.63 mmol) and NaO*t*-Bu (70.7 mg, 0.74 mmol) following the general procedures afforded 102.2 mg (81%) of the title compound as a yellow solid. $R_f$ 0.23 (20% EtOAc:petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.18−8.21 (d, *J* = 9 Hz, 2H, *p*-$NO_2$-*Ph*), 8.04−8.07 (d, *J* = 9 Hz, 2H, *p*-$NO_2$-*Ph*), 7.51−7.54 (d, *J* = 9 Hz, 2H, *p*-$NO_2$-*Ph*), 7.39−7.41 (m, 1H, thienyl), 7.15−7.17 (m, 1H, thienyl), 7.04−7.07 (m, 1H, thienyl), 6.76−6.79 (d, *J* = 9 Hz, 2H, *p*-$NO_2$-*Ph*), 5.29−5.35 (m, 1H, OCH), 4.28−4.29 (m, 1H, NCH), 3.31−3.38 (dd, *J* = 13.5, 9 Hz, 1H, Ar$CH_2$), 3.10−3.16 (dd, *J* = 13.5, 4.8 Hz, 1H, Ar$CH_2$), 2.96−3.00 (m, 1H, $CH_2$), 2.28−2.37 (m, 1H, $CH_2$); $^{13}$C (75 MHz, $CDCl_3$) $\delta$ 155.7, 147.0, 145.7, 141.5, 139.3, 130.5, 127.1, 127.0, 126.6, 125.5, 123.9, 112.4, 76.7, 67.7, 43.5, 41.8; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{17}N_3NaO_5S$ 434.0781, found 434.0806.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The *cis*-configuration was confirmed by NMR NOE and HPLC experiment. See the Supporting Information for further details.

(15) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099.