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Palladium-catalyzed cascade one-pot synthesis of 5-arylmethylisoxazolidines from *N*-homoallylhydroxylamines with aryl bromides

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Abstract

A novel method for the synthesis of 5-arylmethylisoxazolidines via palladium-catalyzed reactions of aryl bromides with *N*-homoallylhydroxylamines is described. This reaction effects intramolecular C–O bond formation with concomitant intermolecular formation of a C–C bond in moderate to good yields. Moderate to excellent diastereoselectivities are observed for the formation of the isoxazolidines. The catalytic system has a tolerance to a wide variety of functional groups.

1. Introduction

The synthesis of isoxazolidine derivatives has received much attention due to the prevalence of this moiety in biologically active molecules and natural products.[1] They also serve as precursors for β-amino alcohols,[2] β-amino ketones,[3] β-amino acids,[4] and 3-isoxazolidones.[5] The 1,3-dipolar cycloaddition of nitrones with alkenes was among these important reactions for the construction of substituted isoxazolidines.[6] However, one of today's challenges in this field is to control the regio-, diastereoselectivity and expand the scope of the reactions to the unactivated alkenes.[7] To avoid these problems in 1,3-dipolar cycloaddition, a number of different synthetic methods have been devised for the preparation, including reaction of *N*-benzylhydroxylamines with α,β-unsaturated esters,[8] reaction of hemiaminals with α,β-unsaturated esters bearing a leaving group on its δ-C,[9] Pd(II)-catalyzed cyclofunctionalization of *O*-homoallylhydroxylamines,[10] and Pd(0)-catalyzed cascade reaction of *O*-homoallylhydroxylamines with aryl iodides.[11]

We have a long-standing and continuing interest in this field. In our laboratory, we recently developed a new method for the stereoselective synthesis of substituted isoxazolidines via Pd-catalyzed sequential reaction of aryl bromides with *O*-homoallylhydroxylamines (Eq. 1) in high yields (up to 90%) and furthermore, selective diarylation of *O*-homoallylhydroxylamines with different aryl bromides was also achieved in one-pot process by an in situ modification of the palladium catalyst via phosphine ligands exchange (Eq. 2).[12] We have found that transformations of *O*-homoallylhydroxylamine substrates provide cis-3,5-disubstituted products with excellent levels of diastereoselectivities. To evaluate the scope of this methodology, we set out to examine the reactions of aryl bromides with *N*-homoallylhydroxylamines containing a less nucleophilic oxygen atom. Herein we describe our preliminary studies on the stereoselective synthesis of 5-arylmethylisoxazolidines via Pd(0)-promoted cascade reaction of *N*-homoallylhydroxylamines with aryl bromides.[13] These studies illustrate the potential utility of this methodology for the construction of various substituted isoxazolidines.

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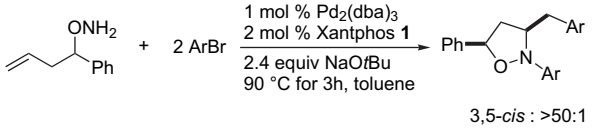
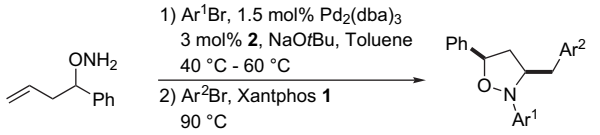


(1)

3,5-*cis* : >50:1



(2)

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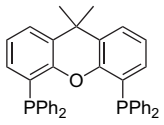

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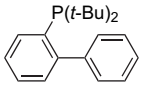

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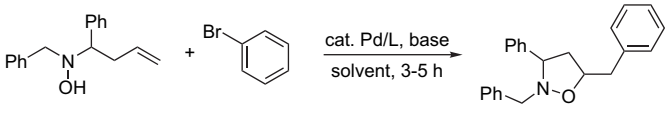
2. Results and discussion

In order to determine the feasibility of this process, we first examined the reaction of *N*-benzyl-*N*-homoallylhydroxylamine[14] **3** with 1.2 equiv of bromobenzene in the presence of NaO-*t*-Bu (1.2 equiv) and catalytic amounts of $Pd_2(dba)_3$ (1 mol %) and Xantphos 1 (2 mol %). These reaction conditions were derived from our earlier studies on Pd-catalyzed synthesis of *N*-aryl-3-arylmethylisoxazolidines.[12a] We were pleased to find that this transformation provided the 5-arylmethylisoxazolidine **8a** in 69% yield, though moderate diastereoselectivity was observed (36:64, cis/trans ratio). To optimize the reaction conditions, we judiciously screened the ligand, base, and catalyst loading. Some results from that study are summarized in Table 1. To our disappointment, an attempted survey of ligands failed to improve the diastereoselectivity (entries 2–9, Table 1). Noteworthy was that when DPE-phos and BINAP were employed as ligands, the major product was reversed to cis-diastereomer (entries 2 and 9), which was also observed by Wolfe in his recent work.[13] Balancing the yield and the diastereoselectivity, the Xantphos **1** was selected as the ligand for the subsequent studies. An attempt to decrease the reaction temperature provided no detectable amounts of the 5-arylmethylisoxazolidine **8a**. NaO-*t*-Bu was proved to be clearly superior to other bases, as Et_3N, Cs_2CO_3, K_2CO_3, and K_3PO_4 gave no desired product while the starting materials simply remained unchanged (entries 10, 11, 13, and 14). This yield was further improved to 84% by adding 2 mol % of $Pd_2(dba)_3$ and 4 mol % of Xantphos to the reaction mixture (entry 12). However, further increase of the catalyst loading gave decreased yield (entry 17). Use of THF as solvent resulted in a significantly lower yield to those obtained in toluene (entry 18). It is worth to note that either palladium or ligand was required for isoxazolidine formation: stirring a mixture of *N*-benzyl-*N*-homoallylhydroxylamine **3**, bromobenzene, and NaO-*t*-Bu in toluene in the

Table 1
Optimization of the reaction conditions in the synthesis of **8a**[a]



3 **8a**

Entry	Ligand	mol % $Pd_2(dba)_3$ /mol % ligand	Base	Solvent	Yield[b] (%)	Cis/trans[c]
1	Xantphos **1**	1:2	NaO-*t*-Bu	Toluene	69	36:64
2	DPE-phos	1:2	NaO-*t*-Bu	Toluene	40	63:37
3	dppe	1:2	NaO-*t*-Bu	Toluene	0[d]	—
4	dppb	1:2	NaO-*t*-Bu	Toluene	11	nd
5	Ph_3P	1:4	NaO-*t*-Bu	Toluene	57	47:53
6	Ph_3P	2:4	NaO-*t*-Bu	Toluene	77	47:53
7	Ph_3P	2:8	NaO-*t*-Bu	Toluene	38	47:53
8	dppf	2:4	NaO-*t*-Bu	Toluene	52	45:55
9	BINAP	2:4	NaO-*t*-Bu	Toluene	68	60:40
10	Xantphos **1**	1:2	Et_3N	Toluene	0[d]	—
11	Xantphos **1**	1:2	Cs_2CO_3	Toluene	0[d]	—
12	Xantphos **1**	2:4	NaO-*t*-Bu	Toluene	84	37:63
13	Xantphos **1**	2:4	K_2CO_3	Toluene	0[d]	—
14	Xantphos **1**	2:4	K_3PO_4	Toluene	0[d]	—
15	—	2:0	NaO-*t*-Bu	Toluene	0[d]	—
16	Xantphos **1**	0:4	NaO-*t*-Bu	Toluene	0[d]	—
17	Xantphos **1**	4:8	NaO-*t*-Bu	Toluene	56	35:65
18	Xantphos **1**	2:4	NaO-*t*-Bu	THF	44	37:63

DPE-phos=bis(2-diphenylphosphinophenyl)ether, dppe=1,2-bis(diphenylphosphino)ethane, dppb=1,4-bis(diphenylphosphino)butane, dppf=1,1′-bis(diphenylposphino)ferrocene.

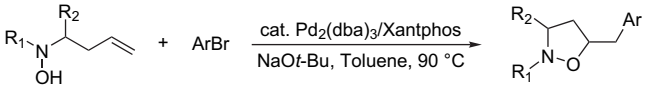
[a] Conditions: 1.0 equiv of hydroxylamine, 1.2 equiv of PhBr, 1.2 equiv of base, solvent (0.1 M), 90 °C.

[b] Isolated yield of **8a**.

[c] The cis/trans ratio of **8a** was based on ^1H NMR analysis.

[d] Complete recovery of starting material.

Table 2
Palladium-catalyzed synthesis of 5-arylmethylisoxazolidines from corresponding hydroxylamines with aryl bromides[a]



Entry	Hydroxylamine	Ar	Product	Cis/trans[b]	Yield[c] (%)
1	**3** (R_1=benzyl, R_2=Ph)	Ph	**8a**	37:63	69 84[d]
2	**3**	*p*-Me−Ph	**8b**	32:68	58 78[d]
3	**3**	*p*-NO_2−Ph	**8c**	45:55	18 32[d]
4	**3**	*p*-Biphenyl	**8d**	23:77	93[d]
5	**3**	2,4-Dimethylphenyl	**8e**	42:58	87[d]
6	**3**	*p*-CH_3CO−Ph	**8f**	40:60	58[d]
7	**3**	*p*-CHO−Ph	**8g**	41:59	40[d]
8	**3**	*o*-Biphenyl	**8h**	62:38	58[d]
9	**4** (R_1=benzyl, R_2=H)	*p*-Me−Ph	**9a**	—	73 75[d]
10	**4**	*o*-Cl−Ph	**9b**	—	76
11	**4**	*p*-MeO−Ph	**9c**	—	78
12	**4**	*p*-NO_2−Ph	**9d**	—	11
13	**5** (R_1=cyclohexyl, R_2=H)	*p*-CN−Ph	**10a**	—	71
14	**5**	*o*-*i*-Pr−Ph	**10b**	—	0
15	**6** (R_1=cyclohexyl, R_2=Ph)	Ph	**11**	30:70	82
16	**7** (R_1=R_2=−$(CH_2)_4$−)	Pyridin-3-yl	**12a**	0:100	72
17	**7**	*o*-Cl−Ph	**12b**	0:100	85

[a] Conditions: 1.0 equiv of hydroxylamine, 1.2 equiv of ArBr, 1 mol % of $Pd_2(dba)_3$, 2 mol % of Xantphos, 1.2 equiv of NaO-*t*-Bu, toluene (0.1 M), 90 °C.
[b] The cis/trans ratio was based on ^{1}H NMR analysis.
[c] Isolated yield. In the case of entries 1−8, it was an isolated yield of two isomers. In the case of entry 12, we were unable to isolate pure cyclized compound **9d**.
[d] Catalyst loading was 2 mol % of $Pd_2(dba)_3$ and 4 mol % of Xantphos instead.

absence of palladium or ligand produced no desired isoxazolidine after 5 h at 90 °C (entries 15 and 16).

With the optimized reaction conditions in hand, we prepared a wide range of 5-arylmethylisoxazolidines (Table 2). A number of *N*-homoallylhydroxylamines and aryl bromides underwent the intramolecular ring closure with generation of a C−O bond, a C−C bond, and a stereocenter in a single step to form the 5-benzylisoxazolidines. In contrast to the conversion of *O*-homoallylhydroxylamines to 3-arylmethylisoxazolidine derivatives,[12a] the high yields were obtained with both electron-neutral and electron-rich aryl bromides (entries 1, 2, 4, 9, 11, and 15), though electron-deficient aryl bromides slightly reduced the yields (entries 6, 7, and 13). However, nitrophenyl bromide served as less effective substrate to form isoxazolidines (entries 3 and 12); in the case of entry 3, a large amount of the imine **13** (Fig. 1) as by-product was detected after stirring at 90 °C for 5 h and in the case of entry 12, the yield was very low, generating lots of complex mixtures that we have not further investigated. Several functional groups are tolerated under these conditions (entries 6, 7, 10, 13, and 17) and the heteroaryl bromide also afforded the corresponding product in good yield (entry 16). Stereo-hindered *o*-methyl (entry 5), *o*-phenyl (entry 8), and *o*-chloro (entries 10 and 17) substituted aryl bromides had little influence on the yield. On the contrary, *o*-isopropylphenyl bromide failed to undergo the palladium-catalyzed cascade conversion (entry 14), presumably due to the large blocking group at the *o*-position of the aryl bromide.

In the cascade transformations of *N*-homoallylhydroxylamine substrates bearing substituents at the position α to nitrogen atom, moderate diastereoselectivities were observed (entries 1−8, Table 2). However, in the case of conversion of the cyclohydroxylamine **7**, a single diastereoisomer[15] was obtained (entries 16 and 17). The stereochemistry of a number of the isoxazolidine products were determined by NOESY studies. For example, the stereochemistry of the major isomer of **8a** was confirmed to be trans because no correlation between the protons H-3 and H-5 was observed in its NOESY experimental data, while a distinct correlation between the two protons was

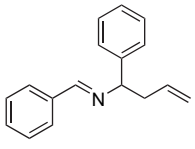


Figure 1. Imine **13**.

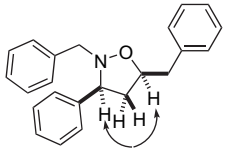
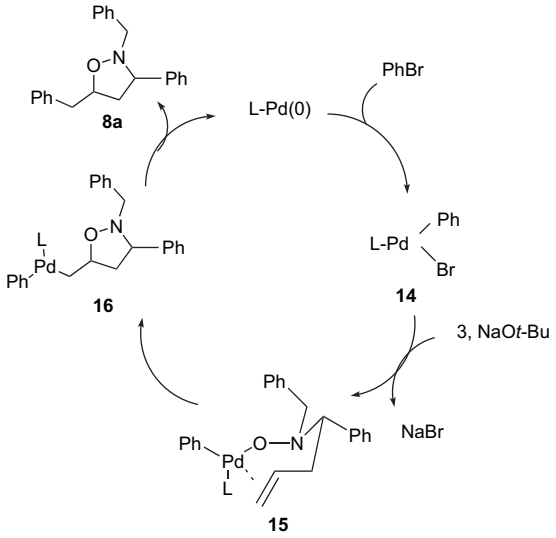


Figure 2. The ^{1}H NOESY experimental data showing a distinct correlation between the protons H-3 and H-5 of the minor isomer of **8a**.

detected in the NOESY experimental data of the minor isomer of **8a** (Fig. 2).

The suggested mechanism of this reaction, taking the transformation of the *N*-homoallylhydroxylamine **3** to isoxazolidine **8a**, as an example, is shown in Scheme 1. Oxidative addition of phenyl bromide to Pd(0) would lead to **14**, which would be transformed to **15** in the presence of NaO-*t*-Bu and hydroxylamine **3**. A *syn* insertion of the alkene into the Pd–O bond would give **16**, which would undergo C–C bond forming reductive elimination to afford the desired compound **8a** and regenerate the Pd(0) catalysis. The reason for transformations of *N*-homoallylhydroxylamines bearing a substituent at 1-position with low level of diastereoselectivities was not clear yet.



Scheme 1. Proposed catalytic cycle.

3. Conclusion

We developed a new, palladium-catalyzed route to 5-benzylisoxazolidines via intramolecular C–O bond formation and intermolecular C-arylation in a single step with concomitant formation of one new stereocenter. The chemistry developed herein together with our previous work should be thus particularly useful in the diversity-oriented synthesis of isoxazolidines. Studies on the mechanism of the diastereoselectivities as well as the applications of this methodology to the synthesis of complex molecules are currently undergoing.

4. Experimental

4.1. General

Chemicals and solvents were all purchased from commercial supplies and purified by standard techniques. NMR spectra were recorded on a Bruker-300 MHz spectrometer; ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts (δ) are given in parts per million (ppm) downfield relative to $CDCl_3$. Coupling constants are given in hertz (Hz). In assignment of the ^{1}H NMR spectra, multiplicities and abbreviations used are as follows: Ar=aromatic, Ph=phenyl, d=doublet, dd=doublet of doublets, m=multiplet, q=quartet, s=singlet, t=triplet. High-resolution mass spectra were recorded on a Bruker BIOTOF Q mass spectrometer.

4.2. General procedure for the preparation of N-homoallylhydroxylamine substrates

A solution of nitrone (1 equiv) in dry ether (0.25 M) was stirred at room temperature as allylmagnesium bromide in ether (0.30 M) was added. The resulting white suspension was stirred for 1 h, and saturated ammonium chloride was added at 0 °C. The ether layer was separated from the aqueous layer, which was extracted twice with ether. The combined ether layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with 5–10% ethyl acetate–petroleum ether.

4.2.1. Compound **3**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.38 (m, 10H), 6.25 (br, 1H), 5.52–5.68 (m, 1H), 4.92–5.02 (m, 2H), 3.72–3.78 (m, 2H), 3.57 (d, J=13.3 Hz, 1H), 2.89–2.92 (m, 1H), 2.58–2.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.2, 135.5, 129.4, 128.9, 128.3, 128.2, 127.5, 127.2, 116.6, 71.8, 61.4, 38.2.

4.2.2. Compound **4**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 7.00 (br, 1H), 5.76–5.82 (m, 1H), 5.01–5.11 (m, 2H), 3.78 (s, 2H), 2.74 (t, J=7.2 Hz, 2H), 2.31–2.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 136.2, 129.9, 128.3, 127.5, 115.7, 64.8, 58.7, 31.4.

4.2.3. Compound **5**

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (br, 1H), 5.78–5.87 (m, 1H), 4.97–5.10 (m, 2H), 2.77 (t, J=7.2 Hz, 2H), 2.49–2.55 (m, 1H), 2.32–2.39 (m, 2H), 1.93–1.95 (m, 2H), 1.78–1.80 (m, 2H), 1.55–1.63 (m, 1H), 1.17–1.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 115.6, 65.7, 54.7, 31.6, 28.7, 26.0, 25.4.

4.2.4. Compound **6**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.33 (m, 5H), 5.61–5.63 (m, 1H), 4.89–5.01 (m, 2H), 4.40 (br, 1H), 3.98 (dd, J=9.0, 5.2 Hz, 1H), 2.77–2.83 (m, 1H), 2.52–2.58 (m, 1H), 2.44–2.52 (m, 1H), 1.85–1.90 (m, 2H), 1.71–1.75 (m, 2H), 1.52–1.56 (m, 1H), 1.35–1.39 (m, 2H), 1.10–1.12 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 135.9, 128.8, 128.1, 127.1, 116.2, 66.8, 61.0, 30.1, 26.0, 25.2, 24.8.

4.2.5. Compound **7**

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br, 1H), 5.69–5.77 (m, 1H), 4.95–5.02 (m, 2H), 3.22–3.26 (m, 1H), 2.73–2.79 (m, 1H), 2.43–2.47 (m, 1H), 2.28–2.29 (m, 1H), 1.97–2.01 (m, 1H), 1.75–1.79 (m, 1H), 1.51–1.63 (m, 3H), 1.09–1.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 116.6, 66.8, 59.6, 37.8, 30.6, 25.7, 23.5.

4.3. General procedure for the palladium-catalyzed cascade synthesis of 5-arylmethylisoxazolidines

A flame-dried two-neck round-bottomed flask equipped with a reflux condenser was cooled under a stream of nitrogen and charged with *N*-homoallylhydroxylamine (1 equiv), $Pd_2(dba)_3$ (1 mol %), Xantphos (2 mol %), and NaO-*t*-Bu (1.2 equiv). The flask was purged with nitrogen and a solution of aryl bromide (1.2 equiv) in toluene (5 mL) was added through syringe. The mixture was heated to 90 °C with stirring until the hydroxylamine was consumed completely as judged by TLC. The reaction mixture was cooled to room temperature, followed by the addition of saturated ammonium chloride and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtrated, and concentrated in vacuo to give the crude product, which was then purified by chromatography on silica gel.

4.3.1. (±)-(3,5-cis)-3-Phenyl-2,5-diphenylmethyl-isoxazolidine (**8a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.47 (m, 15H), 4.43–4.48 (m, 1H), 4.03 (d, J=14.0 Hz, 1H), 3.93 (dd, J=8.4, 8.1 Hz, 1H), 3.84 (d, J=14.0 Hz, 1H), 3.23 (dd, J=13.5, 7.0 Hz, 1H), 2.76–2.86 (m, 2H), 2.16–2.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.5, 137.9, 129.4, 128.8, 128.6, 128.2, 128.0, 127.5, 127.4, 126.9, 126.1, 77.8, 70.6, 60.0, 45.1, 41.8. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{24}NO$, 330.1727; found, 330.1729.

4.3.2. (±)-(3,5-trans)-3-Phenyl-2,5-diphenylmethyl-isoxazolidine (**8a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.44 (m, 15H), 4.51–4.56 (m, 1H), 4.00 (d, J=14.1 Hz, 1H), 3.82 (d, J=14.1 Hz, 1H), 3.77 (dd, 1H), 3.11 (dd, J=13.7, 5.3 Hz, 1H), 2.86 (dd, J=13.7, 7.3 Hz, 1H), 2.31–2.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 137.7, 129.4, 128.9, 128.5, 128.3, 128.2, 128.0, 127.7, 127.5, 127.0, 126.3, 77.4, 69.9, 60.0, 43.8, 40.8. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{24}NO$, 330.1727; found, 330.1729.

4.3.3. (±)-(3,5-cis)-2-Benzyl-3-phenyl-5-(4-methylbenzyl)-isoxazolidine (**8b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.46 (m, 10H), 7.03–7.05 (m, 4H), 4.38–4.43 (m, 1H), 4.00 (d, J=14.1 Hz, 1H), 3.91 (dd, J=7.9, 7.9 Hz, 1H), 3.81 (d, J=14.1 Hz, 1H), 3.16 (dd, J=13.5, 6.9 Hz, 1H), 2.73–2.79 (m, 2H), 2.32 (s, 3H), 2.12–2.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.0, 135.6, 135.5, 129.2, 128.9, 128.8, 128.6, 128.0, 127.7, 127.5, 126.9, 78.0, 70.6, 60.1, 45.1, 41.4, 21.0. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO$, 366.1828; found, 366.1826.

4.3.4. (±)-(3,5-trans)-2-Benzyl-3-phenyl-5-(4-methylbenzyl)isoxazolidine (**8b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.39 (m, 10H), 7.11–7.12 (m, 4H), 4.44–4.48 (m, 1H), 3.95 (d, J=14.1 Hz, 1H), 3.76 (d, J=14.1 Hz, 1H), 3.73–3.75 (m, 1H), 3.04 (dd, J=13.6, 5.1 Hz, 1H), 2.76 (dd, J=13.6, 7.5 Hz, 1H), 2.27–2.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 137.8, 135.8, 134.7, 129.3, 129.0, 128.5, 128.1, 127.9, 127.7, 127.5, 127.0, 77.6, 69.9, 60.1, 43.8, 40.4, 21.0. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO$, 366.1828; found, 366.1826.

4.3.5. (±)-(3,5-trans)-2-Benzyl-3-phenyl-5-(4-nitrobenzyl)-isoxazolidine (**8c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=8.7 Hz, 2H), 7.27–7.40 (m, 12H), 4.47–4.51 (m, 1H), 3.93 (d, J=14.0 Hz, 1H), 3.72 (d, J=14.0 Hz, 1H), 3.67–3.69 (m, 1H), 2.96–3.10 (m, 2H), 2.32–2.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 145.7, 130.3, 129.1, 128.7, 128.1, 127.8, 127.7, 127.2, 125.6, 123.4, 122.6, 76.5, 69.8, 59.8, 43.9, 40.6. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{23}N_2O_3$, 375.1703; found, 375.1717.

4.3.6. (±)-(3,5-trans)-2-Benzyl-3-phenyl-5-(4-phenyl-benzyl)isoxazolidine (**8d**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.58 (m, 4H), 7.29–7.44 (m, 15H), 4.49–4.52 (m, 1H), 3.96 (d, J=14.2 Hz, 1H), 3.78 (d, J=14.2 Hz, 1H), 3.76–3.78 (m, 1H), 3.10 (dd, J=13.7, 5.4 Hz, 1H), 2.86 (dd, J=13.7, 7.1 Hz, 1H), 2.29–2.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 140.0, 139.2, 137.7, 136.9, 129.8, 129.4, 129.0, 128.8, 128.7, 128.6, 128.5, 128.1, 127.7, 127.5, 126.9, 77.4, 69.9, 60.0, 43.8, 40.5. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO$, 428.1985; found, 428.2010.

4.3.7. (±)-(3,5-trans)-2-Benzyl-3-phenyl-5-(2,4-dimethyl-benzyl)isoxazolidine (**8e**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.46 (m, 10H), 6.96–7.06 (m, 3H), 4.48–4.51 (m, 1H), 4.02 (d, J=13.9 Hz, 1H), 3.85 (d, J=13.9 Hz, 1H), 3.78–3.85 (m, 1H), 3.08 (dd, J=14.3, 5.2 Hz, 1H), 2.81 (dd, J=14.3, 6.7, 1H), 2.37–2.40 (m, 2H), 2.32 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 137.7, 136.3, 135.8, 133.0, 131.0, 129.8, 129.0, 128.5, 128.0, 127.7, 127.5, 127.0, 126.4, 77.0, 69.9, 60.1, 44.0, 37.6, 20.7, 19.7. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO$, 380.1985; found, 380.1987.

4.3.8. (±)-(3,5-trans)-2-Benzyl-3-phenyl-5-(4-acetylbenzyl)-isoxazolidine (**8f**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J=8.4, 2H), 7.26–7.38 (m, 12H), 4.47–4.49 (m, 1H), 3.98 (d, J=13.9 Hz, 1H), 3.74 (d, J=13.9 Hz, 1H), 3.71–3.73 (m, 1H), 3.06 (dd, J=13.1, 5.9 Hz, 1H), 2.89 (dd, J=13.1, 6.5 Hz, 1H), 2.59 (s, 3H), 2.30–2.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 143.6, 139.7, 137.6, 135.5, 129.7, 129.0, 128.6, 128.4, 128.1, 127.7, 127.5, 127.1, 76.8, 69.9, 59.8, 43.8, 40.8, 26.5. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{25}NNaO_2$, 394.1778; found, 394.1796.

4.3.9. (±)-4-(((3,5-trans)-2-Benzyl-3-phenylisoxazolidin-5-yl)methyl)benzaldehyde (**8g**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.80 (d, J=8.1 Hz, 2H), 7.29–7.41 (m, 12H), 4.49–4.51 (m, 1H), 3.97

(d, J=13.7 Hz, 1H), 3.73 (d, J=13.7 Hz, 1H), 3.69–3.73 (m, 1H), 3.08 (dd, J=12.8, 6.1 Hz, 1H), 2.95 (dd, J=12.8, 6.2 Hz, 1H), 2.32–2.37 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 145.2, 139.6, 137.5, 134.8, 130.2, 129.7, 129.0, 128.6, 128.1, 127.7, 127.5, 127.1, 77.1, 69.9, 59.8, 43.8, 40.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{23}NNaO_2$, 380.1621; found, 380.1623.

*4.3.10. (±)-(3,5-cis)-2-Benzyl-3-phenyl-5-(2-phenylbenzyl)-isoxazolidine (**8h**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.42 (m, 19H), 4.23–4.27 (m, 1H), 3.92 (d, J=14.1 Hz, 1H), 3.79 (dd, J=8.4, 8.1 Hz, 1H), 3.72 (d, J=14.1 Hz, 1H), 3.15 (dd, J=13.8, 7.2 Hz, 1H), 2.91 (dd, J=13.8, 6.2 Hz, 1H), 2.55–2.59 (m, 1H), 1.90–1.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 141.8, 140.1, 137.9, 135.9, 130.7, 130.0, 129.4, 128.9, 128.5, 128.1, 128.0, 127.5, 127.4, 127.2, 126.9, 126.8, 126.1, 77.2, 70.5, 59.8, 44.9, 38.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO$, 428.1985; found, 428.2007.

*4.3.11. (±)-2-Benzyl-5-(4-methylphenylmethyl)-isoxazolidine (**9a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.41 (m, 5H), 7.10–7.13 (m, 4H), 4.30–4.46 (m, 1H), 3.96–4.05 (m, 1H), 3.75–3.96 (m, 1H), 3.15–3.20 (m, 1H), 3.01 (dd, J=13.7, 5.9 Hz, 1H), 2.74 (dd, J=13.7, 7.1 Hz, 1H), 2.33 (s, 3H), 2.20–2.28 (m, 1H), 1.96–2.02 (m, 1H), 1.82–1.96 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 135.7, 135.0, 129.2, 129.0, 128.9, 128.2, 127.2, 78.1, 62.0, 54.1, 40.7, 33.3, 21.0. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{22}NO$, 268.1696; found, 268.1709.

*4.3.12. (±)-2-Benzyl-5-(2-chlorophenylmethyl)-isoxazolidine (**9b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.39 (m, 7H), 7.15–7.17 (m, 2H), 4.46–4.52 (m, 1H), 3.96 (br, 1H), 3.86 (br, 1H), 3.11 (dd, J=13.9, 6.8 Hz, 1H), 3.08–3.15 (m, 1H), 2.99 (dd, J=13.9, 6.0 Hz, 1H), 2.81–2.86 (m, 1H), 2.35 (br, 1H), 1.97–2.03 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.0, 134.1, 131.7, 129.3, 129.1, 128.3, 127.7, 127.3, 126.6, 76.2, 62.0, 54.1, 38.6, 33.5. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{19}ClNO$, 288.1150; found, 288.1139.

*4.3.13. (±)-2-Benzyl-5-(4-methoxyphenylmethyl)-isoxazolidine (**9c**)*

^{1}H NMR (300 MHz, CD_3OD) δ 7.27–7.36 (m, 5H), 7.13 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 4.45 (br, 1H), 3.99 (br, 1H), 3.81–3.82 (m, 1H), 3.75 (s, 3H), 3.07 (br, 1H), 2.74–2.89 (m, 3H), 2.38 (br, 1H), 1.97–2.01 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 159.7, 133.2, 131.4, 130.6, 129.3, 128.5, 116.9, 114.7, 79.3, 62.5, 55.6, 54.6, 41.0, 34.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{21}NNaO_2$, 306.1465; found, 306.1460.

*4.3.14. (±)-2-Cyclohexyl-5-(4-cyanophenylmethyl)-isoxazolidine (**10a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 4.16–4.25 (m, 1H), 3.22 (br, 1H), 2.99 (br, 1H), 2.80 (br, 1H), 2.31–2.42 (m, 3H), 1.93–2.09 (m, 2H), 1.58–1.90 (m, 4H), 1.21–1.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 132.0, 130.1, 119.0, 110.1, 76.2, 64.9, 52.3, 41.6, 34.4, 31.0, 25.0, 24.5. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{23}N_2O$, 271.1805; found, 271.1808.

*4.3.15. (±)-(3,5-trans)-5-Benzyl-2-cyclohexyl-3-phenylisoxazolidine (**11**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.44 (m, 10H), 4.35–4.38 (m, 1H), 4.18–4.20 (m, 1H), 3.14 (dd, J=13.7, 6.4 Hz, 1H), 2.74 (dd, J=13.7, 6.9 Hz, 1H), 2.67–2.71 (m, 1H), 2.03–2.16 (m, 2H), 1.75–1.79 (m, 2H), 1.64–1.68 (m, 2H), 1.16–1.18 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.5, 129.2, 128.4, 128.3, 128.1, 126.3, 126.2, 78.0, 67.4, 64.5, 46.4, 40.4, 31.1, 29.6, 25.9. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{28}NO$, 322.2165; found, 322.2164.

*4.3.16. (±)-(2,3b-trans)-2-(Pyridin-3-ylmethyl)-piperidino-[1,2-b]isoxazolidine (**12a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.41 (d, J=3.9 Hz, 1H), 7.56 (d, J=7.8 Hz, 1H), 7.16–7.20 (m, 1H), 4.16–4.23 (m, 1H), 3.38–3.41 (m, 1H), 3.04 (dd, J=13.8, 8.0 Hz, 1H), 2.69 (dd, J=13.8, 5.3 Hz, 1H), 2.38–2.39 (m, 2H), 2.31–2.33 (m, 1H), 1.87–1.90 (m, 1H), 1.63–1.73 (m, 4H), 1.38–1.46 (m, 1H), 1.19–1.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 147.5, 136.8, 134.4, 123.2, 76.2, 67.3, 55.1, 41.0, 40.0, 29.1, 24.6, 23.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{18}N_2NaO$, 241.1311; found, 241.1308.

*4.3.17. (±)-(2,3b-trans)-2-(2-Chlorophenylmethyl)-piperidino[1,2-b]isoxazolidine (**12b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.31 (m, 2H), 7.08–7.18 (m, 2H), 4.31–4.36 (m, 1H), 3.39–3.42 (m, 1H), 3.12 (dd, J=13.6, 7.7 Hz, 1H), 2.94 (dd, J=13.6, 5.7 Hz, 1H), 2.28–2.40 (m, 2H), 2.17–2.24 (m, 1H), 1.86–1.90 (m, 1H), 1.66–1.75 (m, 4H), 1.36–1.41 (m, 1H), 1.15–1.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 133.9, 131.6, 129.1, 127.5, 126.5, 74.7, 67.2, 55.1, 40.8, 40.4, 29.0, 24.6, 23.6. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}ClNO$, 252.1150; found, 252.1159.

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