Palladium-catalyzed sequential one-pot reaction of aryl bromides with *O*-homoallylhydroxylamines: synthesis of *N*-aryl-β-amino alcohols†

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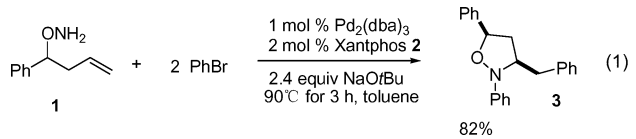
The palladium-catalyzed sequential one-pot *N*-arylation–carbo-amination–*C*-arylation of *O*-homoallylhydroxylamines with two different aryl bromides provides rapid entry to differentially arylated *N*-aryl-3-arylmethylisoxazolidines in good yields with excellent diastereoselectivity. The obtained isoxazolidines can be reductively cleaved to *cis*-*N*-aryl-β-amino alcohols in short times and in high yields at room temperature.

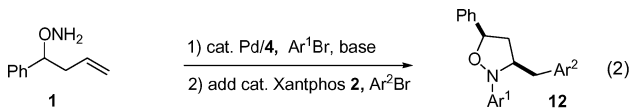
Introduction

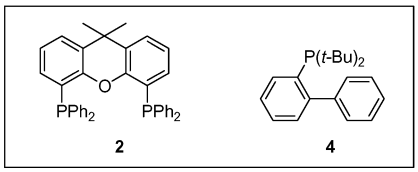
The synthesis of isoxazolidine derivatives has received much attention as they are useful synthons for the construction of biologically important amino acids, *β*-lactams, *β*-amino alcohols, amino carbohydrates and alkaloids.[1] The 1,3-dipolar cycloaddition of nitrones with alkenes was among the important reactions for the construction of substituted isoxazolidines. However, this synthetic methodology usually failed to control the stereoselectivity in reactions of acyclic nitrones with simple terminal alkenes.[2] A number of different synthetic methods have been devised for their preparation.[3] Over the past several years, the palladium-catalyzed tandem synthesis of pyrrolidine derivatives was reported *via* intramolecular insertion of an olefin into a Pd(Ar)(ArNR) intermediate.[4] Recently, Dongol and Tay[3d] reported the Pd-catalyzed cascade reaction of *N*-Boc protected *O*-homoallylhydroxylamines with aryl iodides to afford the corresponding isoxazolidines, contaminated by substantial Heck type side products with modest diastereoselectivity. Herein, we report on stereocontrolled palladium-catalyzed syntheses of differentially arylated *N*-aryl-3-arylmethylisoxazolidines *via* sequential one-pot diarylation of *O*-homoallylhydroxylamines with two different aryl bromides.

Results and discussions

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] To determine the feasibility of the *N*-arylation–carboamination process, we first examined the reaction of *O*-homoallylhydroxylamine (**1**) with 2.05 equiv. of bromobenzene. We were pleased to find that the use of a catalyst comprising $Pd_2(dba)_3$ and Xantphos (**2**)[5] in the presence of NaO*t*Bu (2.4 equiv.) in toluene provided the desired *cis* product **3** in 82% isolated yield (eqn (1)). Having demonstrated the viability of the one-pot diarylation process of *O*-homoallylhydroxylamine, we set out to examine the selective addition reaction of two different aryl bromides (eqn (2)). A transformation of this type would lead to the formation of two C–N bonds, one C–C bond and one ring in a single operation.







In order to carry out this process, we judiciously screened the palladium catalyst, ligand and reaction temperature. Some results from that study are summarized in Table 1. We chose to employ monodentate ligands for the first step of the reaction sequence. Chelating bis(phosphine) ligands, which have been found to be effective in a broad range of carboamination processes,[4e] were employed for the second reaction of the sequence. Using a catalyst comprising $Pd_2(dba)_3$/P(*o*-tol)$_3$/Xantphos, no desired product was formed (entry 1, Table 1). Changing the mono(phosphine) ligand from P(*o*-tol)$_3$ to (furyl)$_3$P, the monoarylation product of the primary hydroxylamine was obtained and the second step of the reaction did not proceed, perhaps due to failure in the ligand exchange (entry 2, Table 1). BINAP, 2-di-*tert*-butylphosphinobiphenyl (**4**) and 2-dicyclohexylphosphinobiphenyl (**5**) were found to be highly effective and selective for the Pd-catalyzed monoarylation of primary aliphatic amines.[4d,6] When we examined this type of phosphine ligands, we were pleased to find that the ligand combination of **4**/Xantphos provided the desired product **12a**[7] in 55% isolated yield (entries 3–5, Table 1). We then carefully screened various bis(phosphine) ligands (dppe, dppb, dppf and DPE-phos[5]) for

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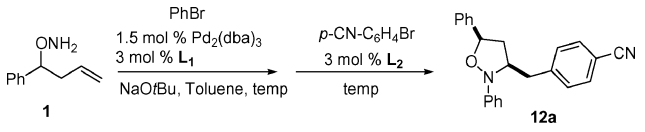
Table 1 Pd-Catalyzed sequential one-pot reaction condition optimization[a]



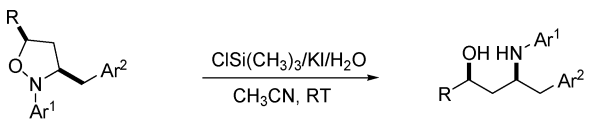
Entry	L_1/Temp	L_2/Temp	Yield (%)[b]
1	P(*o*-tol)$_3$/100 °C	Xantphos/100 °C	0
2	(furyl)$_3$P/100 °C	Xantphos/100 °C	0[c]
3	BINAP/100 °C	Xantphos/100 °C	0[c]
4	**4**/60 °C	Xantphos/90 °C	23[d]
5	**4**/40 °C	Xantphos/90 °C	55
6	**5**/40 °C	Xantphos/90 °C	16
7	**4**/40 °C	Dppe/100 °C	29
8	**4**/40 °C	Dppb/100 °C	27
9	**4**/40 °C	Dppf/100 °C	32
10	**4**/40 °C	DPE-phos/100 °C	18

[a] Conditions: 1.0 equiv. of hydroxylamine, 1.0 equiv. of PhBr, 2.4 equiv. of NaO*t*Bu, 1.5 mol% $Pd_2(dba)_3$, 3 mol% L_1, toluene (0.2 M), then 3 mol% L_2, 1.2 equiv. of *p*-CN–C_6H_4Br. [b] Yield of isolated product. [c] *N*-Phenyl-3-phenyl-*O*-homoallylhydroxylamine was isolated. [d] *N*-Biarylation product was also isolated from the reaction mixture.

the second reaction of the sequence, however, worse results were observed (entries 7–10, Table 1).

With the optimized reaction condition in hand, we prepared a large range of differentially arylated *N*-aryl-3-arylmethylisoxazolidine derivatives (Table 2). As shown in Table 2, this method is effective for the conversion of a variety of *O*-homoallylhydroxylamines to *N*-aryl-3-arylmethylisoxazolidine derivatives. In general, electron-neutral, -deficient or -rich aryl bromides as the first coupling partner are efficiently transformed in the first step of the sequential reaction (entries 1–3, Table 2). Electron-neutral, -deficient, or hetero aryl bromides as the second coupling partner provide the best yield in the second step of the sequential transformation (entries 1–8, Table 2). The tandem transformations of substrates **1** and **6–11**, which bear substituents at the 1-position, proceeded with high levels of diastereoselectivity.[7] Reactions of 1-aryl-*O*-homoallylhydroxylamines **1** and **6–9** exclusively afforded 3,5-*cis*-disubstituted isoxazolidines (entries 1–12, Table 2). Transformation of 1-styryl-*O*-homoallylhydroxylamine **10** also proceeded (entry 13, Table 2), and 1-alkyl-*O*-homoallylhydroxylamine **11** was transformed to 3,5-*cis*-disubstituted products as their *cis* isomers (entry 14, Table 2).

The sequential one-pot differential diarylation of *O*-homoallylhydroxylamine was further utilized for the synthesis of *cis*-*N*-aryl-β-amino alcohols[8] **13a–c** (Scheme 1). The most common methods for the reductive ring opening of isoxazolidines include $LiAlH_4$, catalytic hydrogenation and zinc in acetic acid.[9] Our initial screening with these methods proved unsuccessful in providing the desired *N*-aryl-β-amino alcohols. When *N*-aryl-3-arylmethylisoxazolidines were subjected to a reaction mixture of chlorotrimethyl silane, water and KI in acetonitrile at room temperature,[10] the desired *cis*-β-amino alcohol[11] was formed in high yield (>97%).

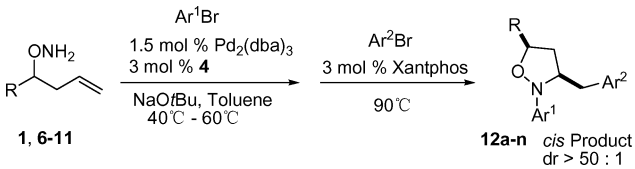


3	R = Ph, Ar^1, Ar^2 = Ph	**13a**	98%
12a	R = Ph, Ar^1 = Ph, Ar^2 = *p*-CN-Ph,	**13b**	97%
12f	R = tolyl, Ar^1 = Ph, Ar^2 = Pyridin-2-yl,	**13c**	98%

Scheme 1 Synthesis of *N*-aryl-β-amino alcohols **13a–c**.

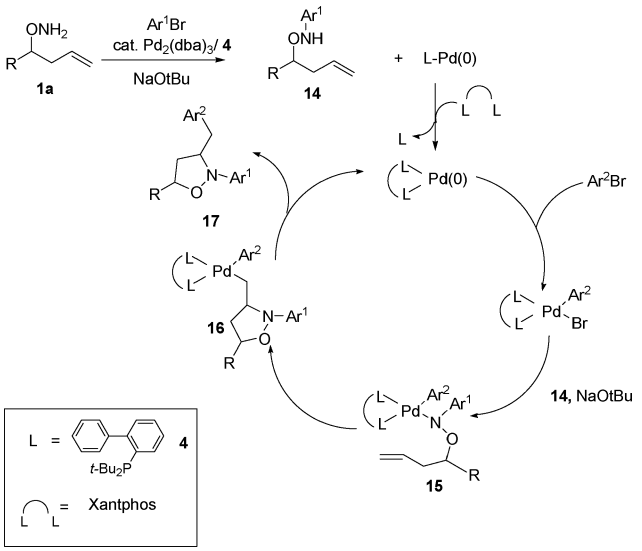
A proposed reaction mechanism of the tandem one-pot arylation of *O*-homoallylhydroxylamines to isoxazolidine derivatives is shown in Scheme 2. This transformation presumably occurs through initial Pd/**4**-catalyzed *N*-arylation of hydroxylamine **1a**

Table 2 Palladium-catalyzed stereoselective synthesis of *N*-aryl-3-arylmethylisoxazolidine derivatives[a]



Entry	R	Ar^1	Ar^2	Product	Yield (%)[b]
1	Ph, **1**	Ph	*p*-CN-Ph	**12a**	55
2	Ph, **1**	*p*-Cl–Ph	*p*-CN–Ph	**12b**	52
3	Ph, **1**	*p*-MeO–Ph	*p*-CN–Ph	**12c**	64
4	Ph, **1**	Ph	*p*-(1,3-Dioxolan-2-yl)phenyl	**12d**	58
5	Ph, **1**	Ph	*p*-Biphenyl	**12e**	63
6	*p*-Me–Ph, **6**	Ph	Pyridin-2-yl	**12f**	66
7	**6**	Ph	Pyridin-3-yl	**12g**	64
8	**6**	Ph	Pyridin-4-yl	**12h**	62
9	2-Thienyl, **7**	*p*-CO_2tBu–Ph	Ph	**12i**	51
10	**7**	*p*-NO_2–Ph	*p*-Me–Ph	**12j**	54
11	*p*-Cl–Ph, **8**	*p*-CN–Ph	*p*-CO_2tBu–Ph	**12k**	67
12	*p*-MeO–Ph, **9**	Ph	*p*-Me–Ph	**12l**	57
13[c]	(*E*)-styryl, **10**	*p*-NO_2–Ph	Ph	**12m**	53
14	$TBSOCH_2$, **11**	*p*-biphenyl	Ph	**12n**	49

[a] Conditions: 1.0 equiv. of hydroxylamine, 1.0 equiv. of Ar^1Br, 2.4 equiv. of NaO*t*Bu, 1.5 mol% $Pd_2(dba)_3$, 3 mol% **4**, toluene (0.2 M), 40–60 °C, then 3 mol% Xantphos, 1.2 equiv. of Ar^2Br, 90 °C. [b] Yield of isolated product. [c] This material contained *ca.* 17% of the corresponding (*E*)-1-phenylhexa-2,5-dien-1-hydroxylamine as an inseparable impurity.



Scheme 2 Proposed catalytic cycle.

with the first aryl bromide to form intermediate **14** and Pd(0), then a key substitution of the Xantphos ligand for **4** is proposed to occur. Oxidative addition of the second aryl bromide to the Xantphos/Pd(0) species is followed by reaction of the resulting complex with **14** and base to afford an intermediate [Pd(Ar)-(RONAr)] complex **15**. A *syn* insertion of the alkene into the Pd–N in **15** then affords the carboamination intermediate **16**. Complex **16** undergoes C–C bond forming reductive elimination to afford the product **17**.

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 **15** (Scheme 2). As shown below (Scheme 3), the conversion of 1-substituted *N*-aryl-*O*-homoallylhydroxylamine **14** to *cis*-3,5-disubstituted isoxazolidine **17a** proceeds *via* conformer **15a**. In this conformer **15a**, the R substituent is oriented in the pseudoequatorial position to minimize nonbonding interactions with the *N*-aryl group and C-3 hydrogen, moreover, *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 **15b** in which the R group is oriented in the pseudoaxial position. The alkene insertion *via* **15a** would afford intermediate **16a**, which would provide the observed *cis*-3,5-disubstituted product **17a** upon C–C bond-forming reductive elimination.

Conclusions

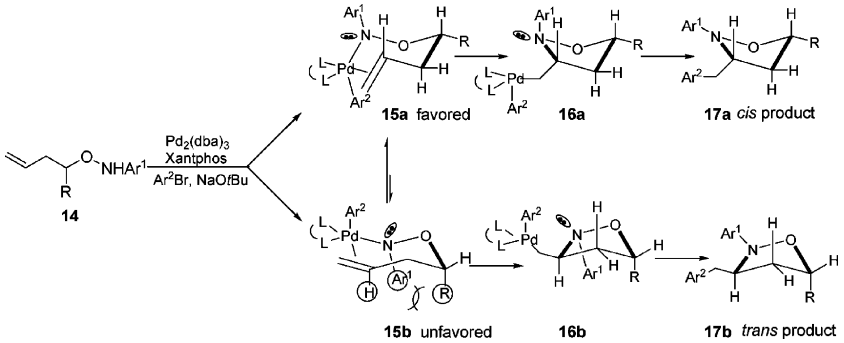
In summary, we have successfully developed an efficient protocol for the palladium-catalyzed stereoselective synthesis of *N*-aryl-3-arylmethylisoxazolidines *via* sequential *N*-arylation–cyclization–*C*-arylation of *O*-homoallylhydroxylamines with two different aryl bromides. The selective diarylation is achieved in a one-pot process by an *in situ* modification of the palladium catalyst *via* phosphine ligand exchange. The obtained isoxazolidines can be reductively cleaved to *N*-aryl-β-amino alcohols in short times and in high yields at room temperature.

Experimental

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). Unless otherwise stated deuterochloroform ($CDCl_3$) was used as solvent. In assignment of the ^{1}H NMR spectra, multiplicities and abbreviations used are as follows; Ar = aromatic, Ph = phenyl, Py = pyridyl, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer.

General procedure for the preparation of *O*-homoallylhydroxylamine substrates

A solution of DEAD (1.5 equiv.) in dry THF (0.25 M) was added dropwise to a solution of the homoallylic alcohol,[3] triphenylphosphine (1.2 equiv.) and *N*-hydroxyphthalimide (1.2 equiv.) in dry THF (0.25 M) under nitrogen at 0 °C. The mixture was allowed to warm to room temperature and stirred for five hours. THF was then evaporated and the residue was purified by flash chromatography on silica gel, eluting with 5–10% ethyl acetate–hexane. The product was dissolved in dichloromethane (*ca.* 0.3 M). Hydrazine hydrate (3 equiv.) was added and the mixture was stirred at room temperature for four hours. The



Scheme 3 Proposed stereochemistry of 3,5-disubstituted isoxazolidines.

mixture was filtered through celite, washing with dichloromethane, and the dichloromethane was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 5–10% ethyl acetate–petroleum ether.

Hydroxylamine 6. ^{1}H (300 MHz, $CDCl_3$) δ 7.17–7.26 (m, 4H), 5.73–5.78 (m, 1H), 5.20 (br, 2H), 5.02–5.11 (m, 2H), 4.50–4.55 (m, 1H), 2.57–2.60 (m, 1H), 2.38–2.44 (m, 1H), 2.36 (s, 3H). ^{13}C (75 MHz, $CDCl_3$) δ 138.2, 137.4, 134.5, 129.1, 126.7, 116.9, 86.4, 40.4, 21.1.

Hydroxylamine 7. ^{1}H (300 MHz, $CDCl_3$) δ 7.28–7.30 (m, 1H), 6.98–7.03 (m, 2H), 5.78–5.80 (m, 1H), 5.32 (br, 2H), 5.05–5.15 (m, 2H), 4.81 (m, 1H), 2.70–2.75 (m, 1H), 2.17–2.56 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 144.6, 133.98, 126.5, 125.6, 125.1, 117.4, 81.7, 40.3.

Hydroxylamine 8. ^{1}H (300 MHz, $CDCl_3$) δ 7.32–7.35 (m, 2H), 7.24–7.27 (m, 2H), 5.68–5.77 (m, 1H), 5.08 (br, 2H), 5.01–5.08 (m, 2H), 4.52–4.56 (t, J = 6 Hz, 1H), 2.52–2.59 (m, 1H), 2.37–2.42 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 139.98, 133.9, 133.4, 128.6, 128.1, 117.4, 85.7, 40.3.

Hydroxylamine 9. ^{1}H (300 MHz, $CDCl_3$) δ 7.23–7.26 (m, 2H), 6.88–6.92 (m, 2H), 5.70–5.79 (m, 1H), 5.18 (br, 2H), 5.00–5.08 (m, 2H), 4.46–4.51 (t, J = 6 Hz, 1H), 3.80 (s, 3H), 2.57–2.62 (m, 1H), 2.39–2.42 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 152.2, 127.4, 126.1, 121.0, 109.9, 106.8, 79.1, 48.1, 33.3.

Hydroxylamine 10. ^{1}H (300 MHz, $CDCl_3$) δ 7.29–7.44 (m, 5H), 6.62–6.67 (d, J = 15 Hz, 1H), 6.12–6.20 (dd, J = 15, 9 Hz, 1H), 5.74 (m, 1H), 5.30 (br, 2H), 5.08–5.17 (m, 2H), 4.15–4.18 (m, 1H), 2.35–2.51 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ 135.2, 134.4, 129.7, 128.7, 128.1, 126.4, 125.5, 116.4, 81.8, 38.5.

Hydroxylamine 11. ^{1}H (300 MHz, $CDCl_3$) δ 5.78–5.87 (m, 1H), 5.38 (br, 2H), 5.02–5.12 (m, 2H), 3.62–3.68 (m, 3H), 2.26–2.32 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C (75 MHz, $CDCl_3$) δ 134.9, 116.8, 84.0, 63.7, 34.5, 25.9, 18.3, −5.4.

General procedure for the palladium-catalyzed sequential one-pot synthesis of *N*-aryl-3-arylmethylisoxazolidines using two different aryl bromides

A flame-dried tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1.5 mol% complex, 3 mol% Pd), 2-di-*tert*-butylphosphinobiphenyl (3 mol%), and NaO*t*Bu (2.4 equiv.). The tube was purged with nitrogen, and toluene (10 mL mmol^{-1} hydroxylamine substrate), the hydroxylamine substrate (1.0 equiv.), and the first aryl bromide (1 equiv.) were added *via* a syringe. The mixture was heated to 40–60 °C with stirring until the hydroxylamine substrate had been consumed as judged by TLC. A 0.01 M toluene solution of Xantphos (3 mol%) was added and the reaction mixture was heated to 90 °C for 15 min to allow the ligand exchange process to occur. The second aryl bromide (1.2 equiv.) in toluene (4 mL mmol^{-1} hydroxylamine substrate) was then added, and heating was continued until the intermediate *N*-aryl hydroxylamine was completely consumed. The reaction mixture was then 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, eluting with 5–30% ethyl acetate–petroleum ether.

(±)-(3*R*,5*R*)-3-(4-Cyanobenzyl)-2,5-diphenylisoxazolidine (12a). Yield 55%; ^{1}H (300 MHz, $CDCl_3$) δ 7.60–7.63 (d, J = 8.1 Hz, 2H), 7.37–7.48 (m, 7H), 7.19–7.24 (m, 2H), 6.93–6.95 (m, 1H), 6.79–6.82 (m, 2H), 5.09–5.15 (m, 1H), 4.12–4.15 (m, 1H), 3.24–3.32 (dd, J = 13.5, 9 Hz, 1H), 2.95–3.01 (dd, J = 13.5, 2 Hz, 1H), 2.82–2.86 (m, 1H), 2.11–2.15 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 151.4, 144.7, 138.4, 132.3, 130.4, 129.1, 128.7, 128.3, 126.5, 121.7, 118.9, 113.8, 110.5, 79.8, 68.8, 43.7, 42.8. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{23}H_{20}N_2NaO$, 363.1468; found, 363.1463.

(±)-(3*R*,5*R*)-2-(4-Chlorophenyl)-3-(4-cyanobenzyl)-5-phenylisoxazolidine (12b). Yield 52%; ^{1}H (300 MHz, $CDCl_3$) δ 7.61–7.63 (d, J = 8.1 Hz, 2H), 7.37–7.46 (m, 5H), 7.32–7.35 (d, J = 9 Hz, 2H), 7.15–7.18 (d, J = 6.9 Hz, 2H), 6.70–6.73 (d, J = 9 Hz, 2H), 5.05–5.11 (m, 1H), 4.07 (m, 1H), 3.21–3.24 (dd, J = 13.5, 9 Hz, 1H), 2.95–3.00 (dd, J = 13.5, 5.1 Hz, 1H), 2.83–2.87 (m, 1H), 2.14 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 150.0, 144.4, 138.1, 133.2, 132.3, 130.4, 128.8, 128.6, 126.6, 126.5, 115.1, 113.3, 110.6, 79.9, 68.9, 43.7, 42.7. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{23}H_{19}ClN_2NaO$, 397.1085; found, 397.1081.

(±)-(3*R*,5*R*)-2-(4-Methoxyphenyl)-3-(4-cyanobenzyl)-5-phenylisoxazolidine (12c). Yield 64%; ^{1}H (300 MHz, $CDCl_3$) δ 7.61–7.64 (d, J = 9 Hz, 2H), 7.34–7.47 (m, 7H), 6.62–6.65 (d, J = 9 Hz, 2H), 6.41–6.43 (d, J = 9 Hz, 2H), 4.95–5.01 (m, 1H), 4.15 (m, 1H), 3.83 (s, 3H), 3.21–3.28 (dd, J = 13.5, 9 Hz, 1H), 3.02–3.08 (dd, J = 13.5, 4.5 Hz, 1H), 2.86–2.90 (m, 1H), 2.14–2.21 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 154.5, 143.8, 142.6, 137.2, 132.6, 130.4, 128.7, 128.6, 126.3, 118.7, 113.4, 110.8, 110.0, 80.5, 67.9, 55.1, 43.6, 42.4. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{24}H_{22}N_2NaO_2$, 393.1578; found, 393.1573.

(±)-(3*R*,5*R*)-3-[4-(1,3-Dioxolan-2-yl)benzyl]-2,5-diphenylisoxazolidine (12d). Yield 58%; ^{1}H (300 MHz, $CDCl_3$) δ 7.32–7.45 (m, 11H), 6.87–6.90 (m, 3H), 5.81 (s, 1H), 5.02 (m, 1H), 4.17 (m, 1H), 4.10–4.14 (m, 4H), 3.28–3.35 (dd, J = 13.5, 8.8 Hz, 1H), 2.82–2.89 (dd, J = 13.5, 5 Hz, 1H), 2.66–2.71 (m, 1H), 2.05 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 151.9, 140.9, 138.4, 135.1, 129.5, 128.7, 128.5, 128.2, 126.6, 126.5, 121.4, 114.0, 109.3, 79.9, 69.6, 67.7, 43.8, 43.0. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{25}H_{25}NNaO_3$, 410.1731; found, 410.1734.

(±)-(3*R*,5*R*)-3-(4-Phenylbenzyl)-2,5-diphenylisoxazolidine (12e). Yield 63%; ^{1}H (300 MHz, $CDCl_3$) δ 7.31–7.64 (m, 16H), 6.95–7.01 (m, 3H), 5.15–5.20 (m, 1H), 4.25 (m, 1H), 3.33–3.40 (dd, J = 13.5, 8 Hz, 1H), 3.01–3.07 (dd, J = 13.5, 6 Hz, 1H), 2.85–2.89 (m, 1H), 2.23–2.27 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 151.3, 139.4, 138.5, 138.1, 134.2, 130.0, 128.6, 128.5, 128.2, 127.6, 127.2, 127.1, 126.6, 126.5, 121.3, 114.3, 80.0, 69.5, 43.9, 42.5. HRMS-ESI (m/z): [M + Na]$^+$ calcd for $C_{28}H_{25}NNaO$, 414.1832; found, 414.1837.

(±)-2-{[(3*R*,5*R*)-2-Phenyl-5-*p*-tolylisoxazolidin-3-yl]methyl}-pyridine (12f). Yield 66%; ^{1}H (300 MHz, $CDCl_3$) δ 8.62–8.64 (m, 1H), 7.59–7.60 (m, 1H), 7.16–7.38 (m, 8H), 6.88–6.92 (m, 3H), 5.06–5.11 (m, 1H), 4.53 (m, 1H), 3.36–3.43 (dd, J = 13.5, 9 Hz, 1H), 3.11–3.17 (dd, J = 13.5, 5.5 Hz, 1H), 2.82–2.86 (m, 1H), 2.38 (s, 3H), 2.15–2.19 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 151.7,

149.3, 138.0, 136.5, 135.6, 129.2, 128.9, 126.7, 124.6, 121.6, 121.2, 113.9, 79.8, 67.8, 45.1, 43.6, 21.2. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{22}H_{22}N_2NaO$, 353.1632; found, 353.1638.

(±)-3-{[(3*R*,5*R*)-2-Phenyl-5-*p*-tolylisoxazolidin-3-yl]methyl}-pyridine (12g). Yield 64%; ^{1}H (300 MHz, $CDCl_3$) δ 8.62–8.64 (m, 2H), 8.17 (br, 1H), 7.68–7.70 (m, 1H), 7.18–7.38 (m, 6H), 6.89–6.93 (m, 3H), 5.05–5.11 (m, 1H), 4.51 (m, 1H), 3.34–3.41 (dd, J = 13.5, 9 Hz, 1H), 3.12–3.18 (dd, J = 13.5, 5 Hz, 1H), 2.81–2.85 (m, 1H), 2.38 (s, 3H), 2.13–2.17 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 151.9, 148.9, 148.6, 138.0, 137.6, 136.1, 135.5, 129.2, 128.9, 126.7, 122.5, 121.2, 113.9, 79.8, 67.8, 45.2, 43.6, 21.2. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{22}H_{22}N_2NaO$, 353.1630; found, 353.1634.

(±)-4-{[(3*R*,5*R*)-2-Phenyl-5-*p*-tolylisoxazolidin-3-yl]methyl}-pyridine (12h). Yield 62%; ^{1}H (300 MHz, $CDCl_3$) δ 8.51–8.53 (d, J = 6 Hz, 2H), 7.27–7.36 (m, 6H), 7.16–7.18 (d, J = 6 Hz, 2H), 6.86–6.90 (m, 3H), 5.03–5.09 (m, 1H), 4.54 (m, 1H), 3.37–3.44 (dd, J = 13.5, 9 Hz, 1H), 3.10–3.16 (dd, J = 13.5, 5.6 Hz, 1H), 2.83–2.87 (m, 1H), 2.38 (s, 3H), 2.14–2.18 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 151.8, 150.3, 144.2, 136.8, 135.5, 129.2, 128.9, 126.7, 124.6, 121.5, 113.9, 79.8, 67.8, 45.1, 43.6, 21.1. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{22}H_{22}N_2NaO$, 353.1631; found, 353.1635.

(±)-*tert*-Butyl-4-[(3*R*,5*R*)-3-benzyl-5-(thiophen-2-yl)isoxazolidin-2-yl]benzoate (12i). Yield 51%; ^{1}H (300 MHz, $CDCl_3$) δ 7.94–7.97 (d, J = 9 Hz, 2H), 7.37–7.40 (m, 6H), 7.13–7.14 (m, 1H), 7.02–7.05 (m, 1H), 6.79–6.82 (d, J = 9 Hz, 2H), 5.26–5.31 (m, 1H), 4.18–4.19 (m, 1H), 3.28–3.35 (dd, J = 13.5, 8.6 Hz, 1H), 2.97–3.03 (dd, J = 13.5, 5.7 Hz, 1H), 2.81–2.85 (m, 1H), 2.22–2.28 (m, 1H), 1.61 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 165.6, 154.5, 140.5, 139.2, 130.7, 129.8, 129.3, 126.9, 126.6, 126.2, 126.0, 124.9, 112.7, 80.3, 76.1, 68.6, 43.5, 42.3, 28.2. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{25}H_{27}NNaO_3S$, 444.1607; found, 444.1612.

(±)-(3*R*,5*R*)-2-(4-Nitrophenyl)-3-(4-methylbenzyl)-5-(thiophen-2-yl)isoxazolidine (12j). Yield 54%; ^{1}H (300 MHz, $CDCl_3$) δ 8.18–8.21 (d, J = 9 Hz, 2H), 7.51–7.54 (d, J = 9 Hz, 1H), 7.15–7.18 (m, 3H), 7.04–7.06 (m, 3H), 6.76–6.79 (d, J = 9 Hz, 2H), 5.27–5.32 (m, 1H), 4.27–4.29 (m, 1H), 3.31–3.38 (dd, J = 13.5, 9 Hz, 1H), 3.09–3.15 (dd, J = 13.5, 4.9 Hz, 1H), 2.94–2.99 (m, 1H), 2.32–2.35 (m, 1H), 2.25 (s, 3H). ^{13}C (75 MHz, $CDCl_3$) δ 155.7, 141.6, 139.2, 136.2, 130.5, 127.3, 127.1, 126.9, 126.5, 125.5, 123.8, 112.5, 76.7, 67.7, 43.5, 41.7, 22.1. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{21}H_{20}N_2NaO_3S$, 403.1093; found, 403.1096.

(±)-*tert*-Butyl-4-{[(3*R*,5*R*)-5-(4-cholorophenyl)-2-(4-cyanophenyl) isoxazolidin-3-yl]methyl}benzoate (12k). Yield 67%; ^{1}H (300 MHz, $CDCl_3$) δ 8.01–8.04 (d, J = 9 Hz, 2H), 7.75–7.78 (d, J = 9 Hz, 2H), 7.32–7.48 (m, 6H), 6.73–6.76 (d, J = 9 Hz, 2H), 4.97–5.03 (m, 1H), 4.27 (m, 1H), 3.25–3.32 (dd, J = 13.5, 9 Hz, 1H), 3.07–3.13 (dd, J = 13.5, 4.8 Hz, 1H), 2.95–2.99 (m, 1H), 2.15–2.21 (m, 1H), 1.62 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 161.5, 154.5, 140.3, 136.9, 135.7, 133.3, 133.2, 131.2, 131.0, 130.4, 126.5, 118.6, 113.2, 103.8, 80.6, 80.3, 68.0, 43.6, 42.5, 29.4. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{28}H_{27}ClN_2NaO_3$, 497.1606; found, 497.1609.

(±)-(3*R*,5*R*)-2-Phenyl-3-(4-methylbenzyl)-5-(4-methoxyphenyl)-isoxazolidine (12l). Yield 57%; ^{1}H (300 MHz, $CDCl_3$) δ 7.56–7.59 (d, J = 9 Hz, 2H), 7.23–7.45 (m, 6H), 7.04–7.07 (d, J = 9 Hz, 2H), 6.88–6.92 (m, 3H), 5.06–5.12 (m, 1H), 4.13–4.14 (m, 1H), 3.85 (s, 3H), 3.26–3.33 (dd, J = 13.5, 7.8 Hz, 1H), 2.92–2.98 (dd, J = 13.5, 6.3 Hz, 1H), 2.76–2.80 (m, 1H), 2.31 (s, 3H), 2.15–2.19 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 161.8, 151.9, 141.4, 139.2, 138.6, 131.6, 129.5, 128.1, 126.4, 121.3, 114.3, 113.7, 79.9, 69.7, 54.2, 43.8, 43.0, 25.1. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{24}H_{25}NNaO_2$, 382.1782; found, 382.1786.

(±)-(3*R*,5*R*)-3-Benzyl-2-(4-nitrophenyl)-5-styrylisoxazolidine (12m). Yield 53%; ^{1}H (300 MHz, $CDCl_3$) δ 8.19–8.22 (d, J = 9 Hz, 2H), 7.33–7.49 (m, 5H), 7.04–7.21 (m, 5H), 6.73–6.80 (m, 3H), 6.18–6.26 (dd, J = 15.9, 7.5 Hz, 1H), 4.66–4.69 (m, 1H), 4.19–4.22 (m, 1H), 3.23–3.31 (dd, J = 13.5, 9 Hz, 1H), 3.03–3.09 (dd, J = 13.5, 4.8 Hz, 1H), 2.74–2.78 (m, 1H), 2.02–2.07 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 156.2, 147.1, 139.3, 135.6, 135.4, 130.2, 128.7, 128.5, 126.7, 126.0, 125.4, 124.6, 123.4, 112.5, 80.2, 67.6, 41.9, 41.8. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{24}H_{22}N_2NaO_3$, 409.1527; found, 409.1531.

(±)-{[(3*R*,5*R*)-2-(*p*-Biphenyl)-3-benzylisoxazolidin-5-yl]methoxy}(*tert*-butyl)dimethylsilane (12n). Yield 49%; ^{1}H (300 MHz, $CDCl_3$) δ 7.51–7.59 (m, 4H), 7.26–7.45 (m, 10H), 6.91–6.94 (d, J = 9 Hz, 2H), 4.42 (m, 1H), 3.88–3.93 (m, 1H), 3.23 (dd, J = 13.5, 8.8 Hz, 1H), 2.87 (dd, J = 13.5, 6 Hz, 1H), 2.42 (m, 1H), 1.97 (m, 1H), 0.96 (s, 9H), 0.15 (s, 6H). ^{13}C (75 MHz, $CDCl_3$) δ 151.3, 139.4, 136.5, 131.2, 129.9, 128.7, 128.2, 127.6, 127.2, 126.0, 125.7, 114.3, 80.1, 69.5, 65.5, 43.9, 42.6, 25.8, 18.1, −5.7. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{29}H_{37}NNaO_2Si$, 482.2493; found, 482.2496.

General procedure for the synthesis of *N*-aryl-β-amino alcohols

Chlorotrimethyl silane (1 equiv.) and potassium iodide (1 equiv.) were stirred in acetonitrile at room temperature for half an hour. To this solution, isoxazolidine (0.5 equiv.) and water (0.25 equiv.) were added and stirred for a further 1 h at room temperature. The reaction mixture was treated with water and stirred for another 1 h, then washed with sodium thiosulfate solution (5%) before extraction with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was then purified by flash chromatography on silica gel, eluting with 40–50% ethyl acetate–petroleum ether, to give the product.

(±)-(1*S*,3*S*)-1,4-Diphenyl-3-(phenylamino)butan-1-ol (13a). Yield 98%; ^{1}H (300 MHz, $CDCl_3$) δ 7.21–7.33 (m, 10H), 7.06–7.09 (m, 2H), 6.84–6.87 (m, 1H), 6.77–6.80 (m, 2H), 4.89–4.94 (m, 1H), 3.87–3.90 (br, 3H), 2.79–2.87 (m, 2H), 1.90–1.96 (m, 1H), 1.72–1.80 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 146.5, 144.3, 137.3, 129.7, 129.5, 128.4, 128.3, 127.5, 126.5, 125.8, 119.1, 115.3, 74.4, 54.4, 42.7, 40.3. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO$, 340.1675; found, 340.1678.

(±)-(1*S*,3*S*)-1-Phenyl-3-(phenylamino)-4-(*p*-cyanophenyl)butan-1-ol (13b). Yield 97%; ^{1}H (300 MHz, $CDCl_3$) δ 7.53–7.56 (d, J = 9 Hz, 2H), 7.16–7.31 (m, 9H), 6.81 (m, 1H), 6.67–6.71 (m, 2H), 4.89–4.90 (m, 1H), 4.11–4.13 (m, 1H), 3.86 (br, 2H), 2.87–2.91 (m, 2H), 1.77–1.86 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ 146.6, 144.5, 142.7, 131.6, 129.6, 129.5, 128.3, 128.2, 125.9, 119.3, 116.4, 115.1, 110.2, 74.3, 54.5, 42.6, 40.2. HRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{23}H_{22}N_2NaO$, 365.1632; found, 365.1637.

(±)-(1*S*,3*S*)-3-(Phenylamino)-4-(pyridine-2-yl)-1-*p*-tolylbutan-1-ol (13c). Yield 98%; ^{1}H (300 MHz, $CDCl_3$) δ 8.52–8.54 (m, 1H), 7.55–7.56 (m, 1H), 7.05–7.24 (m, 8H), 6.73–6.77 (m, 3H), 4.94–4.98 (m, 1H), 4.20–4.90 (br, 2H), 4.03–4.11 (m, 1H), 3.05–3.06 (m, 2H), 2.33 (s, 3H), 1.86–2.05 (m, 2H). ^{13}C (75 MHz, $CDCl_3$) δ 158.8, 149.0, 146.9, 141.7, 136.8, 136.5, 129.3, 128.9, 125.6, 124.3, 121.4, 118.6, 115.1, 73.1, 53.3, 42.9, 41.9, 21.1. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{24}N_2NaO$, 355.1785; found, 355.1787.

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Notes and references

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