Chiral sulfinyl-based olefin ligands for rhodium-catalysed asymmetric conjugate addition of arylboronic acids to cyanoalkenes

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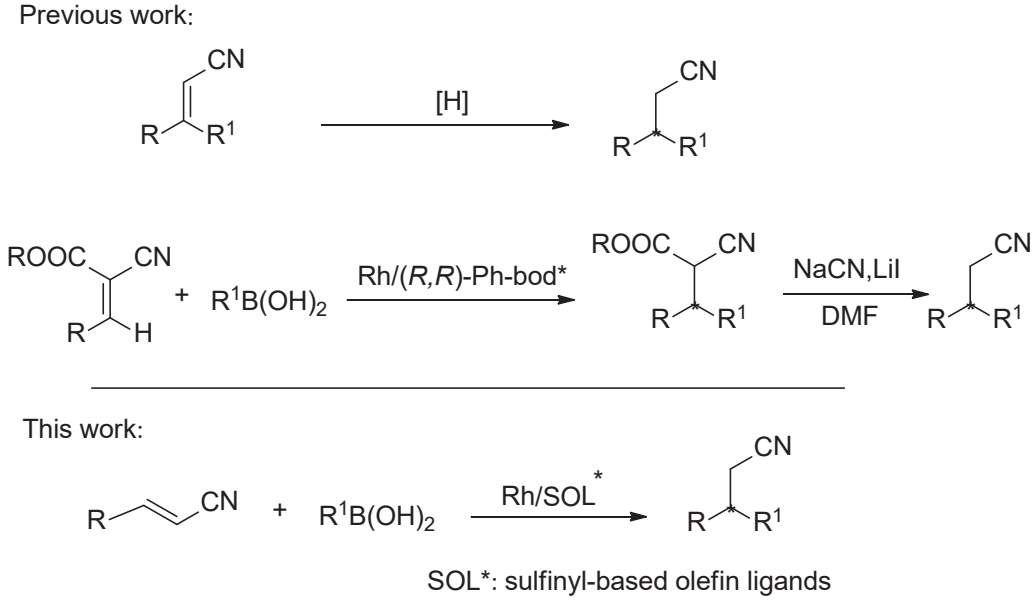
A rhodium/sulfinyl-based olefin ligand-catalysed asymmetric conjugate addition of arylboronic acids to cyanoalkenes without activation groups has been developed, where *p*-tolylsulfinyl-functionalised olefin ligands have been shown to be effective and with moderate enantioselectivities. This is the first example of applying chiral sulfinyl-based olefin ligands in the catalytic asymmetric addition to cyanoalkenes.

Keywords: chiral sulfinyl-based olefin ligands, cyanoalkenes, conjugate addition, asymmetric catalysis

The chiral 3,3-disubstituted propionitriles, which can be readily transformed into other useful functionalities, such as amine, aldehyde and carboxylic acid groups, are versatile synthetic intermediates in many biologically active compounds and pharmaceutical agents, such as *ar*-turmerone,[1] tolterodine,[2] indatraline,[3] vabicaserin[4] and florhydral.[5]

Due to their importance in chemical synthesis, great attention has been drawn to the development of enantioselective synthetic protocols. A predominant route would be the enantioselective hydrogenation of α,β-unsaturated nitriles. However, because of the linear geometry of the nitrile group and the strong binding affinity of the nitrile group to transition metal complexes, reports of efficient catalyst systems for the asymmetric hydrogenation of α,β-unsaturated nitriles remained very limited.[6–8] Moreover, α,β-unsaturated nitriles were restricted to β-alkyl-β-aryl substituted alkenyl nitriles only.[9,10] It was demonstrated that it was more difficult for β,β-diaryl-substituted alkenyl substrates to undergo asymmetric reductions than for other alkenyl substrates, mainly because low enantioselectivity is generally expected from the small steric difference between two aryl substituents and because steric congestion of the aryl groups influences the activity of the catalysts. Thus, until now, there have been only a few reports of the enantioselective conjugate reduction of 3,3-diaryl-substituted propionitriles,[11–13] and so the development of another enantioselective preparation method for such compounds remains highly desirable.

In recent years, the Rh-catalysed asymmetric conjugate addition of organoboronic acids to electron-deficient olefins, pioneered by Carreira, Hayashi and co-workers, has been established as one of the most powerful and convenient tools for the enantioselective synthesis of β-substituted functionalised compounds with chiral olefin ligands.[14–16] Therefore, the most direct and attractive method for obtaining chiral 3,3-diarylpropanenitriles would utilise the asymmetric 1,4-addition reaction of cyanoalkenes and arylboronic acids. So far, however, there have been only two examples involving asymmetric conjugate addition of α,β-unsaturated nitriles, where only chiral diene and *N*-heterocyclic carbene (NHC) ligands were applied.[17,18] Moreover, high enantioselectivities could only be achieved for substrates with activation groups as an assistant coordinating group, such as an ester group attached to the C=C bond. There have been no reports so far of other ligands applied in the asymmetric addition of α,β-unsaturated nitriles, especially for substrates without activation groups. In recent years, chiral sulfinyl-based olefin ligands (SOLs) have been successfully explored and applied in a range of Rh-catalysed asymmetric transformations, which have obvious advantages over some conventional chiral ligands in terms of activity and



Scheme 1 Synthesis of 3,3-diarylpropanenitriles.

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selectivity.[19–23] In spite of recent significant advances, there has still been no report of the use of chiral SOLs in the asymmetric conjugate addition of α,β-unsaturated nitriles. Thus, herein we report on our explorations of these rhodium/SOL complexes in the asymmetric addition of arylboronic acids to cyanoalkenes without activation groups (Scheme 1).

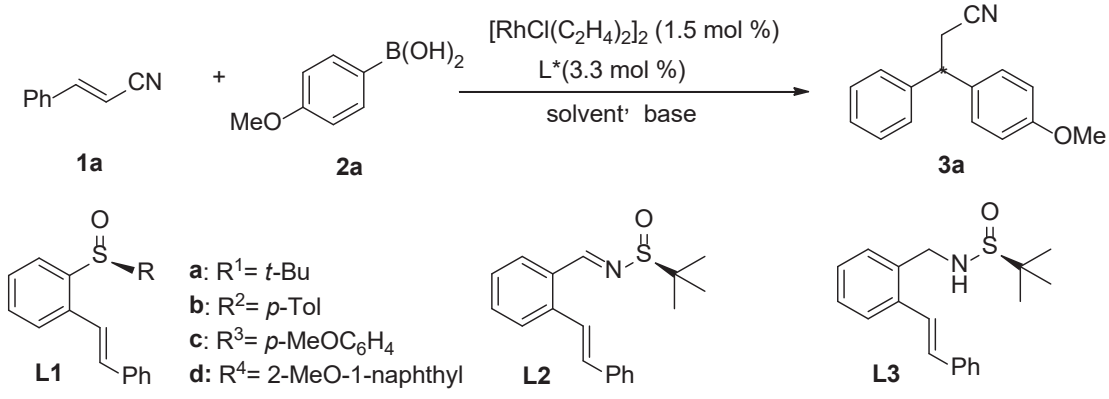
Results and discussion

We began with the Rh-catalysed conjugate addition of *trans*-cinnamonitrile **1a** with *p*-anisylboronic acid **2a** in the presence of SOLs **L1–3** (Table 1). Initially, the reaction proceeded in the presence of 1.5 mol% $[RhCl(C_2H_4)_2]_2$ and 3.3 mol% **L1a**, **L2** or **L3** bearing the *tert*-butylsulfinyl moiety in Et_3N/toluene, giving a trace amount of desired product (entries 1–3). Next, ligands **L1b–d** bearing different sulfinyl moieties were screened: ligand **L1b** with the *p*-tolylsulfiny moiety gave a 35% isolated yield of the expected product **3a** with 40% ee (entry 4), whereas ligand **L1c** bearing the *p*-methoxybenzenesulfinyl moiety and **L1d** bearing the 2-methoxy-1-naphthylsulfinyl moiety gave 32% ee (entry 5) and 37% ee (entry 6), respectively. When the reaction proceeded in aqueous 0.75 M KOH/toluene, ligand **L1b** gave a higher enantioselectivity of 46% ee (entry 7). A survey of other inorganic bases, such as KF, K_2CO_3 and K_3PO_4, did not improve the enantioselectivity of the reaction (entries 8–10). When the reaction was conducted in aqueous KHF_2/toluene, where potassium aryltrifluoroborate can be generated *in situ*, no increase in reactivity or enantioselectivity was observed (entry 11). Moreover, a further screen of other solvents also showed no better results (entries 12–15).

With the *p*-tolylsulfiny moiety established, ligands **L1e–j** with alkene moieties containing substituents with different steric and electronic natures were further synthesised and explored (Scheme 2). When ligand **L1e** was employed, which possessed an electron-donating *p*-methoxy group on the terminal benzene ring, both the catalytic reactivity and the enantioselectivity increased (43% yield and 50% ee, respectively). The use of ligand **1f** with two methoxy groups on its terminal benzene ring gave a higher ee value (58% ee), whereas the 2,4,6-trimethoxy analogue **1g** gave a lower ee value (40% ee). When ligands **1h–j** with electron-withdrawing groups were screened on the *para*-position of the benzene ring, lower reactivities and enantioselectivities were obtained.

Next, we examined the substrate scope under the optimised conditions (Table 2). A range of arylboronic acids with varying electronic and steric demands were reacted smoothly with cyanoalkenes to give the corresponding addition products with moderate enantioselectivities. In general, the electronic properties of the substituent on the substrates did not significantly affect the reaction stereoselectivity significantly. However, the steric hindrance of the substituents on the aromatic ring had an impact on the activity, as in the reaction of 1-naphthylboronic acid and 2-naphthylboronic acid (entries 6,7

Table 1 Screening of ligands, solvents and bases in the conjugate addition reaction[a]



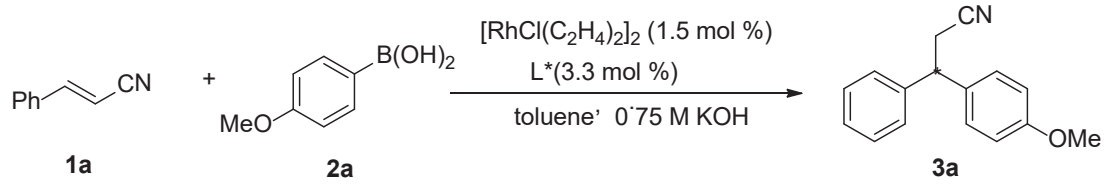
Entry	Ligand	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	**L1a**	Toluene	Et_3N	Trace	n.d.[d]
2	**L2**	Toluene	Et_3N	Trace	n.d.[d]
3	L3	Toluene	Et_3N	Trace	n.d.[d]
4	**L1b**	Toluene	Et_3N	35	40
5	**L1c**	Toluene	Et_3N	30	32
6	**L1d**	Toluene	Et_3N	34	37
7	**L1b**	Toluene	KOH (0.75 M)	40	46
8	**L1b**	Toluene	KF (1.5 M)	35	40
9	**L1b**	Toluene	K_2CO_3 (1.5 M)	41	35
10	**L1b**	Toluene	K_3PO_4 (1.5 M)	36	41
11	**L1b**	Toluene	KHF_2 (1.5 M)	33	42
12	**L1b**	THF	KOH (0.75 M)	35	41
13	L1b	Dioxane	KOH (0.75 M)	43	34
14	**L1b**	CH_2Cl_2	KOH (0.75 M)	41	40
15	**L1b**	CH_3OH	KOH (0.75 M)	Trace	n.d.[d]

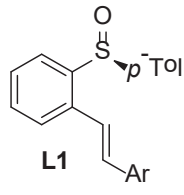
[a]The reaction was carried out with *trans*-cinnamonitrile (0.30 mmol), *p*-anisylboronic acid (0.60 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0045 mmol), ligand (0.0099 mmol, 1.1 equiv. to Rh) and 0.75 M aqueous KOH (0.20 mL) in toluene (2.0 mL) at 80 °C for 12 h.

[b]Yield based on *trans*-cinnamonitrile.

[c]Determined by HPLC analysis.

[d]Not determined.

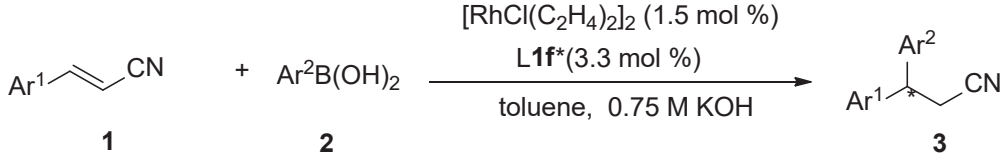




L1e: Ar =4-$MeOC_6H_4$, 43%, 50% ee
L1f: Ar =3,4-$(MeO)_2C_6H_3$, 45%, 58% ee
L1g: Ar =2,4,6-$(MeO)_3C_6H_2$, 30%, 40% ee
L1h: Ar =4-FC_6H_4, 43%, 25% ee
L1i: Ar =4-ClC_6H_4, 42%, 29% ee
L1j: Ar =4-$CF_3C_6H_4$, 45%, 35% ee

Scheme 2 Further ligand screen.

Table 2 Substrate scope in the conjugate addition reaction[a]



Entry	Ar^1	Ar^2	Yield[b] (%)	ee[c] (%)
1	Ph	4-$MeOC_6H_4$	45 (**3a**)	58(*S*)
2	Ph	2-$MeOC_6H_4$	43 (**3b**)	45(*S*)
3	Ph	3-$MeOC_6H_4$	44 (**3c**)	46(*S*)
4	Ph	2-MeC_6H_4	48 (**3d**)	46(*S*)
5	Ph	3-MeC_6H_4	51 (**3e**)	48(*S*)
6	Ph	1-Naphthyl	45 (**3f**)	59(*S*)
7	Ph	2-Naphthyl	53 (**3g**)	56(*S*)
8	Ph	4-FC_6H_4	54 (**3h**)	43(*S*)
9	Ph	4-ClC_6H_4	57 (**3i**)	47(*S*)
10	Ph	4-$CF_3C_6H_4$	55 (**3j**)	46(*S*)
11	4-$MeOC_6H_4$	2-$MeOC_6H_4$	42 (**3k**)	50
12	4-$MeOC_6H_4$	2-MeC_6H_4	44 (**3l**)	57
13	4-$MeOC_6H_4$	1-Naphthyl	44 (**3m**)	52
14	4-$MeOC_6H_4$	2-Naphthyl	52 (**3n**)	59

[a]The reaction was carried out with cyanoalkenes (0.30 mmol), arylboronic acid (0.60 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0045 mmol), ligand **1f** (0.0099 mmol, 1.1 equiv. to Rh) and 0.75 M aqueous KOH (0.20 mL) in toluene (2.0 mL) at 80 °C for 12 h.
[b]Yield based on cyanoalkenes.
[c]Determined by HPLC analysis.

and entries 13,14). Moreover, in the case of arylboronic acids with electron-withdrawing groups, higher reactivities were obtained (entries 8–10).

Conclusions

In summary, we have developed a catalytic system for the rhodium-catalysed addition of arylboronic acids to cyanoalkenes without activation groups, in which chiral sulfinyl-based olefin ligands were applied to give moderate yields and moderate enantioselectivities. Ligands bearing the *p*-tolylsulfinyl group were shown to be more effective than those bearing *tert*-butylsulfinyl, *p*-methoxybenzenesulfinyl or 2-methoxy-1-naphthylsulfinyl groups. Moreover, ligands with electron-donating groups positioned on the terminal benzene ring of the alkene moiety were more beneficial. This study sets the stage for further exploration of these recently developed ligands in other asymmetric transformations and for the development of other kinds of unique olefin ligands. Further studies are underway and will be reported in due course.

Experimental

All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques, unless otherwise noted. Melting points were determined on a Mettler FP5 apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer. Optical rotations were measured with a JASCO P-1020 automatic polarimeter. High resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner System 5303. ^{1}H NMR chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. ^{13}C NMR chemical shifts were recorded in ppm downfield using the central peak of deuterochloroform ($CDCl_3$, 77.2 ppm) as internal standard. Coupling constants (*J*) are reported in hertz (Hz) and refer to apparent peak multiplications. Flash column chromatography was performed on silica gel (300–400 mesh). Thin-layer chromatographic (TLC) analysis was performed using glass-backed plates coated with 0.2 mm silica. Commercially available reagents were used throughout without further purification, other than those procedures detailed below. THF, Et_2O and toluene were distilled over sodium benzophenone ketyl under nitrogen. Methylene chloride (CH_2Cl_2) was distilled over calcium hydride. Arylboronic acids were recrystallised from water.

Preparation of ligands **L1–3***; general procedure*

Ligands **L1–3** were prepared according to literature procedures;[22] the analytical data for **L1a–d** and **L1h** were identical in all respects to those previously reported.[22]

(S,E)-*2-Methyl*-N-*{2-[*(E)-*styryl]benzylidene}propane-2-sulfinamide* **L2**

A solution of (*E*)-2-styrylbenzaldehyde (624 mg, 3 mmol), (*S*)-*tert*-butanesulfinamide (399 mg, 3.3 mmol) and $Ti(OEt)_4$ (1.2 mL, 6 mmol) was refluxed in tetrahydrofuran (THF) for 5 h. The resulting mixture was quenched with cold saturated aqueous NH_4Cl solution. After extracting with CH_2Cl_2, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography gave **L2** as a white solid; 89% yield; m.p. 104–105 °C; $[\alpha]_D^{20}$ = −75.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.97 (s, 1H), 7.94 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.86 (d, *J* = 16.1 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.56–7.48 (m, 3H), 7.37 (dd, *J* = 13.9, 7.0 Hz, 3H), 7.32–7.26 (m, 1H), 7.03 (d, *J* = 16.1 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.8, 139.3, 137.0, 133.4, 132.3, 131.2, 130.3, 128.8, 128.3, 127.8, 127.3, 127.0, 125.3, 57.9, 22.8; HRMS (ESI, *m/z*): Calcd for $C_{19}H_{21}NOSNa$ $[M+Na]^+$: 334.1242; found: 334.1238.

(S,E)-*2-Methyl*-N-*(2-styrylbenzyl)propane-2-sulfinamide* **L3**

$NaBH_4$ (304 mg, 8 mmol) was slowly added to a solution of compound **L2** (933 mg, 3 mmol) in MeOH (10 mL) and continuously stirred at r.t. for 2 h, then cold saturated aqueous NH_4Cl solution was added and the mixture extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography to give **L3** as a white solid; 91% yield; m.p.112–114 °C; $[\alpha]_D^{20}$ = −53.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.52–7.33 (m, 5H), 7.29–7.25 (m, 2H), 7.03 (d, *J* = 16.1 Hz, 1H), 4.50–4.36 (m, 2H), 3.43 (dd, *J* = 8.5, 3.6 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 137.4, 137.0, 135.4, 131.3, 129.9, 128.9, 128.6, 128.0, 127.9, 126.8, 126.2, 125.6, 56.0, 47.6, 22.8; HRMS (ESI, *m/z*): Calcd for $C_{19}H_{23}NOSNa$ $[M+Na]^+$: 336.1398; found: 336.1395.

*(*S,E*)-1-(4-Methoxystyryl)-2-(*p*-tolylsulfinyl)benzene* **L1e**: Light yellow sticky oil; 57% yield; $[\alpha]_D^{25}$ = −163.4 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.89–7.87 (m, 1H), 7.48–7.46 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.36–7.26 (m, 5H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.85–6.78 (m, 3H), 3.69 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.8, 142.5, 142.1, 141.3, 136.2, 131.9, 131.0, 129.9, 129.3, 128.1, 125.7, 125.2, 124.4, 120.6, 114.3, 113.5, 55.1, 21.3; HRMS (ESI, *m/z*): Calcd for $C_{22}H_{20}O_2SNa$ $[M+Na]^+$: 371.1082; found: 371.1078.

*(*S,E*)-1,2-Dimethoxy-4-(2-(*p*-tolylsulfinyl)styryl)benzene* **L1f**: Light yellow sticky oil; 61% yield; $[\alpha]_D^{25}$ = −142.6 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6): δ (ppm) 8.01–7.97 (m, 1H), 7.80–7.74 (m, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.52–7.45 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.15–7.11 (m, 4H), 6.97 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ (ppm) 151.1, 150.7, 144.5, 144.3, 142.5, 137.0, 130.9, 130.6, 128.9, 125.2, 121.5, 121.3, 112.8, 110.6, 56.2, 21.3; HRMS (ESI, *m/z*): Calcd for $C_{23}H_{22}O_3SNa$ $[M+Na]^+$: 401.1187; found: 401.1182.

*(*S,E*)-1,3,5-Trimethoxy-2-(2-(*p*-tolylsulfinyl)styryl)benzene* **L1g**: White solid; 50% yield; m.p. 123–125 °C; $[\alpha]_D^{20}$ = −195.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99–7.84 (m, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.41–7.33 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.17 (s, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.9, 159.9, 158.4, 142.7, 142.3, 141.1, 138.1, 130.8, 127.7, 125.4, 125.2, 124.4, 123.7, 123.1, 107.6, 90.8, 90.4, 55.9, 55.4, 55.0, 21.4; HRMS (ESI, *m/z*): Calcd for $C_{24}H_{24}O_4SNa$ $[M+Na]^+$: 431.1293; found: 431.1299.

*(*S,E*)-1-(4-Chlorostyryl)-2-(*p*-tolylsulfinyl)benzene* **L1i**: White solid; 60% yield; m.p. 100–103 °C; $[\alpha]_D^{20}$ = −125.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.00–7.98 (m, 1H), 7.62–7.60 (m, 1H), 7.53–7.49 (m, 1H), 7.48–7.43 (m, 4H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 16.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 143.1, 142.1, 141.6, 135.8, 134.2, 131.3, 130.0, 128.8, 128.1, 126.2, 125.4, 124.9, 123.8, 21.4; HRMS (ESI, *m/z*): Calcd for $C_{21}H_{17}ClOSNa$ $[M+Na]^+$: 375.0586; found: 375.0591.

*(*S,E*)-1-(*p*-Tolylsulfinyl)-2-(4-(trifluoromethyl)styryl)benzene* **L1j**: White solid; 62% yield; m.p. 91–93 °C; $[\alpha]_D^{20}$ = −152.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.02–8.00 (m, 1H), 7.66–7.62 (m, 4H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.49–7.44 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 16.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 143.4, 142.0, 141.7, 140.2, 135.5, 131.4, 130.9, 129.9 (q, $J^{C,F}$ = 32.6 Hz), 129.3, 127.0, 126.4, 125.9 (q, $J^{C,F}$ = 3.5 Hz), 125.7, 125.4, 125.1, 125.0, 123.1, 21.5; HRMS (ESI, *m/z*): Calcd for $C_{22}H_{17}F_3OSNa$ $[M+Na]^+$: 409.0850; found: 409.0855.

Asymmetric conjugate addition of arylboronic acids to cyanoalkenes: general procedure

Under a nitrogen atmosphere, a mixture of $[RhCl(C_2H_4)_2]_2$ (1.8 mg, 0.0045 mmol) and ligand **L1f** (3.7 mg, 0.0099 mmol) in toluene (1 mL) was stirred at r.t. for 15 min, at which time arylboronic acid (0.60 mmol) was added, followed by cyanoalkenes (0.30 mmol), aqueous KOH (0.75 M in H_2O, 0.20 mL, 0.15 mmol) and toluene (1 mL). The reaction was stirred at 80 °C for 12 h, after which the reaction mixture was concentrated *in vacuo* and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate as eluent) to give the product.

3-(4-Methoxyphenyl)-3-phenylpropanenitrile **3a**[17]: Light yellow liquid; 45% yield, 58% ee; $[\alpha]_D^{20}$ = −3.2 (*c* = 1.0, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (80/20), flow = 1.0 mL min^{-1}, t_R = 19.5 min (major) and 20.5 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32–7.29 (m, 2H), 7.28–7.18 (m, 3H), 7.18–7.10 (m, 2H), 6.86–6.82 (m, 2H), 4.30 (t, *J* = 7.7 Hz, 1H), 3.74 (s, 3H), 2.95 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.8, 141.7, 133.4, 128.9, 128.6, 127.5, 127.3, 118.6, 114.2, 55.3, 46.4, 24.4.

3-(2-Methoxyphenyl)-3-phenylpropanenitrile **3b**[17]: Light yellow liquid; 43% yield, 45% ee; $[\alpha]_D^{20}$ = −22.2 (*c* = 0.8, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (80/20), flow = 1.0 mL min^{-1}, t_R = 7.8 min (major) and 9.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)7.36–7.27 (m, 3H), 7.27–7.20 (m, 3H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.93–6.87 (m, 2H), 4.78 (t, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 3.11–2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.8, 140.9, 129.8, 128.7, 128.6, 128.1, 127.8, 127.1, 120.9, 119.0, 111.0, 55.6, 40.9, 22.8.

3-(3-Methoxyphenyl)-3-phenylpropanenitrile **3c**[17]: Light yellow liquid; 44% yield, 46% ee; $[\alpha]_D^{20}$ = −1.9 (*c* = 0.6, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (70/30), flow = 1.0 mL min^{-1}, t_R = 22.4 min (major) and 25.0 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38–7.30 (m, 2H), 7.29–7.20 (m, 4H), 6.82–6.75 (m, 3H), 4.32 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 2.99 (d, *J* = 7.7, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.9, 142.9, 141.2, 130.0, 128.9, 127.6, 127.5, 119.8, 118.5, 113.9, 112.4, 55.3, 47.2, 24.2.

*3-Phenyl-3-(*o*-tolyl)propanenitrile* **3d**[17]: Light yellow liquid; 48% yield, 46% ee; $[\alpha]_D^{20}$ = +34.3 (*c* = 1.2, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (80/20), flow = 1.0 mL min^{-1}, t_R = 15.1 min (major) and 16.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31–7.27 (m, 2H), 7.23–7.14 (m, 7H), 4.53 (t, *J* = 7.7 Hz, 1H), 2.97 (d, *J* = 7.7 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.0, 139.0, 136.3, 131.1, 128.9, 127.9, 127.4, 127.3, 126.5, 125.9, 118.7, 43.4, 24.4, 19.8.

3-Phenyl-3-(m-tolyl)propanenitrile **3e**[12]: Light yellow liquid; 51% yield, 48% ee; $[\alpha]_D^{20}$ = +1.7 (*c* = 0.5, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (90/10), flow = 1.0 mL min^{-1}, t_R = 16.6 min (major) and 17.5 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32–7.29 (m, 2H), 7.27–7.18 (m, 4H), 7.06–7.00 (m, 3H), 4.30 (t, *J* = 7.7 Hz, 1H), 2.97 (d, *J* = 7.7 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.4, 141.2, 138.6, 128.9, 128.7, 128.4, 128.2, 127.6, 127.4, 124.5, 118.6, 47.1, 24.2, 21.5.

3-(Naphthalen-1-yl)-3-phenylpropanenitrile **3f**: Light yellow liquid; 45% yield, 59% ee; $[\alpha]_D^{20}$ = −17.3 (*c* = 0.7, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 16.1 min (major) and 27.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04–7.90 (m, 1H), 7.89–7.75 (m, 2H), 7.56–7.35 (m, 4H), 7.35–7.17 (m, 5H), 5.13 (t, *J* = 7.5 Hz, 1H), 3.24–3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.4, 136.5, 134.2, 131.3, 129.2, 129.0, 128.5, 127.8, 127.6, 126.7, 125.9, 125.4, 124.2, 123.2, 118.7, 43.1, 24.6; HRMS (ESI, *m/z*): Calcd for $C_{19}H_{15}NNa$ $[M+Na]^+$: 280.1102, found 280.1095.

3-(Naphthalen-2-yl)-3-phenylpropanenitrile **3g**[12]: Light yellow liquid; 53% yield, 56% ee, $[\alpha]_D^{20}$ = +20.6 (*c* = 0.5, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 16.0 min (minor) and 26.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.82–7.77 (m, 3H), 7.71 (s, 1H), 7.54–7.43 (m, 2H), 7.38–7.30 (m, 2H), 7.31–7.20 (m, 4H), 4.53 (t, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.3, 138.7, 133.5, 132.7, 129.1, 128.9, 128.0, 127.8, 127.7, 126.6, 126.3, 126.0, 118.6, 47.3, 24.2.

3-(4-Fluorophenyl)-3-phenylpropanenitrile **3h**[12]: Light yellow liquid; 54% yield, 43% ee; $[\alpha]_D^{20}$ = +0.6 (*c* = 1.0, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 8.5 min (major) and 10.6 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (d, *J* = 7.1 Hz, 1H), 7.52–7.43 (m, 3H), 7.40–7.33 (m, 2H), 7.33–7.27 (m, 1H), 7.25–7.21 (m, 2H), 4.45 (t, *J* = 7.7 Hz, 1H), 3.07 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 142.3, 140.4, 131.6, 131.3, 131.1, 129.6, 129.3, 128.0, 127.6, 124.6–124.4 (m), 118.0, 47.1, 24.3; HRMS (ESI, *m/z*): Calcd for $C_{15}H_{12}FNNa$ $[M+Na]^+$: 248.0851; found: 248.0857.

3-(4-Chlorophenyl)-3-phenylpropanenitrile **3i**[12]: Light yellow liquid; 57% yield, 47% ee; $[\alpha]_D^{20}$ = +3.2 (*c* = 1.0, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 9.4 min (major) and 10.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–7.31 (m, 3H), 7.30–7.25 (m, 2H), 7.21–7.16 (m, 4H), 4.36 (t, *J* = 7.6 Hz, 1H), 3.01 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 140.81, 139.8, 133.5, 129.2, 129.1, 129.0, 127.8, 127.5, 118.3, 46.6, 24.3.

3-Phenyl-3-(4-(trifluoromethyl)phenyl)propanenitrile **3j**[12]: Light yellow liquid; 55% yield, 46% ee; $[\alpha]_D^{20}$ = +2.3 (*c* = 0.8, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 8.1 min (major) and 9.6 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (d, *J* = 8.2 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 4H), 7.32–7.26 (m, 1H), 7.25–7.21 (m, 2H), 4.45 (t, *J* = 7.6 Hz, 1H), 3.06 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 145.2, 140.4, 130.0, 129.7, 129.2, 128.2, 127.9, 127.6, 126.0 (q, *J* = 3.8 Hz), 125.4, 122.7, 118.1, 47.0, 24.1; HRMS (ESI, *m/z*): Calcd for $C_{16}H_{12}F_3NNa$ $[M+Na]^+$: 298.0820; found: 298.0815.

3-(2-Methoxyphenyl)-3-(4-methoxyphenyl)propanenitrile **3k**: Light yellow liquid; 42% yield, 50% ee; $[\alpha]_D^{20}$ = −1.0 (*c* = 1.0, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (80/20), flow = 1.0 mL min^{-1}, t_R = 10.3 min (major) and 13.4 min (minor); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.27–7.17 (m, 3H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.99–6.81 (m, 4H), 4.73 (t, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.07–2.94 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 158.7, 156.8, 133.0, 130.2, 129.0, 128.6, 128.1, 120.9, 119.1, 114.2, 111.0, 55.6, 55.4, 40.3, 23.1; HRMS (ESI, *m/z*): Calcd for $C_{17}H_{17}NO_2Na$ $[M+Na]^+$: 290.1157; found: 290.1162.

*3-(4-Methoxyphenyl)-3-(*o*-tolyl)propanenitrile* **3l**: Light yellow liquid; 44% yield, 57% ee; $[\alpha]_D^{20}$ = +32.6 (*c* = 0.6, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (80/20), flow = 1.0 mL min^{-1}, t_R = 18.9 min (major) and 20.5 min (minor); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26–7.21 (m, 2H), 7.20–7.13 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 2H), 4.49 (t, *J* = 7.6 Hz, 1H), 3.76 (s, 3H), 2.97 (d, *J* = 7.2 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 158.8, 139.4, 136.3, 133.1, 131.2, 128.9, 127.4, 126.5, 125.8, 118.8, 114.3, 55.4, 42.8, 24.6, 19.8; HRMS (ESI, *m/z*): Calcd for $C_{17}H_{17}NONa$ $[M+Na]^+$: 274.1208; found: 274.1221.

3-(4-Methoxyphenyl)-3-(naphthalen-1-yl)propanenitrile **3m**: Light yellow liquid; 44% yield, 52% ee; $[\alpha]_D^{20}$ = −12.6 (*c* = 1.0, $CHCl_3$): Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 19.3 min (major) and 29.1 min (minor); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.95–7.94 (m, 1H), 7.90–7.79 (m, 1H), 7.60–7.35 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.15–3.07 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 158.9, 136.8, 134.3, 133.5, 131.3, 129.2, 128.9, 128.4, 126.7, 125.9, 125.4, 124.0, 123.4, 118.8, 114.5, 55.4, 42.5, 24.9; HRMS (ESI, *m/z*): Calcd for $C_{20}H_{17}NONa$ $[M+Na]^+$: 310.1208; found: 310.1212.

3-(4-Methoxyphenyl)-3-(naphthalen-2-yl)propanenitrile **3n**: Light yellow liquid; 52% yield, 59% ee; $[\alpha]_D^{20}$ = −15.9 (*c* = 0.6, $CHCl_3$); Chiracel OD-H Column, 210 nm, 25 °C, *n*-hexane/*i*-propanol (50/50), flow = 1.0 mL min^{-1}, t_R = 17.3 min (minor) and 29.3 min (major); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.82–7.78 (m, 3H), 7.69 (s, 1H), 7.49–7.45 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.49 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 3H), 3.14 – 3.06 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 158.9, 139.1, 133.4 (d, *J* = 14.1 Hz), 132.7, 128.9 (d, *J* = 5.1 Hz), 128.0, 127.8, 126.6, 126.3, 126.0, 125.8, 118.7, 114.4, 55.4, 46.6, 24.5; HRMS (ESI, *m/z*): Calcd for $C_{20}H_{17}NONa$ $[M+Na]^+$: 310.1208; found: 310.1203.

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