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Transfer of axial chirality through the nickel-catalysed hydrocyanation of chiral allenes

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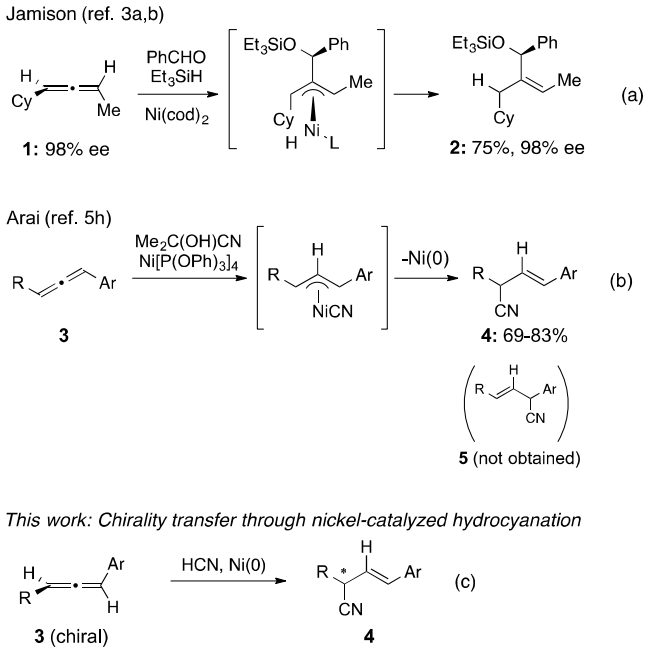
The transfer of axial chirality of allenes is beginning to be exploited as a powerful method for creating central chirality, particularly through the use of transition metal catalysis. In this communication, the transfer of axial chirality of chiral allenes via nickel-catalysed hydrocyanation is achieved through both regio- and face-selective hydronickelation as well as regioselective reductive elimination. This protocol was applied to 12 substrates and gave chiral carbonitriles with up to 97% ee. Further application to hydrocyanative cyclization using a chiral allene-yne is also presented, along with a discussion of the corresponding mechanism of racemization.

Introduction

Allenes continue to attract the attention of chemists because of their unique structural features, including orthogonal □-orbitals composed of sp^2 and sp carbons. They are much more reactive than simple alkenes and therefore have been used in many types of chemical transformations.[1] Allenes also have axial chirality. Due to the remarkable progress in practical synthetic methodologies for chiral allenes over the last few years,[2] transfer of the axial chirality of allenes is beginning to be exploited as a new method for constructing central chirality.[3] Such transfer of axial chirality is difficult because of the need for regio- and face-control of two double bonds. In the case of transition metal-catalysed reaction that generates a π□allylmetal intermediate, regiocontrol in the reductive elimination step is another issue that must be solved for efficient transformation. To the best of our knowledge, the nickel-catalysed 3-component coupling of chiral allene **1** with aldehyde and silane reported by Ng and Jamison[3a,b] is the only example of a chirality-transfer reaction through a chiral π□allylmetal intermediate (Scheme 1a). We previously reported that allenes were more reactive than other C-C unsaturated bonds in nickel-catalysed hydrocyanation, and successfully developed a hydrocyanative cyclization as well as a 3-component coupling reaction.[4, 5a-g] We also found that the aryl groups on allenes strongly influenced the regio- and stereoselectivity in hydrocyanation;[5h] the hydride selectively added to the electron-deficient sp carbon to form a π-allylnickel intermediate, and subsequent reductive elimination exclusively gave **4** to maintain the conjugation of C-C double bonds with the aryl group, while **5** was not observed (Scheme 1b). Thus, we next turned our attention to the synthesis of optically active carbonitriles through regio- and stereoselective hydrocyanation with the use of chiral allenes (Scheme 1c).[6]



Scheme 1 Chirality transfer via chiral π-allylnickel complexes

Results & discussion

The hydrocyanation of (*R*)-**3a**[7] was performed using $Ni[P(OPh)_3]_4$ and acetonecyanohydrin to give (*R*)-**4a** with 69% ee, although the

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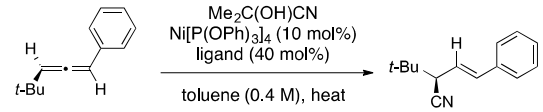
reaction was messy and did not complete even after 20 h (Table 1, entry 1). Because both the yield and ee were significantly increased upon the addition of $P(OPh)_3$ as an external ligand (entry 2), we next investigated several phosphorous ligands to study how they influenced in chirality transfer. Both the yield and ee decreased to 57% and 72%, respectively, with $P(O\text{-}o\text{-tolyl})_3$ (entry 3), whereas the axial chirality of (*R*)-**3a**[7] was almost completely transferred to give (*R*)-**4a** in 88% yield with 96% ee when $P(OMe)_3$ was used (entry 4). While PPh_3 did not give any improvement (entry 5), $PMePh_2$ gave (*R*)-**4a** with 95% ee (entry 6). A greater amount of acetonecyanohydrin (5 equiv) dramatically increased the reaction rate, and the reaction was completed within 15 min (entry 7). However, with a bidentate ligand such as dppb, the reaction was not complete even after 20 h (entry 8). Further optimization at 80 °C using $P(OMe)_3$ and $PMePh_2$ revealed that the former gave lower conversion and with the latter the reaction was completed within 30 min to achieve 97% ee (entries 9, 10). Therefore, we concluded that $PMePh_2$ was the best ligand of choice.[8] Another feature of this reaction is the observed racemization in the recovered allenes. There information may be useful for elucidating the reaction pathway, which will be discussed below.



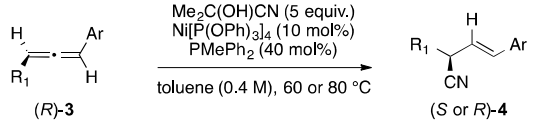
(*R*)-**3a** (98% ee) (*R*)-**4a**

entry	ligand	temp. (°C)	time (h)	$Me_2C(OH)CN$ (equiv.)	(*R*)-**4a** yield (%) (ee %)	(*R*)-**3a** recov. (%) (ee %)
1	none	100	20	2	22* (69)	15 (37)
2	$P(OPh)_3$	100	4	2	83 (89)	-
3	$P(O\text{-}o\text{-tolyl})_3$	100	20	2	57 (72)	9 (50)
4	$P(OMe)_3$	100	4	2	88 (96)	-
5	PPh_3	100	20	2	65 (85)	4 (35)
6	$PMePh_2$	100	20	2	54 (95)	6 (70)
7	$PMePh_2$	100	0.25	5	90 (95)	-
8	dppb**	100	20	2	76 (92)	5 (27)
9	$P(OMe)_3$	80	20	5	32 (96)	38 (2)
10	$PMePh_2$	80	0.5	5	95 (97)	-

*ca. 50% purity **20 mol%

Table 1 Condition screening

Next, we investigated the substrate scope under the optimum conditions (Table 2). Catalytic hydrocyanation proceeded smoothly with a 4-CF_3 group on the benzene ring to give (*R*)-**4b** in 89% yield with 94% ee (entry 2). A 4-MeO group could also be used to give (*R*)-**4c** with good transfer of chirality (entry 3). Although the ee was decreased, a cyclohexyl group gave the corresponding carbonitriles ((*S*)-**4d-j**) at 60 °C in 78-93% yields with 65-82% ee (entries 4-10). Allenes with primary alkyl substituents such as (*R*)-**3k** and (*R*)-**3l** also gave the corresponding products with respective ee values of 47% and 63% at 80 °C and 60 °C (entries 11-12).[9] As observed in the reaction of (*R*)-**3e,h,l** a CF_3 group enhances the reactivity to enable smooth conversion at lower temperature to achieve higher ee in the corresponding products (entries 5, 8, 12).



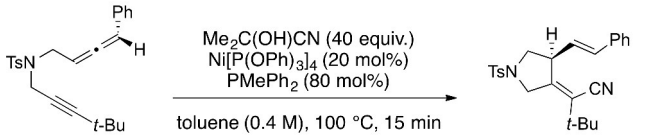
(*R*)-**3** (*S* or *R*)-**4**

entry	(*R*)-**3** R_1	Ar	ee %	temp. (°C)	time (min)	**4** yield (%) (ee %)
1	*t*-Bu	C_6H_5	98	80	15	(*R*)-**4a:** 95 (97)
2	*t*-Bu	4-$CF_3C_6H_4$	98	80	20	(*R*)-**4b:** 89 (94)
3	*t*-Bu	4-$MeOC_6H_4$	88	80	15	(*R*)-**4c:** 84 (84)
4	Cy	C_6H_5	97	60	45	(*S*)-**4d:** 80 (72)
5	Cy	4-$CF_3C_6H_4$	98	60	15	(*S*)-**4e:** 84 (82)
6	Cy	4-$MeOC_6H_4$	85	60	90	(*S*)-**4f:** 79 (65)
7	Cy	4-BrC_6H_4	97	60	180	(*S*)-**4g:** 78 (66)*
8	Cy	3-$CF_3C_6H_4$	97	60	20	(*S*)-**4h:** 84 (80)
9	Cy	3-$MeOC_6H_4$	94	60	90	(*S*)-**4i:** 89 (74)
10	Cy	2-naphthyl	96	60	30	(*S*)-**4j:** 93 (72)*
11	*n*-Hep	C_6H_5	97	80	5	(*S*)-**4k:** 68 (47)
12	*n*-Hep	4-$CF_3C_6H_4$	96	60	15	(*S*)-**4l:** 74 (63)

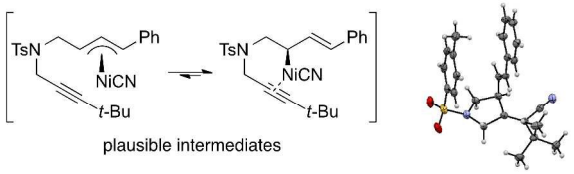
* The ee of (*S*)-**4g**, **j** were determined after conversion to the corresponding alcohols (See SI).

Table 2 Substrate scope

This protocol was also applied to hydrocyanative cyclization[5a, b] using (*R*)-**6** (Scheme 2). The reaction is triggered by hydronickelation to allene followed by 5-exo cyclization and reductive elimination. Although ee was decreased, (*S*)-**7** was obtained in 66% yield. This result suggests that a chiral Ni(II) intermediate from (*R*)-**6** remains in an optically active form to give the chiral product. The absolute stereochemistry of **7** was unambiguously confirmed to be S by X-ray crystallographic analysis after recrystallization.[10]



(*R*)-**6** (92% ee) (*S*)-**7**: 59%, 64% ee



ORTEP diagram of (*S*)-**7**

Scheme 2 Hydrocyanative cyclization of (*R*)-**6**

The racemization of the recovered allenes observed in Table 1 prompted us to investigate the time course of this reaction and particularly ee (Figure 1). Fortunately, the ee values of the products were constant and racemization under the optimum conditions was negligible.[11] However, the starting allenes begin to undergo partial racemization within 30 min.[12] The rate of racemization seems to depend on the substituents; allenes with primary and secondary alkyl groups undergo racemization faster than those with tertiary alkyl groups.

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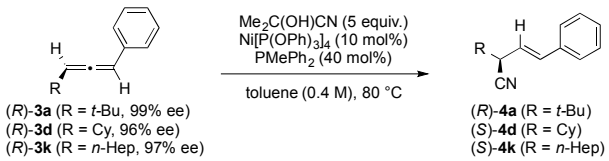
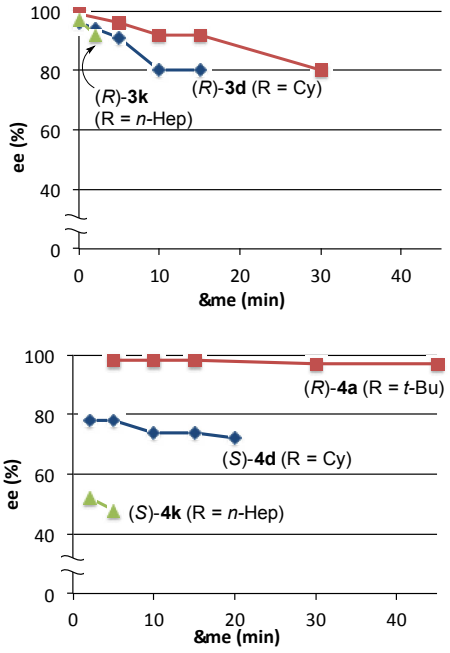
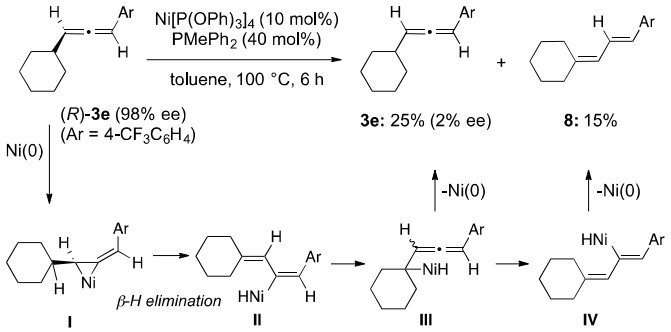
Figure 1. Time course profiling



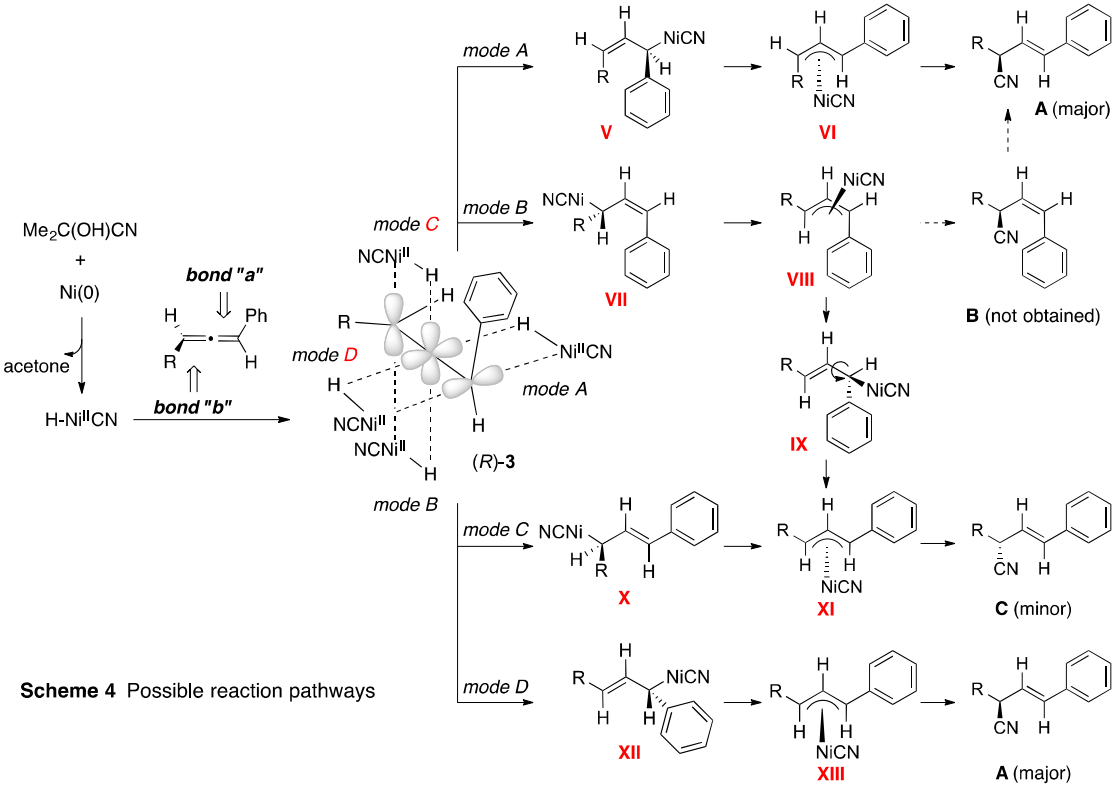


To elucidate the mechanism of racemization of chiral allenes, we next examined the reaction of (*R*)-**3e** in the absence of acetonecyanohydrin. The reaction gave conjugated diene **8** along with recovered (*R*)-**3e** with 2% ee (Scheme 3). The former is a key product in the following plausible reaction pathway of allene racemization. The formation of **I** *via* oxidative addition[3a,b] followed by β–H elimination gives **II**. Reductive elimination through **III** would then give **3e** together with **8** that is produced *via* **III** and **IV**. This proposed mechanism reasonably explains why substrates with Csp^3-H bonds at an allylic position (**3d** and **3k** in Figure 1) are more favorable for partial racemization than **3a**.



Scheme 3 Reaction of (*R*)-**3e** in the absence of cyano source

Based on the above results, a plausible reaction mechanism for the transfer of chirality by hydrocyanation is shown in Scheme 4. Because C-H bonds in products preferentially form at the sp carbon of the starting allenes, 4 possible modes for the initial hydronickelation can be proposed. Mode A includes the addition to *bond "a"* to avoid the steric effect of R to give **V**, which could be converted to **A** *via* **VI**. Mode B is triggered by hydronickelation to *bond "b"*, which would give **B** *via* **VII** and **VIII**. However, **B** was not obtained at all. Both modes C and D would be unfavorable due to steric repulsion between the Ni(II) complex and substituents such as R and Ar groups even though the observed enantiomer could be obtained (mode D). The minor enantiomer **C** would be produced by mode B *via* **IX** and **XI** to give **C** from **VIII**. We also confirmed that isomerization from **B** to **A** would be slower (80 °C, 2 h) and



Scheme 4 Possible reaction pathways

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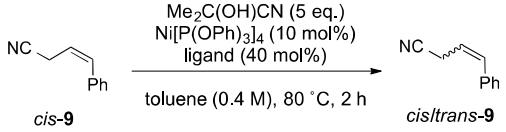
unlikely to be promoted under the reaction conditions with the use of *cis*-**9**.[13] The isomerizaion of *cis*-**9** partially proceeded with $PMePh_2$. However, intact *cis*-**9** was recovered in almost quantitative yield when $P(OPh)_3$ was used (Scheme 5).



ligand	*cis*-**9**	*trans*-**9**
$PMePh_2$	67%	23%
$P(OPh)_3$	95%	1%

Scheme 5 The isomerization reaction of *cis*-**9**

Therefore, the most suitable pathway should be mode A, which explains why a tertiary alkyl group is the most favorable for obtaining products with higher ee. The enhanced reactivity observed in a CF_3 group on the benzene ring could be due to the partial activation of *bond "a"* to smooth hydronickelation in the initial step. Although the nature of the influence of partial racemization is unclear, we assume that the transfer of axial chirality could be predominantly controlled by the hydronickelation step because racemization seems to be slower than conversion to **4** even at higher temperature.

Conclusions

In conclusion, we have demonstrated the transfer of axial chirality of allenes through Ni-catalysed hydrocyanation. This protocol enables a facile access to the corresponding chiral carbonitriles with up to 97% ee. We concluded that the steric bulkiness of the alkyl substituents plays an important role in determining the efficiency of the transfer of axial chirality from allenes because such substituents would be more strongly influenced regio- and face-selectivity in the initial hydronickelation step. A detailed mechanistic study and further applications are currently underway.

Experimental

General: All reactions were performed with dry solvents and reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel (Fuji Silysia, PSQ-60B). IR spectra were recorded on a JASCO FT/IR-230 Fourier transform spectrophotometer. NMR spectra were recorded on JEOL JMN-ECS-400, ECP-400, ECA-600 and ECP-600 at 400 and 600 MHz for 1H NMR and at 100 and 150 MHz for 13C NMR, with calibration using residual undeuterated solvent as an internal reference. Mass spectra were recorded using ESI mode with JEOL JMS-T100LP and APPI mode with Thermo Fisher Exactive. The enantiomeric excess was determined by HPLC analysis using JASCO HPLC LC-2000Plus series (PU-2089, CO-2065, UV-2075). Optical rotations were measured using JASCO P-1020 and P-2200 Polarimeter. X-ray crystal data were collected with Rigaku VariMax with RAPID diffractometer at –180±1 °C using filtered Cu-Kα radiation.

Typical procedure for nickel-catalized hydrocycnation: A solution of $PMePh_2$ (14.0 μL, 0.075 mmol) and $Ni[P(OPh)_3]_4$ (24.4 mg, 0.019 mmol) in toluene (190 μL) was heated under an Ar atmosphere at 100 °C for 10 min. After the mixture was cooled to room temperature, a solution of (*R*)-**3a** (32.4 mg, 0.19 mmol) and acetonecyanohydrin (84.0 μL, 0.94 mmol) in toluene (280 μL) was added and the mixture was heated at 80 °C for 30 min. The reaction mixture was filtrated through Celite®, concentrated under vacuo and purified by column chromatography (Hexane/AcOEt = 40/1) to provide (*R*)-**4a** as a colorless solid (36.3 mg, 0.18 mmol, 95% yield, 97% ee).

(*R*,*E*)-2-(*tert*-Butyl)-4-(4-(trifluoromethyl)phenyl)but-3-enenitrile ((*R*)-4b): Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (s, 9H), 3.22 (dd, 1H, *J* = 7.2, 1.2 Hz), 6.22 (dd, 1H, *J* = 16.0, 7.2 Hz), 6.76 (d, 1H, *J* = 16.0 Hz), 7.49 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.3, 34.8, 46.7, 119.0, 123.5, 124.0 (q, *J* = 270.2 Hz), 125.6, (q, *J* = 3.8 Hz), 126.7, 130.0 (q, *J* = 33.5 Hz), 133.7, 139.2; IR (ATR) ν□□2968, 2309 cm^{-1}; HRMS (APPI) m/z calcd for $C_{15}H_{17}NF_3$ $[M+H]^+$ 268.1308, found 268.1300; mp. 50-52 °C; $[\alpha]_D^{25}$ = +27.0 (*c* = 1.0 , $CHCl_3$, 94% ee); HPLC conditions; Chiralcel OJ-H, hexane/*i*-PrOH = 99:1, f: 1.0 mL/min, tR: 15.2, 18.8 min (94% ee).

(*R*,*E*)-2-(*tert*-Butyl)-4-(4-methoxyphenyl)but-3-enenitrile ((*R*)-4c): Colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (s, 9H), 3.15 (d, 1H, *J* = 7.2 Hz), 3.82 (s, 3H), 5.97 (dd, 1H, *J* = 15.6, 7.2 Hz), 6.63 (d, 1H, *J* = 16.0 Hz), 6.87 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.3, 34.6, 46.7, 55.3, 114.0, 118.4, 119.5, 127.7, 128.6, 134.4, 159.6; IR (ATR) ν□□2964, 2235 cm^{-1}; HRMS (APPI) m/z calcd for $C_{15}H_{20}ON$ $[M+H]^+$ 230.1539, found 250.2539; mp. 72-73 °C; $[\alpha]_D^{25}$ = +22.7 (*c* = 1.0, $CHCl_3$, 84% ee); HPLC conditions: Chiralpak IA, hexane/*i*-PrOH = 98:2, f: 1.0 mL/min, tR: 9.1, 9.8 min (84% ee).

(*S*,*E*)-2-(4-(Trifluoromethyl)styryl)nonanenitrile ((*S*)-4l): Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (t, 3H, *J* = 7.2 Hz), 1.29-1.37 (m, 9H), 1.43-1.60 (m, 1H), 1.79 (dt, 2H, *J* = 7.2, 7.2 Hz), 3.46 (dt, 1H, *J* = 6.4, 6.4 Hz), 6.14 (dd, 1H, *J* = 16.0, 6.4 Hz), 6.78 (d, 1H, *J* = 16.0 Hz), 7.48 (d, 2H, 8.0 Hz), 7.59 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.0, 22.5, 26.8, 28.91, 28.93, 31.6, 33.1, 34.4, 199.8, 124.0 (q, *J* = 270.2), 125.6 (q, *J* = 3.8 Hz), 126.0, 126.7, 130.0 (q, *J* = 32.6 Hz), 131.8, 139.2; IR (ATR) ν□□ 2928, 2858, 2242 cm^{-1}; HRMS (APPI) m/z calcd for $C_{18}H_{22}F_3N$ $[M]^+$ 309.1699, found 309.1694; $[\alpha]_D^{25}$ = +6.8 (*c* = 1.15, $CHCl_3$, 63% ee); HPLC conditions*: Chiralcel AD-H, hexane/*i*-PrOH = 99:1, f: 1.0 mL/min, tR: 10.3, 11.3 min (63% ee).

(*E*)-3,3-Dimethyl-2-((*S*)-4-((*E*)-styryl)-1-tosylpyrrolidin-3-ylidene)butanenitrile ((*S*)-7): Colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.21 (s, 9H), 2.45 (s, 3H), 3.16 (dd, 1H, *J* = 11.4, 6.0 Hz), 3.51 (d, 1H, *J* = 9.6 Hz), 3.78 (dd, 1H, 7.8, 6.0 Hz), 3.96 (d, 1H, *J* = 16.2 Hz), 4.33 (d, 1H, *J* = 16.2 Hz), 5.99 (dd, 1H, *J* = 16.2, 7.8 Hz), 6.57 (d, 1H, *J* = 16.2 Hz), 7.23-7.25 (m, 1H), 7.30-7.31 (m, 4H), 7.37 (d, 2H, *J* = 7.8 Hz), 7.73 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.6, 29.6, 35.4, 49.5, 50.0, 51.8, 117.1, 120.0,

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125.9, 126.6, 127.8, 128.5, 129.9, 130.0, 132.0, 132.4, 136.3, 144.3, 153.3; IR (ATR) ν□□ 2968, 2212, 1348, 1161 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{28}N_2NaO_2S$ $[M+Na]^+$ 443.1769, found 443.1771; mp. 123-124 °C; $[\alpha]_D^{25}$ = -59.6 (*c* = 0.51, $CHCl_3$, 42% ee); HPLC conditions: Chiralpak IB, hexane/*i*-PrOH = 75:25, f: 1.0 mL/min, tR: 6.6, 8.1 min (64% ee).

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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11. No racemization of (*R*)-**4a**, (*S*)-**4d** or (*S*)-**4k** was observed at all under the optimum hydrocyanation conditions.
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