

Scalable Organocatalytic One-Pot Asymmetric Strecker Reaction Via Camphor Sulfonyl Functionalized Crown-Ether-Tethered Calix[4]arene

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7.1. Introduction

The asymmetric Strecker reaction is the most pivotal organic synthesis reaction documented in the literature. It is one of the first multicomponent one-pot, economically viable reactions that provide robust and direct access to optically active α -amino nitriles. The nitrile precursor is essentially preferred because of its linear geometry and hydrogen bond acceptor properties for the synthesis of chiral α -amino acids, tetrazoles, which are recurrent scaffolds in many biologically important chiral drugs. Representative examples that contain chiral α -amino nitrile moiety include antiplatelet agent the largest selling drug clopidogrel, anti-tumor and antibiotic saframycin A, and indole alkaloids -like- reserpine and hirsutine as potent antihypertensive agents. Accordingly, significant efforts have been made towards the employment of new and efficient catalysts that involve state-of-the-art in the synthesis of cyano adducts such as organocatalytic metal complexes polymeric materials, and resins. Out of these, organocatalysis has gained noteworthy attention due to its efficiency, selectivity, and gratifying results at sub-stoichiometric amounts of chiral catalysts. Therefore, it is crucial to create chiral organocatalysts that are synthetically varied and scalable for a broad range of substrates.

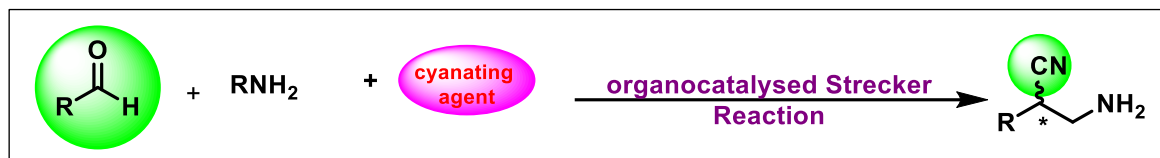


Figure 7.1: General representation of organocatalyzed Strecker reaction

7.1.1 Our work

A detailed study was carried out to study the newly designed camphor sulfonyl functionalized crown appended calix[4]arene organocatalysts for the synthesis of chiral α -amino nitriles via a three-component Strecker reaction through cyanation of an in-situ generated imine under ambient conditions. Furthermore, the potential utility of this strategy is highlighted by the preparation of S-Clopidogrel.

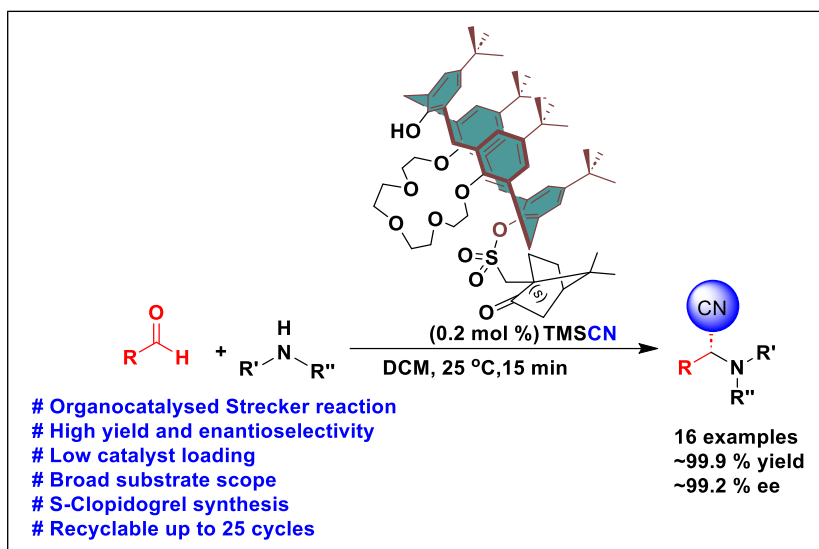


Figure 7.2 Organocatalysed Asymmetric Strecker reaction of aldehydes

7.2 Experimental Section

General Remarks

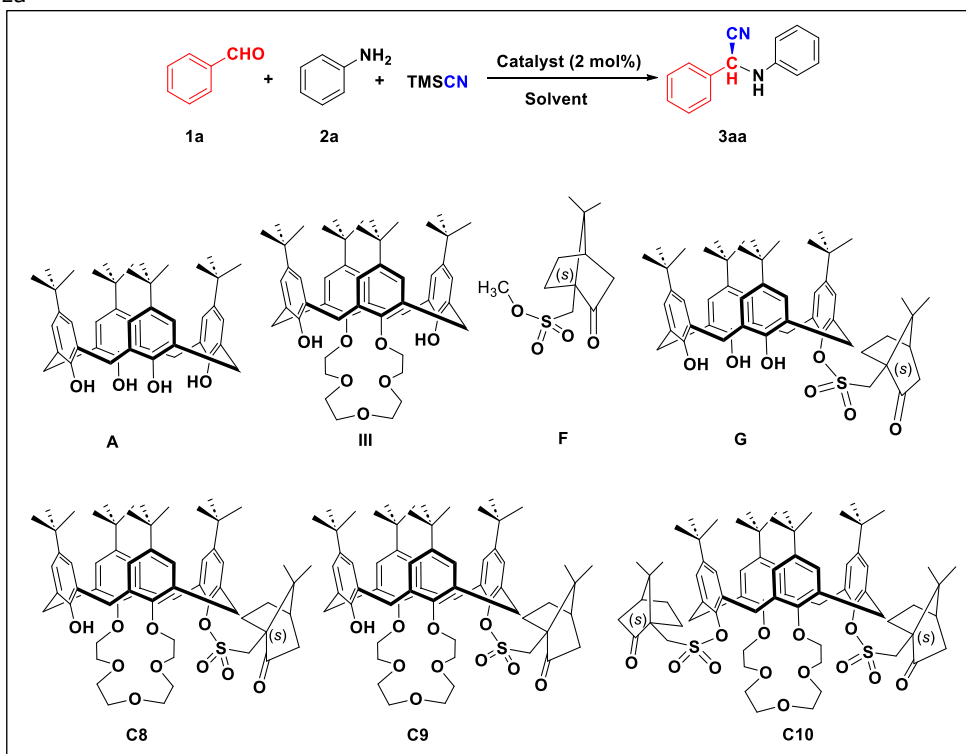
Reaction temperatures were measured externally; reactions were monitored by analytical thin layer chromatography (TLC), Merk 60 F₂₅₄ Aluminium coated plates and visualized by UV light. Column chromatography was performed on silica gel (60-120 mesh) and the solvents employed were of analytical grade purified before Use. The enantiomeric excess (ee) of the cyanated products was determined by HPLC measurements carried out using a thermos scientific Vanquish detector Model: VC-D11-A equipped with chiral columns DAICEL 4.6 mm × 250 mm Chiralpak- AD-H using condition n-Hexane/isopropanol solvent system. Optical rotation values were measured on a JASCO P-1010 polarimeter at $\lambda = 589$ nm, corresponding to the sodium D line, at the temperatures indicated. NMR spectra were recorded on a Bruker 500 spectrophotometer ¹H NMR, ¹³C and ²⁹Si spectra were recorded on 500, 126, and 500 MHz respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (¹H CDCl₃, $\delta = 7.26$; ¹³C CDCl₃, $\delta = 77.0$) and the following abbreviations designate the multiplicity of each signal: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet; bd, broad doublet. Coupling constants (J) are quoted in Hertz. High-resolution mass spectra (HRMS) were acquired using an Agilent technologies model G6564 QTOF. The samples were ionized in positive ion mode using a MALDI or ESI ionization source.

7.2.1 Enantioselective Strecker reaction of aldehyde with amine and effect of catalysts

We started our investigation with a reaction of benzaldehyde **1a** and aniline **2a** using equimolar of TMS-CN as a model reaction in the presence of 2 mol % catalyst **C8** to form enantiopure compounds. The yields are compromised by altering the amount of TMS-CN or aniline (Table 7.2) The reaction proceeds cleanly without any additive and does not form cyanohydrin trimethylsilyl ether side product (Rulli et al., 2011). At the outset, catalysts **A** and **III** were tested and gave incomplete conversion (Table 1, entries 1 and 2). While the pure Methyl (1S)-(+)-10-Camphorsulfonate (**F**) gave 45% yield and 37% ee (Table 1, entry 3). Further calix [4] arene appended with (+)-10-camphor sulfonyl (**G**) without having crown substitution, gave better yield, and improved ee at longer reaction time (Table 1 entry 4) due to hydrogen bond assistance from hydroxyl groups of calixarene. Surprisingly calix[4]arene tethered with crown and (+)-10-camphorsulfonyl (**C8**) moiety gave excellent results with 99% yield and ~98% ee in just 15 minutes (Table 1 entry 5). Noticeably in the case of **C9** when the opposite enantiomer was used it showed the opposite value (Table 1, entry 6). Doubly substituted **C10** gave a good yield but lower

ee (Table 1 entry 7) possibly because of the absence of hydrogen bond donor phenolic OH group. Other chlorinated solvents such as 1,1,2,2-tetrachloroethane and chloroform proved to be good reaction media (Table 1 entries 8 and 9, respectively). The reactions in other polar protic and aprotic solvents like acetonitrile, methanol, dimethyl sulfoxide, and water yielded good but very low enantioselectivities (Table 1 entry 10-13) probably due to unfavorable noncovalent interaction to destabilize enantioselective transition state. The poor miscibility of the catalyst in Et₂O gave poor conversion without any chiral induction (Table 1, entry 14). Although in THF some optical initiation was observed (Table 1, entry 15). Both DMF and toluene did not lead to the completion of the reaction even after 1 h (Table 1 entries 16 and 17, respectively). We next investigated the impact of reaction temperature on selectivity under optimized conditions. Lowering the temperature (10 and 5 °C) gave decelerated reactions with low ee due to the limited solubility of the catalyst (Table 1, entries 18-19). Interestingly, low catalyst loading gave enhanced selectivity (Table 1, entries 20-22) with best enantioselectivity 99.2% with 0.2 mol% catalyst loading (entry 22), indicating the kinetic control nature of chirality transfer. Further decreasing the catalyst loading led to a drop in selectivity (Table 1, entry 23). Thus, the optimal reaction conditions were found to be benzaldehyde **1a** (0.8 mmol), **2a** (0.8 mmol), catalyst **C8** (0.2 mol%), TMSCN (0.8 mmol) in CH₂Cl₂ (0.4 mL) at 25°C for 15 min, under air (entry 22). Under optimal conditions, we extend the scope of the reaction by investigating a series of aldehydes in combination with aniline and diphenylamine (Scheme 2), achieving good to high yields and ee (up to 99% yield and 99% ee; **3aa-3ha** & **3ab-3hb**). Higher yield was observed for unsubstituted benzaldehyde **3aa** and **3ab**. Substituted chlorobenzaldehyde with aniline showed lower enantioselectivity **3ba** and **3ca** on the contrary substituted chlorobenzaldehyde with diphenylaniline gave higher ee **3bb** and **3cb** (95.5 %, 98.5% ee). Strong electron withdrawing group p-NO₂ resulted in low enantioselectivity in **3da** and **3db** (47.0 %, 66.4% ee). o-hydroxy benzaldehyde gave comparatively lower yield and ee than expected might be because of the steric effect **3ea** (92% yield, 89.1% ee). Surprisingly o-hydroxy benzaldehyde with diphenylaniline higher ee was observed **3eb** (95% yield, 98% ee). At the same time, para-hydroxy benzaldehyde and anisaldehyde also participated well and gave appreciable yields and ee **3fa,3fb,3ga**, and **3gb**. The reaction of cyclohexanecarbaldehyde gave the desired product in good yield and ee **3ha** (99.9% yield, 98.5% ee) and **3hb** (92% yield, 96.1% ee).

Table 7.1. Screening of catalysts and further optimizations for asymmetric Strecker reaction of benzaldehyde (**1a**) and Aniline **2a**^a



entry	catalyst	solvent	time (min)	temp (° C)	% yield	%ee ^d (Config.)
1	A	CH ₂ Cl ₂	60	25	56	n.d.
2	III	CH ₂ Cl ₂	60	25	62	n.d.
3	F	CH ₂ Cl ₂	60	25	45	37 (S)
4	G	CH ₂ Cl ₂	60	25	68	75 (S)
5	C8	CH ₂ Cl ₂	15	25	>99	98 (S)
6	C9	CH ₂ Cl ₂	15	25	98	98 (R)
7	C10	CH ₂ Cl ₂	15	25	95	78 (S)
8	C8	TeCA	15	25	94	82 (S)
9	C8	CHCl ₃	15	25	91	72 (S)
10	C8	CH ₃ CN	15	25	78	25 (S)
11	C8	CH ₃ OH	15	25	71	10 (S)
12	C8	H ₂ O	15	25	82	11 (S)
13	C8	DMSO	15	25	75	12 (S)
14	C8	Ether	15	25	28	n.d.
15	C8	THF	15	25	54	23
16	C8	DMF	60	25	24	15 (S)
17	C8	Toluene	60	25	20	12 (S)
18	C8	CH ₂ Cl ₂	15	10	78	64 (S)
19	C8	CH ₂ Cl ₂	60	5	69	60 (S)
20 ^e	C8	CH ₂ Cl ₂	15	25	>99	99 (S)
21 ^f	C8	CH ₂ Cl ₂	15	25	>99	>98 (98.8, S)
22 ^g	C8	CH ₂ Cl ₂	15	25	>99	>99 (99.2, S)
23 ^h	C8	CH ₂ Cl ₂	15	25	97	90 (S)

^aReaction condition: benzaldehyde (0.8 mmol) and Aniline (0.8 mmol) were stirred for 15-120 min at a given temperature in the presence of 2 mol% of catalyst. Then TMSCN (0.8 mmol) was added. ^c Isolated yield. ^d Determined by chiral HPLC on a Chiralpak AD-H column. ^eCatalyst (1 mol%), ^fCatalyst (0.5 mol%), ^gCatalyst (0.2 mol%) and ^hCatalyst (0.1 mol%).

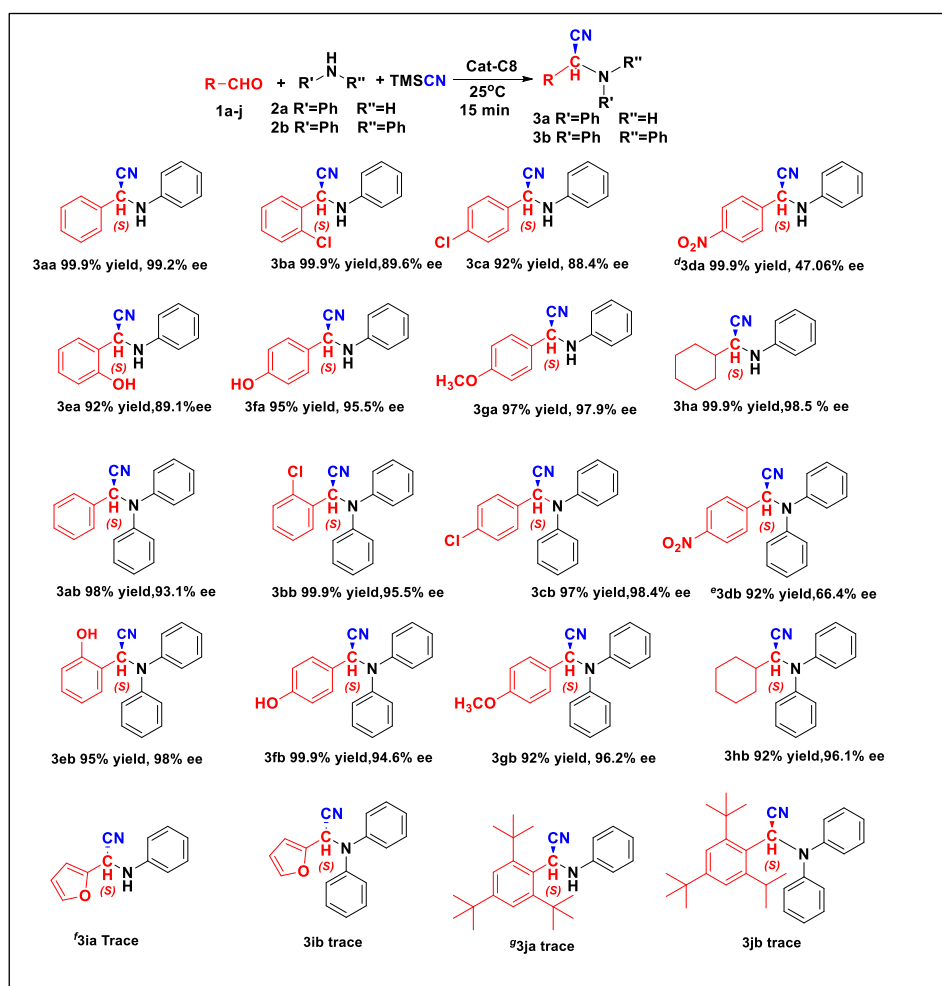
Heterocycles and bulky substituents adjacent to the carbonyl group did not go well with our catalytic system despite increasing the catalyst loading and time of the reaction as we did not get the expected α -amino nitriles as in **3ia**, **3ja**, **3ib**, and **3jb**

Table 7.2-Effects of the ratio of aldehyde/amine to TMSCN on enantioselective Strecker reaction*

Entry ^[a]	Ratio of benzaldehyde/aniline /TMSCN	Time[min]	%Yield ^[b]	%ee ^[c]
1	1/1/1	15	99.9	99.2
2	1/0.9/1.2	15	99.9	99.1
3	1/0.9/1.5	30	99.9	98.9

*Reaction Conditions: 1 equiv of catalyst **C8**, aldehyde, aniline and TMSCN in DCM at 25°C ^[b] Isolated yield. ^[c] Optical rotation values were measured on a JASCO P-1010 polarimeter at $\lambda = 589$ nm.

Scheme 2: Substrate scope using catalyst **C8** under optimized conditions. ^{a,b,c}



^aReaction conditions: **1** (0.8 mmol), **2** (0.8 mmol), catalyst **C8** (0.2 mol%), TMSCN (0.8 mmol), DCM (0.4 mL, 25°C, 15 min, under air). ^bIsolated yield. ^c% ee determined by HPLC equipped with AD-H chiral columns and configuration was determined by relative retention time and specific rotation with literature data; See Supporting Information for details. ^d5 mol% catalyst loading. ^eReaction time 48 h. ^fReaction completed in 10 h. ^g5 mol% catalytic loading, 72 h. ^h5 mol% catalytic loading, 48 h

7.3 Mechanistic Explanation

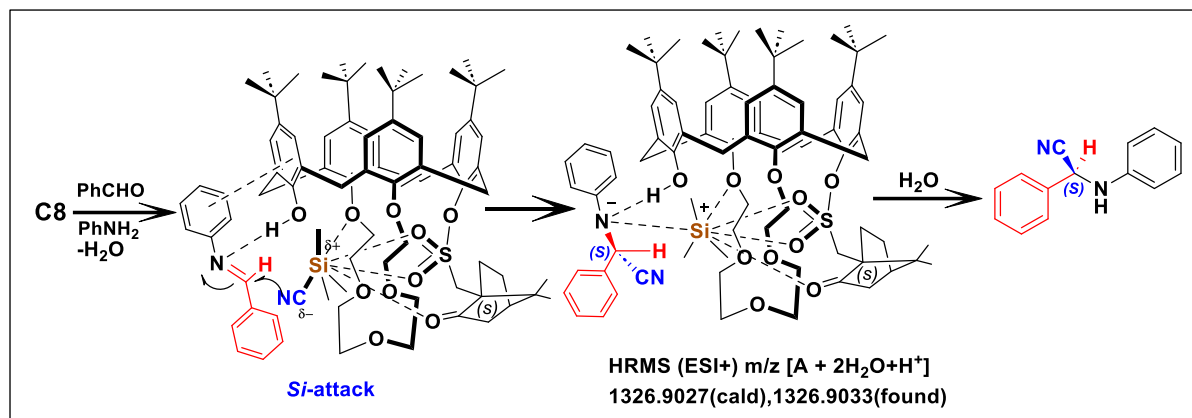


Figure 7.3: Plausible mechanism for asymmetric Strecker reaction. The mechanism involves the chiral induction via non-covalent approach (H-bonding, pi-pi, cation-lp, and electrostatic), creating *Si*-attack on imine intermediate to form *S*-isomer of **3**. (Pan et al., 2023, Shinohara et al., 2019)

7.4 Application of camphor sulfonyl catalysed asymmetric cyanation reaction in the synthesis of Clopidogrel^a

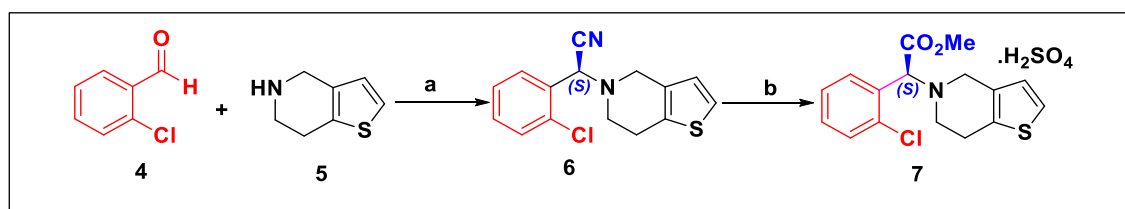


Figure 7.4: ^aReaction Conditions (a) **4** (3g, 21mmol), **5** (2.9g, 21 mmol), TMSCN (2.0 g, 21 mmol), catalyst **C8** (0.2 mol%), DCM (20 ml) to give **6** (98% yield, 99.3% ee); (b) MeOH, H₂SO₄ to give **7** (73.2% yield, 98.5% ee); % ee of **6** and **7** determined by HPLC equipped with AD-H chiral columns and configuration was determined by relative retention time and specific rotation

7.4.1 Procedure for the Synthesis of *S*-Clopidogrel

In an inert environment 2-Chlorobenzaldehyde (3 g, 21mmol), 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (2.9 g, 21 mmol) TMSCN (2.0 g, 21 mmol), were introduced in a round bottom flask with dichloromethane (20 ml) as a solvent and catalyst **C8** (0.2 mol%). The reaction mixture was stirred continuously for 15 minutes and monitored through TLC. The reaction mixture was treated with chloroform and washed with a saturated solution of sodium bisulphite. The organic phase was dried over anhydrous sodium sulphate. The solvent was then evaporated under reduced pressure and the crude was purified through column chromatography (n-hexane/ethyl acetate 80:20) to give (*S*)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetonitrile (**6**, 5.9 g, 98% yield). To this compound **6** esterification was done with MeOH (40 ml), and H₂SO₄ (1 ml) and the reaction was continued for 4 days and monitored through TLC. The reaction mixture was treated with water followed by the addition of sodium carbonate and dichloromethane. After drying over Na₂SO₄ solvent was evaporated to obtain *S*-Clopidogrel (4.8 g, 73.2% yield). The enantiomeric excess was determined by chiral stationary-phase HPLC analysis using AD-H chiral column.

7.5 Recyclability of catalysts

In an inert environment, benzaldehyde (84 mg, 0.8 mmol), aniline (74 mg, 0.8 mmol), trimethylsilyl cyanide (79 mg, 0.8 mmol), and catalyst (2 mol%) were introduced in a dry glass tube with dichloromethane (0.4ml) as a solvent. The reaction mixture was stirred continuously for 15 minutes and monitored through TLC. The reaction mixture was treated with chloroform and washed with a saturated solution of sodium bisulphite. The organic phase was dried over anhydrous sodium sulphate. The solvent was then evaporated under reduced pressure and the crude was purified through column chromatography (hexane/Ethyl acetate 80/20). The enantiomeric excess was determined by chiral stationary-phase HPLC analysis.

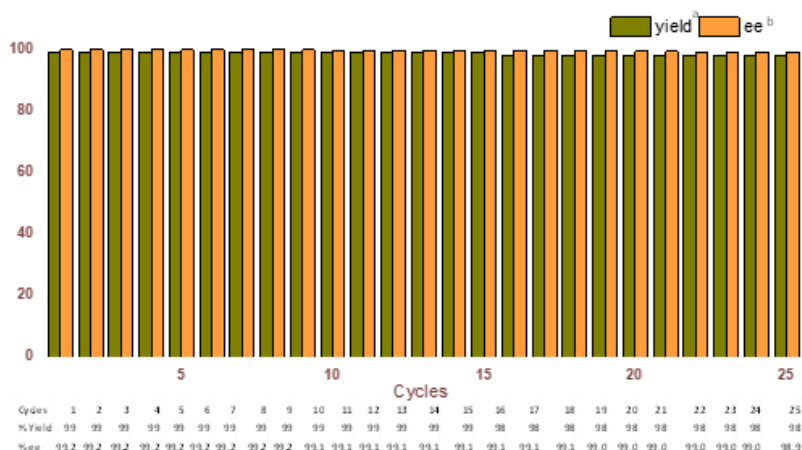
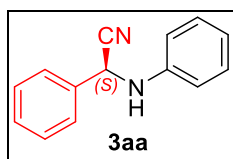


Figure 7.5: Recyclability test of catalyst **C8** for **3a**. Reaction condition: **1a** (80 mmol), **2a** (80 mmol), TMSCN (80 mmol), DCM 120 mL, catalyst **C8** (0.2 mol%), rt, 30 min, under air. ^aIsolated yield. ^bee was determined by HPLC equipped with Daicel Chiralpak AD-H column

7.6 Conclusion

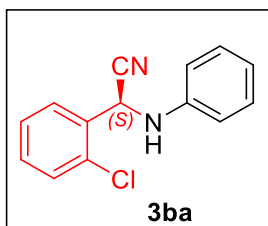
A newly designed camphor sulfonyl functionalized crown ether strapped calix[4]arenes as organocatalysts (**C8**) for asymmetric Strecker reaction for cyano-adduct that show promising adaptability to high-throughput screening with remarkable efficiency and selectivity under ambient conditions (99% Yield and > 99% ee). We were also able to synthesize (S)-Clopidogrel the most selling drug worldwide with 73% yield and 98.5 % ee. Here the sulfonyl moiety transfers the chirality to the substrate through non-covalent interactions, π - π stacking, and the crown ether pendulum serves as a useful tool for control of asymmetric reaction which enhances enantioselectivity. Unlike most organocatalysts, the catalyst could be recovered and reused up to 25 test cycles without a significant drop in enantioselectivity.

7.7 Product Analysis

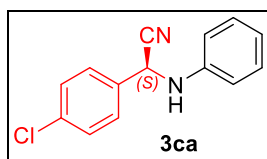


(S)-2-phenyl-2-(phenylamino)acetonitrile(3aa). Colourless solid; 164.3 mg, 99.9% yield; 99.2% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) =12.5min, tR (minor) = 18.9 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 3H), 7.31 – 7.27 (m, 2H), 7.17 (dd, *J* = 8.5, 7.4 Hz, 1H), 6.96 – 6.88 (m, 1H), 6.82 – 6.77 (m, 2H), 6.73 – 6.69 (m, 1H), 5.44

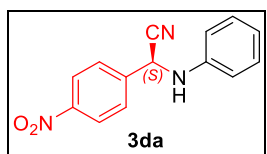
(s, 1H), 4.00 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.62, 132.87, 128.54, 128.51, 128.31, 126.23, 119.24, 113.09, 49.16. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$, 208.1000; found 208.1009.



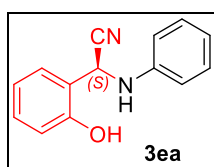
(S)-2-(2-chlorophenyl)-2-(phenylamino)acetonitrile(3ba). Colourless solid; 171.8 mg, 99.9% yield; 89.6% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 4.1 min, tR (minor) = 7.1 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 5H), 7.31 – 7.28 (m, 4H), 5.75 (s, 1H), 4.07 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.39, 135.64, 132.43, 129.65, 128.63, 126.25, 120.60, 117.86, 114.33, 49.69. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{ClN}_2$, 242.0600; found 242.0602.



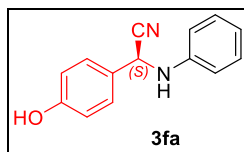
(S)-2-(4-chlorophenyl)-2-(phenylamino)acetonitrile (3ca). Colourless solid; 151.4 mg, 92% yield; 88.4% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 4.2 min, tR (minor) = 4.4 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.48 – 7.39 (m, 5H), 7.29 (d, J = 7.9 Hz, 1H), 7.24 – 7.20 (m, 2H), 6.93 (t, J = 7.4 Hz, 1H), 5.42 (s, 1H), 4.10 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.92, 150.67, 143.37, 136.41, 133.69, 131.42, 128.98, 128.65, 128.57, 128.23, 128.11, 127.62, 125.24, 119.87, 119.62, 116.82, 113.32, 48.68, 28.73. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{ClN}_2$, 242.0600; found 242.0603.



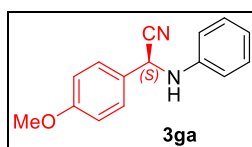
(S)-2-(4-nitrophenyl)-2-(phenylamino)acetonitrile(3da). Yellow solid; 207.3 mg, 99.9% yield; 47.0% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 26.3 min, tR (minor) = 39.3 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.30 (d, J = 8.7 Hz, 2H), 8.09 – 8.06 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 13.4, 6.9 Hz, 3H), 6.94 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 2H), 5.64 – 5.48 (m, 1H), 4.22 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.59, 138.75, 129.73, 129.51, 129.43, 129.36, 129.15, 128.68, 128.24, 127.11, 124.49, 124.21, 124.04, 120.98, 120.79, 114.62, 49.76. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2$, 253.0900; found 253.0907.



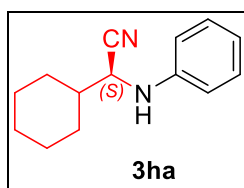
(S)-2-(2-hydroxyphenyl)-2-(phenylamino)acetonitrile(3ea). Colourless solid; 157.9 mg, 92% yield; 89.1% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 8.9 min, tR (minor) = 18.8 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.63 (s, 1H), 7.56 (dd, J = 7.8, 1.6 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.31 – 7.27 (m, 3H), 7.03 (dd, J = 7.7, 3.6 Hz, 3H), 6.92 (d, J = 8.0 Hz, 2H), 5.63 (d, J = 9.1 Hz, 1H), 4.23 (d, J = 9.6 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.66, 153.76, 132.15, 131.26, 128.71, 128.40, 127.13, 125.89, 121.23, 120.15, 118.07, 116.30, 115.41, 47.61. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$, 224.0900; found 224.0903



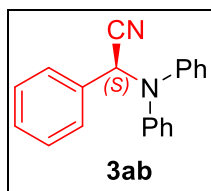
(S)-2-(4-hydroxyphenyl)-2-(phenylamino)acetonitrile(3fa). Colourless solid; 171.3 mg, 95% yield; 95.5% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 26.9 min, tR (minor) = 33.3 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.46 (d, J = 8.5 Hz, 2H), 7.31 – 7.27 (m, 2H), 6.91 (t, J = 8.1 Hz, 3H), 6.78 (dt, J = 7.7, 3.4 Hz, 2H), 5.36 (d, J = 7.5 Hz, 1H), 4.01 (d, J = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.65, 143.66, 128.56, 127.85, 124.99, 119.22, 117.38, 115.13, 113.08, 48.66. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$, 224.0900; found 224.0905



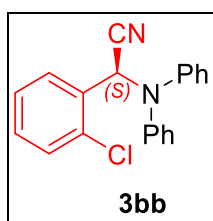
(S)-2-(4-methoxyphenyl)-2-(phenylamino)acetonitrile(3ga). Colourless solid; 151.5 mg, 97% yield; 97.9% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 11.8 min, tR (minor) = 12.5 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.51 (d, J = 8.7 Hz, 2H), 7.28 (dd, J = 8.5, 7.3 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.80 – 6.75 (m, 2H), 5.37 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.38, 143.69, 128.52, 127.60, 124.88, 119.13, 117.39, 113.59, 113.04, 54.39, 48.60. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$, 238.1100; found 238.1107.



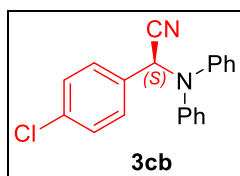
(S)-2-cyclohexyl-2-(phenylamino)acetonitrile(3ha). Colourless solid; 141.1 mg, 99.9% yield; 98.5% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 22.9 min, tR (minor) = 25.6 min; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.27 (m, 2H), 7.20 – 7.17 (m, 1H), 6.90 – 6.87 (m, 1H), 6.73 (ddt, J = 11.0, 8.5, 1.1 Hz, 3H), 3.88 – 3.79 (m, 1H), 1.36 – 1.21 (m, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.19, 129.55, 119.89, 118.86, 114.06, 51.75, 40.80, 29.69, 28.94, 25.94, 25.66, 25.59. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2$, 214.1500; found 214.1504



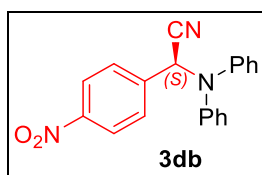
(S)-2-(diphenylamino)-2-phenylacetonitrile(3ab). Colourless solid; 217.1 mg, 98% yield; 93.1% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: t_R (major) = 18.8 min, t_R (minor) = 34.2 min; ¹H NMR (500 MHz, CDCl₃) δ 7.53 – 7.50 (m, 2H), 7.43 (s, 3H), 7.07 (d, *J* = 7.9 Hz, 9H), 6.93 (d, *J* = 7.4 Hz, 5H), 5.50 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 143.19, 135.38, 129.41, 126.81, 126.63, 121.12, 121.11, 121.01, 118.89, 117.88, 63.76. HRMS (ESI+) *m/z* [M + H]⁺ calcd for C₂₀H₁₆N₂, 284.1300; found 284.1308.



(S)-2-(2-chlorophenyl)-2-(diphenylamino)acetonitrile(3bb). Colourless solid; 225.8 mg, 99.9% yield; 95.5% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: t_R (major) = 9.1 min, t_R (minor) = 19.1 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.8 Hz, 6H), 7.10 (d, *J* = 8.0 Hz, 6H), 6.96 (t, *J* = 7.4 Hz, 3H), 5.85 (d, *J* = 4.6 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 144.17, 142.09, 130.13, 130.03, 129.59, 129.10, 128.85, 128.31, 127.41, 126.69, 125.78, 122.95, 121.98, 119.97, 116.78, 59.99. HRMS (ESI+) *m/z* [M + H]⁺ calcd for C₂₀H₁₅ClN₂, 318.0900; found 318.0902.

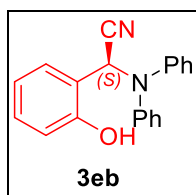


(S)-2-(4-chlorophenyl)-2-(diphenylamino)acetonitrile(3cb). Colourless solid; 209.8 mg, 97% yield; 98.4% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: t_R (major) = 17.2 min, t_R (minor) = 22.4 min; ¹H NMR (500 MHz, CDCl₃) δ 7.07 (d, *J* = 7.9 Hz, 9H), 6.92 (t, *J* = 7.4 Hz, 5H), 5.51 (s, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 143.12, 133.73, 131.09, 129.38, 127.98, 121.09, 120.97, 118.38, 117.81, 63.08. HRMS (ESI+) *m/z* [M + H]⁺ calcd for C₂₀H₁₅ClN₂, 318.0900; found 318.0909.

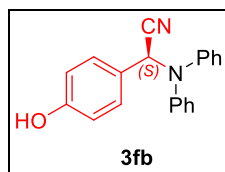


(S)-2-(diphenylamino)-2-(4-nitrophenyl)acetonitrile (3db). yellow solid; 248.1 mg, 92% yield; 66.4% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: t_R (major) = 17.0 min, t_R (minor) = 18.6 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 8.8 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.29 (s, 1H), 7.28 (d, *J* = 1.2 Hz, 2H), 7.27 (s, 3H), 7.11 – 7.06 (m, 4H), 6.94 (s, 2H), 5.71 (s, 1H). ¹³C NMR (126 MHz,

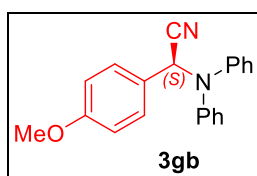
Chloroform-*d*) δ 143.13, 141.44, 129.36, 127.51, 124.37, 121.03, 117.83, 62.54. HRMS (ESI+) m/z [M + H]⁺ calcd for C₂₀H₁₅N₃O, 329.1200; found 329.1204.



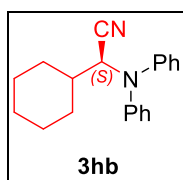
(S)-2-(diphenylamino)-2-(2-hydroxyphenyl)acetonitrile(3eb). Colourless solid; 218.4 mg, 95% yield; 98% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) =18.1 min, tR (minor) = 20.8 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.48 (m, 1H), 7.27 (d, *J* = 7.8 Hz, 4H), 7.08 (d, *J* = 7.9 Hz, 7H), 6.94 (t, *J* = 7.4 Hz, 3H), 5.70 (s, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 163.07, 141.56, 130.46, 128.39, 127.77, 126.75, 119.42, 116.24, 112.97, 112.76, 61.82, 54.03. HRMS (ESI+) m/z [M + H]⁺ calcd for C₂₀H₁₆N₂O, 300.1300; found 300.1304.



(S)-2-(diphenylamino)-2-(4-hydroxyphenyl)acetonitrile(3fb) Colourless solid; 241.3 mg, 99.9% yield; 94.6% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 18.8 min, tR (minor) =28.3 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 5H), 7.08 (d, *J* = 8.0 Hz, 5H), 6.95 (q, *J* = 8.0 Hz, 3H), 5.73 (s, 1H); ¹³C NMR (126 MHz, Chloroform-*d*) 163.59, 142.07, 131.00, 128.91, 128.31, 127.29, 119.95, 116.75, 113.50, 113.29, 62.36. HRMS (ESI+) m/z [M + H]⁺ calcd for C₂₀H₁₆N₂O, 300.1300; found 300.1305.



(S)-2-(diphenylamino)-2-(4-methoxyphenyl)acetonitrile(3gb). Colourless solid; 189.5 mg, 92% yield; 96.2% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) =5.0 min, tR (minor) = 5.6 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 4H), 7.11 – 7.07 (m, 6H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.96 – 6.90 (m, 3H), 5.76 (s, 1H), 3.90 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 163.59, 142.07, 131.00, 128.31, 127.29, 119.95, 116.75, 113.50, 113.29, 62.36, 54.56. HRMS (ESI+) m/z [M + H]⁺ calcd for C₂₁H₁₈N₂O, 314.1400; found 314.1402.



(S)-2-cyclohexyl-2-(diphenylamino)acetonitrile(3hb). Colourless solid; 176.1 mg, 92% yield; 96.1% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) = 9.5 min, tR (minor) = 13.0 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.8 Hz, 3H), 7.08 (d, *J* = 7.9 Hz, 5H), 6.93 (t, *J* = 7.4 Hz, 2H), 4.27 (d, *J* = 6.2 Hz, 1H), 1.89 (s, 1H), 1.85 – 1.80 (m, 2H), 1.75 – 1.70 (m, 3H), 1.27 (q, *J* = 5.0 Hz, 5H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 141.55, 127.77, 119.43, 116.24, 64.84, 40.72, 26.52, 26.20, 24.35, 23.87, 23.84 HRMS (ESI+) *m/z* [M + H]⁺ calcd for C₂₀H₂₂N₂, 290.1800; found 290.1800.