

α -Methylbenzylamine Functionalized Crown-Ether-Appended Calix[4]arene Phase Transfer Catalyst for Enantioselective Henry Reaction

This work described in this chapter has been published in *Chem. Eur. J.* 2023, **29**, e202302638

6.1. Introduction

The nitroaldol or Henry reaction is one of the traditional named reactions in organic synthesis among various C-C bond formation reactions. Since its discovery in 1895, the coupling of the nucleophile obtained from nitroalkane with a carbonyl electrophile to give product β -nitroalcohol has essentially been commonly employed as a versatile intermediate in organic synthesis. The first asymmetric version was introduced by Shibasaki in 1992 (Sasai et al., 1992). Nitroaldol reaction has seen a resurgence of activity for the direct transformation of C-H into C-C bonds due to synthetic versatility and operational simplicity (Luzzio, 2001, Marcelli et al., 2006a). The Henry product, hydroxy nitroalkanes, are useful building blocks for important unnatural amino acids and bioactive molecules (Kudyba et al., 2003, Dodda et al., 2008) with special reference to β -adrenergic receptor blockers toliprolol (Howe and Rao, 1968, Roy et al., 2014), and propranolol (Dukes and Smith, 1971, Sasai et al., 1995). Generally, the enantioselective Henry reaction is proceeded by a chiral catalyst, although attaining high enantiomeric excess under mild reaction conditions is synthetically challenging. Limited success has met with phase transfer catalysts (PTCs) with good enantioselectivity. We conceived that enantioselective installation by supramolecule-derived PTC could provide a generalizable state-of-the-art auxiliary approach with catalytic recyclability while avoiding stoichiometric use of catalytic amounts. The application of calix[4]arene as PTCs for the catalytic asymmetric nitro-aldol reaction is still infancy. The catalytic versatility of the calix[4]arene-based catalysts arises from two key factors: conformational flexibility and bifunctionality. Conformational flexibility makes calix[4]arene easily tunable with different groups and the bifunctionality is attributed by the calix crown which encapsulates the K^+ ion and the NH proton of the chiral scaffold attached to calix[4]arene. The product contains two important functional groups nitro and hydroxy groups, nitro alcohols can easily be transformed into useful synthons for the synthesis of variety of structural scaffolds which holds importance for pharmaceutically active compounds

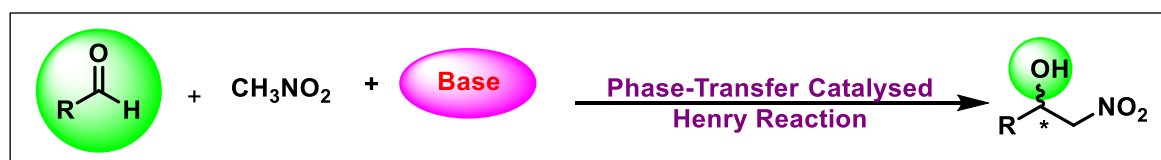


Figure 6.1 General scheme for phase transfer catalyzed asymmetric Henry reaction

6.1.1 Earlier work

Interest in this area has grown significantly, considering several studies on the development of various metal and non-metal-based catalysts for the asymmetric Henry reaction such as zeolite-Y (Deka et al., 2015), Organocatalytic asymmetric Henry reaction of 1H-pyrrole-2, 3-diones with bifunctional amine-thiourea catalysts bearing multiple hydrogen-bond donors. (Zhang et al., 2016). A new class of urea-substituted cinchona alkaloids promotes highly enantioselective nitroaldol reactions of trifluoromethylketones. (Palacio and Connon, 2011) (Yao et al., 2012). Hongming Li et al. reported the nitroaldol reaction of R-ketoesters catalyzed by cinchona

alkaloids. (Li et al., 2006). However, there have only been a few reports of asymmetric Henry reactions employing chiral phase transfer catalysts. (Corey and Zhang, 1999, Palomo et al., 2004) Highly enantioselective asymmetric Henry reaction catalyzed by novel chiral phase transfer catalysts derived from cinchona alkaloids. (Vijaya et al., 2016).

Calixarene derived PTCs for asymmetric Henry reaction is virtually absent in the literature. To the best of our knowledge, the only reported examples pertaining to calix[4]arene functionalized organocatalysts for Henry reaction are reported with poor enantioselectivities (7.5% ee) (Chang et al., 2017) and Li (22.3% ee) (Peng et al., 2021b) Hence the design of effective PTCs for Henry reaction with high enantioselectivity under mild conditions remains the sine qua non to date.

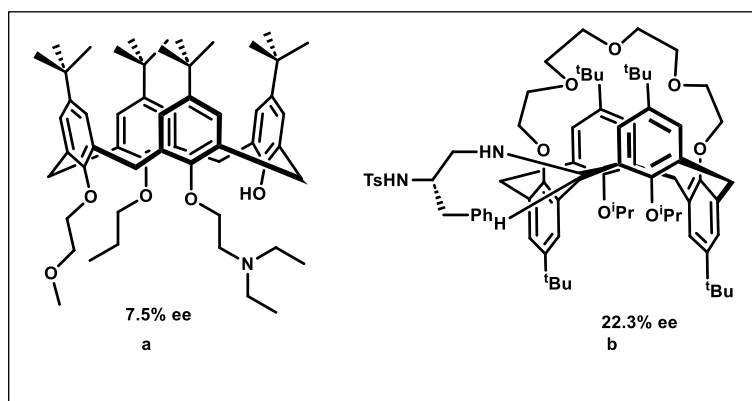


Figure 6.2 Catalyst prepared for asymmetric henry reaction using calix[4]arene scaffold (a) Chang; (b) Li

6.1.2 Our work

A highly selective α -methylbenzylamine functionalized crown-ether-appended calix[4]arene derived phase transfer catalyst for asymmetric nitroaldol reaction to provide the desired nitroaldol adducts in high yields (up to 99% yield) with good to excellent enantioselectivities (up to 99.8 % ee)

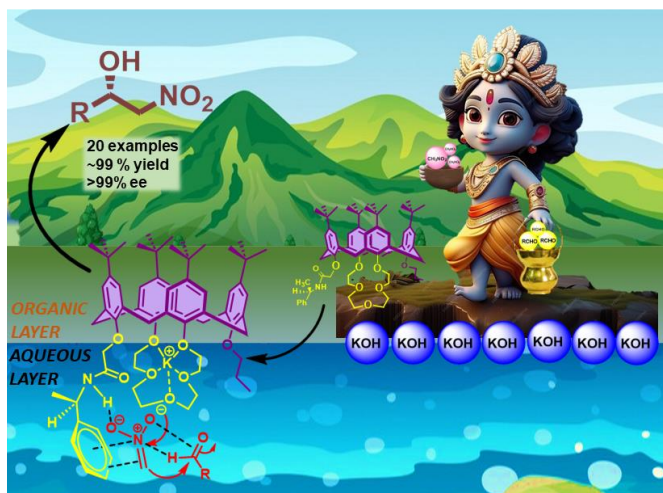


Figure 6.3 Pictorial representation of Phase transfer catalysed asymmetric Henry reaction catalysed by α -methylbenzylamine functionalized crown-ether-appended calix[4]arene

6.2 Experimental Section

General Remarks

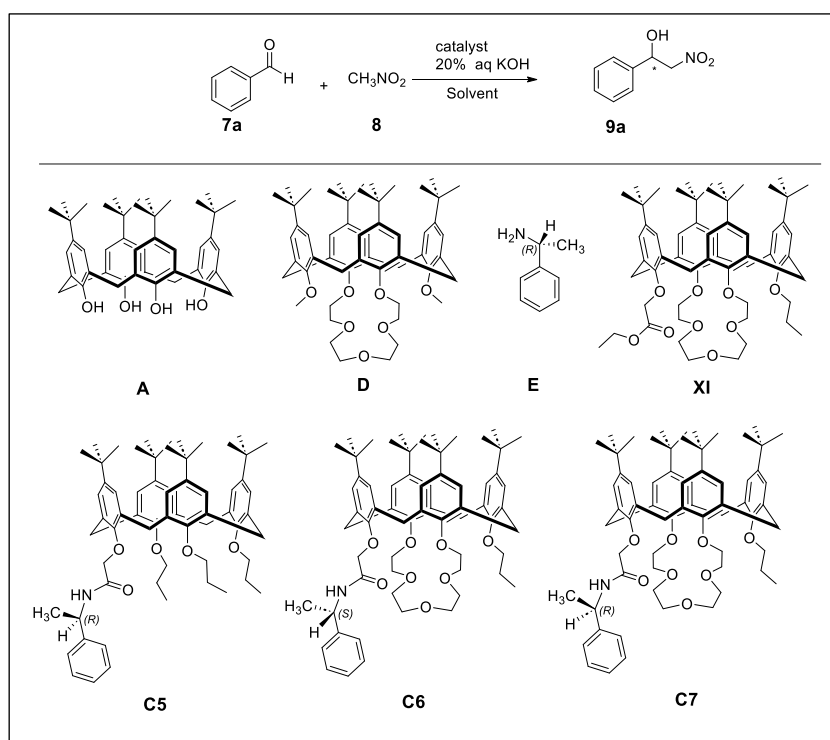
Catalysts were prepared under a nitrogen atmosphere, while Henry reactions were carried out in open air. To a mixture of various aldehydes **7** (a–y, 0.3 mmol.), nitromethane **8** (0.183g, 3 mmol.) and PTCs (0.033g, 0.1 mmol%) **C7** were dissolved in 2 mL cyclohexane and 0.5 mL of 20% aqueous KOH was added. Then the reaction mixture was stirred for 12 h at room temperature (25 °C), after that the reaction mixture was extracted with chloroform, washed with water (3 $\times$ 2 ml), then

washed with brine solution (5 ml), dried over Na₂SO₄ and then concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate and petroleum ether (1: 9) as an eluent), to afford the corresponding products **9a-y**. An enantiomeric excess of **6a-y** was determined by chiral stationary-phase HPLC analysis carried out using a Waters Model 2489 equipped with various chiral columns (DAICEL 4.6 mm × 250 mm Chiralpak-OD-H, OB, AD, AD-H, and OJ) using condition n-Hexane/isopropanol solvent system at room temperature.

6.2.1 Enantioselective Henry reaction of aldehyde to nitromethane and effect of catalysts

At the onset of our study, we first employed benzaldehyde **7a** as a model substrate with nitromethane in cyclohexane at RT to obtain chiral 1-Phenyl-2-nitroethanol **9a** using 5 mol% catalysts (Table 6.2.1). While the calix[4]arene (**A**) is catalytically inactive as expected (Entry 1), PTC with crown pendulum accelerated the reaction rate considerably due to K⁺ recognition and produced 70% nitroaldol product (entry 2). Interestingly, pristine (R)- α -methylbenzyl amine (**D**) showed negligible conversion with a preference towards rapid formation of undesired imine (entry 3). Ester functionalization of phenolic OH of calixarene improved the yield due to a favorable steric effect (catalyst **XI**; entry 4). Moderate yield and low enantioselectivity were realized in the absence of crown in catalyst **C5**, indicating its crucial role in catalytic conversion

Table 6.1. Screening of catalysts and further optimizations for asymmetric Henry reaction of benzaldehyde (**7a**) and nitromethane **8**^a



Entry	Cat	Solvent	Time [h] ^b	T [°C]	Yield [%] ^c	ee [%] ^d
1	A	cyclohexane	12	25	trace	n.d
2	D	cyclohexane	12	25	70	n.d
3	E	cyclohexane	12	25	trace	n.d
4	XI	cyclohexane	12	25	75	n.d
5	C5	cyclohexane	12	25	60	45 (S)
6	C6	cyclohexane	8	25	98	95 (R)
7	C7	cyclohexane	8	25	> 99	98 (S)
8	C7	CH ₃ CN	12	25	67	35 (S)
9	C7	CHCl ₃	12	25	55	42 (S)
10	C7	CH ₂ Cl ₂	12	25	56	38 (S)
11	C7	toluene	12	25	76	15 (S)
12	C7	Et ₂ O	24	25	trace	n.d.
13	C7	THF	12	25	35	57 (S)
14	C7	EtOAc	12	25	71	62 (S)
15	C7	MeOH	12	25	23	n.d
16	C7	cyclohexane	8	0	60	92 (S)
17	C7	cyclohexane	12	-5	20	10 (S)
18	C7	cyclohexane	24	-10	trace	n.d
19 ^e	C7	cyclohexane	8	25	> 99	99.7 (S)
20 ^f	C7	cyclohexane	8	25	> 99	99.6 (S)
20 ^g	C7	cyclohexane	8	25	> 99	99.8 (S)
21 ^h	C7	cyclohexane	8	25	> 99	99.8 (S)
22 ⁱ	C7	cyclohexane	8	25	92	89 (S)

^aUnless otherwise stated, the reactions were executed with **7a** (0.031g, 0.3 mmol), MeNO₂ (**8**, 0.183g, 3 mmol), in 2 mL of solvent in the presence of 5 mol% catalyst and 20% aq KOH (0.5 mL) at room temperature for 12 h.

^bBased on TLC analysis of **7a** consumption ^cIsolated yield, rest starting materials. ^dDetermined by HPLC analysis using Chiralcel OD-H column with n-hexane/2-propanol (80: 20) and the configuration was assigned by relative retention time and specific rotation with literature data.⁸ ^ecatalyst (1 mol%), ^fcatalyst (0.5 mol%), ^gcatalyst (0.2 mol%), ^hcatalyst (0.1 mol%), ⁱcatalyst (0.05 mol %).

(entry 5). Calix-crown anchored (S)- α -methylbenzyl amine catalyst C6 gave an appreciable 98% yield and 95% ee of **9a** with opposite configuration in a shorter reaction time (entry 6). To our pleasure, excellent yield (> 99%) and selectivity (98.2% ee) were afforded with catalyst C7 in 8 h (entry 7). A survey of solvents revealed that the reaction medium had a significant impact on the conversion and selectivity in nitroaldol reaction (entry 8-15). Acetonitrile as a solvent resulted **9a** in moderate yield (67%) and low selectivity (35% ee, entry 8). While chlorinated solvents like

chloroform and dichloromethane gave slightly improved enantioselectivity (entries 9 and 10, respectively), toluene performed poorly (entry 11). We could not get any conversion in Et₂O due to poor miscibility of the catalyst (entry 12), although moderate activity was observed in THF (35%, 57% ee; entry 13). The reaction carried out in polar solvent ethyl acetate gave 71% yield and 62% ee (entry 14), whereas MeOH essentially gave the racemic product with low conversion (entry 15). We next investigated the impact of reaction temperature on selectivity under standard conditions. Lowering temperatures (0, -5, and -10 °C) gave sluggish reactions with poor conversion due to the inferior solubility of the catalyst (entry 16-18). Interestingly, low catalyst loading gave improved selectivity (entry 19-21) with the best enantioselectivity. Further lowering of catalyst loading led to a decrease in the yield and enantioselectivity (entry 22). Among the bases examined, 20% KOH gave the best conversion Table 6.2 Thus, the optimal reaction conditions were found to be 0.3 mmol benzaldehyde, 3 mmol nitromethane and 20% aqueous KOH in 2 mL of cyclohexane with 0.1 mol % PTC C7 loading at 25°C for 8 h (entry 21).

Table 6.2. Screening of bases

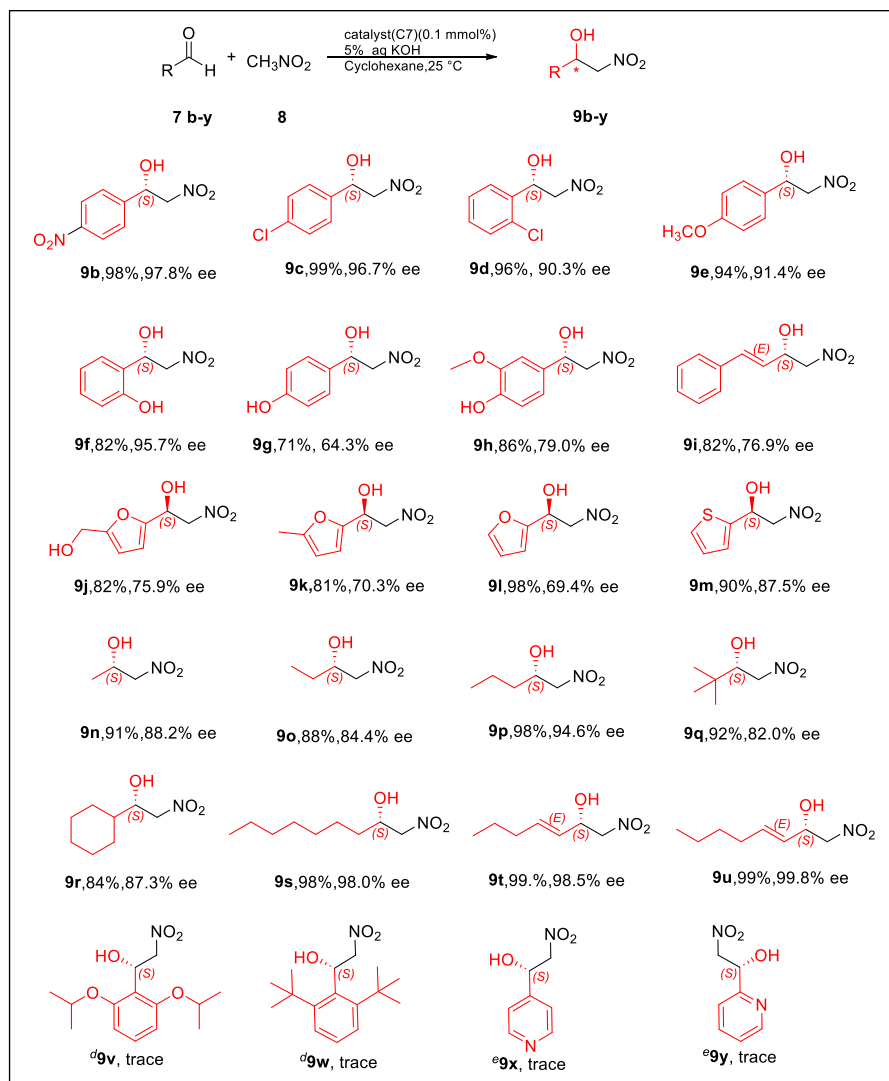
Entry	Base	% Base	Time (h) ^a	Yield (%) ^b	ee (%) ^c
1	n.a	-	24	-	-
2	NaOH	20	12	80	87
3	KOH	20	12	99	98.5
4	CsOH	20	12	81	85
5	K ₂ CO ₃	20	12	62	49
6	Na ₂ CO ₃	20	12	54	52
7	Cs ₂ CO ₃	20	12	61	51
8	CsF	20	12	60	30
9	KOH	30	8	99	98.4
10	KOH	20	8	99	98.6
11	KOH	10	10	94	98.3

^aDetermined by monitoring the consumption of benzaldehyde **7a** by TLC. ^bIsolated yield. ^cDetermined by HPLC equipped with Daicel Chiralpak OD-H

The scope of this reaction using catalyst **C7** under optimized conditions (Scheme 6.1). Significantly, the majority of the reactions with aromatic, aliphatic, and heterocycles **7b-y** afforded the corresponding nitroaldol products **9b-y** with high yields and selectivities with few exceptions (**9v-y**). Phenyl substituted aldehydes **7b-i** yielded enantioenriched nitroaldol products **9b-i** in good to excellent yield and enantiopurities. When the phenyl moiety of benzaldehyde is substituted with chloro, corresponding adducts were obtained with high yields and enantioselectivities (**9c** and **9d**, respectively). Similar tendencies were observed for electron-donating substituents, *p*-CH₃O- (**9e**, 94% yield, >91% ee). The *o*-HO- substituted phenyl **7f** gave high optical purity 95.7% ee while *para*-hydroxy **7g** provided modest enantioselectivity due to loss of hydrogen bonding assistance of hydroxyl group. The exact reason is not clear, but apparently, strong hydrogen bond donor *o*-HO- could create favorable interactions, leading to high enantioselectivity. Vanillin improved enantiopurity of **7h** due to the positive directing of 3-methoxy group. Cinnamaldehyde with conjugated double bond was well tolerated with

comparable yield and selectivity of **6i**. Hydrogen bond interactive heterocyclic aldehydes (**7j-m**) gave high yields with moderate enantioselectivities (**9j-m**). These results are in coherence with **9f-g** with phenolic aldehydes. Higher enantioselectivity of **6m** could be due to the higher aromaticity of 2-Thienylaldehyde **7m** with a soft sulfur center. Interestingly, unactivated and linear and cyclic aliphatic aldehydes (**4n-u**) offered remarkable enantioselectivities (82-99.8%) except for **9q** (82% ee), where *tert*-butyl group might offer steric hindrance. The high enantioselectivities could be pertaining to the good fit of linear alkyl groups within the chiral parasol of the catalyst without offering intrusive steric interaction with preference to odd carbons. It is noteworthy that linear conjugated aldehydes (*E*)-pentyl **7t** and (*E*)-hexyl **7u** produced corresponding nitro alcohol adducts (**9t-u**) with excellent enantiopurities by facilitating enantio-face control with π -donor double bond.

Scheme 6.1. Substrate scope using catalyst **C7** under optimized conditions ^{a,b,c}



^aReaction conditions: **7** (0.3 mmol), **8** (3 mmol), catalyst **C7** (0.1 mol%), cyclohexane (2 mL), 20% aq KOH (0.5 mL), 25 °C, 1 h, under air. ^bIsolated yield, rest starting material. ^c% ee determined by multiple chiral columns and configuration was assigned by relative retention time and specific rotation with literature data;^{8,11} see supporting information for details. ^d5 mol% catalyst loading, 24 h. ^e10 mol% catalyst loading, 24 h.

6.3 Mechanistic explanation

³⁹K NMR of the reaction mixture at different time intervals and observed ~8.7 ppm downfield shift in 6 h (see supporting information for details), indicating selective recognition of K⁺ by calix-crown that swiftly generated nitronate anion. The nitronate anion is conceivably involved in non-covalent interactions with -O, N-H, and aryl groups of the catalyst to generate a chiral environment for the enantioselective addition of nitronate anion to the carbonyl group.

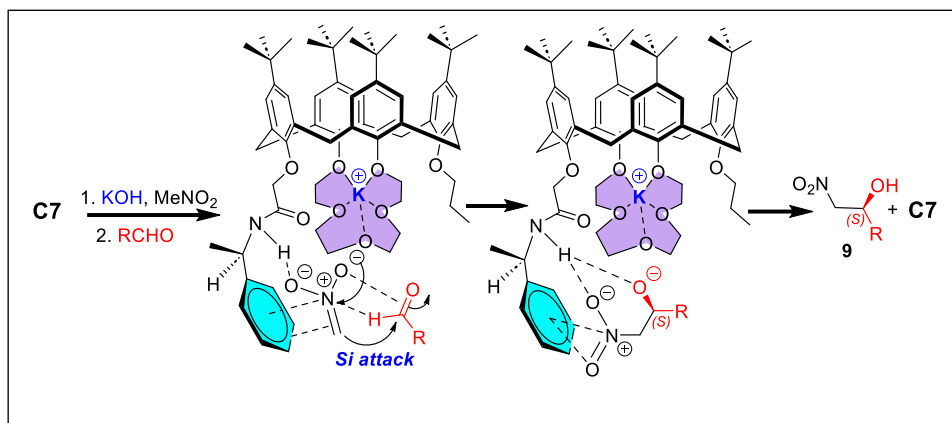


Figure 6.4: Possible mechanism of asymmetric nitroaldol reaction. This mechanism invokes a chiral induction via a selective recognition of K^+ that generate nitronate anion participating in non-covalent interactions (cation-p, p-p, lp-p, electrostatic, hydrogen bonding etc.) for the subsequent *Si* attack on aldehyde to form *S*-isomer of **9**.

6.4 Recyclability of catalysts

The reaction was carried out in a 500 mL round bottom flask at 25 ± 0.5 °C (using Julabo FL300 circulator) with benzaldehyde **7a** (3.05 mL, 3.18 g, 30 mmol; density 1.04 g/mL), nitromethane **8** (16 mL, 18.31 g, 300 mmol; density 1.14 g/mL), 20 % aq KOH (50 mL) in cyclohexane (200 mL) with catalyst **C7** (3.3 g, 0.1 mol%). After completion of the reaction, the cyclohexane was removed under vacuum at 40 °C from the reaction flask, followed by product extraction with cold diethyl ether (50X 8 mL) to afford **9a** (4.96 g, 99% yield). The same reaction flask (containing catalyst and aq KOH) was utilized for successive catalytic cycles using identical reaction ingredients under similar conditions as indicated above.

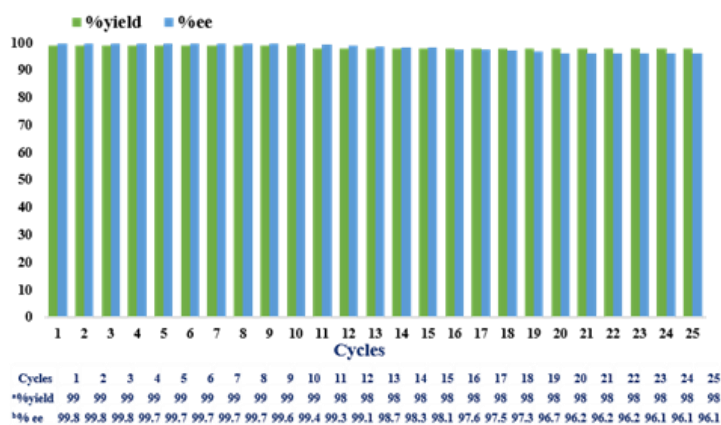
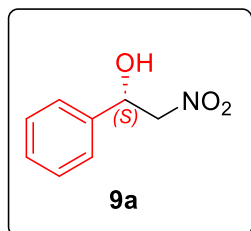


Figure 6.5 . Recyclability test of catalyst **c7** for **9**. Reaction condition: **7** (3.18 g, 30 mmol), **8** (16 mL, 18.31 g, 300 mmol), Cyclohexane (200 mL), 20% aq KOH (50 mL), catalyst **c7** (3.3g, 0.1 mol%), cyclohexane (200 mL), at 25 °C, 8 h

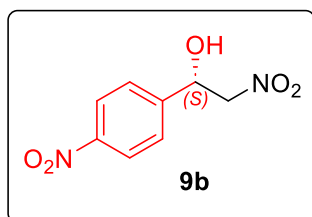
6.5 Conclusion

In conclusion, we have developed the highly efficient Henry reaction of various aldehydes with nitromethane using a novel bifunctional phase transfer catalyst bearing calixarene moiety with a chiral NH donor. A wide range of aldehydes were investigated, and the corresponding nitroaldol adducts were obtained in high yields and excellent enantioselectivities employing very low catalytic loading. Importantly the catalyst was recovered and recycled at gram scale up to 25 test cycles without substantial drop-in catalytic activity

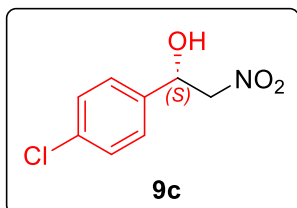
6.6 Product Analysis



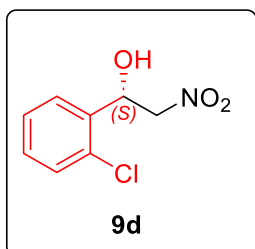
(S)-2-Nitro-1-phenyl ethan-1-ol (9a). Colourless oil; 49.6 mg, 99% yield, 99.8% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol= 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 29.6 min, tR (minor) 36.5 min; ^1H NMR (500 MHz, Chloroform- d) δ 7.38 – 7.27 (m, 5H), 5.85 (dd, J = 9.7, 2.4 Hz, 1H), 4.62 (dd, J = 13.6, 2.4 Hz, 1H), 4.45 (dd, J = 13.6, 9.6 Hz, 1H), 3.17 (s, 1H). ^{13}C NMR (126 MHz, Chloroform- d) δ 137.56, 129.95, 128.72, 127.55, 83.28, 75.14. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_9\text{NO}_3$, 167.0612; found 167.0618.



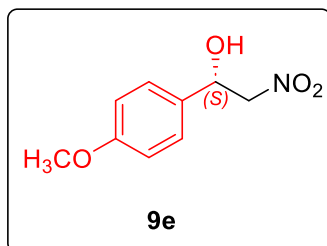
(S)-2-nitro-1-(4-nitrophenyl)ethan-1-ol (9b). Colourless oil; 61.91 mg, 98% yield, 97.8% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol= 95/5, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 11.3 min, tR (minor) 14.2 min; ^1H NMR (500 MHz, Chloroform- d) δ 8.27 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 5.61 (dd, J = 8.7, 3.6 Hz, 1H), 4.60 – 4.58 (m, 2H), 3.21 (s, 1H). ^{13}C NMR (126 MHz, Chloroform- d) δ 144.10, 128.72, 127.55, 81.28, 74.51. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$, 212.0410; found 212.0414.



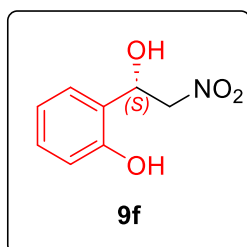
(S)-1-(4-Chlorophenyl)-2-nitro ethan-1-ol (9c). Colourless oil; 59.6 mg, 99% yield, 96.7% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10 flow rate: 1 mL/min, wavelength=210 nm; tR (major) 18.3 min, tR (minor) = 34.5 min; ^1H NMR (500 MHz, Chloroform- d) δ 7.83(d, J = 9.0 Hz, 2H), 7.63(d, J = 9.0 Hz, 2H), 5.60 (dd, J = 10.3, 3.3 Hz, 1H), 4.58 (m, 2H), 3.26 (s, 1H); ^{13}C NMR (126 MHz, Chloroform- d) δ 147.59, 135.56, 131.50, 130.89, 129.95, 79.35, 75.14. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_8\text{ClNO}_3$, 201.0205; found 201.0208.



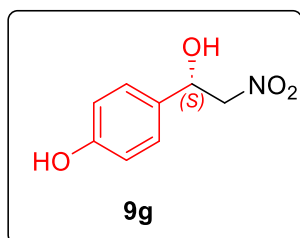
(S)-1-(2-Chlorophenyl)-2-nitro ethan-1-ol (9d). Colourless oil; 57.7 mg, 96% yield, 90.3% ee ; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 85/15, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 19.9 min, tR (minor) = 36.5 min; ^1H NMR (500 MHz, Chloroform-d) δ 7.66 (dd, J = 7.6, 1.8 Hz, 1H), 7.39 – 7.32 (m, 4H), 5.85 (dd, J = 9.7, 2.4 Hz, 1H), 4.67 (dd, J = 13.6, 2.4 Hz, 1H), 4.45 (dd, J = 13.6, 9.6 Hz, 1H), 3.17 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 135.56, 129.95, 129.72, 127.63, 127.55, 79.35, 67.84 . HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_8\text{ClNO}_3$, 201.0206; found 201.0208.



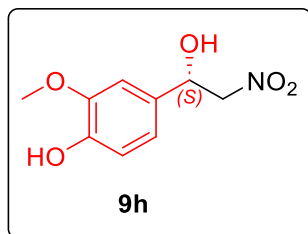
(S)-1-(4-Methoxyphenyl)-2-nitroethan-1-ol (9e). Colourless oil; 55.0 mg, 94% yield, 91.4% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 4.8 min, tR (minor) 7.3 min; ^1H NMR (500 MHz, Chloroform-d) δ 7.36 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0, 2H), 5.81 (d, J = 6.6 Hz, 1H), 4.22–4.11 (m, 3H), 2.28 (s, 3H), 2.04 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 159.84, 135.56, 133.59, 83.28, 70.84, 55.06. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{11}\text{NO}_4$, 197.0710; found 197.0712.



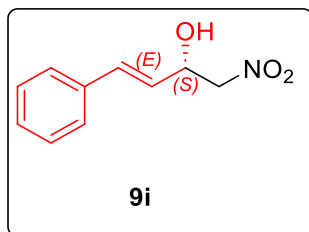
(S)-2-(1-Hydroxy-2-nitroethyl)phenol (9f). colorless oil; 45.0 mg, 82% yield, 95.7% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 0.7 mL/min, wavelength=210 nm: tR (major) 37.2 min, tR (minor) 54.6 min; ^1H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.29 (m, 4H), 5.84 (dd, J = 10.3, 3.3 Hz, 1H), 4.67 (dd, J = 7.3, 13.2 Hz, 1H), 4.45 (dd, J = 3.2, 12.8 Hz, 1H), 3.17 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 142.49, 133.28, 132.31, 129.55, 83.28, 69.55. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_9\text{NO}_4$, 183.0502; found 183.0506.



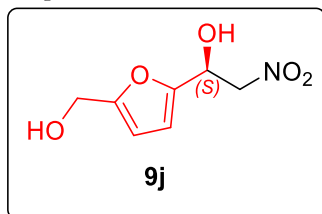
(S)-4-(1-Hydroxy-2-nitroethyl)phenol (9g). colorless oil; 38.9 mg 71% yield, 64.3% ee ; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 92/8, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 26.8 min, tR (minor) 29.6 min. ^1H NMR (500 MHz, Chloroform-d) δ 7.47 (d, J = 9.6 Hz, 2H), 7.04 (d, J = 9.6 Hz, 2H), 5.44 (dd, J = 9.0, 3.0 Hz, 1H), 4.66 (dd, J = 9.0, 13.2 Hz, 1H), 4.42 (dd, J = 3.0, 13.2 Hz, 1H), 3.69 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 155.06, 135.28, 129.55, 117.31, 83.28, 69.80. HRMS (ESI+) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_9\text{NO}_4$, 183.0512; found 183.0516.



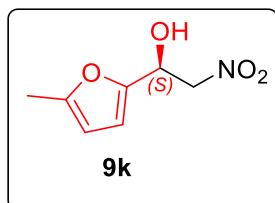
(S)-4-(1-Hydroxy-2-nitroethyl)-2-methoxyphenol (9h). colorless oil ;54.91mg,86% yield,79.0% ee; determined by HPLC analysis (Daicel Chiralpak OJ-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 14.8 min, tR (minor) = 17.3 min. ¹H NMR (500 MHz, Chloroform-d) δ 7.53-7.39(m, 3H), 5.84-5.79(m, 1H), 4.66 (dd, J =9.0, 13.2 Hz, 1H), 4.42 (dd, J = 3.0, 13.2 Hz, 1H), 3.75 (s, 3H),3.17 (s,br,2H). ¹³C NMR (126 MHz, Chloroform-d) δ 150.35, 149.25, 129.25, 122.50, 117.05, 115.25, 107.92, 79.86, 71.86, 56.30. HRMS (ESI+) m/z [M + H]⁺ calcd for C₉H₁₁NO₅, 213.0611; found 213.0614.



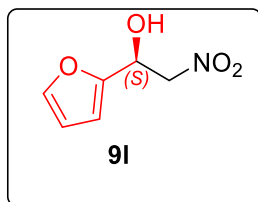
(S,E)-1-Nitro-4-phenylbut-3-en-2-ol (9i). dark yellow oil; 47.4 mg,82% yield ,76.9% ee; determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol= 95/5, flow rate: 0.8 mL/min, wavelength=210 nm: tR (major) 37.9 min, tR (minor) 43.3 min. ¹H NMR (500 MHz, Chloroform-d) δ 7.51 – 7.29 (m, 3H), 7.16 (dd, J = 8.5, 7.3 Hz, 2H), 6.83 – 6.73 (m, 1H), 6.73 – 6.67 (m, 1H), 5.32 (d, J = 20.2 Hz, 1H), 4.76 – 4.54 (m, 2H), 2.62 (s, 1H). ¹³C NMR (126 MHz, Chloroform-d) δ 135.56, 131.50, 129.95, 129.72, 127.63, 127.55, 87.28, 75.14. HRMS (ESI+) m/z [M + H]⁺ calcd for C₁₀H₁₁NO₃, 193.0710; found 193.0714.



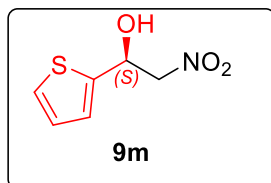
(S)-1-(5-(hydroxymethyl)furan-2-yl)-2-nitroethan-1-ol(9j). yellow oil ;56.1 mg,82% yield,75.9% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 16.9 min, tR (minor) 26.1 min. ¹H NMR (500 MHz, Chloroform-d) δ 6.28 (s, 2H), 4.79(s, 2H),4.66 (m,1H), 4.43(m,1H), 4.26(s, 2H). ¹³C NMR (126 MHz, Chloroform-d) δ 158.77, 150.87, 128.15, 108.44, 72.84, 56.15. HRMS (ESI+) m/z [M + H]⁺ calcd for C₇H₉NO₅, 187.0513; found 187.0515.



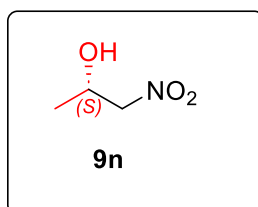
(S)-1-(5-methylfuran-2-yl)-2-nitroethan-1-ol (9k). yellow oil;41.5 mg 81% yield,70.3% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1.5 mL/min, wavelength=210 nm : tR (major) 7.2 min, tR (minor) = 11.2 min. ¹H NMR (500 MHz, Chloroform-d) δ 6.21 (dd, J = 3.4, 1.1 Hz, 1H), 6.10 (dd, J = 3.3, 1.1 Hz, 1H), 5.02 – 5.00 (m, 1H), 4.97 (d, J = 2.0 Hz, 1H), 4.94 (d, J = 2.1 Hz, 1H), 4.92 – 4.91 (m, 1H), 2.44 (s, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 158.25, 150.30, 107.92, 79.86, 71.86, 12.50. HRMS (ESI+) m/z [M + H]⁺ calcd for C₇H₉NO₄, 171.0518; found 171.0519.



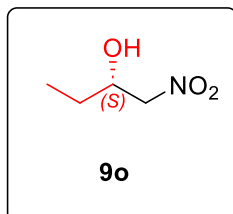
(S)-1-(furan-2-yl)-2-nitroethan-1-ol (9l). yellow oil ,46.1 mg,98% yield, 69.4% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol= 90/10, flow rate: 1 mL/min, wavelength=210 nm: tR (major) 22.5 min, tR (minor) 26.5 min. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.68 (dd, J = 1.1, 4.8 Hz , 1H), 7.25 (dd, J = 1.1, 4.8 Hz, 1H), 6.60 (m, 1H), 5.60 (d, J = 8.4 Hz, 1H), 4.60 - 4.55 (m, 2H), 3.17 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) 151.38, 143.53,123.53, 103.73, 79.86, 71.38. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_6\text{H}_7\text{NO}_4$, 157.0410; found 157.0412.



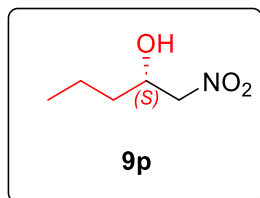
(S)-2-nitro-1-(thiophen-2-yl)ethan-1-ol (9m). yellow oil; 46.76 mg,90% yield, 87.5% ee; determined by HPLC analysis (Daicel Chiralpak AD column, hexane/2-propanol= 88/12, flow rate: 1.2 mL/min, wavelength=210 nm: tR (major) 20.5 min, tR (minor) 29.1 min ^1H NMR (500 MHz, Chloroform-*d*) δ 7.64 (d, J = 4.9 Hz, 1H), 7.02 (d, J = 4.9 Hz, 2H), 5.84 (m, 1H), 4.66 (dd, J = 3.4, 9.0 Hz, 1H), 4.45 (dd, J = 9.1, 13.4 Hz, 1H), 3.14 (s, br, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) 143.53, 128.25,126.80, 125.50, 103.73, 79.86, 66.80. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_6\text{H}_7\text{NO}_3\text{S}$, 173.0106; found 173.0108.



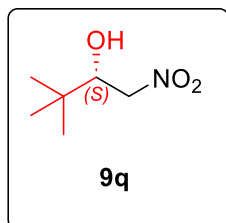
(S)-1-nitropropan-2-ol (9n). yellow oil; 28.8 mg 91%, 88.2% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1.5 mL/min, wavelength = 210 nm: tR (major) 9.2 min, tR (minor) 10.7 min. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.74 (d, J = 5.9 Hz, 3H), 3.74 (s, 1H), 1.21 (d, J = 6.2 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 73.00, 29.72, 14.13. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_3\text{H}_7\text{NO}_3$, 105.0402; found 105.0405.



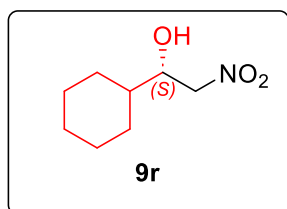
(S)-1-nitrobutan-2-ol (9o). colorless oil ;31.4 mg,88% yield, 84.4% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength = 210 nm: tR (major) 28.6 min ,tR (minor) 34.0 min, ^1H NMR (500 MHz, Chloroform-*d*) δ 5.08-5.06 (m, 1H), 4.96-4.90 (m, 1H), 4.61-4.44 (m, 2H), 2.48-2.43(m, 2H), 1.11-1.07 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 81.28, 70.14, 31.06, 14.55 .HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_4\text{H}_9\text{NO}_3$, 119.0610; found 119.0612.



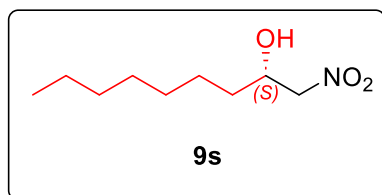
(S)-1-nitropent-2-ol (9p). yellow oil; 39.0 mg, 98%, 94.6% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength = 210 nm: tR (major) 12.4 min, tR (minor) 16.0 min. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.45 – 4.36 (m, 3H), 2.54 (s, 1H), 1.49 – 1.40 (m, 4H), 0.97 (t, J = 7.0 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 79.64, 67.37, 34.72, 17.42, 12.74. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_5\text{H}_{11}\text{NO}_3$, 133.0710; found 133.0712.



(S)-3,3-Dimethyl-1-nitro-2-butanol (9q). colorless oil 92%, 82.0% ee ;determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol= 90/10, flow rate: 1.5 mL/min, wavelength = 210 nm: tR (minor) 14.0 min ,tR (major) 17.0 min. ^1H NMR (500 MHz, Chloroform-*d*) δ : 5.29-5.22(m, 1 H), 4.69-4.66 (m, 2H), 4.48-4.43(m, 1H), 3.52(s, 1H), 2.55 (m, 1H),1.10 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 79.86, 71.86, 16.23. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_6\text{H}_{13}\text{NO}_3$, 147.0915; found 147.0918.

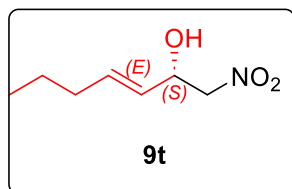


(S)-1-Cyclohexyl-2-nitroethanol (9r). Colorless oil ;43.5 mg,84% yield,87.3% ee; determined by HPLC analysis (Daicel Chiralpak OB column, hexane/2-propanol = 88/12, flow rate: 1.5 mL/min, wavelength = 210 nm: tR (major) 21.1 min ,tR (minor) 23.1 min; ^1H NMR (500 MHz, Chloroform-*d*) δ , 4.69 – 4.43 (m, 2H), 4.00 (s, 1H), 2.21 (s, 1H), 1.85-1.82 (m, 2H), 1.73 – 1.68 (m, 2H),1.67-1.60 (m,3H) 1.30 – 1.23 (m, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 79.86, 69.55, 41.80, 28.66 , 27.44, 24.94 , 24.88 , 24.84. HRMS (ESI+) m/z [M + H]⁺ calcd for $\text{C}_8\text{H}_{15}\text{NO}_3$, 173.1101; found 173.1105.

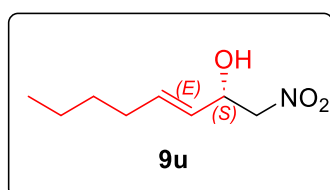


(S)-1-nitrononan-2-ol (9s). yellow oil; 55.4 mg, 98%, 98.0% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 90/10, flow rate: 1.2 mL/min, wavelength = 210 nm: tR (major) 10.9 min, tR (minor) 14.0 min. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.48 – 4.28 (m, 4H), 2.54 (s, br, 1H), 1.65 – 1.45 (m, 13H), 1.00 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz,

Chloroform-*d*) δ 80.67, 68.64, 41.12, 33.75, 31.72, 29.28, 29.10, 25.19, 22.61, 14.05. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_9H_{19}NO_3$, 189.1408; found 189.1409.



(S, E)-1-nitrohept-3-en-2-ol (9t). yellow oil ;42.9 mg, 99%, 98.5% ee; determined by HPLC analysis (Daicel Chiralpak OD-H column, hexane/2-propanol = 95/5, flow rate: 1.2 mL/min, wavelength = 210 nm: tR (major) 20.5 min, tR (minor) 33.5 min. ^1H NMR (500 MHz, Chloroform-*d*): δ 5.58 (dt, J = 15.5, 6.8 Hz, 1H), 4.84 (m, 2H), 4.66 (d, J = 10.9 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H), 2.92 (s, 1H), 2.29 (qd, J = 7.2, 1.6 Hz, 2H), 1.52 (q, J = 7.4 Hz, 2H), 0.94 (tt, J = 7.5, 1.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ : 138.73, 125.02, 82.03, 71.61, 34.61, 21.03, 13.55. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_7H_{13}NO_3$, 159.0910; found 159.0912.



(S, E)-1-nitrooct-3-en-2-ol (9u). yellow oil ; 51.3 mg, 99%, 99.8% 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) 4.3 min ,tR (minor) 36.2 min. ^1H NMR (500 MHz, , Chloroform-*d*): δ 5.21 (dt, J = 15.5, 6.8 Hz, 2H) ,4.91 (m,1H), 4.67 (d, J = 10.9 Hz, 1H), 2.25 (ddd, J = 9.2, 7.4, 5.9 Hz, 2H),1.44 – 1.36 (m, 2H), 1.33 – 1.24 (m, 2H), 0.83 (td, J = 7.4, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ : 132.71, 121.97, 81.97, 72.18, 32.18, 29.67, 21.97,13.53. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_8H_{15}NO_3$, 173.1104; found 173.1107.