4

Experimental and computational studies on the *Cinchona* anchored Calixarene catalysed Asymmetric Michael addition reaction

This work described in this chapter has been published in ***Chem. Commun.***, 2022,**58**, 7249-7252

4.1 Introduction

The primary goal of synthetic organic chemistry has evolved as the creation of novel chemical transformations for the effective and practical synthesis of complex structures. Numerous organic reactions have been investigated for this aim, enabling the stereo-controlled synthesis of a variety of significant scaffolds. The asymmetric Michael reaction stands out as one of the most versatile tools for the production of carbon-carbon bonds. It has been extensively employed in organic synthesis to produce useful building blocks since the resulting γ-nitro carbonyl compounds are valuable intermediates that could be used for the preparation of a large number of chiral biological and pharmaceutical substances. Conversely, asymmetric organocatalyst has been a popular field of study for the production of optically active molecules using affordable organocatalysts under benign reaction circumstances. (Zhang and Wang, 2012) .Chiral supramolecular organocatalysts anchored with a Brønsted base with the hydrogen-bond donor unit are powerful for asymmetric C–C bond formation. Related *Cinchona* and its thio(urea)/squaramide derivative catalysed Michael addition of carbanions to β-nitrostyrenes has seen resurgence of activity. Impressive advances in vinylogous Michael addition and tandem cyclization have also been made *via* *Cinchona*-mediated catalysts. The *Cinchona* based organocatalysts have a wide range of applications in various asymmetric reactions, including aldol,(Ogawa et al., 2007, Singh et al., 2010, Meninno et al., 2014, Huang and Zhang, 2021) Morita–Baylis–Hillman,(Iwabuchi et al., 1999, Liu et al., 2010, Ran et al., 2016) Mannich(Song et al., 2006),(Bahlinger et al., 2014, Zhu et al., 2020, Bora et al., 2021) and dihydroxylation(Hentges and Sharpless, 1980, Breman et al., 2016) where the quinuclidine portion works as an activator for nucleophiles.

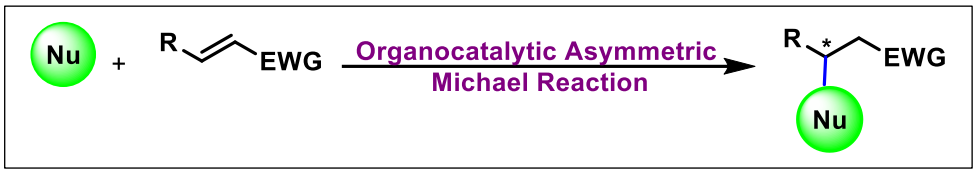


Figure 4.1 General scheme for organocatalytic Asymmetric Michael Addition reaction

The third generation of supramolecules known as Calixarenes have found extensive use because it pertains the creation of novel chiral receptors for asymmetric recognition and provides and offers potent tools for the stereochemical understanding of biochemical systems. The introduction of chiral substituents into the calixarene macrocyclic ring by attaching chiral units at one of the calix rims could, in turn, lead to chirality. In this way calixarene might be good candidates as chiral catalysts for the organocatalytic preparation of chiral compounds. Calixarene supramolecules have a stable aromatic cavity to titivate substrate functional groups. Additionally, their lower-rim phenolic hydroxyl groups offer synthetic flexibility along with noncovalent and secondary interactions, important for organocatalysis.

4.1.1 Earlier work

Little attention has been paid to the calixarene-driven C–C bond formation with specific reference to Michael addition. Only reported examples pertaining to the calixarene functionalized thiourea(Durmaz and Sirit, 2013b, Durmaz et al., 2016, De Simone et al., 2018, Li et al.,

2018), trisulfonamide(Cera et al., 2020) and squaramide(Cera et al., 2020, Yang et al., 2020) catalysts for β-nitrostyrene based Michael addition are reported with moderate enantioselectivities at high catalyst loading and long reaction time. Notably, very recently a *Cinchona* thiourea catalyzed asymmetric Michael addition of α-aminomaleimides to β-nitrostyrenes has been reported with good enantioselectivity (92% ee) to selective substrates. (Sakai et al., 2021)

4.1.2 Our work

A detailed study was carried out to study the Newly designed mono and dicationic *Cinchona* alkaloid-anchored calix[4]arenes as organocatalysts for the asymmetric conjugate addition of acetylacetone to nitroolefins. (Figure)The catalyst provided the chirality to the product. The enantioselectivity can be explained by the computational studies

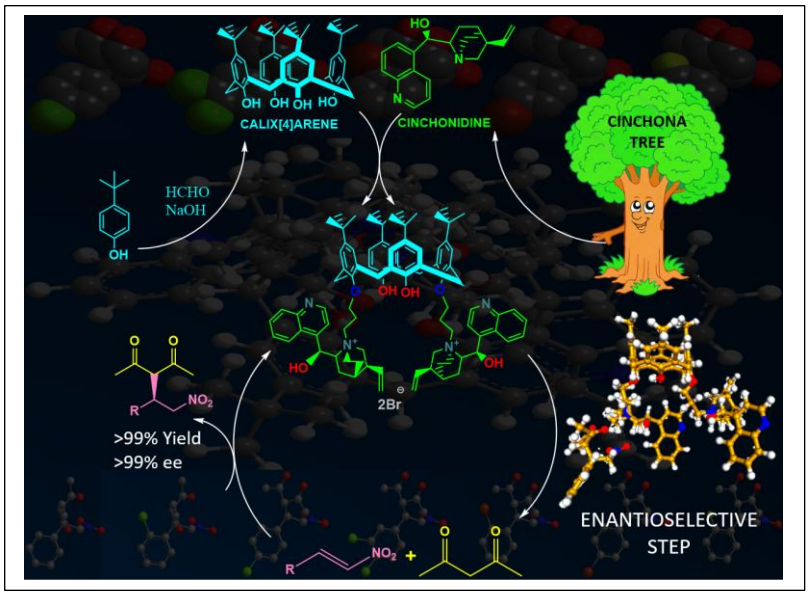


Figure 4.2 Pictorial representation of our work

4.2 Experimental Section

General Remarks

Catalysts were prepared under a nitrogen atmosphere, while Michael addition reactions were carried out in open-air. The enantiomeric excess of the Michael products were determined by HPLC measurements carried out using a Waters Model 2489 equipped with chiral columns DAICEL 4.6 mm × 250 mm Chiralpak- IA, IB and AD-H using condition n-Hexane/isopropanol solvent system. The enantiomeric excess of the Michael products were determined by HPLC measurements carried out using a Waters Model 2489 equipped with chiral columns DAICEL 4.6 mm × 250 mm Chiralpak- IA, IB and AD-H using condition n-Hexane/isopropanol solvent system. Analytical techniques that were used for characterization of products are described in chapter 3

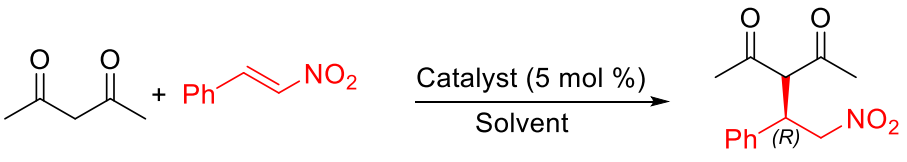
4.2.1 Enantioselective Michael Addition of acetylacetone to nitroolefins and effect of catalysts

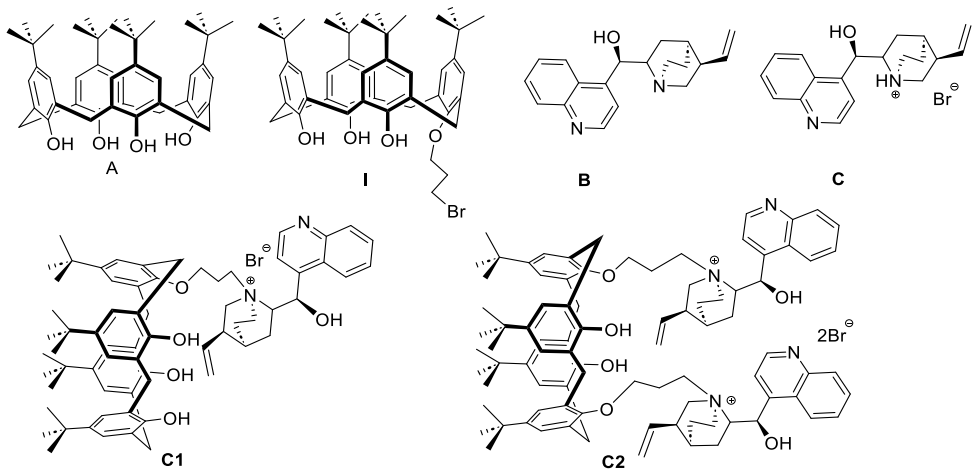
To a pre-cooled stirred solution of the nitrostyrenes 1 (0.1 mmol) and 2,4-pentanedione 2a-u (0.1 mmol), a toluene solution of organocatalyst (0.5 mL 0.0005 mmol) was added and stirred for 24 h at -5 ^{o}C. after the reaction was completed (monitored by TLC), the resulting mixture was concentrated and product was extracted by diethyl ether followed by purification via flash

chromatography on silica gel (eluent with ethyl acetate/heaxane,1:5 to 1:2) to afford the product 3a-u.

Our studies started with an examination of β-nitrostyrene as a Michael acceptor to optimize organocatalysts (Table 4.1) in toluene at rt. As expected with neat calixarene(A) and alkylated calixarene (I), negligible conversion of Michael adduct was acquired . Moderate yields and poor ees were obtained when unmodified cinchonidine and cinchonidine bromide were used as organocatalysts. In contrast, calix[4]arene appended cinchonidine bromide **C1** afforded promising results in 4 hours (entry 7) under similar reaction conditions (entries 5-8). Other solvents gave moderate to good conversion but poor enantioselectivity (entries 9–16) after 24 h. When protic solvents are used, only 30% (water) and 26% (MeOH) yields were obtained (entries 11 and 16, respectively). In contrast, when halogenic ($CHCl_3$ and CH_2Cl_2) and aprotic polar solvents (CH_3CN, EtOAc, THF and ether) were used, 3a was obtained with low enantioselectivity with moderate conversion (entries 9, 10 and 12–15). The reaction also works under solvent free conditions with incomplete conversion (entry 17). Based on the investigation, toluene is found to be an optimal solvent for the catalytic reaction. The reaction conditions were further optimized by lowering the temperature -10 °C (entries 18–20). High yield (~96%), and enantioselectivity (92%) were realized at −5 °C in 24 h (entry 19). Catalyst **C2**, calix[4]arene anchored with two cinchonidine bromide moieties, also shows a similar trend (entries 21–24) with excellent yield and selectivity (98%, >97% ee) as shown in entry 23 of Table 4.1. Interestingly, high yields and enantioselectivities (99%, >99% ee) were obtained even when the catalyst loading decreased to 0.5 mol % (entries 25–27). Further reduction in catalyst to 0.3 mol % compromised both the yield and the enantioselectivity to 94% and ~92% ee, respectively (entry 28).

Table 4.1. Screening of catalysts and further optimizations for asymmetric Michael addition of acetylacetone (1a) and β-nitrostyrenes (2a)





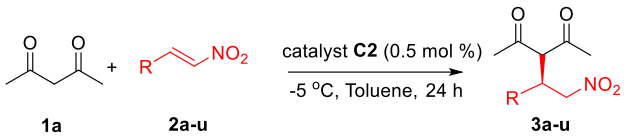
Entry	Catalyst	Solvent	Time (h)	Temp (° C)	% Yield[e]	%ee[f] (Config.)
1	A	Toluene	24	25	< 5	n.d.
2	I	Toluene	24	25	<10	n.d.
3	B	Toluene	24	25	41	16 (*R*)
4	C	Toluene	24	25	53	27 (*R*)
5	C1	Toluene	24	25	97	44 (*R*)
6	C1	Toluene	8	25	97	44 (*R*)
7	C1	Toluene	4	25	97	45(*R*)
8	C1	Toluene	3	25	89	39 (*R*)
9	C1	$CHCl_3$	6	25	83	12 (*R*)
10	C1	CH_2Cl_2	4	25	87	08 (*R*)
11	C1	H_2O	24	25	30	00
12	C1	CH_3CN	24	25	55	23 (*R*)
13	C1	EtOAc	24	25	75	13 (*S*)
14	C1	THF	24	25	69	05 (*R*)
15	C1	Et_2O	24	25	60	00
16	C1	MeOH	24	25	26	00
17	C1	Neat	24	25	70	00
18	C1	Toluene	12	0	98	70 (*R*)
19	C1	Toluene	24	-5	96	87 (*R*)
20	C1	Toluene	48	-10	63	82 (*R*)
21	C2	Toluene	4	25	93	34 (*R*)
22	C2	Toluene	12	0	95	55 (*R*)
23	C2	Toluene	24	-5	98	97 (*R*)
24	C2	Toluene	48	-10	53	92 (*R*)
25[a]	C2	Toluene	24	-5	96	>99 (99.2, *R*)
26[b]	C2	Toluene	24	-5	98	>99 (99.1, *R*)
27[c]	C2	Toluene	24	-5	99	>99 (99.2, *R*)
28[d]	C2	Toluene	24	-5	94	92 (*R*)

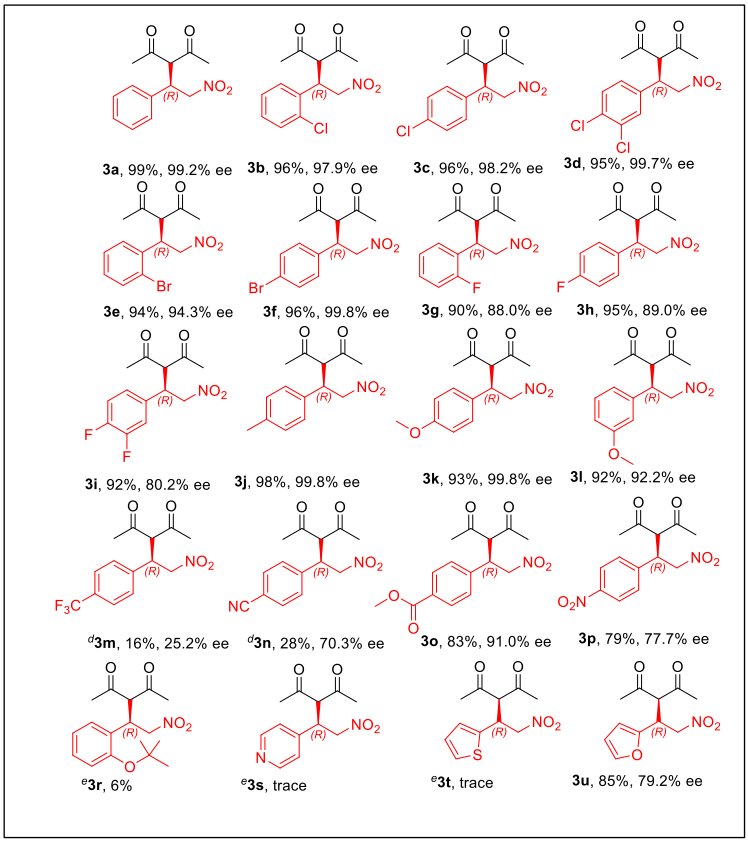
The reactions were performed with **1a** (0.1 mmol) and **2a** (0.1 mmol) in 0.5 mL solvent in presence of 5 mol% catalyst at given temperature for 4-24 h. [a]catalyst (3 mol%), [b]catalyst (1 mol%), [c]catalyst (0.5 mol%), [d]catalyst (0.3 mol%), [e]Isolated yield. [f]Determined by chiral HPLC with a Chiralpak AD-H and the configuration was assigned by relative retention time and specific rotation with literature data.

Thus, the optimal reaction conditions were found to be 0.1 mmol β-nitrostyrene and 0.1 mmol acetylacetone in 0.5 mL of toluene with 0.5 mol % catalyst loading at −5 °C for 24 h. The optimized reaction conditions using catalyst **C2** have broad applicability for β-nitrostyrene derivatives, as shown in Scheme 4.1. When the phenyl moiety of β-nitrostyrene is substituted with mono (o-, m-) and di (m- & p-) chloro groups, the corresponding Michael adducts were obtained with high yields and enantioselectivities (3b–d). Similar tendencies were observed in the case of o- and p-bromo (3e–f) and o-, p- and m-, p-fluoro (3g–i) substituted β-nitrostyrenes. However, moderate enantioselectivities were obtained (o-88% ee, p-89% ee and m-, p-80.2% ee) possibly due to the electron withdrawing effect of fluorine. Electron donating substituents, p-CH_3– and m-, p-CH_3O–

on β-nitrostyrene gave good yield and enantioselectivities (3j–l). Electron withdrawing groups, p-F_3C– and p-CN– gave incomplete reactions and lower enantioselectivities even with higher catalytic loading up to 5 mol % catalyst and longer reaction time (3m–n). However, oxygen-rich electron-withdrawing groups, p-NO_2– and p-COOMe– are tolerated with moderate yields and decent ee's of Michael adducts (3o–p). Attempts were unsuccessful to synthesize Michael adduct with a large group, o-t-butyl substitute β-nitrostyrene (3r), which could be due to steric hindrance, preventing catalyst–substrate interactions. The pyridyl and thienyl groups were not tolerated even at higher catalytic loading (10 mol%), and desired Michael adducts were rarely obtained (3s–t). However, the 2-furyl derivative gave 85% yield and 79% ee (3u), possibly due to good hydrogen bonding accepting nature of furyl oxygen towards catalyst All substrates gave high yield and ee except the pyridyl and thienyl groups. However, 2-furyl derivative gave 85 % yield and 79 % ee (3u), possibly due to good hydrogen bonding accepting nature of furyl oxygen towards catalyst.

Scheme 4.1: Substrate scope using catalyst C2 under optimized conditions[a,b,c]





[a]Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), catalyst **C2** (0.5 mol%), toluene (0.5 mL), -5 °C, 24 h, under air. [b]Isolated yield, rest starting materials. [c]%ee determined by multiple chiral columns and the configuration was assigned by relative retention time and specific rotation with literature data.[9b,11,13]; see Supporting Informations for details. [d]5 mol% catalyst loading. [e]10 mol% catalyst loading.

4.3 Mechanistic explanations

In order to determine the catalytic reactivity differences, B3LYP-D3/6-31G(d,p) studies have been carried out on mono- and di-anchored calix[4]arenes for the asymmetric addition of acetylacetone to β-nitrostyrene To identify the mechanistic pathways, both catalysts (**C1** and **C2)** were optimized and modelled DFT. To elucidate the plausible mechanism, firstly,

catalysts **C1** and **C2** associate with β-nitrostyrene "**a**" and keto-enol "**b**" to form an association complex **C1a** and **C2a** (Fig.4.5). In (Figure 4.4) the β-nitrostyrene in the associate complex **C1a** and **C2a** (Figure. 4.5) both expose their Re-face to the addition of acetylacetone (**b**) rather than Se-face. In the Re-face configuration, β-nitrostyrene and keto-enol "**b**" forms strong hydrogen bonds with both **C1** and **C2** catalysts in the association complexes. According to hydrogen bonding distances, the strongest interactions between β-nitrostyrene and catalyst **C1** occur via hydrogen bonding (N(O)···H(C) and secondary hydrogen bonding interactions were found between the quinolone moiety (–HC). As shown in Figure. 4.5, in the association complex **C2a**, the closest association between β-nitrostyrene and catalyst **C2** is 2.24 Å and 2.28 Å. Due to the energetically favourable Re-face, the addition of acetylacetone to β-nitrostyrene results in an *R*-configured product. The Re-face involves a stronger intramolecular hydrogen bond than the Se-face. For keto-enol "**b**" addition to **C2** in the association complex, we considered three different conformations. One is the enol-form of acetylacetone hydrogen bonding with cinchonidine. The second is the enol-form of acetylacetone hydrogen bonding with –OH of the Calix[4]arene conjugate. The third is the keto form of acetylacetone hydrogen bonding with –OH of the Calix[4]arene conjugate. For the three conformations, the relative energy difference was computed as 0.0, 0.3, and 2.7 kcal mol^{-1}. A cinchonidine hydrogen bonding with acetylacetone enol-form has been taken into account for the transition states (**C1-TS** and **C2-TS**). The DFT energy calculations predict that the formation of **C1a** and **C2a** from corresponding reactants is considerably more energetic with a value of −20.77 kcal mol^{-1} and −18.33 kcal mol^{-1} at the B3LYP level of theory (Figure.4.5), an energetically more favorable process. In the next step, the reaction coordinate proceeds with a tightening of the interaction between β-nitrostyrene and mono- and di-anchored catalysts.

At the same time, the addition of keto-enol **b** to the association complexes **C1a** and **C2a** led to the transition states **C1a-TS** and **C2a-TS**. The C–C bond formation transition state (TS) is the most crucial step on the potential energy surface; in**C1-TS** (Figure. 4.4,) and **C2a-TS** (Figure. 4.5), the distances of C–C is 1.76 Å, 1.96 Å. The computed activation energy barrier (**C1a** → **C1a-TS**; **C2a** → **C2a-TS**) at the B3LYP level of theory. *i.e.* 18.02 and 14.25 kcal mol^{-1}. Additionally, the formation of reaction complexes from these transition states represents an energetically more favourable step; the corresponding relative energies are −18.0 and −15.78 kcal mol^{-1}. The reaction complexes **C1b** and **C2b** are stabilized by hydrogen bonding with mono- and di-anchored catalysts in reaction complexes.

In the final step of the reaction, chiral products are generated from complexes **C1b** and **C2b** and calix[4]arene conjugate catalysts **V** and **VI** are regenerated (Fig. 4.5, **Pr**). Gas-phase relative energy for the formation of the chiral products Pr from **C1b** (**C1b** → **Pr**) and **C2b** (**C2b** → **Pr**) is negative *i.e.* −14.06 and −14.0 kcal mol^{-1}; thus, the formation of final products is a more favorable process. For both reaction pathways that are energetically favorable processes, the DFT calculation indicates the overall relative energy to form chiral products "**Pr**" from "**C1 + a**" (**C1 + a** → **Pr**) and "**C2 + a**" (**C2 + a** → **Pr**) is −32.3 kcal mol^{-1} and −33.8 kcal mol^{-1} respectively. Both these catalysts work well energetically, but the catalyst **C2** is slightly more favourable than **C1** towards Michael addition of acetylacetone to β-nitrostyrene.

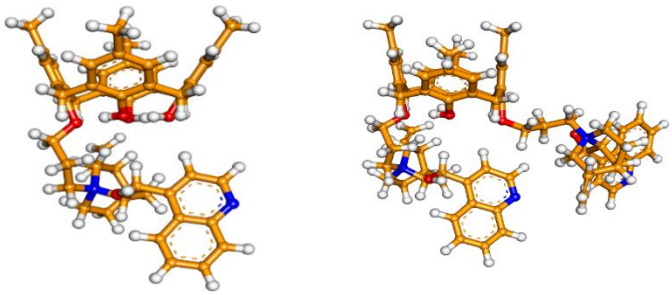


Figure 4.3: Fully optimized structures at B3LYP/6-31G(d,p) of mono- and di-conjugate anchored Calix[4]arene catalyst.

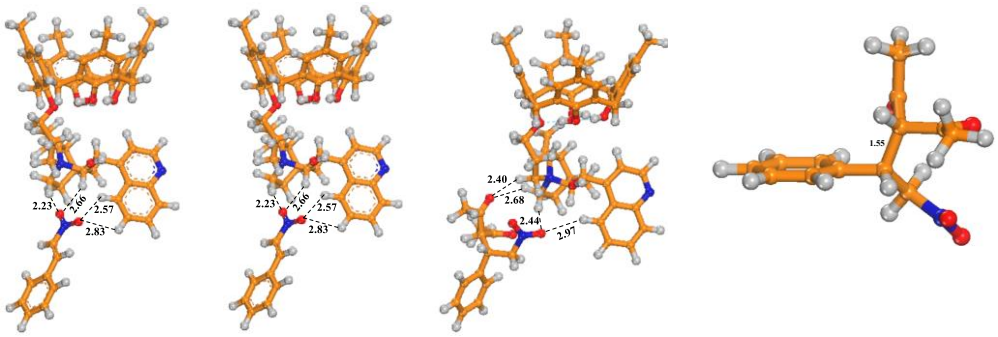


Figure 4.4: Fully optimized association complex "C1a" , Michael addition transition state "C1a-TS" and corresponding reaction complex "C1b" and final product "Pr" using Calix[4] arene single- strand catalyst "C1" involved addition reaction. Important H-bonding interactions (in Å) are indicated with dotted lines.

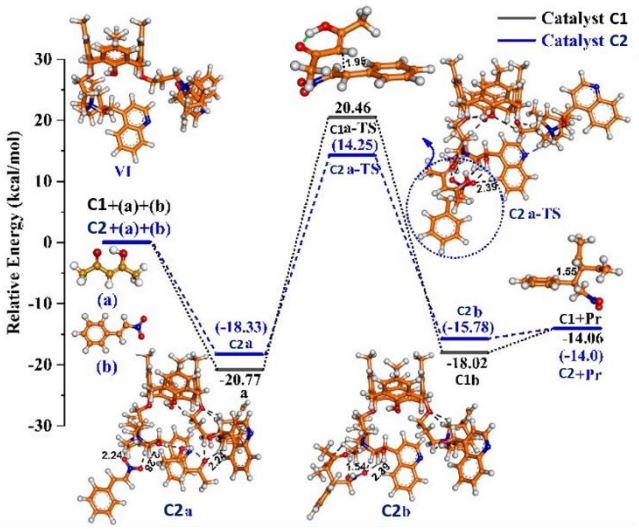


Figure. 4.5: The reaction coordinate for Calix[4]arene conjugate catalyzed Michael addition of enols to β-nitrostyrene, using single-strand catalyzed (Catalyst C1, black line) and double-strand catalyzed Michael addition reaction (Catalyst C2, blue line). Fully optimized association complex C1a, Michael addition transition state C2a-TS and corresponding reaction complex C2b and final product Pr using Calix[4] arene double-strand catalyst C2" involved addition reaction**.** Important H-bonding interactions (in Å) are indicated with dotted lines.

4.4 Recyclability of catalysts

The calix[4]arene scaffold gives a special advantage due to its selective solubility profile. Hence, catalyst **C2**, being poorly soluble in cold diethyl ether, could be easily separated from the reaction mixture via removal of Michael adduct dissolving in diethyl ether and recycled up to 20 times without compromising the yield and enantioselectivity.

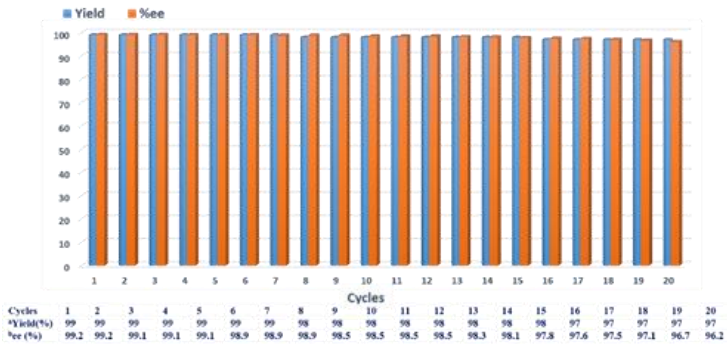
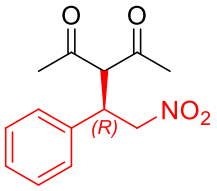


Figure 4.6: Recyclability of catalyst C2 for Michael adduct 3a.

4.5 Conclusion

In conclusion, two new lower rim anchored *Cinchona* calix [4] arene organocatalysts (**C1** and **C2**) were developed and used for asymmetric Michael addition reaction of acetylacetone to β-nitrostyrenes for the first time with a quantitative yield and >99% ee of the Michael adduct. The reaction tolerated diverse substrate scope maintaining high yields and enantioselectivities. The catalyst could be recovered and reused up to 20 cycles without a significant drop-in activity and selectivity. Furthermore, DFT investigations revealed substrate–catalyst interactions, mechanistic insights, and energetics for high enantioselectivities. Further studies are underway to expand the scope of the reaction and role of the calixarene scaffold.

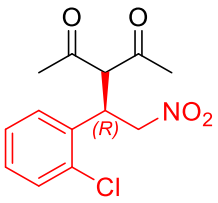
4.6 Product analysis



(*R*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione

3a

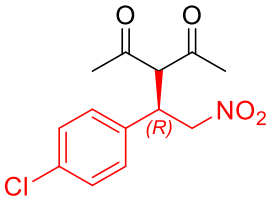
3a) White solid; 0.123g yield 99%; 99.2% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol/Methanol = 90/9/1, flow rate: 1 mL/min, wavelength = 210 nm: tR (minor) = 7.26 min, tR (major) = 8.69 min). 1H NMR (500 MHz, Chloroform-d) δ 7.32-7.27 (m, 3H), 7.11-7.07 (m, 2H), 4.61 (d, J = 6.3 Hz, 2H), 4.33 (d, J = 10.7 Hz, 1H), 4.25 (d, J = 9.0 Hz, 1H), 2.30 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 201.80, 201.02, 135.99,129.37,128.59, 127.95, 78.21, 70.75, 42.80, 30.46, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{15}NO_4Na$ 272.0899; found 272.0896.



(*R*)-3-(1-(2-chlorophenyl)-2-nitroethyl)pentane-2,4-dione

3b

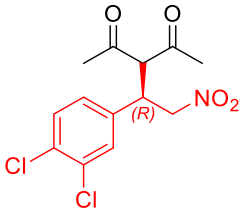
3b) White solid; 0.136 g yield 96%; 97.9% ee determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 89/11, flow rate: 0.9 mL/min, wavelength = 210 nm: tR (minor) = 4.23 min, tR (major) = 6.24 min).). 1H NMR (500 MHz, Chloroform-d) 7.44-7.43 (m, 2H), 7.16-7.86 (m, 2H, CH), 4.87-4.58 (m, 4H), 2.29 (s, 3H), 2.03 (s, 3H,) ppm. ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = 201.9, 200.9, 142.80,135.99,129.37,128.59, 127.95,125.71, 78.21, 70.75, 42.80, 30.46, 29.72,29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}ClNO_4Na$ 306.0509; found 306.0500



(*R*)-3-(1-(4-chlorophenyl)-2-nitroethyl)pentane-2,4-dione

3c

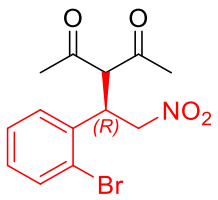
3c) White solid; 0.136g, yield 96%; 98.2% ee determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol = 90/9, flow rate: 1.2 mL/min, wavelength = 210 nm: tR (minor) = 9.12 min, tR (major) = 11.50 min). 1H NMR (500 MHz, Chloroform-d) 7.31 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.63-4.60 (m, 2H), 4.34 (d, J = 10.2 Hz, 1H), 4.27-4.19 (m, 1H, CH), 2.30 (s, 3H), 1.98 (s, 3H) ppm. ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = 201.80, 201.02, 135.99, 129.37, 128.59, 78.21, 70.75, 42.80, 30.46, 29.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}ClNO_4Na$ 306.0509; found 306.0489.



(*R*)-3-(1-(3,4-dichlorophenyl)-2-nitroethyl)pentane-2,4-dione

3d

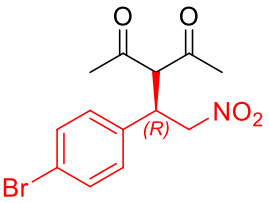
3d) White solid;0.154 g, yield 97%; 99.7% ee determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol/Methanol = 90/9/1, flow rate: 1 mL/min, wavelength = 210 nm: tR (minor) = 16.79 min, tR (major) = 19.59 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.42-7.41 (m, 2H), 7.31 (m,1H),7.05(m,1H), 4.63-4.60 (m, 2H), 4.34 (d, J = 10.2 Hz, 1H), 4.23-4.21 (m, 1H, CH), 2.30 (s, 3H), 2.03 (s, 3H) ppm. ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = 201.80, 201.02, 135.99, 129.37, 128.59, 78.21, 70.75, 42.80, 30.46, 29.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{13}Cl_2NO_4Na$ 340.0119; found 340.0117.



(*R*)-3-(1-(2-bromophenyl)-2-nitroethyl)pentane-2,4-dione

3e

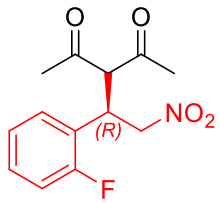
3e) Orange solid;0.154 g yield 94%; 94.3% ee determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/2-propanol/Methanol= 90/9/1, flow rate: 1.1 mL/min, wavelength =210 nm: tR (minor) = 3.48 min, tR(major) = 5.81 min). ^{1}H NMR (500 MHz, Chloroform-d) δ7.56(d, J = 7.3 Hz, 1H), 7.17 (m, 1H), 7.03 (s, 2H), 4.61 (d, J = 6.3 Hz, 2H),4.83(m,1H),4.61-4.60(m,1H),4.34-4.32 (d, J = 10.7 Hz, 1H), 2.30 (s, 3H), 1.97(s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 201.80, 201.02, 135.99, 132.80, 129.37, 128.59, 78.21, 70.75, 42.80, 31.06, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}BrNO_4Na$ 350.0004; found 350.0010.



(*R*)-3-(1-(4-bromophenyl)-2-nitroethyl)pentane-2,4-dione

3f

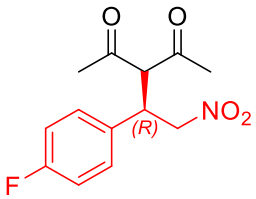
3f) White solid; 0.157g, yield 96%; 99.8% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 0.9 mL/min, wavelength =210 nm: tR (minor) = 15.63 min, tR(major) = 18.21 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.41 (d, J = 8.1 Hz), 7.03 (d, J = 8.1 Hz), 4.61-4.60 (m, 2H), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H), 2.30 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02,164.47,160.75,132.80, 129.37, 128.59, 78.21, 70.75, 42.80, 31.06, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}BrNO_4Na$ 350.0004; found 350.0001.



(*R*)-3-(1-(2-fluorophenyl)-2-nitroethyl)pentane-2,4-dione

3g

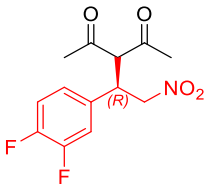
3g) Colorless oil; 0.120 g,yield 90%; 88.0% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 0.8 mL/min, wavelength =210 nm: tR (minor) = 4.23 min, tR(major) = 6.24 min). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.17 (s, 2H), 7.03 (s, 2H), 4.61 (d, J = 6.3 Hz, 2H), 4.33 (d, J = 10.7 Hz, 1H), 4.25 (d, J = 9.0 Hz, 1H), 2.30 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 201.80, 201.02, 135.99, 132.80,129.37,129.37, 127.95,127.57, 78.21, 70.75, 42.80, 31.06, 30.46, 29.72, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}FNO_4Na$ 290.0805; found 290.0767



(*R*)-3-(1-(4-fluorophenyl)-2-nitroethyl)pentane-2,4-dione

3h

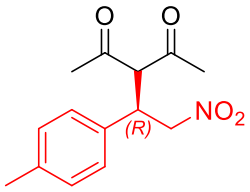
3h) Colorless oil; 0.126g, yield 95%; 89.0 % ee determined by HPLC analysis (Daicel Chiralpak IA column, hexane/2-propanol = 90/10, flow rate: 1.1 mL/min, wavelength = 210 nm: tR (minor) = 9.00 min, tR (major) = 11.33 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.17(m,2H),7.03 (m,2H), 4.61(m,2H,)4.34-4.32 (m, 1H,), 4.25-4.22 (m, 1H), 2.30 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02, 164.47, 170.75, 135.99, 129.37, 128.59, 116.59, 116.37, 78.21,70.75, 42.80, 30.46, 29.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}FNO_4Na$ 290.0805; found 290.0803



(*R*)-3-(1-(3,4-difluorophenyl)-2-nitroethyl)pentane-2,4-dione

3i

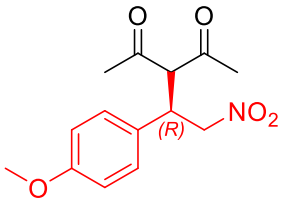
3i) Colorless oil;0.131g, yield 92%; 80.2 % ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 0.8 mL/min, wavelength = 210 nm: tR (minor) = 16.20 min, tR (major) = 19.00 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.17(m,1H),7.03 (m,1H), 6.99 (m, 1H), 4.61-4.60 (m, 2H, CH_2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02, 149.80, 148.59, 147.80, 129.37,116.59, 116.37, 78.21, 70.75, 42.80, 30.46, 29.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{13}F_2NO_4Na$ 308.0710; found 308.0706



(*R*)-3-(2-nitro-1-(*p*-tolyl)ethyl)pentane-2,4-dione

3j

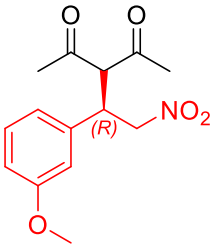
3j) White solid; 0.129 g, yield 98%; 99.8% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength =210 nm: tR (minor) = 15.63 min, tR(major) = 18.21 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.11-7.07 (d, J = 8.1 Hz, 2H, CH), 7.03 (d, J = 8.1 Hz, 2H, CH), 4.61-4.60 (m, 2H, CH_2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02,138.21,132.80,129.37,128.59, 78.21, 70.75, 42.80, 31.06, 29.55,22.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}NO_4Na$ 286.1055; found 286.1050



(*R*)-3-(1-(4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione

3k

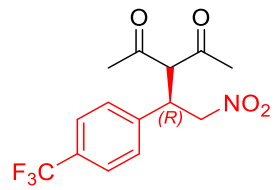
3k) White solid; 0.129g, yield 93%; 99.8% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 92/8, flow rate: 1.2 mL/min, wavelength =210 nm: tR (minor) = 14.80 min, tR(major) = 18.10 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.11 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.61-4.60 (m, 2H, CH2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH),3.76(s,3H, OCH_3) 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02,160.59,129.37,127.95,114.13, 78.21, 70.75,60.59, 42.80, 30.46, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}NO_5Na$ 302.1004; found 302.1001.



(*R*)-3-(1-(3-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione

3l

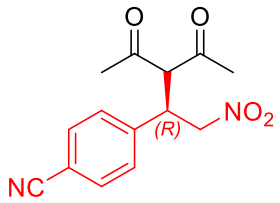
3l) White solid; 0.129, yield 93%; 92.2% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength =210 nm: tR (minor) = 6.20 min, tR(major) = 8.69 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.24 (m,1H), 6.83-6.67 (m, 3H), 4.61-4.60 (m, 2H, CH_2), 4.34- 4.26 (m, 1H), 4.25-4.24 (m, 1H, CH),3.76(s,3H, OCH_3) 2.30 (s, 3H, CH3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02,160.59,129.37,127.95,119.55,114.59,113.46, 78.21, 70.75,60.59, 42.80, 30.46, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}NO_5Na$ 302.1004; found 302.1006.



(*R*)-3-(2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)pentane-2,4-dione

3m

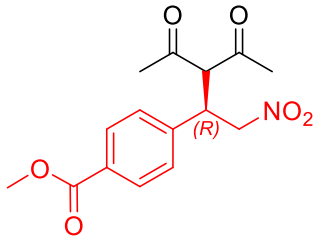
3m) Colorless oil; 0.025g, yield 16%; 25.2 % ee determined by HPLC analysis (Daicel Chiralpak IA column, hexane/2-propanol = 95/5, flow rate: 0.9 mL/min, wavelength =210 nm: tR (minor) = 3.48 min, tR(major) = 5.81 min). ^{1}H NMR (500 MHz, Chloroform-d) 7.44 (d, J = 8.1 Hz,2H), 7.38 (d, J = 8.1 Hz, 2H), 4.61-4.60 (m, 2H, CH_2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm)= δ 201.80, 201.02,135.99,132.80,129.37,127.95,127.57, 78.21, 70.75,



(*R*)-4-(3-acetyl-1-nitro-4-oxopentan-2-yl)benzonitrile

3n

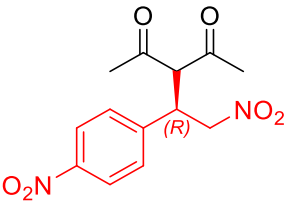
3n) Colorless oil; 0.038 g, yield 28%; 70.3% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol/Methanol= 90/9.8/0.2, flow rate: 1.1 mL/min, wavelength =210 nm: tR (minor) = 8.00 min, tR(major) = 15.45 min). 1H NMR (500 MHz, Chloroform-d) 7.41 (d, J = 8.5 Hz,2H), 7.38 (d, J = 8.5 Hz, 2H), 4.61-4.60 (m, 2H, CH2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02, 135.99, 132.80, 129.37, 128.59, 127.57, 119.55, 78.21, 70.75,60.59, 42.80, 31.06, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{14}N_2O_4Na$ 297.0851; found 297.0853.



methyl (*R*)-4-(3-acetyl-1-nitro-4-oxopentan-2-yl)benzoate

3o

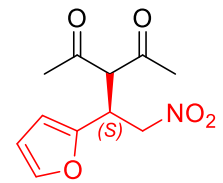
3o) Colorless oil; 0.127g, yield 83%; 91.0% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol/Methanol = 90/9/1, flow rate: 0.8 mL/min, wavelength =210 nm: tR (minor) = 14.80 min, tR(major) = 18.10 min).1H NMR (500 MHz, Chloroform-d) 7.82 (d, *J* = *8.2 Hz*,2H), 7.60 (d, *J* = *8.2 Hz*, 2H), 4.61-4.60 (m, 2H, CH_2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH),3.87(s,1H) 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02, 176.78, 129.37, 128.59, 127.57, 125.71, 78.21, 70.75,51.06, 42.80, 31.06, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{17}NO_6Na$ 330.0954; found 330.0950.



(*R*)-3-(2-nitro-1-(4-nitrophenyl)ethyl)pentane-2,4-dione

3p

3p) Yellow solid; 0.116 g,yield 79%; 77.7% ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 1 mL/min, wavelength =210 nm: tR (minor) = 28.99 min, tR(major) = 32.80 min).^1H NMR (500 MHz, Chloroform-d) 7.48 (d, *J* = *8.5 Hz*,2H), 8.16 (d, *J* = *8.5 Hz*, 2H), 4.61-4.60 (m, 2H, CH_2), 4.34-4.26 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.97 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) = δ 201.80, 201.02,142.55,128.29,128.08,128.00,127.88,127.78, 78.21, 42.80, 31.06, 29.55. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{14}H_{14}N_2O_6Na$ 317.0750; found 317.0749.



(*S*)-3-(1-(furan-2-yl)-2-nitroethyl)pentane-2,4-dione

3u

3u) White solid; 0.101 g, yield 85%; 79.2 %ee determined by HPLC analysis (Daicel Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate: 0.7 mL/min, wavelength = 210 nm: tR(major) = 18.21 min and tR(minor) = 21.26 min). ^1H NMR (500 MHz, Chloroform-d) 7.56(t,1H, J=1.2 Hz),7.03 (m,1H), 6.27 (t, 1H, J=2.2 Hz),6.17(d,1H, J=3.6 Hz) 4.83(m,1H,)4.61-4.60 (d, 2H,J=5.4 Hz), 4.36-4.32 (m, 1H), 4.25-4.24 (m, 1H, CH), 2.30 (s, 3H, CH3), 2.03 (s, 3H, CH3). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) 201.80, 201.02, 160.59, 141.46, 114.59, 113.46, 78.21,70.75, 42.80, 30.46, 29.72. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{11}H_{13}NO_5Na$ 262.0691; found 262.0693