

Declaration

This is to certify that the thesis titled “*Calix[4]arene Derived Catalysts for Asymmetric Organic Transformations*” submitted by Apoorva Malik to the Indian Institute of Technology Jodhpur for the award of the degree of *Doctor of Philosophy* is a bonafide record of the research work done by her under my supervision. To the best of our knowledge the contents of this report, in full or in parts, have not been submitted to any other institute or university for the award of any degree or diploma.



Rakesh Kumar Sharma
Ph.D. Thesis Supervisor

Declaration

I hereby declare that the work presented in this Thesis "*Calix[4]arene Derived Catalyst for Asymmetric Organic Transformations*" submitted to the Indian Institute of Technology Jodhpur in partial fulfillment of the requirements for the award of the degree of Doctor of Philosophy, is a bonafide record of the research work carried out under the supervision of Prof. Rakesh Kumar Sharma. The contents of this thesis in full or in parts, have not been submitted to, and will not be submitted by me to, any other Institute or University in India or abroad for the award of any degree or diploma.



Apoorva Malik

P19CY012

Abstract

This study draws attention to supramolecular catalysts. Cram, Lehn, and Pedersen's pioneering works evolved around the use of supramolecules for molecular recognition and catalysis. Supramolecules offer defined binding pockets and noncovalent interactions such as hydrogen bonding, van der Waals forces, and π - π interactions, thus generating a reaction microenvironment for catalysis. Moreover, macrocycles can provide a preorganized arrangement of functional groups, such as binding sites or catalytically active groups, thus enabling a defined and possibly multivalent binding and activation of substrates. Various supramolecules such as calixarene, cryptands, cucurbiturils, and COFs, have been studied for a variety of applications for environmental and catalytic applications.

Among various supramolecules, calixarene is the most important molecule for constructing conformationally rigid supramolecular catalysts. The unique properties of calix[4]arene lead to a rational design of homogeneous catalysts and due to the absence of metals, these methods are attractive for the preparation of pharmaceutical compounds, and chemical reactions that are of high value in the biological, and chemical industries. With the increasing demand for chiral products, many efficient catalysts have been developed for a wide range of organic transformations. The major part of asymmetric catalysis is homogeneous catalysts as they facilitate molecular reactions in an efficient manner with high chirality transfer. Calix[4]arene appended catalysts are easily recoverable, separable, and can be purified as well and these catalysts could be recycled with a good number of recyclable cycles.

Out of various studies on asymmetric homogeneous organocatalyzed reactions, asymmetric Michael addition of acetylacetone to β -nitrostyrene is one of the key reactions with wide applications in pharmaceutical industries. Mono and dicationic *Cinchona* alkaloid-anchored calix[4]arenes as organocatalysts were effective and gave high enantiomeric induction (~99% yield and >99% ee). Phase Transfer catalysts (PTC) based on calixarene supramolecules offer special advantages due to their unique properties with a rigid and stable aromatic cavity. Additionally, four phenolic hydroxyl groups of calix [4] arene provide synthetic adaptability and noncovalent interactions and a new catalyst designed utilizing quaternary ammonium *Cinchona*-functionalized crown ether-strapped calix[4]arenes as PTCs for asymmetric α -alkylation of glycine imines to α -alkylated glycines with remarkable selectivity under ambient conditions (~98% yield and >99% ee). Another PTC designed a highly selective α -methylbenzylamine functionalized crown-ether-appended calix [4]arene is harnessed for asymmetric nitroaldol reaction to provide nitroaldol adducts in high yields (up to 99 % yield) with good to excellent enantioselectivities (up to 99.8 % ee). Organocatalysis has gained noteworthy attention due to its efficiency, selectivity, and gratifying results at sub-stoichiometric amounts of the chiral catalyst and calixarene-derived enantioselective organocatalytic one-pot Strecker reaction catalyzed by camphor sulfonyl functionalized crown-ether-tethered calix [4] arene and provide the desired cyano adducts in high yields up to 99.9% yield and 99.2% ee. The synthetic utility of the Strecker reaction was used in the synthesis of Clopidogrel.

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List of Symbols

Symbol	Description
Å	Angstrom
C=O	Carbonyl group
e ⁻	Electron
Kcal	Kilocalorie
cm	Centimeter
mm	Millimeter
nm	Nanometer
μM	Micromolar
μL	Microliters
mL	Milliliter
Hz	Hertz
MHz	Mega hertz
V	Voltage
M	Molarity
N	Normality
mol	Mole
mmol	Millimole
%	Percentage
°C	Degree Celsius
K	Kelvin
ppm	Parts per million

List of Abbreviations

a.u.	Arbitrary Unit
Ar	Aromatic ring
cc	Cubic centimeter
AcCN	Acetonitrile
CDCl ₃	Deuterated chloroform
CD	Cinchonidine
CN	Cinchonine
DCM	Dichloromethane
DMF	Dimethylformamide
d	Days
d	Doublet (NMR)
Dd	Doublet of doublet(NMR)
ee	Enantiomeric excess
Et	Ethyl
Et ₂ O	Diethyl Ether
EA	Elemental Analysis
EI	Electron impact
ESI	Electrospray ionization
eq	Equivalent
HPLC	High-Performance liquid chromatography
HRMS	High resonance magnetic spectroscopy
KOH	Potassium hydroxide
MeOH	Methanol
MALDI	Matrix-Assisted laser desorption ionisation
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
o	ortho
-OH	Hydroxyl group
-O-CH ₃	Methoxy group
p	para
Ph	Phenyl
PTC	Phase Transfer catalyst
q	Quartet (NMR)
QD	Quinidine
QN	Quinine
R.T	Room temperature
s	Singlet (NMR)
t-Bu	Tert-Butyl
t	Triplet (NMR)
T	Temperature
TEA	Triethylamine
THF	Tetrahydrofuran
TS	Transition state
Wt	Weight

