Total synthesis of recently isolated bioactive natural products

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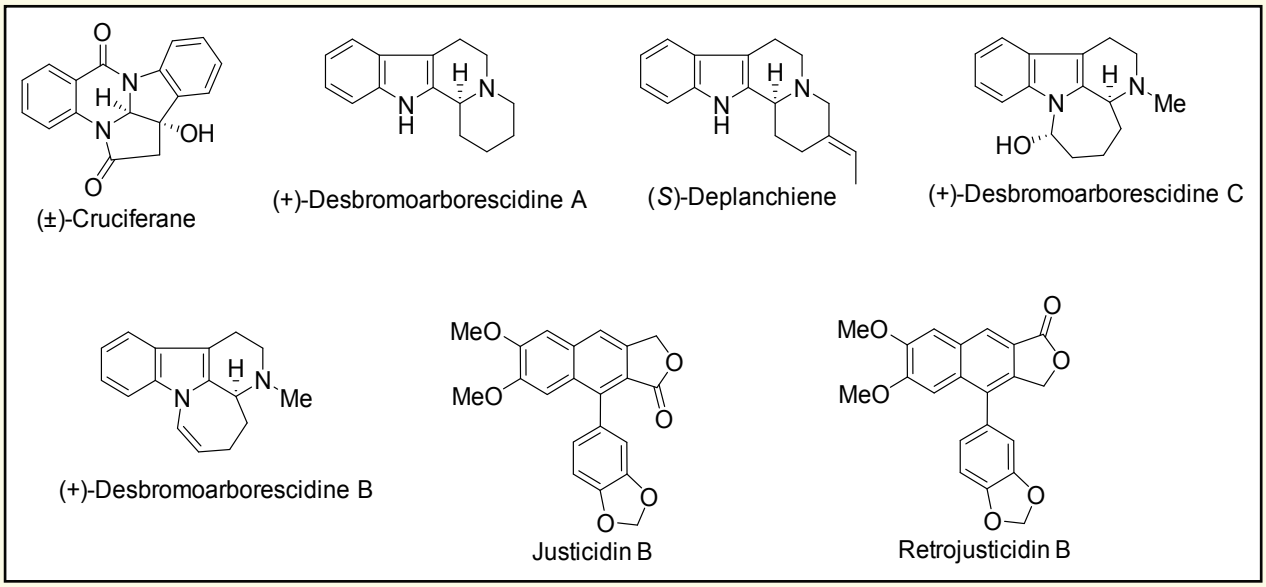
Publications: Org. Lett., 2013, 15, 14, 4006; J. Org. Chem., 2013, 78, 6802

Total synthesis of bioactive natural products occupies a keystone position in organic chemistry. The real challenge was to design these molecules with highly efficient practical routes. Total synthesis of several desired, complex bioactive natural and unnatural products, pseudo natural products and natural product hybrids using cyclic anhydrides as potential precursors was done by employing variety of new synthetic strategies.

The list of natural products synthesized included cruciferane, desbromoarborescidines A–C, deplancheine, justicidin B and retrojusticidin B. The remarkable selective aryne insertion reactions, stereoselective reductive intramolecular cyclization, exchange of nitrogen regioselectivity in intramolecular cyclization and the palladium-promoted [2+2+2] cocyclization were the involved key steps.



Research & Development Reports

Transition-metal-free carbon-carbon bond forming reactions using aryne chemistry and N-heterocyclic carbene organocatalysis

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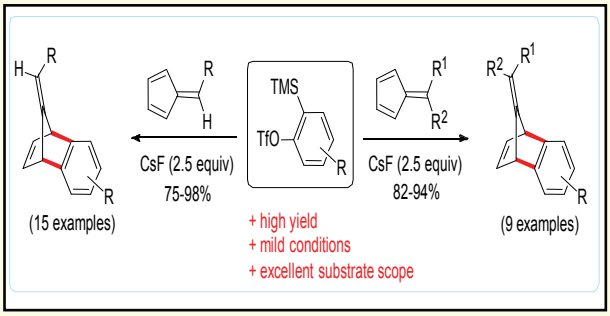
Publications: Org. Lett. 2012, 14, 2830, 6238, 2013, 14, 1756; Adv. Synth. Catal., 2013, 355, 1089; Green Chem., 2013, 15, 1608

The transition-metal-free carbon-carbon bond-forming reactions using arynes resulted in the one-pot construction of molecular complexity, which were applied to the synthesis of various heterocyclic scaffolds and 1,2-disubstituted arenes. The application of arynes in transition-metal-free multicomponent coupling reactions, pericyclic reactions and insertion reactions were examined. The group has been working on NHC-organocatalyzed umpolung (reversal of normal mode of reactivity) of aldehydes, which can lead to the formation of nucleophilic acyl anion intermediates, homoenolate intermediates and enolate intermediates depending on the reaction conditions. It resulted in the construction of various carbocycles and heterocycles via unique carbon-carbon and carbon-heteroatom bond-forming reactions.

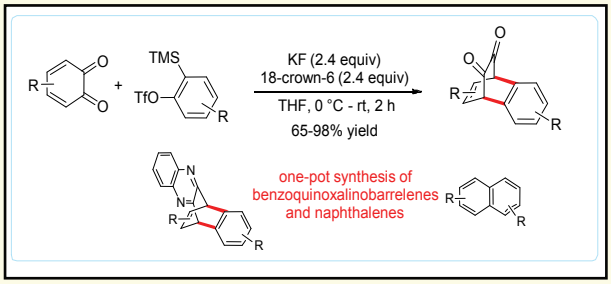
Diels-Alder reaction of pentafulvenes with arynes

A high-yielding, versatile and practical Diels-Alder reaction of pentafulvenes with arynes under mild reaction conditions was developed. The aryne generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates undergoes efficient cycloaddition with 6-substituted and 6,6-disubstituted pentafulvenes leading to the formation of benzonorbornadiene derivatives. Broad substrate scope, high yields, and mild reaction conditions are the noteworthy features of the present reaction. The benzonorbornadienes have potential applications in organic chemistry. Ring opening metathesis polymerization (ROMP) by using Mo carbene initiators afforded highly stereoregular polymers. Also, the addition of benzonorbornadienes to 4-phenyl-4H-1,2,4-triazole-3,5-dione (PTAD) resulted in a convenient entry to polycyclic azoalkanes, which were valuable target molecules.



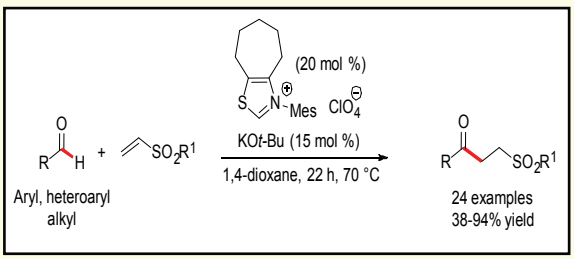
Diels-Alder reaction of 1,2-benzoquinones with arynes

A new protocol for the efficient Diels-Alder reaction of 1,2-benzoquinones with arynes was reported. The aryne generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates undergone a facile Diels-Alder reaction with 1,2-benzoquinones affording the dioxobenzobicyclooctadienes in good to excellent yields. In addition, this methodology was applied to the one-pot synthesis of benzoquinoxalinobarrelene and naphthalene derivatives. The dioxobenzobicyclooctadiene derivatives are potentially amenable to a number of synthetic transformations including various photochemical reactions of the bicyclo [2.2.2] octadiene moiety as well as the reaction of 1,2-diketo group.



Synthesis of γ-Keto sulfones by NHC-catalyzed intermolecular stetter reaction

In the area of NHC-organocatalysis, a transition-metal-free NHC-organocatalyzed intermolecular Stetter reaction of aldehydes was developed with γ-unsaturated sulfones, the first intermolecular hydroacylation of γ-unsaturated sulfones, leading to the efficient formation of γ-keto sulfones in good yields. The product formation took place in spite of various selectivity issues under basic conditions. Key to success for this unique transition-metal-free carbon-carbon bond-forming reaction is the right choice of the NHC precursor and base. The reaction tolerated a broad range of different aldehydes.

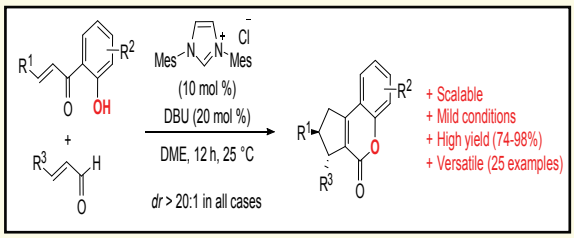


Research & Development Reports

Transition-metal-free carbon-carbon bond forming reactions using aryne chemistry and N-heterocyclic carbene organocatalysis

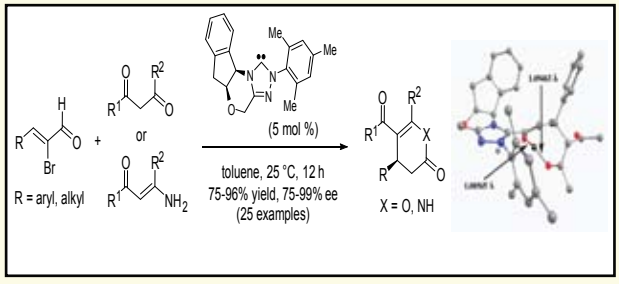
NHC-catalyzed reaction of enals with hydroxy chalcones: Diastereoselective synthesis of functionalized coumarins

The N-Heterocyclic carbene-catalyzed annulation of enals with 2'-hydroxy chalcones was uncovered which afford cyclopentane-fused coumarin derivatives with excellent level of diastereocontrol. The reaction tolerated a broad range of functional groups and proceeded under mild conditions; 25 examples were given and a preliminary mechanistic investigation was done. Notably, functionalized coumarin derivatives are important synthetic targets due to their biological properties and some of them are endowed with important fluorescent properties.



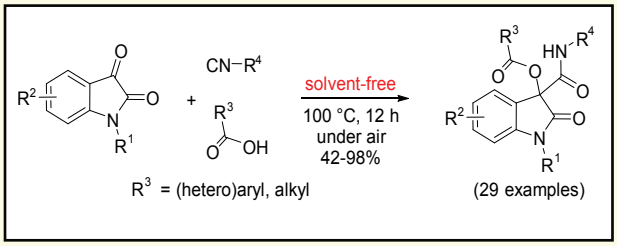
Enantioselective NHC-catalyzed annulations of 2-bromoenals with 1,3-dicarbonyl compounds and enamines via chiral α,β-unsaturated acylazoliums

The NHC-catalyzed generation of chiral α, β-unsaturated acyl azoliums from 2-bromoenals followed by its interception with 1,3-dicarbonyl compounds or enamines, the formal [3+3] annulation reaction was exposed. The reaction resulted in the enantioselective synthesis of synthetically and medicinally important dihydropyranones and dihydropyridinones and tolerated a wide range of functional groups. It was noteworthy that the reaction took place under mild reaction conditions utilizing relatively low catalyst loadings. In addition, based on DFT calculations, a mechanistic scenario involving the attack of nucleophile from below the plane of the α, β-unsaturated acyl azoliums, and the mode of enantioinduction was realized.



Engaging isatins in solvent-free, sterically congested passerini reaction

A facile, atom-economic and environmentally-benign protocol was developed for the synthesis of biologically important 3-acyloxy 3-carbamoyl indol-2-ones in high yields by employing isatins as carbonyl compound surrogates in Passerini reaction carried out under solvent-free conditions. In addition, electron-deficient phenols can also be used as the acid component in this reaction. Notably, oxindoles having a quaternary benzylic centre represent a common structural motif in many natural products and biologically active compounds.



Methodologies, asymmetric synthesis and organometallics

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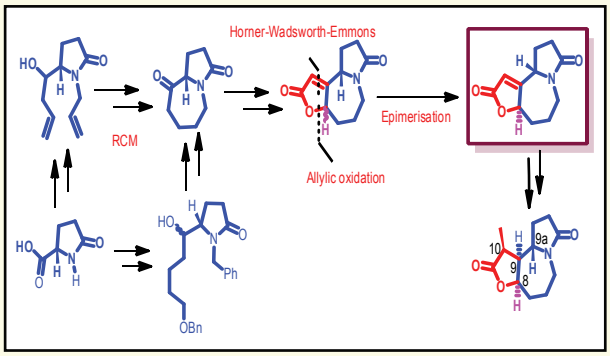
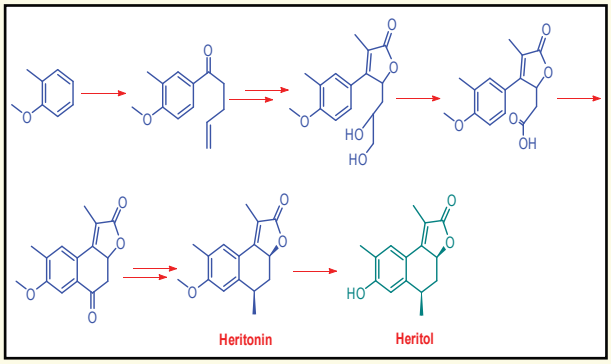
Publications: Tetrahedron Lett., 2012, 53, 2647, 4683, 2013, 54, 1528, 2137; Tetrahedron, 2012, 68, 8509; Tetrahedron-Asymmetr., 2012, 23, 1410, 1496; Eu. J. Org. Chem., 2012, 6841

Synthesis of natural products and biologically active compounds

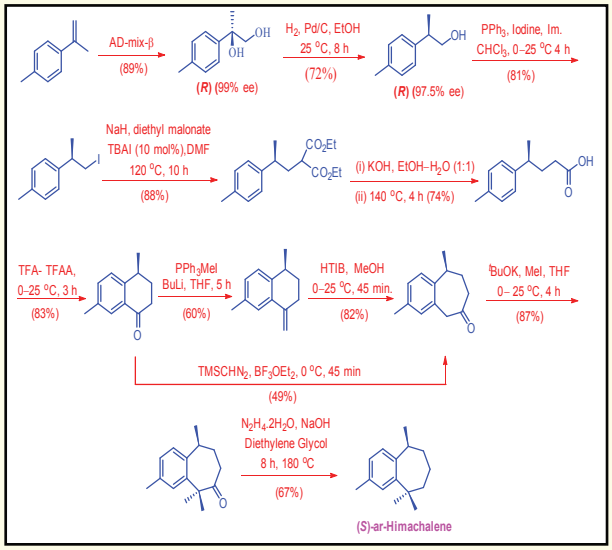
Synthesis of stemoamide: (–)-Stemoamide, one of the stemona alkaloids was isolated by Xu and coworkers in 1992 from *Stemona tuberosa* Lour and related stemona species. The research group accomplished the formal total synthesis of (–)-stemoamide by taking advantage of Ring closing Metathesis (RCM) and allylic oxidation in eleven steps in 15% overall yield. The alternate route to seven membered ring construction was developed using Grignard reaction and base induced cyclisation to furnish butenolide in fourteen steps in 11% overall yield.



Diastereoselective synthesis of (±) heritonin and (±) heritol: Miles and co-workers have isolated cadinane sesquiterpene lactones Heritol and Heritonin from the sap of the mangrove plant *Heritiera littoralis* of Philippines and other tropical countries. These plants possess ichthyotoxicity in ppm quantities to *Tilapia nilotica* fingerlings and are used by native fishermen to kill fish. The highly distereoselective total synthesis of racemic heritonin and heritol was achieved from cheap and commercially available starting materials in eight and nine purification operation in 43% and 33% overall yield, respectively which was highest overall yield reported so far.



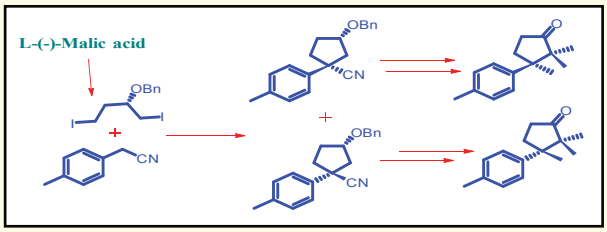
Enantioselective synthesis of pheromonal component *ar*-Himachalene: Himachalene is a structurally and biologically important class of the naturally occurring sesq-uiterpene hydrocarbons containing the synthetically challenging benzoannulene ring system. The essential oil and different constituents of *C. deodara* account for the insecticidal and larvicidal action therefore it can be used in pest management. The research group accomplished the enantioselective synthesis of both isomers of ar-himachalene. The synthetic sequence involved a sharpless asymmetric dihydroxylation reaction, hydrogenolysis, and the use of TMSCHN2 or a hypervalent iodine reagent for the ring expansion. This protocol could be of general interest and also useful for the synthesis of several complex bioactive natural and unnatural products.



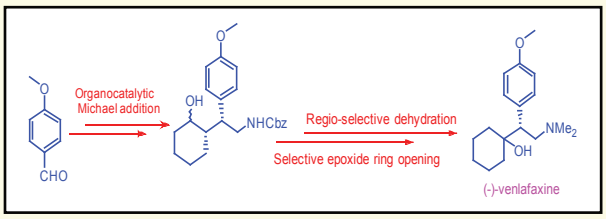
Synthesis of (+) cuparenone and (-) cuparenone: α-Cuparenone is a bicyclic sesquiterpene which exhibits itself in two isomeric forms. This sesquiterpene is a synthetic challenge to organic chemists due to presence of two contiguous quaternary centers, one of which is stereogenic in cyclopentane ring. The synthesis of both the enantiomers of α-αuparenone was achieved in ten steps involving one diastereomeric separation, starting from L- Malic acid and 4-methyl benzyl cyanide, led to (*S*)-(+)-cuparenone and (*R*)-(-)-cuparenone in ⩾99 % and 15 % overall yield.

Research & Development Reports

Methodologies, asymmetric synthesis and organometallics

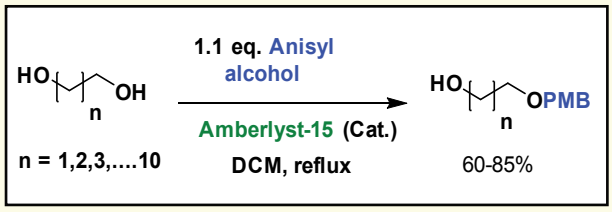


Asymmetric synthesis of antidepressant venlafaxine: Venlafaxine, a new generation antidepressant drug is being used for the treatment of major depressive disorder (MDD), generalized anxiety disorder and comorbid indications in certain anxiety disorders for depression. Research group accomplished asymmetric total synthesis of (–)-venlafaxine from commercially available, cheap starting material by using an environmentally friendly proline-based catalyst. By using different enantiomers of proline-based catalyst both the enantiomers of venlafaxine in a very concise manner can be accessed.

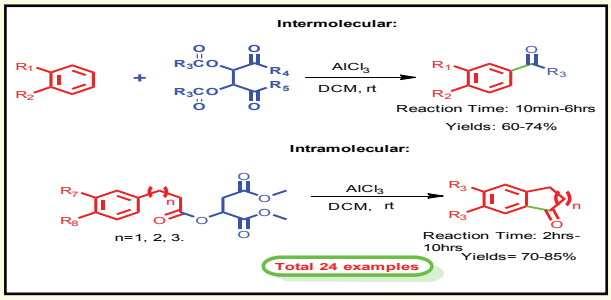


Development of synthetic methodologies

A mild, convenient and practical methodology for PMB protection of alcohols: 4-Metho-xybenzyl (PMB) protection of alcohols is an important step in the synthetic sequence. Conventional methods for the PMB protection of alcohols require the use of strong bases like NaH, *n*-BuLi *etc* and the use of unstable *p*-methoxy benzyl bromide/chloride as the reactant. A methodology was devised which utilized a commercially available Ambertlyst-15 resin as a heterogenous catalyst and anisyl alcohol as the reactant. The use of heterogenous catalyst offers advantages over conventional reagents in terms of selectivity, ease of operation and reusability of the resin and simple work-up after the reaction is over. This methodology allows selective mono PMB protection of diols and di-PMB protection of diols as per requirement.



Unprecedented, mild, efficient and simple Friedel-Crafts acylation reaction using esters: Esters normally do not undergo Fridel-Craft's acylation reactions. An important synthetic methodology was developed for the inter- and intra-molecular Friedel-Crafts acylation reaction of wide variety of activated esters with different aromatic compounds and mechanistic aspects were studied carefully by both theoretically and experimentally.



Research & Development Reports

Development of synthetic methods and total synthesis of natural products

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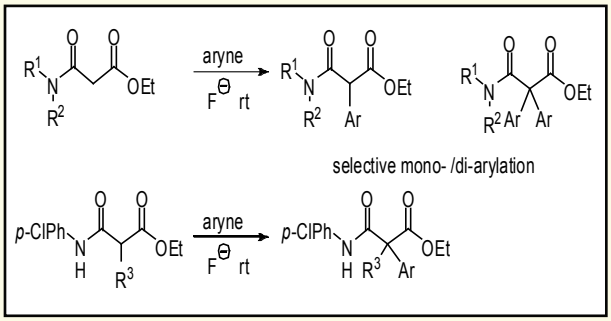
Publications: Org. Lett., 2012, 14, 3994, 5804; 2013, 15, 2218; Synth. Commun., 2013, 43, 1

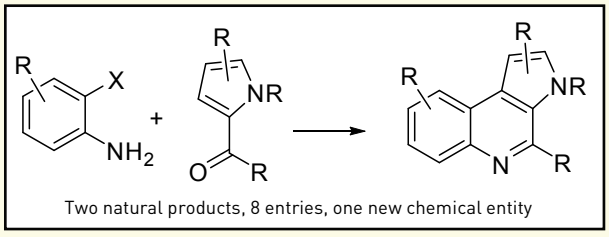
A facile, fluoride-induced transition-metal-free chemoselective α-arylation of β-dicarbonyl compounds (malonamide esters) at room temperature using aryne intermediates was demonstrated. Selective mono- or diarylation and generation of a quaternary benzylic stereocenter were also achieved. The methodology is useful for the synthesis of a library of CNS depressant barbiturate drugs like Phenobarbital.

Facile C-arylation using arynes

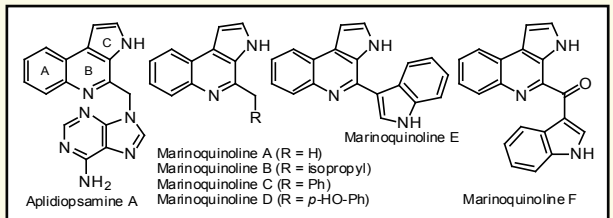


C-H activation: Direct access to pyrroloquinolines

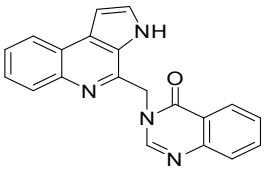
A method for palladium-catalyzed cyclization of imines was developed to construct the extremely rare 3*H*-pyrrolo[2,3-*c*]quinoline ring system for diversity oriented first total synthesis of antimalarial marine natural product Aplidiopsamine A, Marinoquinoline A and potential natural product hybrid NCLite-M1.



Two natural products, 8 entries, one new chemical entity



PDE4 inhibitors for CNS disorders

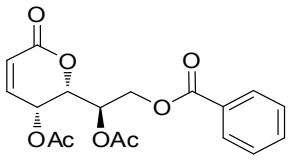


NCLite-M1

CNS / Malaria
NCE of pharmaceutical interest

Protecting group-free total synthesis of celistenolide

A short, efficient and expedient protecting group-free diastereoselective total synthesis of (±)-Cleistenolide was achieved in five steps with 60% overall yield. Achmatowicz reaction, chemoselective oxidation of secondary alcohol and diastereoselective 1,3-*anti* reduction of β-hydroxy ketone are the key features of this linear total synthesis. The synthetic strategy demonstrated herein has a potential to explore it for an asymmetric total synthesis of (–)-Cleistenolide and related bioactive natural products.



(-)-Cleistenolide

Anti-Tuberculotic

Research & Development Reports

Asymmetric synthesis of biologically important compounds

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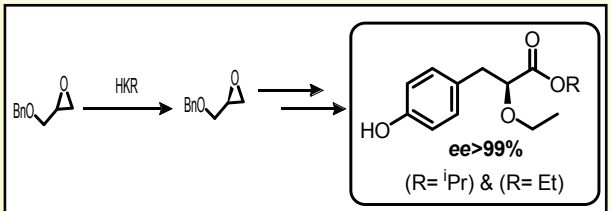
Publications: Bioorg. Med. Chem. Lett., 2013, 23, 1416; Tetrahedron Asymmetr., 2011, 22, 1353, 2012, 23, 1512; Tetrahedron Lett., 2011, 52, 2387

Hydrolytic kinetic resolution (HKR) method is one such elegant strategy, which utilizes chiral (salen) Co complex catalysts for the preparation of terminal epoxides and vicinal diols in high enantiopurity. Easy access of terminal epoxides, high levels of selectivity, low loading and easy availability of the catalyst made this method well amenable for the preparation of plethora of biologically important compounds. The group has utilized the elegant HKR strategy for the preparation of many pharmaceutically important compounds.

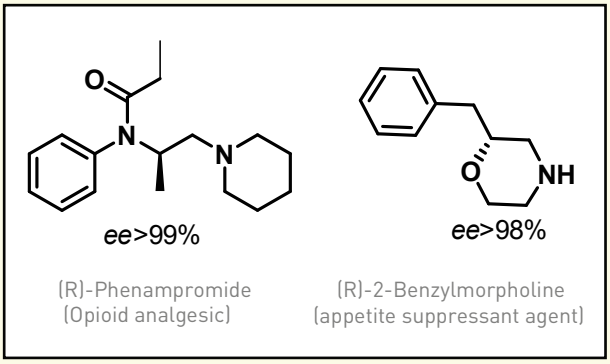
Asymmetric synthesis of ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), a key intermediate of PPAR agonists

Ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), is an important pharmaceutical intermediate, present in many PPAR (Peroxime proliferator-activated receptors) agonists. PPAR plays a significant role in regulating lipid and carbohydrate metabolism and their agonists have shown therapeutic application for the treatment of diabetes and dyslipidemia. In addition EEHP derivatives found application in photosensitive materials, sweetening agents, treatment of certain eating disorders, etc. Development of a practical and highly enantioselective synthetic route to EEHP was done by employing HKR strategy as a key step and a source of Chirality.



Asymmetric synthesis of EEHP employing HKR strategy

Similarly, group has utilized the HKR strategy for the synthesis of some other chiral drugs as following.

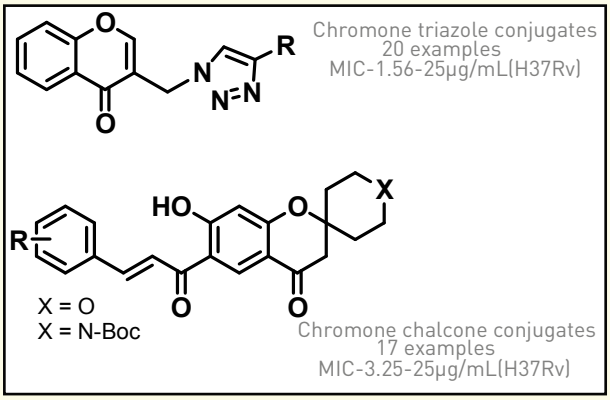


(R)-Phenampromide (Opioid analgesic)

(R)-2-Benzylmorpholine (appetite suppressant agent)

Development of novel chromone based derivatives as potent antitubercular agents

Chromone is recognized as a privileged structural motif, observed in plethora of natural products and in various therapeutic agents. Although many of the naturally occurring chromones exhibit interesting anti-TB properties, but no systematic investigations were carried out to explore its anti-TB potential. As part of research program, focus was on design and synthesis of structurally new class of compounds based upon privileged chromone scaffold and studying their anti-TB properties.



Research & Development Reports

Methodologies, asymmetric total synthesis of biologically active compounds

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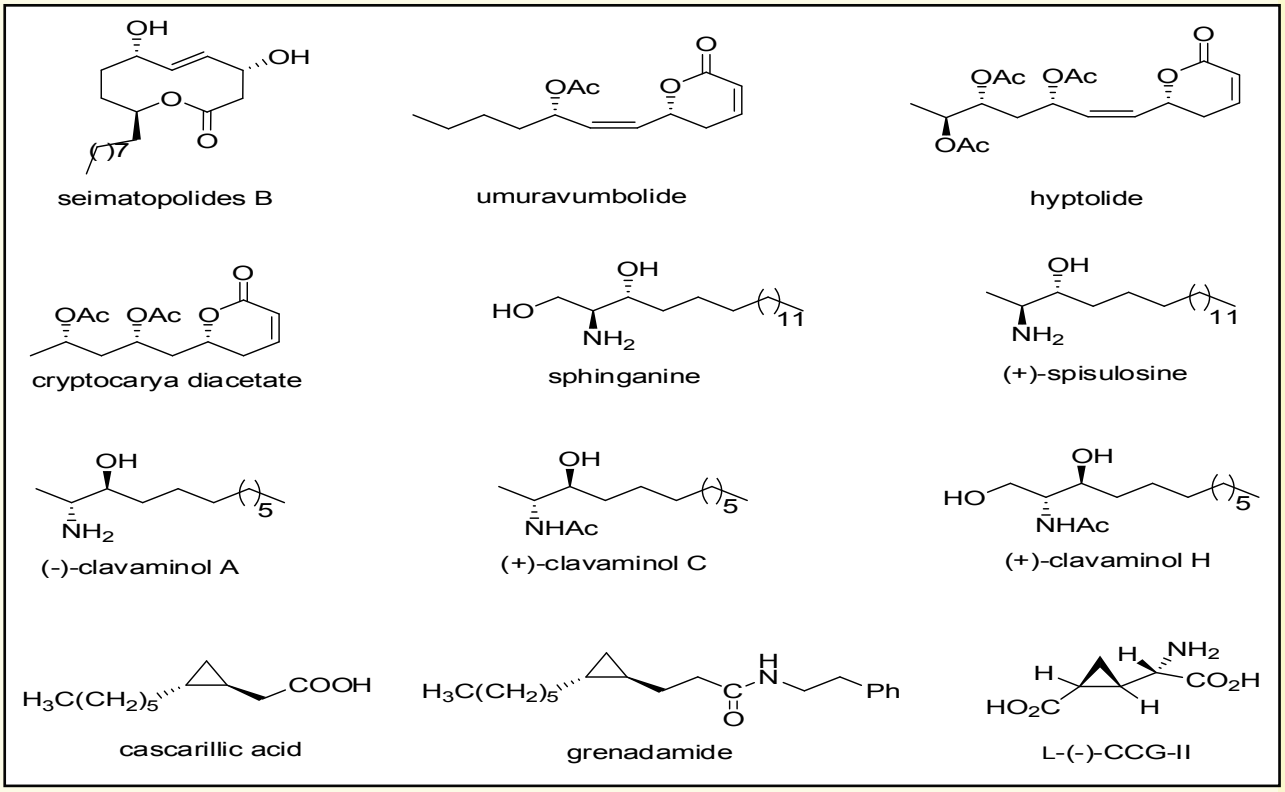
Publications : RSC Adv., 2012, 2, 11231; 2013, 3, 15442; Eur. J. Org. Chem., 2013, 4586; Adv. Synth. Catal., 2013, 355, 1719; Accounts Chem. Res., 2013, 46, 289

Research was focused on asymmetric synthesis of naturally occurring lactones and amino alcohols. New methodologies for the preparation of *syn/anti*-1,5-diols and *syn/syn*-1,3,5-triols were developed which serve as useful building blocks for enantioselective synthesis of biologically active natural products.

Research was done on the enantio- and diastereocontrolled conversion of chiral epoxides to trans-cyclopropane carboxylates and applied the methodology to the successful synthesis of cascarillic acid, grenadamide and L-(-)-CCG-II. The total asymmetric synthesis of a wide variety of biologically useful compounds was achieved by employing the Jacobsen hydrolytic kinetic resolution, organocatalysis, indium mediated allylation of α-hydrazino aldehyde as the source of chirality and silicon-tethered ring closing metathesis, cross-metathesis as the key steps. The target molecules including seimatopolide B, aculeatins F, solenopsin, umuravumbolide, hyptolide, cryptocarya diacetate, clavaminols, sphinganine and (+)-spisulosine. Seimatopolide B were synthesized by generating the stereogenic centers by means of Jacobsen`s HKR. In the case of umuravumbolide and hyptolide, the stereogenic centers were generated via proline-catalyzed α-aminoxylation of aldehydes and Brown's asymmetric allylation method and the olefins were constructed by exploiting temporary silicon-tethered ring-closing metathesis (TST-RCM) and Ando's protocol.

A desymmetrization approach was used for the synthesis of enantiopure *syn/anti*-1,5-diols via hydrolytic kinetic resolution (HKR) of functionalized meso bis-epoxides which was further elaborated to the synthesis of *syn/syn*-1,3,5-triols and subsequently applied to the formal synthesis of cryptocarya diacetate. A conceptually different approach was employed for the synthesis of 1,2-amino alcohols such as clavaminol A–H, sphinganine and (+)-spisulosine by proline catalyzed α-amination of aldehyde and one-pot indium mediated allylation of the crude α-hydrazino aldehydes. A DFT based quantum chemical calculations were performed to obtain a quantitative explanation of the stereoselectivity of the reaction. Some of the molecules accomplished in the total synthesis using above reactions were following.



Research & Development Reports

Total synthesis and metal catalysis

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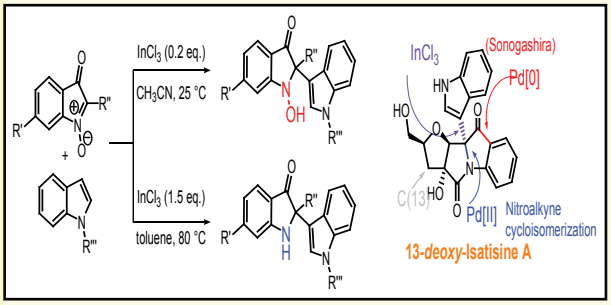
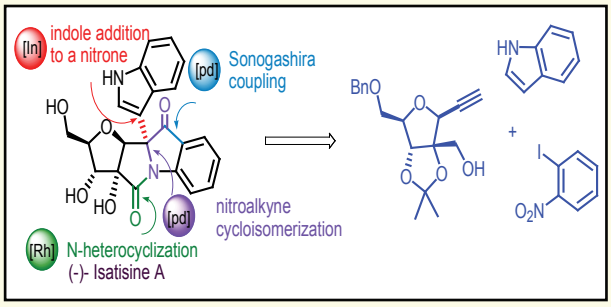
Publications: Chem. Eur. J., 2012, 18, 9601, 13288; J. Org. Chem., 2012, 77, 1566, 2169, 10509; Tetrahedron Lett., 2012, 53, 6347

Total synthesis is focused on creativity in development of new methodologies, modular strategies and providing effective platforms for the synthesis of natural products like small molecule libraries. The use of metal complexes as catalysts addressing the construction of the polycyclic frame works present in the bioactive small molecules in another active area.

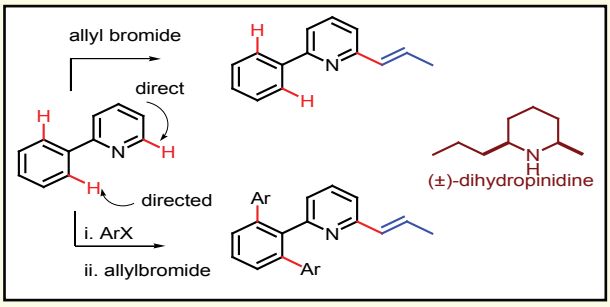
A strategy directed towards the total synthesis of isatisine A was executed. The research group has developed the selective methods for the addition of indoles to isatogens leading to either 2,2-disubstituted-N-hydroxy-indolin-3-one or 2,2-disubstituted-indolin-3-one compounds. The present methods provide the first example of the addition of indoles to the isatogen nucleus. The earlier methodology for the isatogen synthesis, taken together with the current methods has helped to synthesize the 13-deoxy-isatisine A in ten steps from an easily available sugar building block. The strategy that have developed is unique in its own and features several late-stage metal-mediated transformations (coupling, cyclization and additions, the later two being developed in this context) addressing the key carbon–carbon and carbon–hetero atom bond formations, thereby making it highly modular.



The recent total synthesis of isatisine A is a classic example wherein the compatibility of four [metal]-catalyzed / mediated transformations have been executed in a sequence by the group. This is a rare feat in total synthesis. Amongst them were the unprecedented nitroalkyne / nitroalkynol cycloisomerizations, were designed based purely on the mechanistic hypothesis. Also, the application of a [Rh]-catalyzed oxidative γ-aminoalcohol cyclization leading to the γ-lactam in the synthesis of a complex natural product was established for the first time. This paper was appeared as a "Featured article in the Journal of Organic Chemistry.



Dealing with the development of complementary C – H activations, research group has revealed the direct C – H activation of pyridine ring which was unprecedented. As an off-shoot to this exercise, the (±)–dihydropinidine was synthesized in two steps, both being catalyzed by the complexes of ruthenium and platinum in sequence. A one-pot directed and direct C–H activation comprising a total three C-H activations in one-pot were explored successfully.

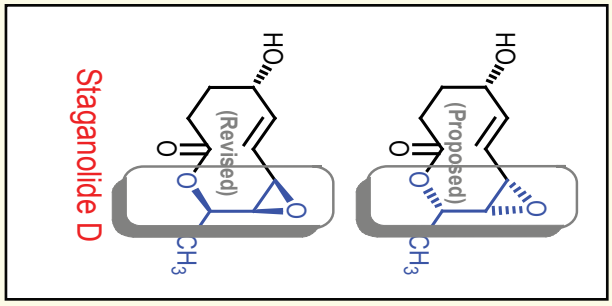


A simple protocol was developed for the stereospecific synthesis of C-arabinofuranosides featuring a furan ring transposition as the key reaction. The stereochemistry present at the C(5) of the starting hexofuranose was translated to the anomeric configuration of the resulting C-glycosides. The carba-disaccharide analogue of motif C (of cell wall AG complex of M.Tb) was also synthesized by applying a double furan ring transposition, where a C(2)-symmetric bis-hexofuranoside was explicitly converted to the corresponding disaccharide. This double furan ring transposition reported herein is the first of its kind.

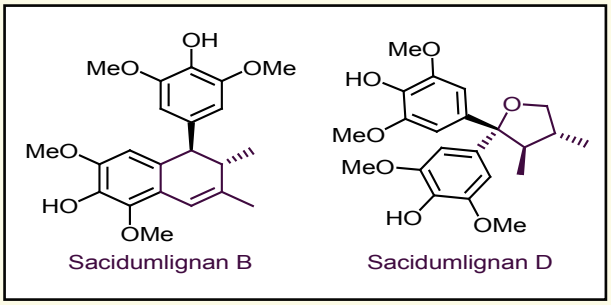
Research & Development Reports

Total synthesis and metal catalysis

Staganolide D, a target was selected for the (first) total synthesis in order to demonstrate the proposal on how the stereochemistry of the allylic substituents can influence the outcome of a ring closing metathesis (RCM) reaction. The group showed that the proposed structure was not the right one, despite the fact that an earlier total synthesis confirmed its proposed structure. It proved that the group that isolated staganolide D overlooked its existence as equilibrating conformational isomers.



The first total synthesis of naturally occurring sacidumlignans B and D was completed and their relative or absolute configurations were established. The synthesis of sacidumlignan A from an intermediate was executed which was used in the synthesis of sacidumlignan B. For the total synthesis of the sacidumlignan B, a dehydrative cyclization of a γ-arylaldehyde leading to the aryldihydronaphthalene units were used–which was the first of its kind. The adopted strategy employed a single advanced intermediate for all the targets executed. A diastereoselective γ-methylation of a lactone was used as the key step for the control of the chiral centers of the central lignan core.



Research & Development Reports

Total synthesis of biologically active compounds and medicinal chemistry

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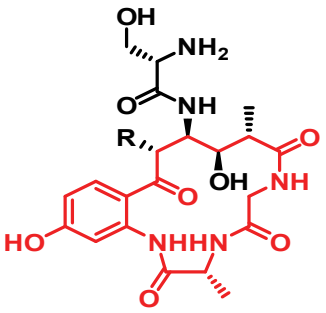
Publications: Chem. Commun., 2013, 49, 3242; Org. Lett., 2012, 14, 6222; Tetrahedron Lett., 2012, 53, 6343; WO 2013054275 A1, 2013054366 A1

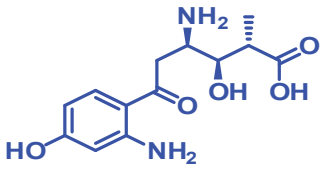
The research was focused mainly on total synthesis of biologically active compounds such as anti-inflammatory, anti-bacterial and anti-cancer agents. Significant progress on "Silicon-switch approach" was made in the medicinal chemistry front.

Synthesis of anti-inflammatory cyclic peptides solomonamides A and B

Two cyclic peptides solomonamide A and solomonamide B with unprecedented chemotype were recently isolated from the marine sponge *Theonella swinhoei* from Italy. Solomonamide A showed significant reduction (~ 60%) of inflammation in the carrageenan induced paw edema model properties at a very low concentration of 100g/kg. Because of potent *in vivo* biological activity, novel chemotype, and scarcity of the material, it is significant to access these important classes of molecules by means of total synthesis and their analog in sufficient quantities for further biological evaluation. The synthesis was accomplished of macrocyclic core and key fragment AHMOA in the program. The feasibility of key reactions was tested and established a synthetically viable route. The total synthesis, synthesis of analogues, and its biological evaluation are currently ongoing.



R = OH Solomonamide A
R = H Solomonamide B

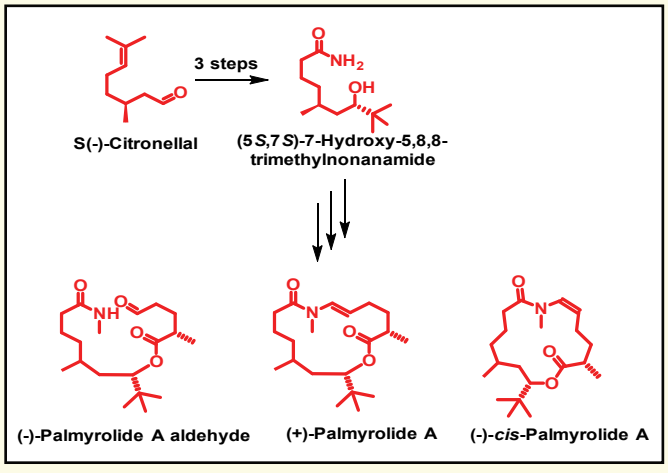


4-amino-6-(2'-amino-4'-hydroxyphenyl)-3-hydroxy-2-methyl-6-oxohexanoic acid (AHMOA)

Highlights:
- macrocyclic core synthesis
- key fragment AHMOA synthesis

Synthesis of palmyrolide A and its cis-Isomer, potential voltage-gated sodium channel blocker

Palmyrolide A, a neuroactive macrolide was isolated from the marine organism by Gerwick and co workers in 2010. Based on findings from initial *in vitro* biological screening, palmyrolide A and their analogues qualify for further biological evaluation as they may function as voltage-gated sodium channel (VGSC) blockers. The interesting biological profile along with its two rare structural units as the tertiary butyl group adjacent to lactone moiety and *trans-N*-methyl-enamide motif, make this compound as an attractive target for synthetic chemists. The total synthesis of (-)-palmyrolide A aldehyde and (+)-palmyrolide A and (-)-*cis*-palmyrolide A was accomplished using chiral pool approach, Zhu's oxidative homologation of an aldehyde to primary amide, access to (–)-*cis*-palmyrolide A, and the protecting group-free total synthesis. Calculations with DFT (with the help of Dr. Vanka Kumar) have provided insight into the *trans-cis* conversion process and corroborated experimental findings.

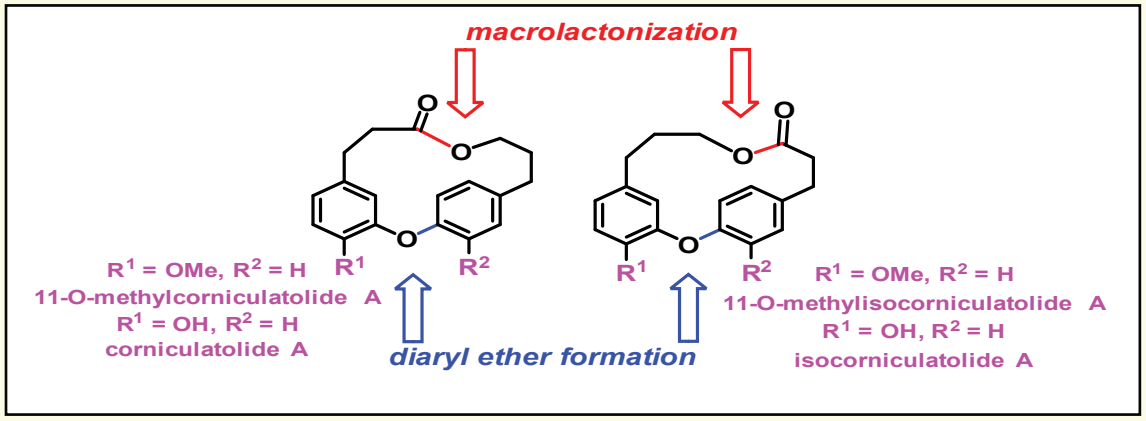


Research & Development Reports

Total synthesis of biologically active compounds and medicinal chemistry

Synthesis of isomeric corniculatolides

Synthesis of three natural macrolides 11-*O*-methylcorniculatolide A, 11-*O*-methylisocorniculatolide and isocorniculatolide A were reported using simple, straight forward and high-yielding route. The present synthesis confirms the assigned molecular structures and provided an access to sufficient quantities of natural products for the biological evaluation. In addition, it has determined the anti-TB potential of the three natural compounds using Alamar-blue assay (H_37R_v) and found no significant inhibitory activity at 100g/ml. Excellent yield, short sequence, and useful SAR information are the highlights of this work.



Medicinal chemistry: Silicon-switch approach

Significant progress on "Silicon-switch approach" was made in the medicinal chemistry front. The strategic replacement of carbon with silicon within marketed drugs or pre-validated drug scaffolds provided an exciting approach to search for new chemical entities (NCEs) in drug discovery. This approach can be cost-effective and of minimum risk because the corresponding carbon analogues (starting points) are known drugs or drug-like compounds with proved pharmacology/toxicity profiles. Another highlight of this approach is in the anti-infective area, where research group could possibly address the problem of drug resistance through introduction of silicon-based drugs.

Research & Development Reports

Asymmetric synthesis of bioactive molecules and synthetic methodologies

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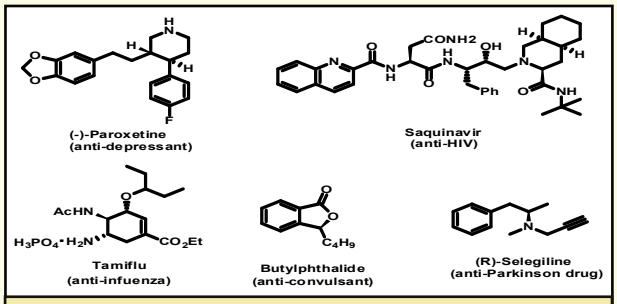
Publications: Org. Biomol. Chem., 2012, 10, 3655, 3988; 2013, 11, 1280, 3608; Tetrahedron Asymmetr., 2012, 23, 240, 898, 1534; Tetrahedron Lett., 2012, 53, 148, 3213, 4195; 2013, 54, 2679; RSC Adv. 2013, 3,1695

The research included development of new synthetic methodologies using organocatalysis and transition metal catalysis, newer synthetic methods for C-C and C-N bond formations and their application in multi-step asymmetric synthesis of pharmaceuticals, large number of bioactive natural products from readily available non-chiral sources and metal-free processes for key organic transformations.

Asymmetric synthesis of pharmaceuticals and bioactive molecules

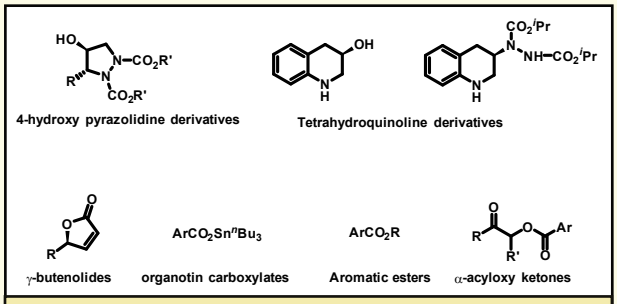
New methods for synthesis of optically active drugs were developed. Drugs such as Tamiflu (anti-influenza), Amprenavir and Saquinavir (anti-HIV), Paroxetine (anti-depressant), (*R*)-Selegiline (anti-Parkinson), Benzphetamine (anerotic drug), Butylphthalide (anti-convulsant drug) and a large number of bioactive natural products such as Stagonolid C (phytotoxic nonenolide), (-) Aspinolide A, Ro 67-8867 (NMDA receptor antagonist), (+)-Elanolide (attractant pheromone), (+)-Deoxoprosophylline (glycosidase inhibitory), Demethyl pestaphthalide, first synthesis of Matteucen C (relieving ostalgia), (–)-Sumanirole (anti-Parkinson), (*S*)-903 (inotropic agent).



Compounds synthesized

Synthetic methodologies involving organocatalysis

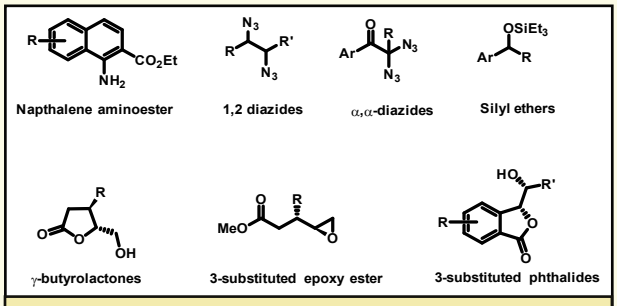
It involved asymmetric synthesis of biologically active molecules using organocatalysts, novel synthetic methods were developed using proline as catalyst for the synthesis of bioactive 4-hydroxy pyrazolidine derivatives through α-amination/Corey-Chaykovsky reaction of aldehydes, γ-butenolides *via* α-aminoxylation and *cis* wittig olefination of aldehydes, tetrahydroquinoline derivatives by α-aminoxylation or amination/ reductive cyclization method. N-heterocyclic carbenes (organocatalyst) were used for oxidative stannylation and esterification of aromatic aldehydes and for regioselective oxo-acyloxylation of alkenes to give α,α acyloxyketones and esters under aerobic condition.



Key organic frameworks synthesized under transition metal catalysis

Synthetic methodologies involving transition metal catalysis

A simple methodology was developed that affords substituted naphthalene amino esters, important building blocks for the synthesis of pharmaceuticals and polycyclic aromatic electronic materials *via* CuCN-promoted cyclization in high yields. Also, it was reported that Pd salts were highly effective catalysts in the presence of triethylsilane as hydride source for selective hydrosilylation of aryl ketones and aldehydes. A flexible, novel single-step method that employs Co-catalyzed HKR to produce substituted γ-butyrolactones and epoxy esters in high optical purities was developed. Additionally, demonstration of a highly practical, novel CN-assisted oxidative cyclization method was done for the synthesis of a wide variety of 3-substituted phthalides. A simple procedure with $NaIO_4$–NaN_3 as a new combination for the 1,2-diazidation of alkenes and α,α-diazidation of aryl ketones, that provides direct and efficient entry to vicinal 1,2-diazidoalkanes and geminal 1,1-diazidoarylketones was reported.



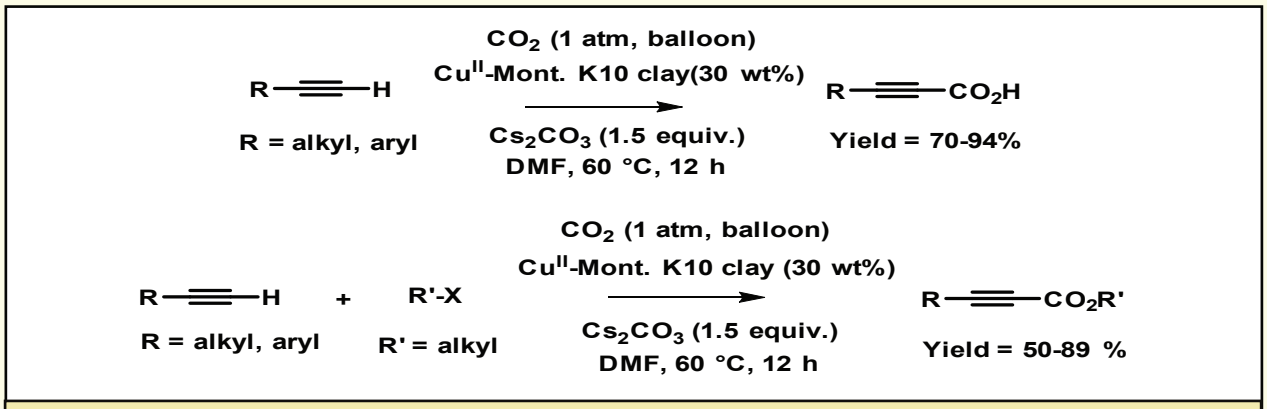
Key organic compounds synthesized using organocatalysis

Research & Development Reports

Asymmetric synthesis of bioactive molecules and synthetic methodologies

Carboxylation of terminal alkynes with carbon dioxide under heterogeneous catalysis

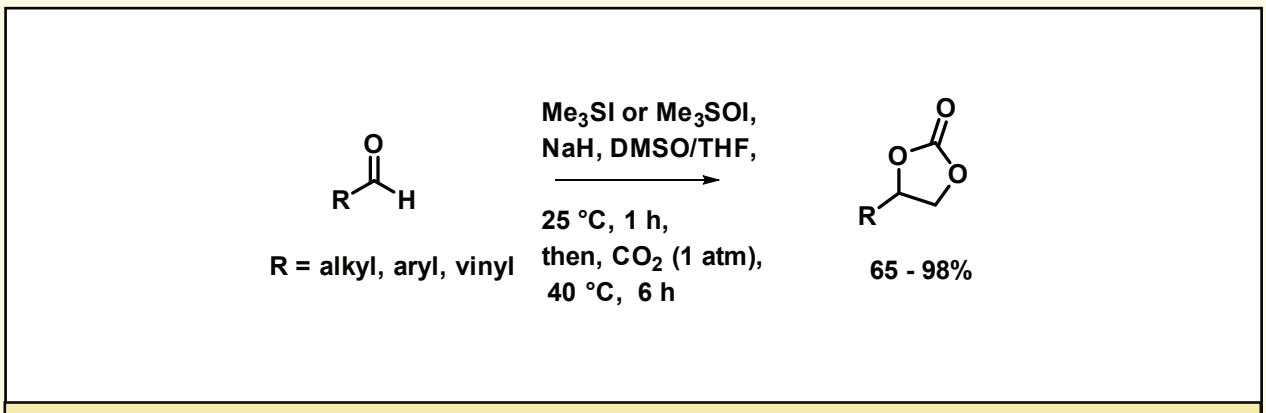
A new protocol for direct carboxylation of terminal alkynes was developed using reusable Cu^{II}-Mont. K10 clay as heterogeneous catalyst and CO_2 as the C1 carbon feedstock (Scheme 1). And also coupling of terminal alkynes with CO_2 (1 atm) in the presence of alkyl halides was achieved under the same reaction conditions, thereby providing access to a variety of functionalized alkyl-2-alkylnoates in high yields.



Scheme 1: Direct carboxylation of terminal alkynes with carbon dioxide

Metal-free one-pot synthesis of cyclic carbonates from aldehydes

An elegant one-pot synthetic method was developed for the preparation of cyclic carbonates in high yields involving reaction of aldehyde with sulphur ylides, followed by CO_2 insertion (Scheme 2). The salient features of the methodology are as follows: (1) inexpensive starting materials, (2) metal-free synthesis, (3) no costly reagents or complex co-catalyst needed, (4) water soluble NaI (by-product) acts as promoter, (5) utilization of CO_2 (1 atm) under ambient reaction conditions at 40°C, and (6) functional group tolerance, and high yields of cyclic carbonates.



Scheme 2: Synthesis of cyclic carbonates from aldehydes and CO_2

Research & Development Reports

Open source drug discovery and outreach programs

The objective of OSDD was to develop an open platform for researchers across the globe to contribute to the cause of fighting against neglected diseases. TB is a disease which is a major threat for the developing and the tropical countries and has been a neglected target in the majority of the Pharmaceutical Industries. The first disease target taken up by OSDD was Tuberculosis (TB). Apart from the lack of any new drugs (for almost the last 40 years), the recent emergence of MDR TB has posed even more challenges. It was aimed to develope new drug candidates for certain diseases like TB in the OSDD platform.

Efforts were made to contribute for the synthesis of small molecules for screening, and for the in-silico modeling for further modulation of the identified hits. Along with this, it has developed a platform for the science students to contribute to the cause of OSDD from their under-graduate phase onwards by participating in the outreach program for synthesis of small molecules.

A diverse array of small molecules comprising of natural products, their analogues, novel heterocyclic scaffolds, derivatives of steroids and carbohydrate analogues were synthesized across the 12 groups (470 compounds) and were screened against the growth of *M. Smegmatis.* The initial screening led to the identification of a good number of initial hits which was sent for further screening against H_37R_v.

OSDD outreach program

It was aimed to attract the young talent to participate in the open source drug discovery program. As part of this training program, the selected students were exposed to the advancements in the scientific research and were informed how to carry out the modern synthetic reactions that they study in their courses to get encouraged to pursue their career in research.

The first batch of the OSDD Outreach Program started from the May 1, 2012. Twelve students who were pursuing B.Sc/M.Sc integrated participated in this program. These students were trained in the selected research groups of CSIR-NCL to carry out the synthesis of small-molecule libraries using simple and easy-to-do reactions in 2-3 steps. Each student or a group of students made a few compounds and learned how to carry out the purification of the compounds by chromatography and also take the NMR, mass spectra, etc. and characterize them. These compounds were screened for anti-tuberculosis activity at CSIR-IICT. A certificate of appreciation was issued to each student.

Having successfully conducted the first Outreach Program over a period of two months, the next program was planned for a period of four–six months for students of M. Sc or M. Pharm during December 2012 to April, 2013. Four students were participated during this session.

Research & Development Reports