# Details of Research Work by the Applicant

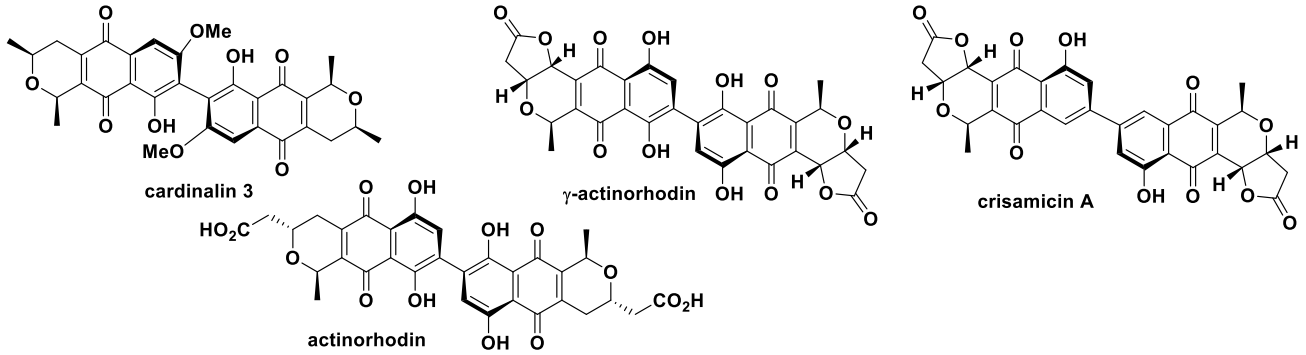
## (Dr. Rodney A. Fernandes)

The Applicant has made significant contributions in three major areas of organic synthesis:

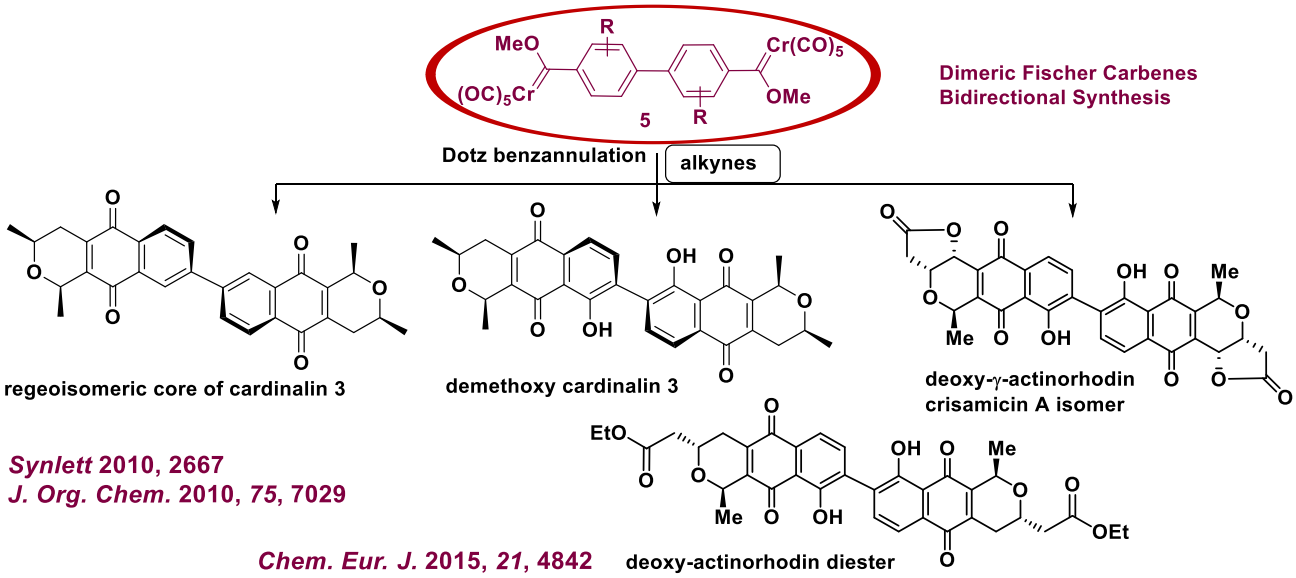
1] Total Synthesis, 2] Drugs and Analogues Synthesis, and 2] New Method Development.

## 1] Total Synthesis

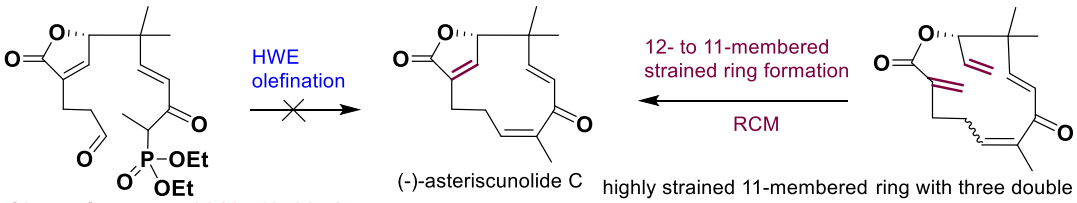
**A]** Total synthesis of several natural products by designing unique strategies have been achieved by the Applicant. The total synthesis of complex natural products like actinorhodins, crisamicin A and cardinalins has been executed. The synthetic strategies have been elegantly designed based on Dötz benzannulation of dimeric Fischer carbenes with requisite chiral alkynes (***Chem. Eur. J.* 2015,** *21*, 4842, ***Synlett* 2010**, 2667, ***J. Org. Chem.* 2010**, *75*, 7029, ***Eur. J. Org. Chem.* 2016**, 5778).




This work has led to the total synthesis of regioisomeric core structure of cardinalin 3 and demethoxy cardinalin 3. The bidirectional Dötz benzannulation of dimeric Fischer carbenes **5** was extended to the synthesis of deoxy-actinorhodin diester and deoxy-γ-actinorhodin. The latter is iso-crisamicin A.

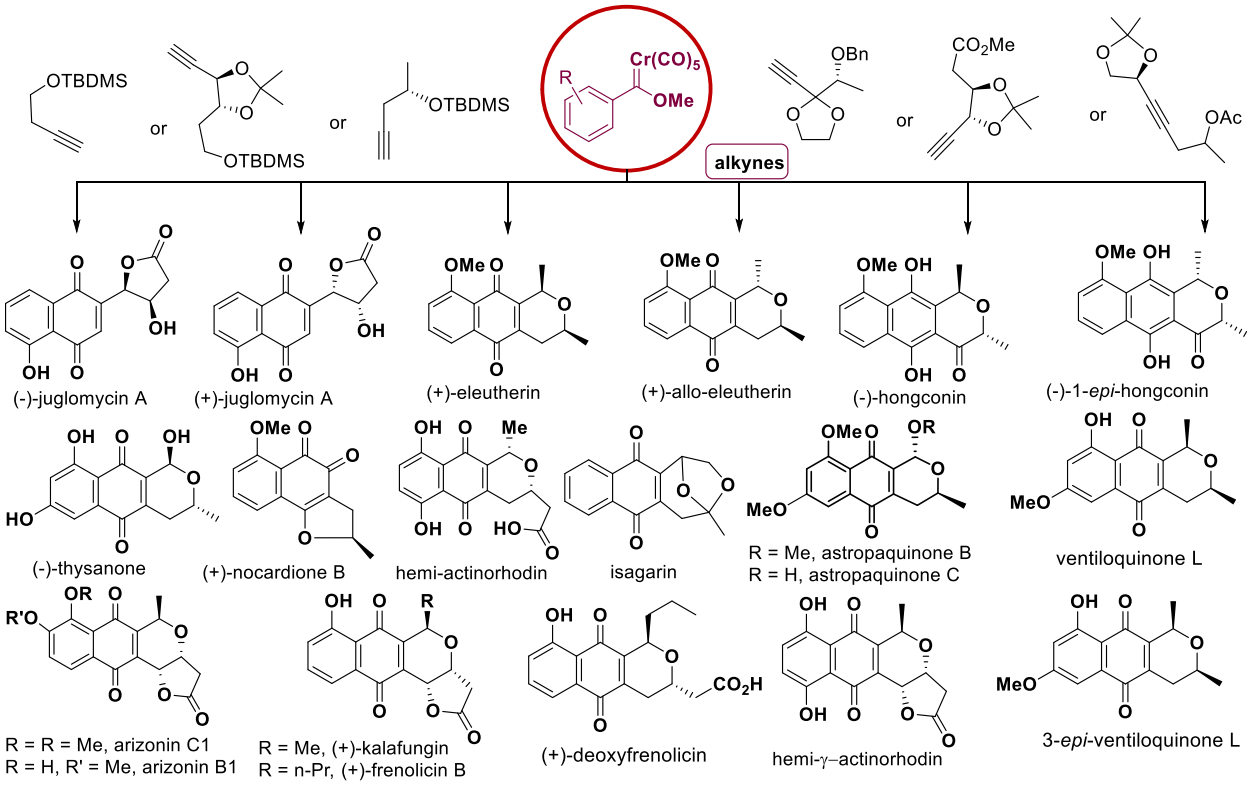



The first stereoselective total synthesis of strained 11-membered astericunolide C (anticancer) was achieved with a unique ring-contracting strategy from a 12-membered to strained 11-membered ring based on ring-closing metathesis (***Chem. Commun.* 2013**, *49*, 3354).

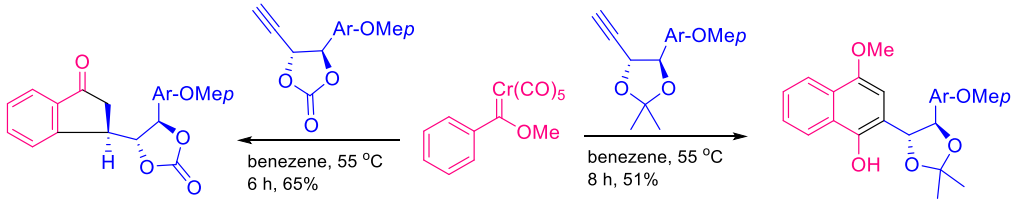



*Chem. Commun.* **2013**, *49*, 3354

The total synthesis of other natural products like various pyranonaphthoquinones has been achieved based on Dötz benzannulation of Fischer carbenes as shown below (***Eur. J. Org. Chem.*** **2015**, 4931, ***Asian J. Org. Chem.*** **2015**, *4*, 560, ***Synthesis*** **2014**, *46*, 1836, ***Tetrahedron: Asymmetry*** **2013**, *24*, 1281, ***Tetrahedron: Asymmetry*** **2013**, *24*, 1548, ***Org. Biomol. Chem.*** **2012**, *10*, 4462, ***J. Org. Chem.*** **2012**, *77*, 10455, ***Eur. J. Org. Chem.*** **2011**, 6624, ***Tetrahedron: Asymmetry*** **2011**, *22*, 1312, ***Tetrahedron: Asymmetry*** **2011**, *22*, 487, ***Eur. J. Org. Chem.*** **2010**, 4306).



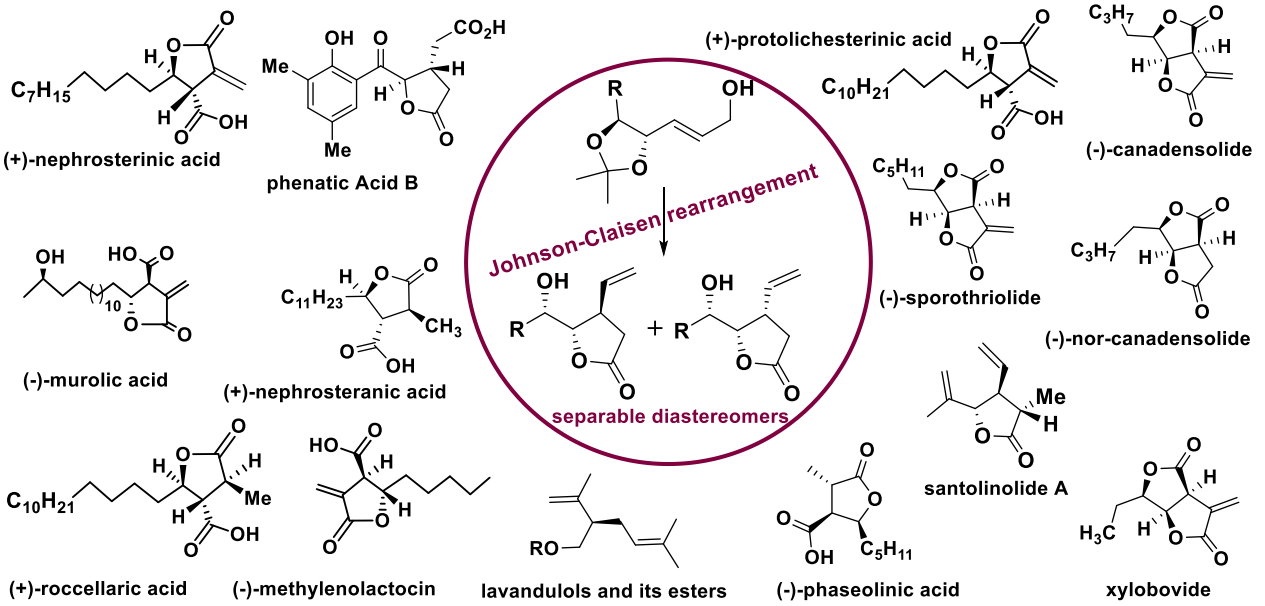

The Fischer carbene-based pentannulation has also been developed (***Org. Lett.*** **2020,** *22*, 3438).



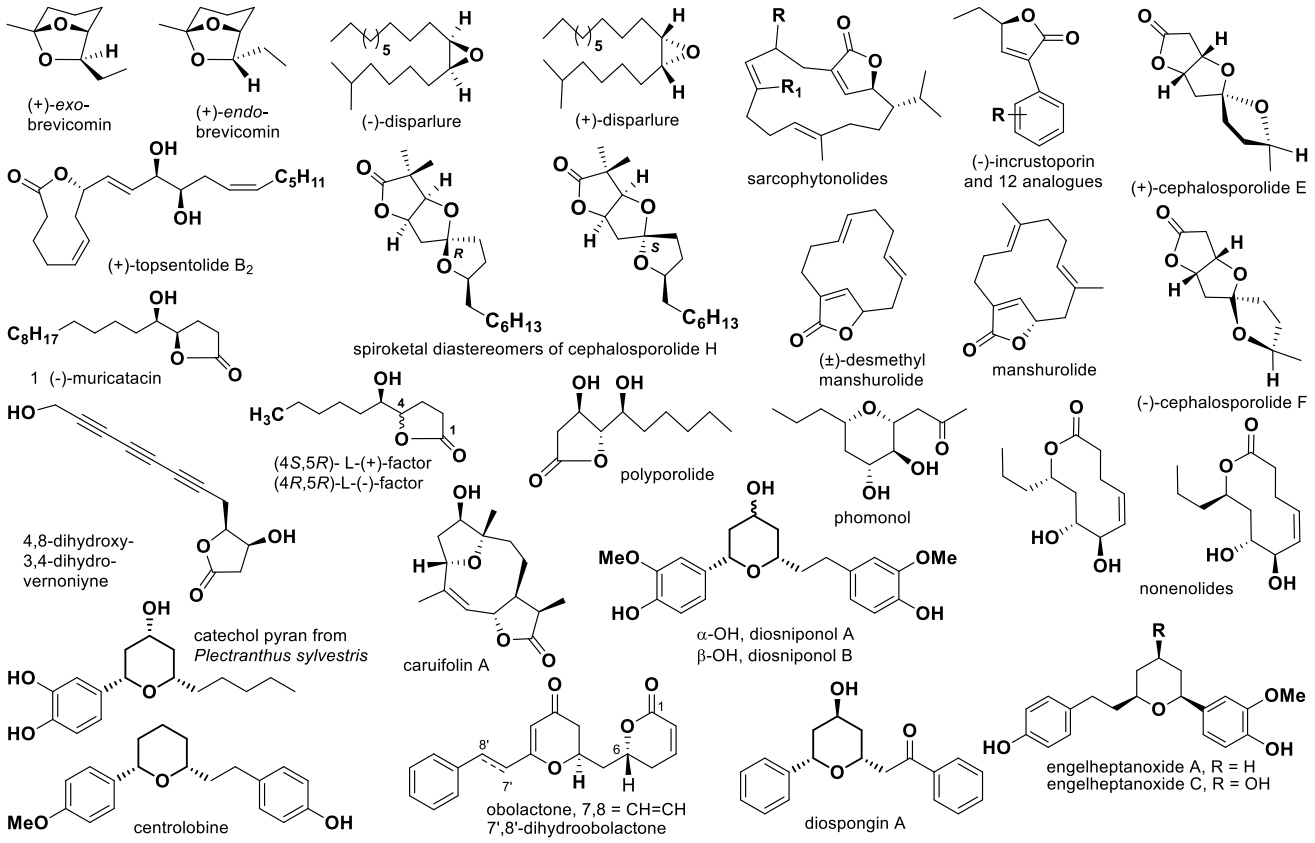

**Cyclopentannulation vs Dötz benzannulation, Synthesis of 3-substituted indanones**
**Orthogonal reactivity of acetonide vs carbonate/acyloxy-based alkynes**

***Org. Lett.*** **2020,** *22*, 3438

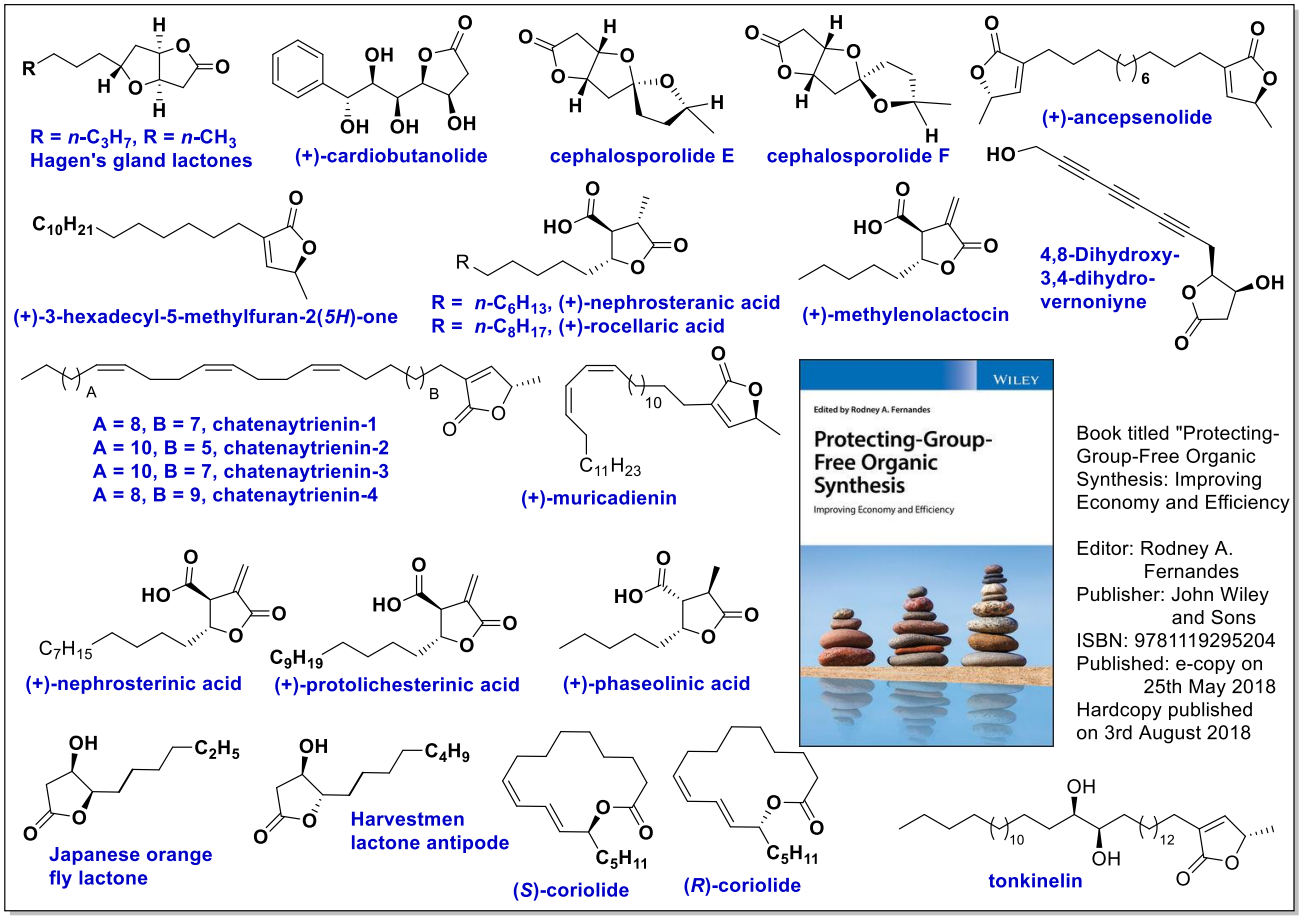
The total synthesis of phenatic acids, various paraconic acids and related natural products has been achieved based on ortho-ester Johnson-Claisen rearrangement strategy (***Eur. J. Org. Chem.*** **2014**, 237, ***Eur. J. Org. Chem.*** **2014**, 2833, ***Eur. J. Org. Chem.*** **2013**, 5165, ***Eur. J. Org. Chem.*** **2012**, 1047, ***Tetrahedron: Asymmetry*** **2012**, *23*, 60, ***Tetrahedron: Asymmetry*** **2011**, *22*, 1114, ***Eur. J. Org. Chem.*** **2011**, 1106, ***Tetrahedron: Asymmetry*** **2009**, 20, 2835, ***J. Org. Chem.*** **2009**, *74*, 8826).




Synthesis of many other natural products as shown below has also been achieved by developing efficient and short strategies (***Org. Lett.* 2019**, *21*, 5827, ***J. Org. Chem.* 2019**, *84*, 3537, ***Tetrahedron* 2021, 96, 132375**, ***Eur. J. Org. Chem.* 2020**, 6909, ***Eur. J. Org. Chem.* 2020**, 6922, ***Asian J. Org. Chem.* 2016**, *5*, 839, ***Tetrahedron Lett.* 2016**, *57*, 3694, ***Tetrahedron: Asymmetry* 2016**, *27*, 114, ***RSC Advances* 2015**, *5*, 49189, ***RSC Advances* 2014**, *4*, 63342, ***Eur. J. Org. Chem.* 2014**, 3249, ***RSC Advances* 2014**, *4*, 14507, ***Asian. J. Org. Chem.* 2014**, *3*, 58, ***Asian J. Org. Chem.* 2013**, *2*, 74, ***Tetrahedron: Asymmetry* 2011** *22*, 1930, ***Tetrahedron Lett.* 2011**, *52*, 1788, ***Tetrahedron Lett.* 2011**, *52*, 458).



**B]** An ideal synthesis demands no use of protecting groups, enabling shorter synthesis and overall economy. Keeping this in mind, many of the earlier synthesis involving lengthy sequences have been shortened based on efficient protecting-group-free (PGF) based synthetic strategies. The research work based on **"Protecting-Group-Free"** strategies has been commendable for total synthesis of Hagen's gland lactones, cardiobutanolide, cephalosporolides, muricadienin, ancepsenolide and several paraconic acids, dihydroxy-dihydrovernoniyne, chatenaytrienins, tonkinelins, harvestmen lactones, etc (***Asian J. Org. Chem.*** **2013**, *2*, 74 ***featured article*****, *J. Org. Chem.*** **2012**, *77*, 9357, ***RSC Advances*** **2015**, *5*, 42131, ***Org. Biomol. Chem.*** **2016**, *14*, 9072, ***Org. Biomol. Chem.*** **2017**, *15*, 708), ***J. Org. Chem.*** **2019**, *84,* 14127, ***J. Org. Chem.*** **2019**, *84*, 12216, ***J. Nat. Prod.*** **2021**, *84*, 120). A full book has been edited by me on "Protecting-Group-Free Organic Synthesis: Improving Economy and Efficiency, John Wiley & Sons, 2018.




For a few of them process patents have been granted.

1] A Process for Preparation of Cephalosporolides E and F. **Patent Granted No. 327987**. Indian process patent application No. 2595/MUM/2015. Rodney A. Fernandes*, Dipali A. Chaudhari and Pullaiah Kattanguru.

2] A Novel Process for the Four-Step Protecting Group Free Synthesis of (+)-Hagen's Gland Lactones. **Patent Granted No. 292674.** Indian process patent application filed, No. 1908/MUM/2012. Rodney A. Fernandes* and Pullaiah Kattanguru.

3] Process for the Three Step Synthesis of (+)-Cardiobutanolide from D-Glucono-δ-lactone. **Patent Granted No. 285997.** Indian process patent application filed, No. 1780/MUM/2012. Rodney A. Fernandes* and Pullaiah Kattanguru.

## 2] Drugs and Analogues Synthesis and Bioactivity Study

Organic Synthesis enables drug synthesis, development and medicinal synthesis. Several drug molecules and analogs have been uniquely synthesized by the Applicant's research group (***Chem. Commun.* 2019, *55*, 2313**). Many of them have been tested for bioactivity like anti-bacterial and anti-tuberculosis (Unpublished results).

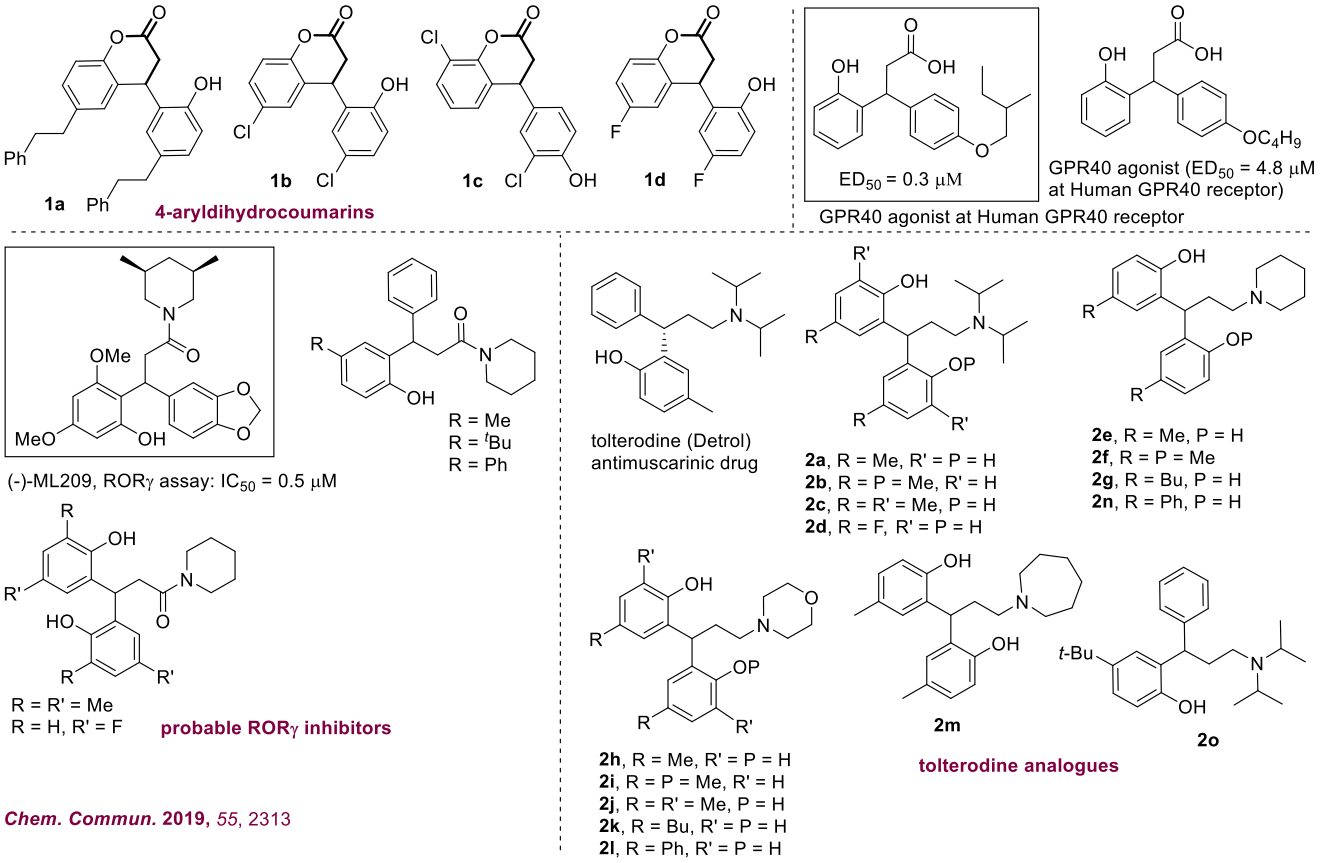



**Table 1.** Antibacterial studies of selected 4-aryldihydrocoumarins **1a-d** and tolterodine analogues (Unpublished results).

| **Compound** **4-Aryldihydrocoumarins and Tolterodine analogues** | **MIC (μg/mL)** | | | | |
|---|---|---|---|---|---|
| | ***E. coli*** **ATCC 25922** | ***S. aureus*** **ATCC 29213** | ***K. pneumoniae*** **BAA 1705** | ***A. baumannii*** **BAA 1605** | ***P.aeruginosa*** **ATCC 27853** |
| **1a** | >64 | 2 | >64 | >64 | >64 |
| **1b** | >64 | 16 | >64 | >64 | >64 |
| **1c, 1d** | >64 | 32 | >64 | >64 | >64 |
| Levofloxacin | 0.015 | 0.125 | 64 | 8 | 0.5 |
| | | | | | |
| **2a, 2b, 2d, 2e, 2g, 2h, 2i** | >64 | >64 | >64 | >64 | >64 |
| **2l** | >64 | 2 | >64 | >64 | >64 |
| **2n** | >64 | 1 | >64 | >64 | >64 |

We have synthesized several 2,6-disubstituted and 2,4,6-trisubstituted pyran natural products like centrolobine, engelheptanoxides A and C, diospongins and various analogues as shown below. These molecules were tested for antituberculosis activity (***Tetrahedron* 2020, *96*, 132375**).

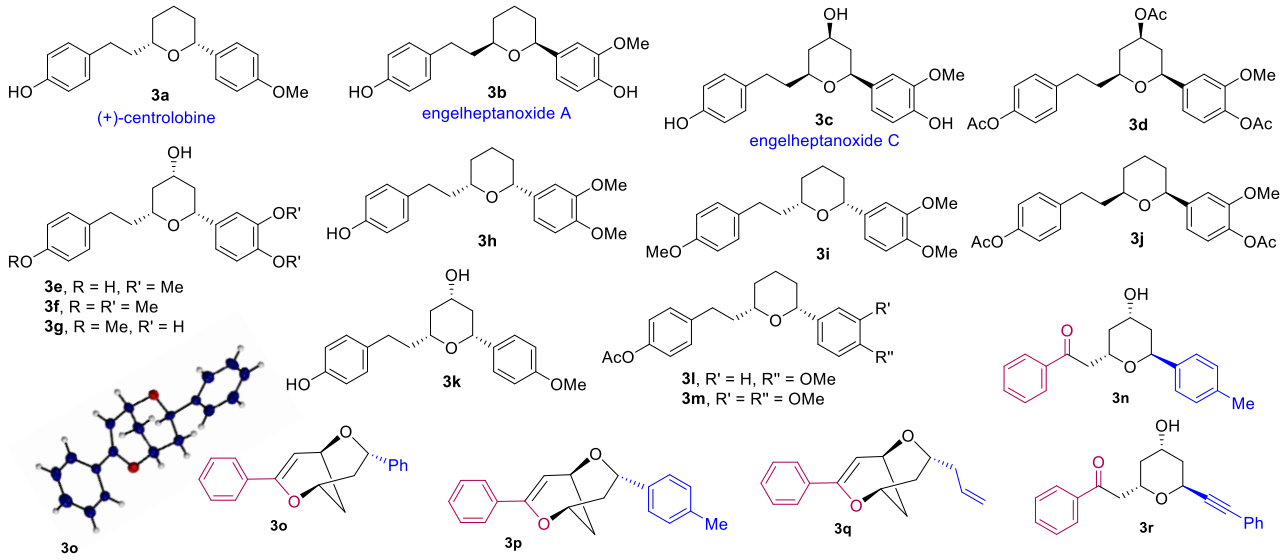
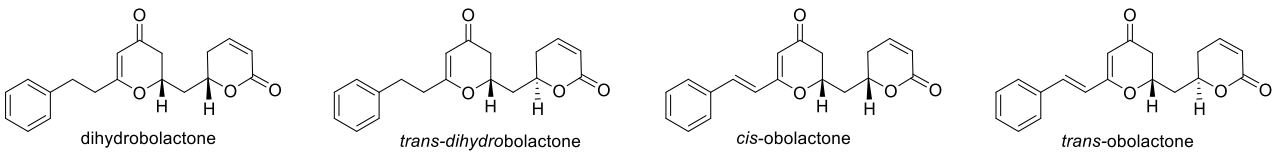



**Table 2:** Antitubercular activities of **1**-**3** and their analogues and acetate derivatives against *M. tuberculosis* $H_{37}Rv$ ATCC 27294

| Compounds | MICs reported | MICs (μg/mL) |
|---|---|---|
| **3a, (+)-centrolobine** | - | >64 |
| **3b, (-)-engelheptanoxide A** | 168.6 μM or 55.4 μg/mL | 32 |
| **3c, (-)-engelheptanoxide C** | ≥581.4 μM or ≥200.2 μg/mL | >64 |
| **3d** | - | 64 |
| **3e** | - | >64 |
| **3f** | - | >64 |
| **3g** | - | >64 |
| **3h** | - | 64 |
| **3i** | - | 32 |
| **3j** | - | 64 |
| **3k** | - | >64 |
| **3l** | - | 32 |
| **3m** | - | 16 |
| **3n** | - | 64 |
| **3o** | - | 64 |
| **3p** | - | 32 |
| **3q** | - | 32 |
| **3r** | - | 64 |
| Ethambutol (positive control) | - | 1 |

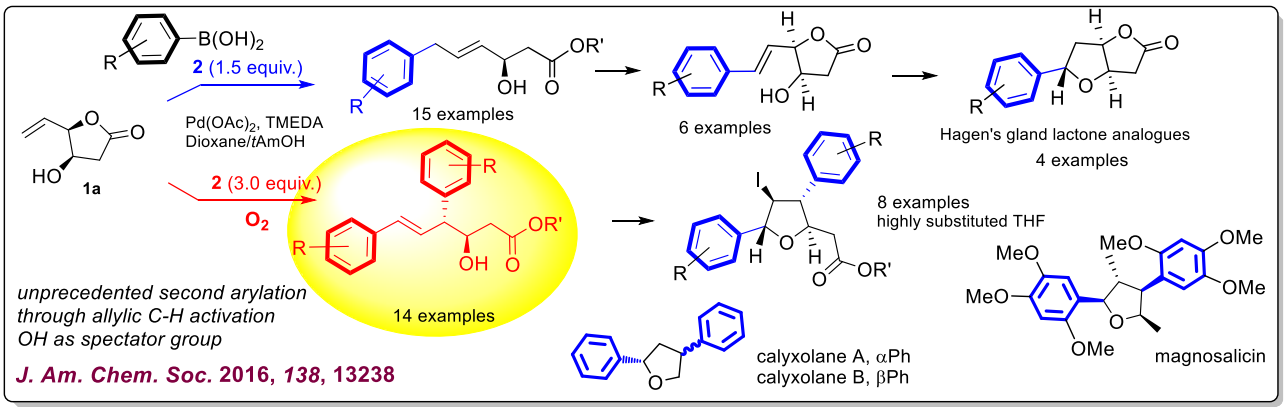
Several more natural products like obolactones, dihydroobolactones and 4-aryldihydrocoumarins and analoges are in development for bioactivity studies. Similarly, structure activity studies are ongoing for 4-arylcoumarins, acetogenins, lactone natural products and analogues.



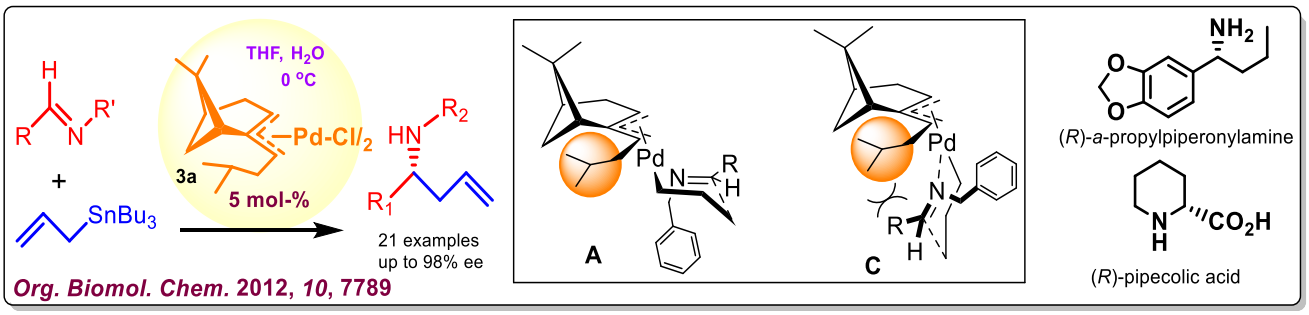

We have also initiated in collaboration with a Russian institute and CDRI Lucknow the development of anticancer compounds based on bioactive acetogenins and related molecules.

## 3] New Method Development in Organic Synthesis

**A]** The Applicant has worked in the area of asymmetric synthesis and metal-catalysis. He has explored an unprecedented double arylation through π-allylpalladium formation by synergistic Pd(II) and Pd(0) dual-catalysis (***J. Am. Chem. Soc.* 2016**, *138*, 13238). The γ-vinyl-γ-lactone **1a** has been envisaged as allyl electrophile donor for allylic arylation *via* π-allylpalladium intermediate using 1.5 equiv. of aryl boronic acid **2**. Use of 3.0 equiv. of the latter resulted in monoarylation by allylic substitution and subsequent site-selective second arylation by directed allylic C-H activation giving stereoselectively *anti*-γ-(aryl,styryl)-β-hydroxy acids. Presence of $O_2$ was crucial for the second arylation via Pd(II) catalysis. The unique feature of this work is the opening of lactone **1a** for first arylation is atom-economic as the leaving acyl group is part of the molecule. Secondly the unprecedented second arylation with untouched OH group with defined stereochemistry adds to the functionality in the product. This methodology has been elaborated to synthesize highly substituted THFs including aryl-Hagen's gland lactone analogs via intramolecular iodoetherification of the OH group and pendant olefin bond.

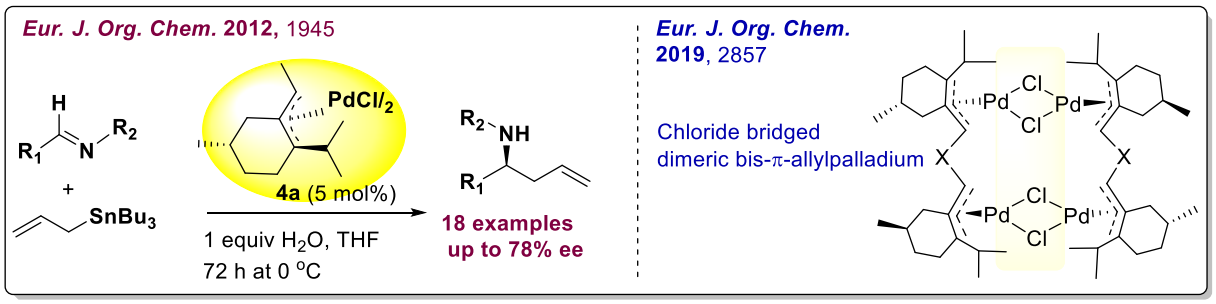



The pinane and menthane skeletons have been exploited for development of π-allylpalladium catalysis. The newly developed π-allylpalladium catalyst with (–)-*β*-pinene framework **3a** with isobutyl side chain catalyzed the enantioselective allylation of imines in good yields and enantioselectivities (21 examples, up to 98% ee). The isobutyl group rendered steric crowding for complexation of imine from the front side as in model **A** exhibiting higher enantioselectivities. An efficient enantioselective synthesis of (*R*)-α-propyl piperonylamine part of DMP 777, a human leukocyte elastase inhibitor and the α-amino acid (*R*)-pipecolic acid have been achieved as a useful application of this methodology (***Org. Biomol. Chem.* 2012**, *10*, 7789).

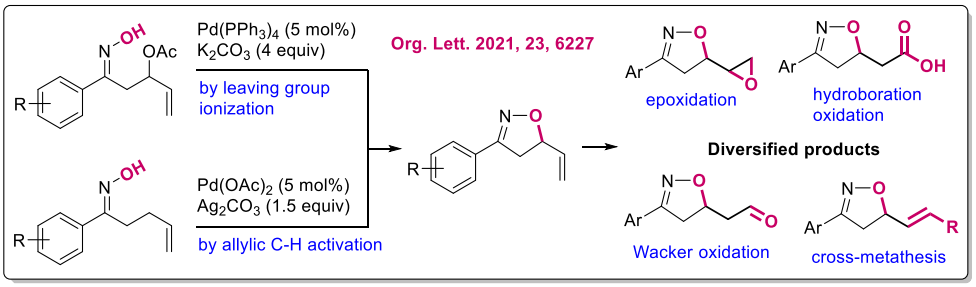



The menthane skeleton has been widely used as chiral auxiliary in organic synthesis. We have for the first time explored the menthane moiety for similar chiral induction by synthesizing the menthane based π-allylpalladium catalyst **4a**. This could catalyze the enantioselective allylation of imines in good

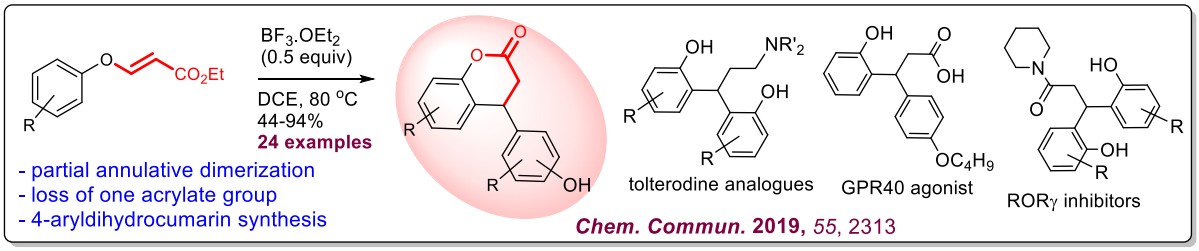
yields and enantioselectivities (18 examples, up to 78% ee, ***Eur. J. Org. Chem.* 2012**, 1945). Menthane based dimeric π-allylpalladium catalyst have also been developed (***Eur. J. Org. Chem*. 2019**, 2857).



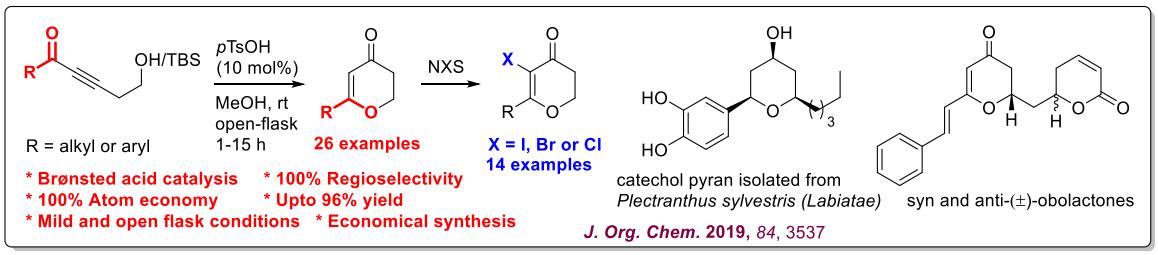

**B]** The Applicant has developed the efficient method for the synthesis of 5-vinyl-2-isoxazolines via two different strategies based on Pd-catalysis (***Org. Lett.* 2021**, 23, 6227). Both the methods converge to the electrophilic π-allylpalladium formed either by leaving group ionization or the more efficient allylic C-H activation. This is then attacked intramolecularly by the suitably placed oxygen nucleophile of the ketoxime giving efficiently the 5-vinyl-2-isoxazolines. Various other useful compounds were synthesized from the latter using the olefin or imine handles by functional group addition. The acid obtained is an analogous intermediate for roxifiban and ISO-I drug molecules.



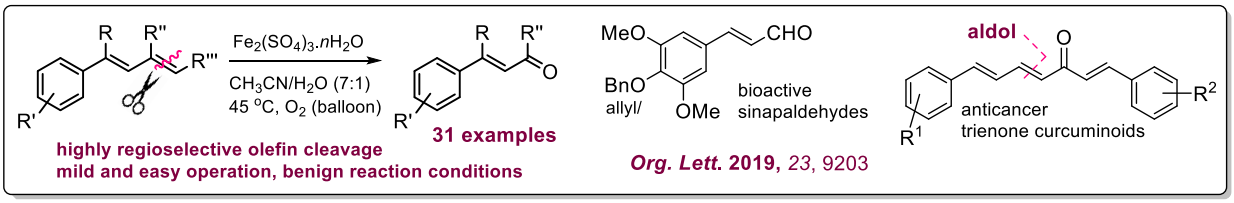

The Lewis acid catalysis has been explored in a beguiling annulative partial dimerization/ rearrangement of 3-aryloxyacrylates to 4-arylchroman-2-ones (4-aryldihydrocoumarins), which are important structural motifs in many natural products (***Chem. Commun*. 2019**, *55*, 2313). The reaction occurs through C3–O aryloxy bond cleavage, electrophilic aromatic substitution, O–C aryl-migration and lactonization. This method is important, as the addition of a phenol to an alkyl/aryl propiolate and one-step rearrangement provide 4-arylchroman-2-ones. The methodology has been elaborated to various analogues of the drug tolterodine, RORγ-inhibitors and a GPR40 agonist.

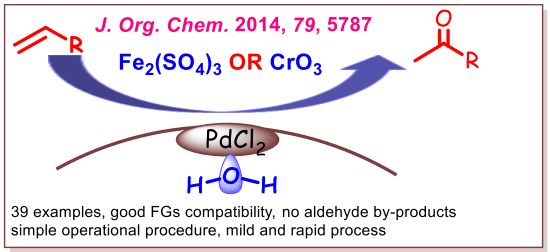


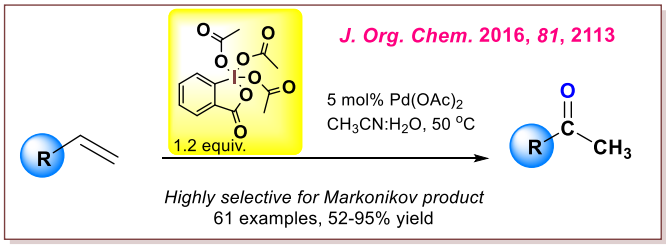

Similarly, the metal-free and cost-effective *p*TsOH-catalyzed intramolecular rearrangement of δ-hydroxyalkynones to substituted 2,3-dihydro-4*H*-pyran-4-ones has been developed (***J. Org. Chem*. 2019**, 84, 3537). The scope has been illustrated by synthesizing several mono- and disubstituted-2,3-dihydro-4*H*-pyran-4-ones in up to 96% yield with 100% atom economy. A regioselective and chemoselective vinylic halogenation has also been achieved on the synthesized dihydropyranones. Further application of this rearrangement in the total synthesis of *syn*/*anti*-(±)-obolactones and a catechol pyran isolated from *Plectranthus sylvestris* (*Labiatae*) has been demonstrated.

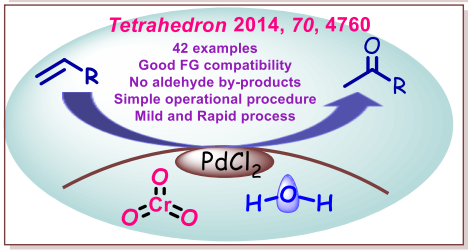


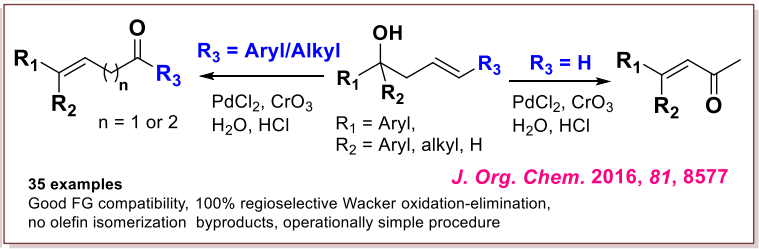

**C]** The new methods development by the nominee has resulted in new and useful organic reactions like oxidative cleavage of olefins (***Org. Lett.* 2019**, *21*, 9203), Wacker process and oxidation reactions (***J. Org. Chem.* 2016**, *81*, 8577, ***J. Org. Chem.* 2016**, *81*, 2113, ***J. Org. Chem.* 2014**, *79*, 5787, ***Tetrahedron* 2014**, *70*, 4760). These works have been abstracted in ChemInform 2016, vol. 47, issue 30, ChemInform 2014, vol. 45, issue 50. Highlighted in Organic Chemistry Portal, Highlights 2015, March 30 by Douglass F. Taber and Highlights 2016 by Reto Mueller. **A Process for Synthesis of Methyl Ketones by Wacker-Type Oxidation Reaction.** Patent granted No. 314743, dated 26/06/2019. Patent application No. 2965/MUM/2015. Selective new oxidation methods have also been developed. 1] An expedient method for chemoselective osmium(VI) catalyzed oxidation of benzylic, allylic and propargylic alcohols using $K_3Fe(CN)_6$ as a secondary oxidant was developed. 2] Similarly a tandem benzylic oxidative dihydroxylation of α-vinyl and α-alkenylbenzyl alcohols was also explored.

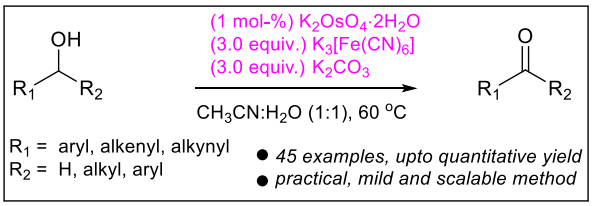


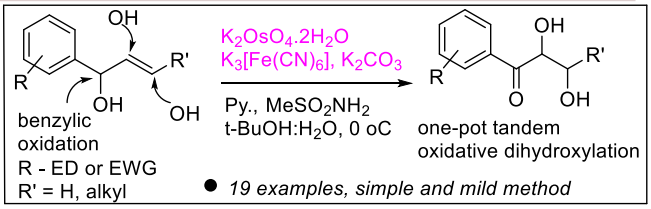



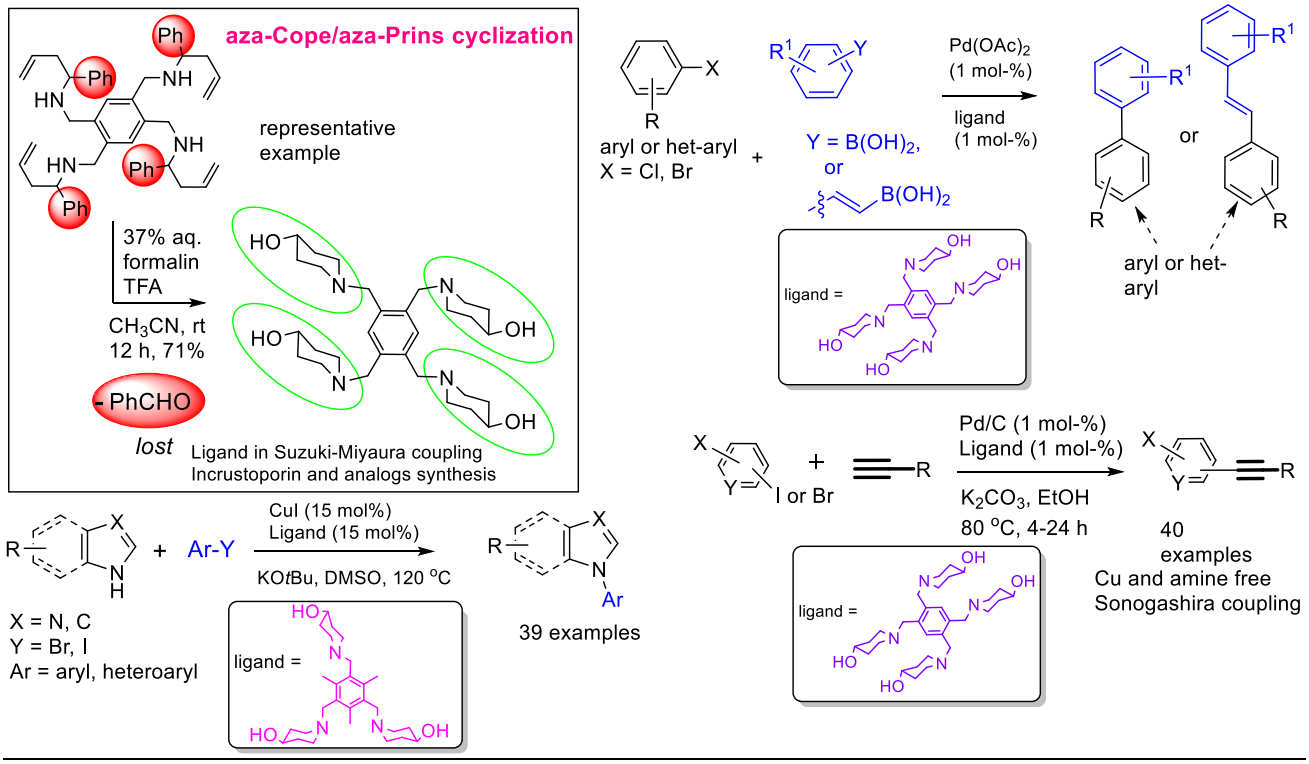




A new cascade reaction involving Aza-Cope/Aza-Prins cyclization leading to piperidine derivatives has been explored. The reaction works well on even four allyl groups on tetrabenzyl amine giving a crucifix type piperidine-4-ols (see figure). Some of these served as excellent ligands in Ulmann coupling, Sonogashira and Suzuki couplings (***Eur. J. Org. Chem.* 2015**, 2012, ***Asian J. Org. Chem.* 2015**, *4*, 552, ***Eur. J. Org. Chem.* 2015**, 3558, ***RSC Advances* 2015**, *5*, 54037).




## Summary:

The Applicant, Dr. Rodney A. Fernandes has worked extensively in asymmetric synthesis, catalysis, total synthesis and new synthetic methods development in the broad area of Synthetic Organic Chemistry. He has developed elegant synthetic routes based on Protecting-Group-Free strategies, as an approach towards "*ideal synthesis*". Many of the previous routes are shortened by avoiding protecting groups. The short processes developed have been granted patents. The total synthesis of challenging and complex natural products like actinorhodins, crisamicin A, cardinalins, asteriscunolides, paraconic acids, cephalosporolides, dihydrovernoniyne, chatenaytrienins, muridienins, etc is also commendable. The new oxidative methods like Wacker Process and development of asymmetric synthesis and catalysis based on π-allylpalladium chemistry, acid-catalysis, oxidative cleavage, pentannulation are also noteworthy. The research work has resulted in high-end publications like *J. Am. Chem. Soc.* **2016**, *138*, 13238, *Org. Lett.* **2021**, *23,* 6227, *Org. Lett.* **2020**, *22,* 3438, *Org. Lett.* **2019**, *21,* 9203, *Chem. Commun*. **2019**, *55*, 2313, *J. Org. Chem*. **2019**, *84*, 3537, *Org. Lett*. **2019**, *21*, 5827, *J. Org. Chem*. **2019**, *84*, 12216, *Chem. Eur. J.* **2015,** *21*, 4842, *J. Org. Chem.* **2012**, 77, 10455, *Chem. Commun.* **2013**, *49*, 3354, *J. Org. Chem.* **2012**, *77*, 9357, etc.

He has also edited a book titled "**Protecting-Group-Free Organic Synthesis: Improving Atom-Economy and Efficiency",** Publisher: John-Wiley & Sons, Editor: **Rodney A. Fernandes.**

**Total Publications = 137, Includes 8 Patents, 1 Book and 5 Book Chapters.**

Sincerely,

Rodney A. Fernandes

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