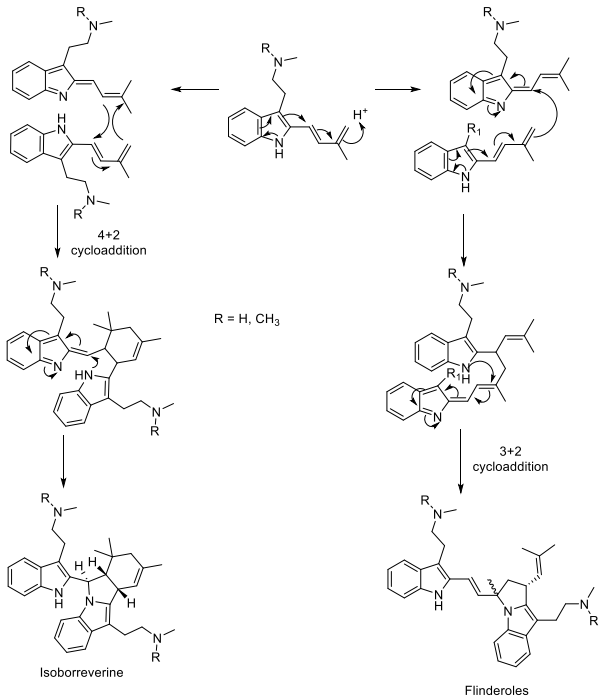
Details of the research work – Prof. Dattatraya Dethe, IIT Kanpur

Synthetic organic chemistry has several applications in a range of different sectors. The discovery and design of novel molecules offer great potential for cutting-edge technology to take over scientific research and industry. Synthetic organic chemistry as integration of total synthesis and chemistry gives rise to novel substances, natural products that can be modified, new therapies, novel methods of synthesis and analysis. Synthetic chemistry gives us the ability to mimic some of the most complex and intriguing compounds in nature and develop their variations in the laboratory using synthetic technologies and strategies. Prof. Dattatraya Dethe has made outstanding contributions in the field of "**total synthesis of bioactive complex natural products and their analogues**". His group has also developed novel reactions and methodologies for the Carbon-Carbon and Carbon-Hetero atom bond formations.

1. **Total Synthesis of Indole alkaloids and indoloterpenoid natural Products:**

   His research group has made outstanding contribution to the synthesis of indole alkaloids, antimalarial complex natural products flinderoles and borreverrines using a selective biomimetic [3+2] cycloaddition and Diels-Alder reaction. Switchable reaction patterns of dimerization of indole substituted butadienes via *Lewis* acid and thermal activation was developed by his group. While under acidic conditions dimerization occurred around the internal double bond of the dienophile, a complete switch of regioselectivity was observed under thermal conditions, where dimerization occurred around the terminal double bond of the dienophile. This switch of regioselectivity was further exploited for the divergent total synthesis of structurally diverse indole alkaloid natural products.

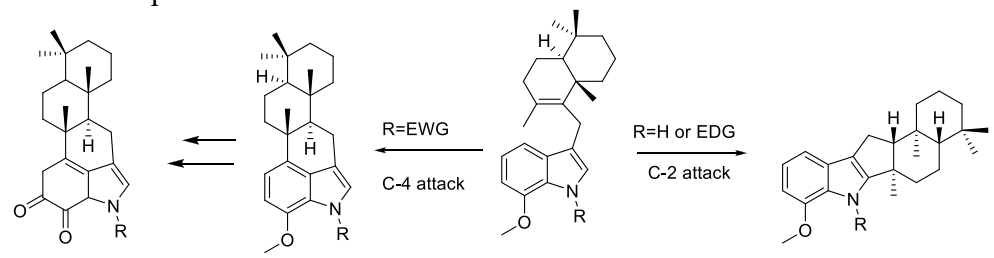
   Scheme 1: Photoswitchable dimerization of indole dienes and its application for the synthesis of indole alkaloids (*J. Am. Chem. Soc.* **2011**, *133*, 2864-2867, *J. Org. Chem.* **2015**, *78*, 10106, *Org. Lett.* **2014**, *16*, 2764−2767)



Their research group also developed an intramolecular Friedel−Crafts reaction at C-4 of the indole derivative driven by the EDG/EWG within a compound that was rationally designed to prevent the cyclization reaction at the C-2 positon of indole, The strategy was applied to total synthesis of two indoloterpene natural products (−)-mycoleptodiscin A and Petromindole starting from the enantiopure key intermediate, which was prepared by Friedel−Crafts reaction between 7-methoxyindole and chiral primary allylic alcohol. This intramolecular Friedel−Crafts reaction at C-4 of indole derivative developed by his group could be applied for the synthesis of many other C-4-substituted indole alkaloid natural products.

Scheme 2: Biomimetic total Synthesis of (−)-mycoleptodiscin A (*Org. Lett.* **2016**, *18*, 6392−6395)

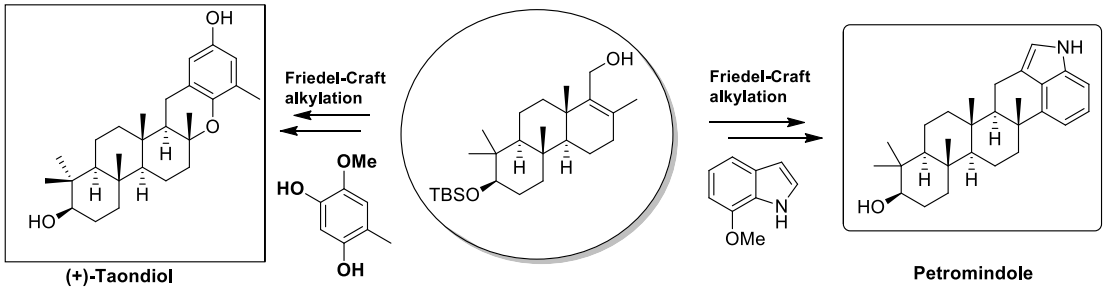
Biomimetic total synthesis of (−)-mycoleptodiscin A (1) was achieved starting from the enantiopure key intermediate, which was prepared by Friedel–Crafts reaction between 7-methoxyindole and chiral primary allylic alcohol. The crucial step in this synthesis was an intramolecular Friedel–Crafts reaction at C-4 of the indole derivative driven by the EDG/EWG within a compound that was rationally designed to prevent the cyclization reaction at the C-2 positon of indole, thereby successfully providing the complete carbon framework of 1. This intramolecular Friedel–Crafts reaction at C-4 of indole derivative could be applied for the synthesis of other C-4-substituted indole alkaloid natural products.



Mycoleptodiscin A

Org. Lett., 2016, 18, 6392–6395.

Scheme 3: Biomimetic first Enantioselective Total Synthesis of (−)-Petromindole (*Org. Lett.* **2018**, *20*, 3, 632-635)



(+)-Taondiol

Org. Lett. **2018**, *20*, 9, 2766-2769

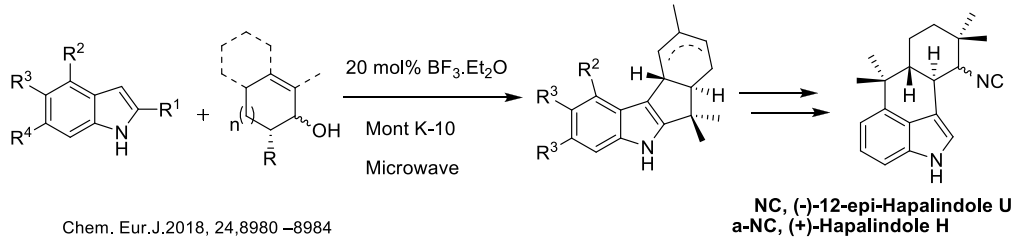
Petromindole

Org. Lett. **2018**, *20*, 3, 632-635

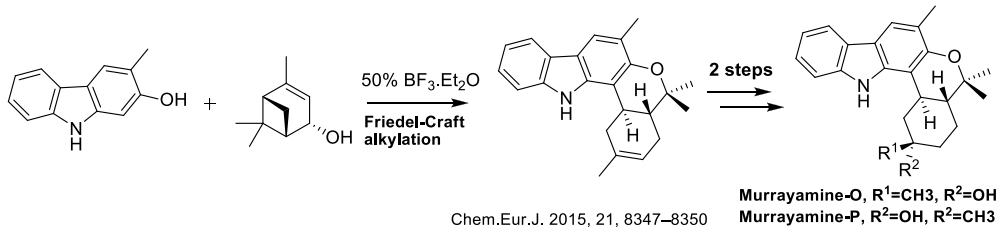
Hapalindoles and fischerindoles are members of a class of indole alkaloid natural products that have been isolated from the Stigonematales order of cyanobacteria. These compounds possess a polycyclic ring system, unique functional groups and various

stereo- and regiochemical isomers. Since their initial isolation in 1984, they have been explored as potential therapeutics due to their wide variety of biological activities.
Dethe's group also achieved enantiospecific total syntheses of (+)-hapalindole-H and (-)-12-epi-hapalindole U as well as the formal syntheses of (+)-hapalindole Q and (+)-12-epi-fischerindole U isothiocyanate. Key steps of our approach feature expedient, highly regio- and diastereoselective *Lewis* acid catalyzed Friedel–Crafts reaction of indole with cyclic allylic alcohols and intramolecular reductive Heck reaction. Efficiency of the synthetic route also relies on an alkynyl aluminate complex driven regioselective nucleophilic epoxide opening from a sterically hindered site.

Scheme 4: Enantiospecific total Synthesis of (+)-hapalindole-H and (-)-12-epi-hapalindole U (*Chem. Eur. J.* **2018**, *24*, 8980-8984)



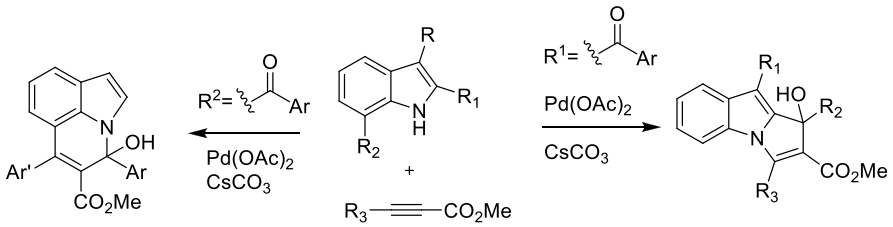
Scheme 5: Total Synthesis of murrayamine-O and murrayamine-P (*Chem. Eur. J.* **2015**, *21*, 8347-8350)



Dethe Group have achieved first enantiospecific total syntheses of representatives of cannabinol-skeletal carbazole alkaloids murrayamine-O and -P. Synthesis of both natural products and their enantiomers were achieved in highly atom economical, gram scale, protecting group free manner, in six steps longest linear sequence starting from (-)-(S)- and (+)-(R)-cis-verbenol.

Scheme 6: Synthesis of pyrrolo-[1,2-a]-indoles and pyrroloquinolines (*Chem. Eur. J.* **2016**, *22*, 106-110)

Pd-catalysed annulations reactions between indole derivatives and internal alkyne esters leading to various pyrrolo-[1,2-a]-indoles and pyrroloquinolines have been developed. The strategy involves an intermolecular addition of the indole nitrogen on to the internal alkyne ester followed by an intramolecular insertion of a vinyl–palladium complex into the carbonyl group. This method offers a facile and practical approach to pyrrolo-[1,2-a]-indoles and pyrroloquinolines.



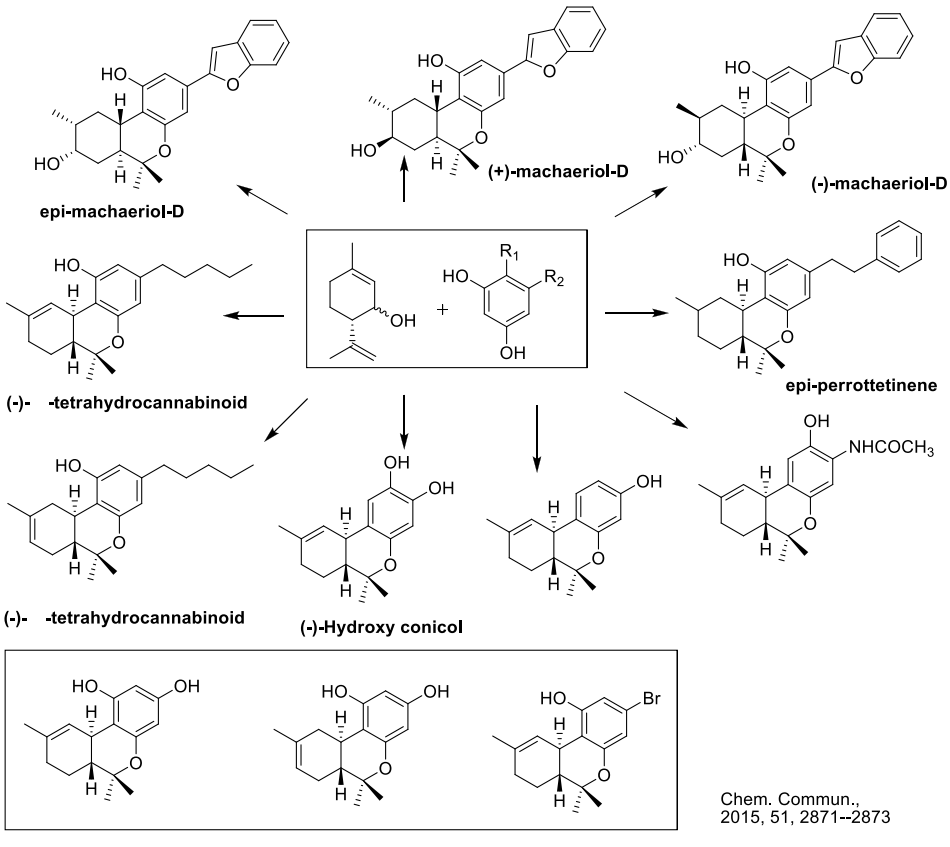
Chem. Eur .J. 2016, 22, 106 –110.

2. Total Synthesis of Meroterpenoid Natural Products:

Dethe's group has developed novel reactions and strategies for the C-C bond formation between phloroglucinol derivatives and terpene moieties and applied it for structurally diverse and biologically active natural meroterpenoids.

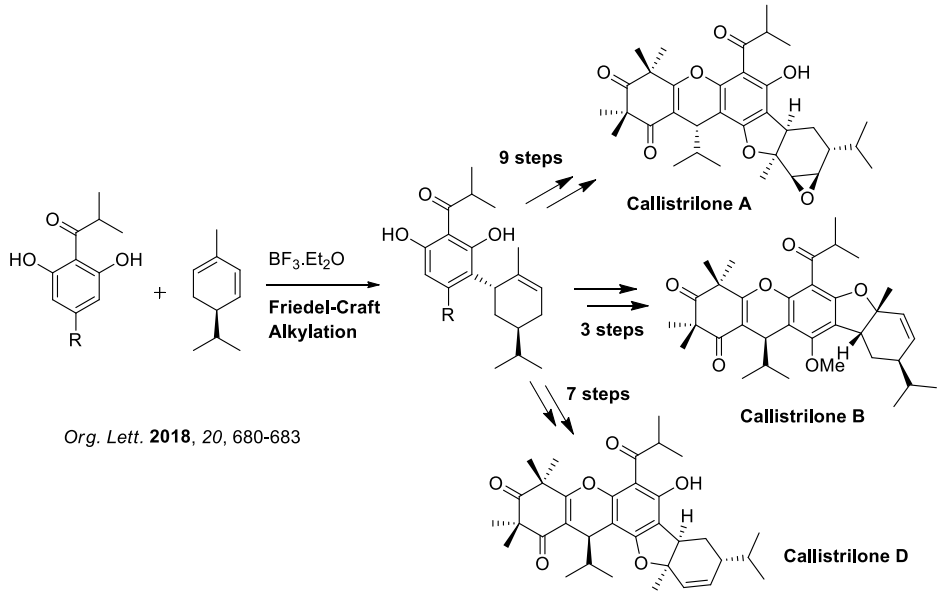
Scheme 7: Lewis acid catalysed Friedel-Crafts coupling of allylic alcohols and synthesis of tetrahydrocannabinoid analogues (*Chem. Commun*., **2015**, *51*, 2871-2873)

A simple, highly diastereoselective, Lewis acid catalyzed Friedel–Crafts coupling of a cyclic allylic alcohol with resorcinol derivatives has been developed. The method was applied for the enantiospecific total syntheses of structurally diverse natural products such as machaeriol-D, Δ^8 -THC, Δ^9 -THC, *epi*-perrottetinene and their analogues. Synthesis of both natural products and their enantiomers was achieved with high atom economy, in a protecting group free manner and in less than 6 steps, the longest linear sequence, in a very good overall yield starting from R-(+) and S-(-)-limonene.



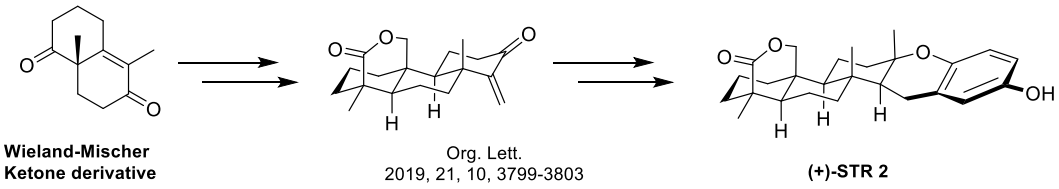
Chem. Commun., 2015, 51, 2871--2873

Scheme 8: Biomimetic total synthesis Callistrilone A, B and D (*Org. Lett.* **2018**, *20*, 3, 680-683)



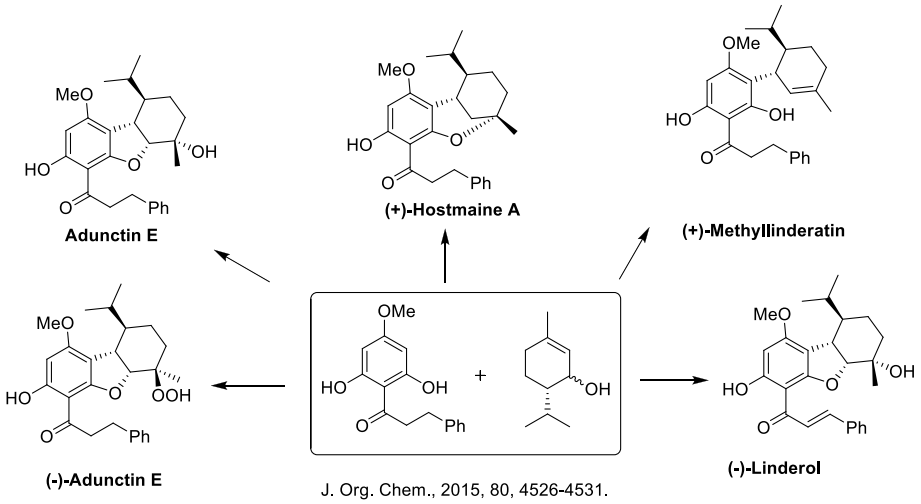
A biomimetic total synthesis of callistrilones (±)-A, B, and D and the postulated biosynthetic intermediate were achieved using a highly regio- and diastereoselective Friedel−Crafts alkylation, palladium-catalyzed Wacker-type oxidative cyclization, and stereoselective epoxide formation from extremely hindered β face as a key reaction. This method is fairly general to the synthesis of other natural products of this class as well as their analogues.

Scheme 9: Total Synthesis of (+)-Strongylophorines 2 and 9 (*Org. Lett.* **2019**, *21*, 3799−3803)



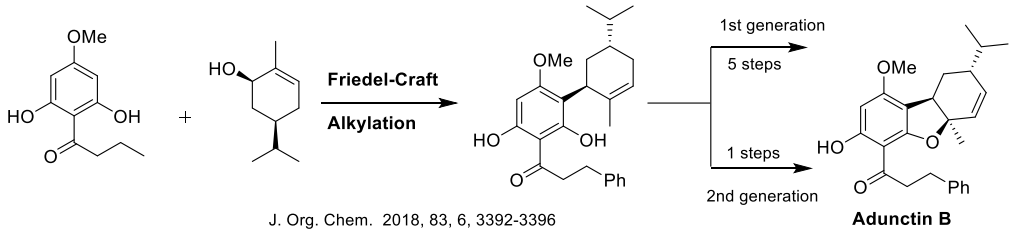
Recently Dethe group reported the first enantioselective total syntheses of strongylophorine-9 and strongylophorine-2 in 27 and 29 steps, respectively, as the longest linear sequences, which in addition to confirming the structure of the molecule also established their absolute configurations. The notable points of the synthesis include application of the Robinson-type annulation for attaining the diterpene moiety in a concise manner from an enantiopure Wieland-Miescher ketone derivative and a highly fascinating sp3 C−H activation on axial methyl to install the lactone moiety. It is presumed that the overall synthetic sequence can provide a useful guide for the synthesis of the other congeners of the strongylophorine family and their analogues.

Scheme 10: Synthesis of benzofuran derivatives (*J. Org. Chem.* **2015**, *80*, 4526−4531)



They have developed one-step protocol for the enantioselective synthesis of hexahydro dibenzofuran derivatives using a modified Friedel−Crafts reaction. The developed method was successfully applied to the synthesis of a series of natural products including (+)-hostmanin A, (+)-methyllinderatin, and (−)-linderol A. The synthetic and spectroscopic data investigations led to the structural reassignment of natural product adunctin E, which was further confirmed by single-crystal X-ray analysis.

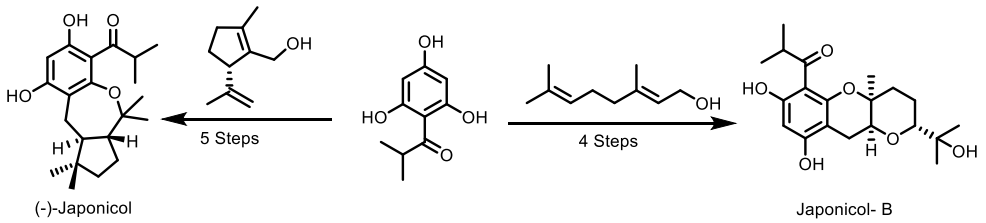
Scheme 11: Total Synthesis of Adunctin B (*J. Org. Chem.* **2018,** *83***,** 3392−3396)



Also complete the total synthesis of (±)-adunctin B, a natural product isolated from Piper aduncum (Piperaceae) was achieved using two different strategies, in seven and three steps. The efficient approach features highly atom economical and diastereoselective Friedel−Crafts acylation, alkylation reaction and palladium catalyzed Wacker type oxidative cyclization.

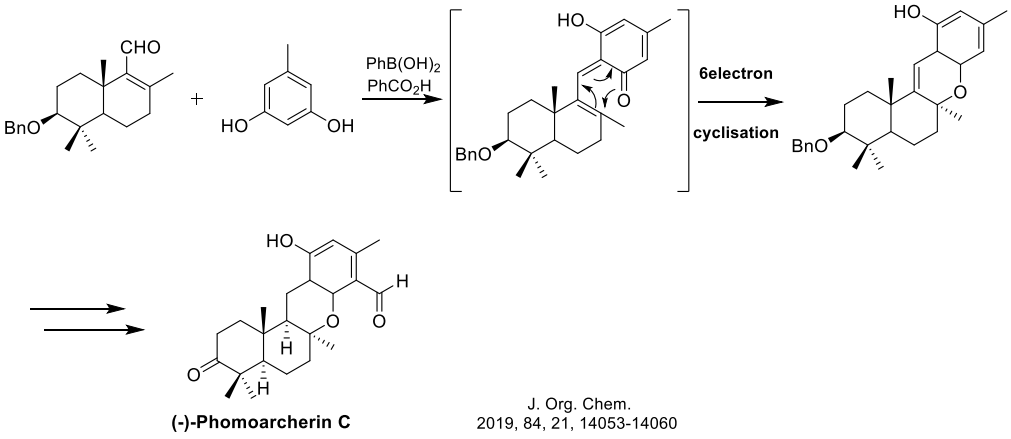
Scheme 12: Enantiospecific Total Synthesis of (−)-Japonicol C (*Org. Lett.* **2021**, 23, 7, 2648–2653)

Recently they have completed an efficient and convergent first total syntheses of (±)-japonicol B and (−)-japonicol C. The notable points of the synthetic route are Lewis-acid-catalyzed Friedel–Crafts reaction for one pot C–C and C–O bond formations resulting in construction of the tricyclic meroterpenoid skeleton, one pot Pd(OH)2/C-catalyzed isomerization/hydrogenation, and site selective sp3 C–H oxidation.



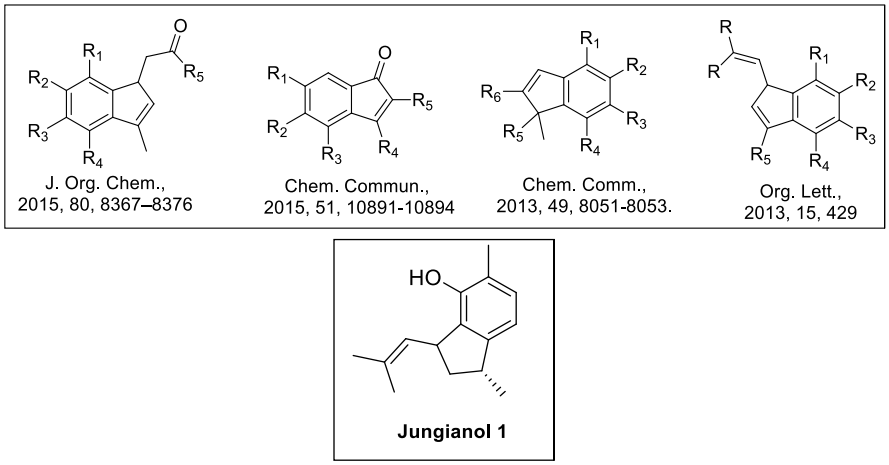
Scheme 13: First total synthesis of a chroman meroterpenoid, (−)-phomoarcherin C (*J. Org. Chem.* **2019**, 84, 21, 14053–14060)

They have also worked on a structurally intriguing benzopyran natural product phomoarcherin C synthesis for the first time in a considerably concise route. A 6π-electrocyclization strategy catalyzed by boronic acid−Bronsted acid cocatalyst system was employed for the synthesis of the natural product in nine steps from the known ketone 12 in 29.83% overall yield. With the synthesis of this natural product confirmed the structure of the molecule, also established its absolute configuration.
. 2019, 84, 14053−14060)



Scheme 14: $FeCl_3$ catalysed synthesis of Indenes, Indenones and total synthesis of (±)-jungianol and 1-epi-jungianol (*Org. Lett.* **2013**, *15*, 429, *Chem. Commun*., **2013**, *49*, 8051-8053, *J. Org. Chem.* **2015**, *80,* 8367-8376, *Chem. Commun*., **2015**, *51*, 10891-10894)

They have used $FeCl_3$ as Lewis acid catalysed [2+2] Cycloaddition for the synthesis of substituted indenes and indenones. An intramolecular $FeCl_3$-catalyzed Michael addition reaction of styrene, a poor nucleophile, onto α,β-unsaturated ketones was developed for the synthesis of highly substituted indene derivatives. The method was further applied to the total synthesis of the sesquiterpene natural products (±)-jungianol and 1-epi-jungianol.

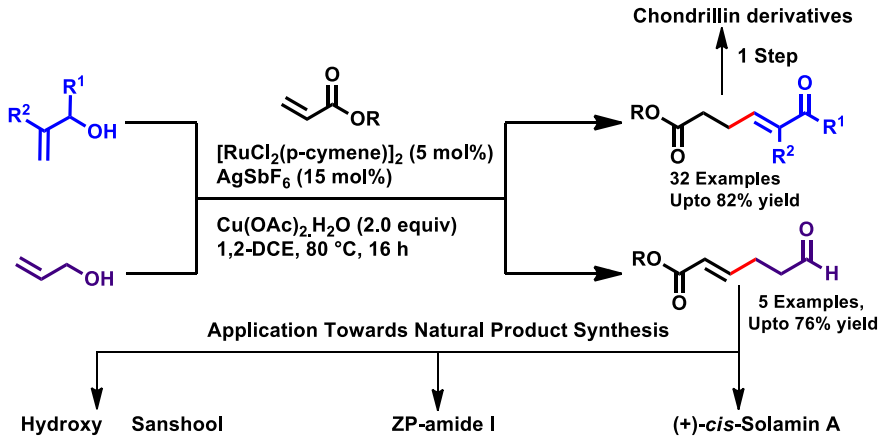


A novel $FeCl_3$ mediated formal [2+2] cycloaddition/ring opening cascade of o-keto-cinnamates was also developed for the synthesis of indenones. The reaction tolerates a broad range of functional groups, including bromide, chloride, amide, acid and ester groups.
followed by Lewis acid-catalyzed Friedel−Crafts reaction for one-pot C−C and C−O bond formations resulting in construction of the pentacyclic meroterpenoid skeleton.

3. Ruthenium catalysed C-H activation and its application to total synthesis of natural products.

Recently Dethe's group shown interest in Ruthenium catalysed C-H activation reactions and are getting very good results. They have published 5 publications in last 1.5 years in this area only. They developed new methodology of metal-catalysed reations and used them in total synthesis of natural products.

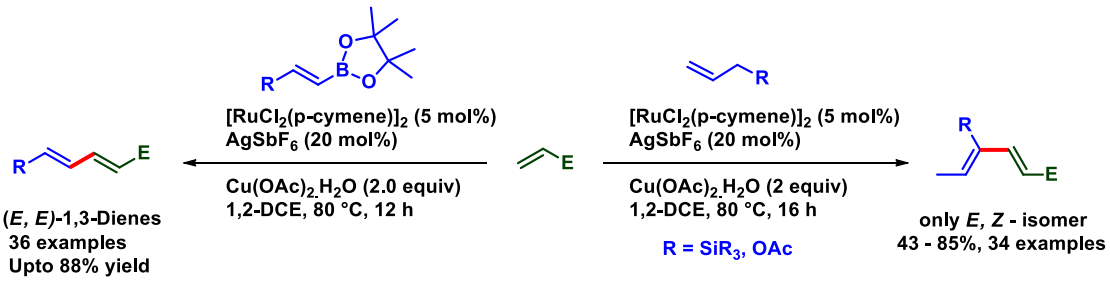
Scheme 15: Ruthenium-Catalyzed Direct Dehydrogenative Cross-Coupling of Allyl Alcohols and Acrylates: Application to Total Synthesis of Hydroxy β-Sanshool, ZP-Amide I, and Chondrillin (*Org. Lett.* **2020**, 22, 4, 1618–1623)



Ru-catalyzed oxidative coupling of allyl alcohols and activated olefins has been developed by C(allyl)−H activation of allyl alcohols providing efficient and direct

access to synthetically useful α,β-unsaturated enone intermediates. Synthetic utility of this method was demonstrated by its application to synthesis of bioactive natural products such as Hydroxy-β-sanshool, ZP-amide I, Chondrillin, Plakorin, and (+)-cis-Solamin A.

Scheme 16: Ruthenium-catalyzed formal sp3 C–H activation of allylsilanes/esters with olefins and Ruthenium-Catalyzed Oxidative Cross-Coupling Reaction of Activated Olefins with Vinyl Boronates (*J. Org. Chem.* **2021**, *86*, 3444–3455), (***Chem. Sci.***, 2021,**12**, 4367-4372)



J. Org. Chem. **2021**, *86*, 3444–3455 ***Chem. Sci.***, 2021,**12**, 4367-4372

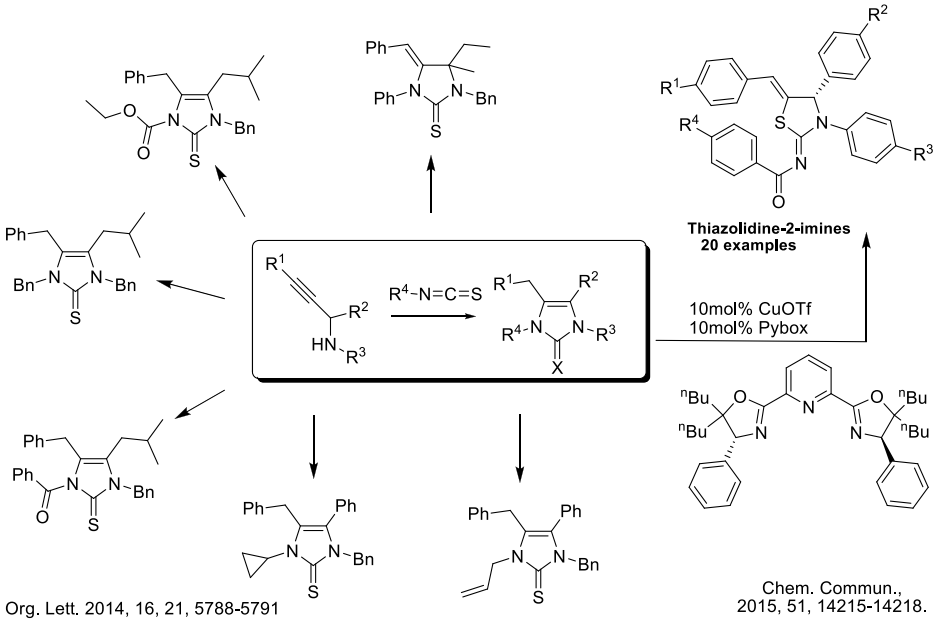
Ru-catalysed oxidative coupling of allylsilanes and allyl esters with activated olefins has been developed via isomerization followed by C(allyl)–H activation providing efficient access to stereodefined 1,3-dienes in excellent yields. Mild reaction conditions, less expensive catalysts, and excellent regio- and diastereoselectivity ensure universality of the reaction. In addition, the unique power of this reaction was illustrated by performing the Diels–Alder reaction, and enantioselective synthesis of highly functionalized cyclohexenone and piperidine and finally synthetic utility was further demonstrated by the efficient synthesis of norpyrenophorin, an antifungal agent.

An oxidative cross-coupling reaction between activated olefins and vinyl boronate derivatives has been developed for the highly stereoselective construction of synthetically useful (*E*,*E*)-1,3-dienes. The highlight of this reaction is that exclusive stereoselectivity (only *E*,*E*-isomer) was achieved from a base-free, ligand-free, and mild catalytic condition with a less expensive $[RuCl_2(p\text{-cymene})]_2$ catalyst.

Scheme 17: Synthesis of diversely substituted imidazole-2-thione and spirocyclic imidazolidine-2-thione (*Org. Lett.* **2014**, *16*, 5788-5791, *Chem. Commun*., **2015**, *51*, 14215-14218)

Also developed a multicomponent reaction between imines, terminal alkynes, and isothiocyanates in the presence of a catalytic chiral copper–pybox complex proceeded to enantiopure thiazolidine2-imines (60–99% *ee*) via a highly regioselective intramolecular 5-exo-dig hydrothiolation reaction.

An intramolecular transition-metal-free base-mediated hydroamination of propargylamine with isothiocyanates was achieved. This atom-economical, regioselective intramolecular 5-exo-dig cycloisomerization was further utilized for the one-pot synthesis of diversely substituted imidazole-2- thione and spirocyclic imidazolidine-2-thione. The reaction was performed at room temperature via propargylthiourea and 65−97% isolated yields were obtained.



Overall, Dethe's research group has developed novel synthetic methodologies for the total synthesis of complex natural products of biological relevance.