




REVIEW ARTICLE

Special Section on Transition Metal Catalyzed Synthesis of Medicinally Relevant Molecules

Transition metal catalyzed C-H activation for the synthesis of medicinally relevant molecules: A Review

DEBJIT BASU*, SARVESH KUMAR, SAI SUDHIR V and RAKESHWAR BANDICHHOR
Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Bachupally, Qutubullapur,
Ranga Reddy District, Telangana 500 090, India
E-mail: debjitbasu@drreddys.com

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Abstract. C-H activation in the synthesis of medicinally relevant molecules is reviewed. C-H activation is one of the most powerful components in the C-C or C-heteroatom bond formation tool box. This represents such an alternative which has provided the greener solutions to the organometallic/synthetic organic chemistry aiming to the synthesis of complex molecules. In recent years, there has been explosive growth in this area. In this review article we have presented effective methods of C-H activation employed in the synthesis of medicinally relevant molecules since 2010.

Keywords. C-H activation; organometallic synthesis; effective methods; greener solution; pharmaceutical targets.

1. Introduction

Carbon-carbon bond formation event is one of the most important reactions considering their significance in the key steps to architect more complex molecules from relatively less functionalized starting materials. Among the recent methodological advancement, transition metal mediated C-H functionalization represents a paradigm shift from the regular methods of organic synthesis.¹ This relies on the controlled functionalization of specific and remote C-H bonds, even in the presence of supposedly more reactive functional groups. The classical way of achieving remote C-H functionalization had been either by free-radical pathway or by intramolecular hydrogen abstraction. The recent advancements in organometallic chemistry have made it possible to achieve site-selective C-H functionalization. The initial approaches tend to focus on developing methods for the functionalization of relatively simple hydrocarbons, but in recent years, C-H functionalization has matured to the point where it can be contemplated as a viable strategy for the synthesis of complex targets.² In particular, functionalized or un-functionalized aromatic carbons can be used for the

construction of biaryls, which are considered to be the important structural motifs in many naturally occurring and medicinally relevant organic molecules. The quest that gained significance over the period of time is to develop carbon-carbon bond formation without functionalization. These strategies are poised to fulfill this need for green and sustainable chemistry.³

The metal catalyst is involved throughout each stage of a C-H transformation and duly plays a fundamental role in determining its mildness.⁴ The identity and oxidation state of the metal largely dictates which C-H activation mechanism operates in any given reaction.⁵ Mechanisms for common C-H activations mainly fall under four general categories: (i) Oxidative addition, this is the most common mechanism by which a R-H bond cleaves and a M-C bond and a M-H bond are formed. The mechanistic pathway starts by coordination of the R-H bond to the metal vacant site (Figure 1). This mechanism is common for electron-rich, low-valent complexes of the late transition metals (Re, Fe, Ru, Os, Ir, Pt) for which the higher oxidation state of the metal in the product and the required change in geometry upon formation of the two new bonds are energetically favourable. (ii) Sigma-bond metathesis, oxidative addition is not possible with transition metals having with d^0 electronic configuration (groups 3 and 4, lanthanides and actinides) and thus preferred mechanism is σ -bond metathesis involving usually an alkyl or a

*For correspondence

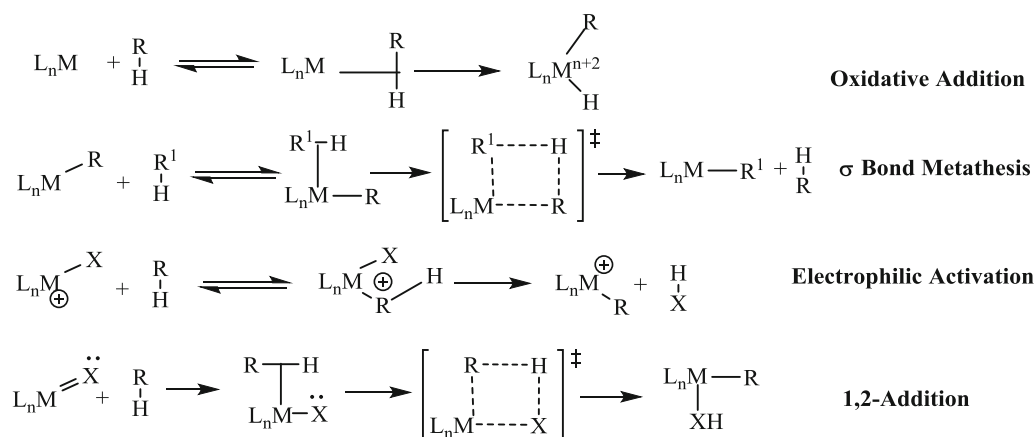


Figure 1. Mechanisms of C-H activation.

hydride complex (Figure 1). The concerted mechanistic pathway of σ -bond metathesis involves concerted formation of M-R¹ and R-H bonds and breaking of M-R and R¹-H bonds at the transition state. This is usually common for late or post-transition metals (Pd²⁺, Pt²⁺ or Pt⁴⁺, Hg²⁺). (iii) Electrophilic addition, the intermediate formed in this mode of C-H activation is by the electrophilic attack of the metal. This classification of electrophilic substitution has emerged from the mechanistic pathway by which the hydrogen atom of the substrate is replaced by a metal and thus it acts as a Lewis acid. (iv) 1, 2 addition, in this mechanistic pathway—the C-H bond directly adds across an unsaturated M-X bond in a 1,2 addition fashion (Figure 1). This mechanism is closely similar to σ -bond metathesis; however the newly formed X-H bond does not lead to release of XH because the M-X σ -bond is still present in the product. The complexes of early to middle transition metals have been shown to activate C-H bonds by 1, 2-addition.

To position better in terms of carbon-carbon or carbon-heteroatom bond formation it becomes imperative in most of the cases to employ transition metal as a catalyst for cross-dehydrogenative coupling (CDC) reaction with two C-H bonds as a greener choice. CDC is also aimed to avoid the installation of functional groups, thus making synthetic routes shorter, greener and efficient.⁶ Here in, we have reviewed the C-H activation followed by carbon-carbon bond formation by using Pd, V, Ru and Rh metals in the synthesis of several medicinally relevant molecules. This review does not necessarily categorize C-H functionalization reactions on the basis of the mechanism by which they occur, but provides a selective overview of C-H functionalization strategies that has been employed for the rapid synthesis of medicinally relevant molecules as pharmaceutical targets since 2010.

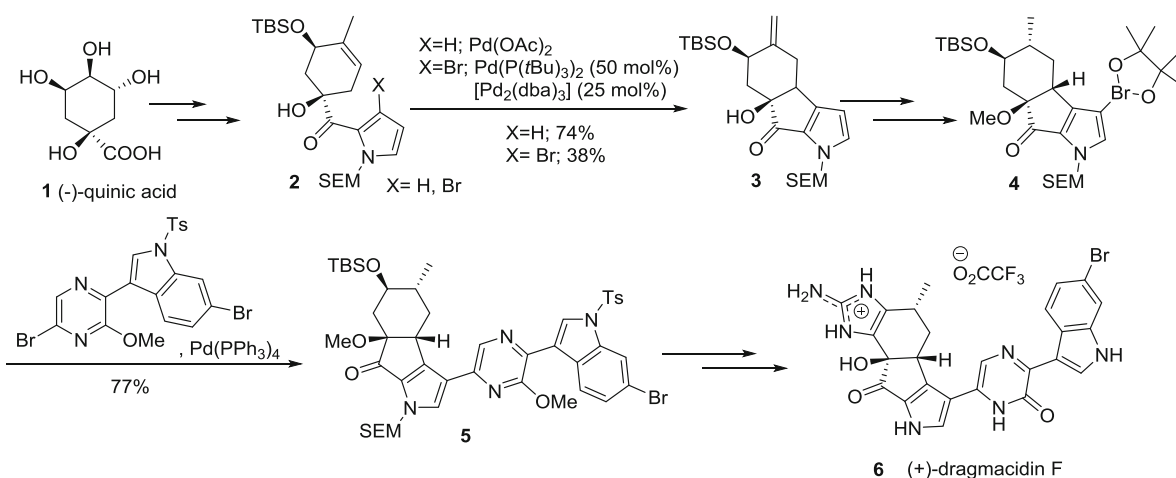
2. C-H activation in medicinally relevant molecules

2.1 Palladium catalyzed C-H activation

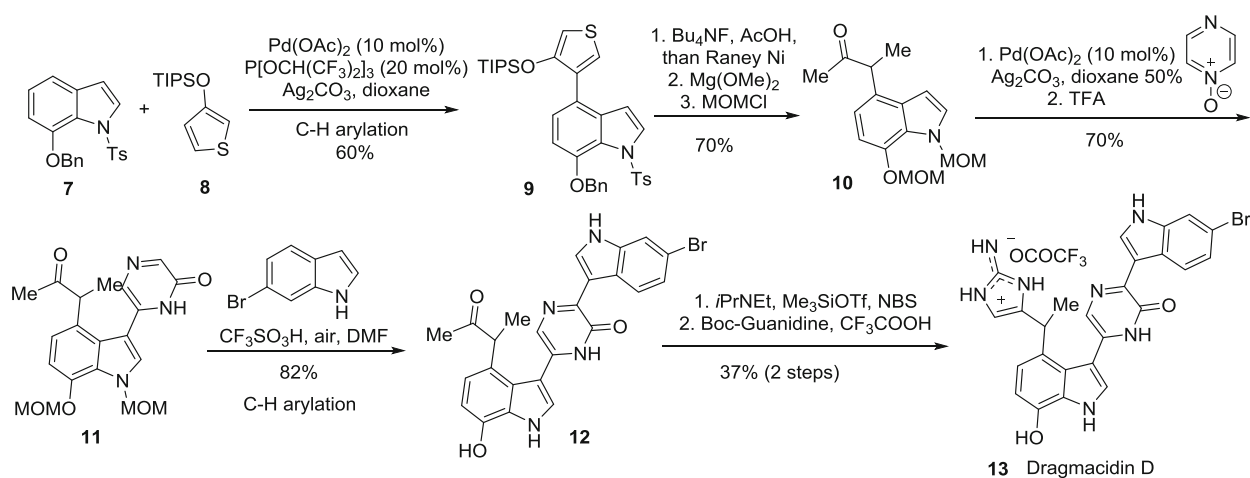
2.1a Synthesis of dragmacidins: Synthetic studies towards the marine alkaloids dragmacidins have been successfully attempted by several research groups and several valuable synthetic methods were developed for the preparation of the homo- or heterodimerization of precursors.⁷ Among them, most notably is the asymmetric aminohydroxylation of vinyl indoles in Jiang's total synthesis of dragmacidin A.⁸ However, the lengthy synthetic sequence involved in the preparation of functionalized precursors proved less attractive. Stoltz laboratory has conducted an extensive and systematic study for the synthesis of several analogues of dragmacidin.⁹ Among them, it is noteworthy to mention C-H activation-based oxidative coupling strategy applied in Stoltz's dragmacidin campaign that employed halogen-selective (Scheme 1), sequential Suzuki–Miyaura coupling for the synthesis of the structurally more challenging dragmacidin F.¹⁰

The concise total synthesis of dragmacidin D **13** was accomplished by Itami and co-workers through C-H coupling reactions in 15 steps synthesis,¹¹ which is 10 steps shorter than the preceding synthesis that employed Suzuki–Miyaura coupling reactions (Scheme 2). The state of art methodological developments that was employed in this elegant synthesis include (i) Pd-catalyzed thiophene–indole C–H/C–I coupling, (ii) Pd-catalyzed indole–pyrazine N-oxide C–H/C–H coupling, and (iii) acid-catalyzed indole–pyrazinone C–H/C–H coupling. These regio selective catalytic C–H couplings had been used to rapidly assemble simple building blocks to construct the core structure of dragmacidin D **13** in a step-economical fashion.

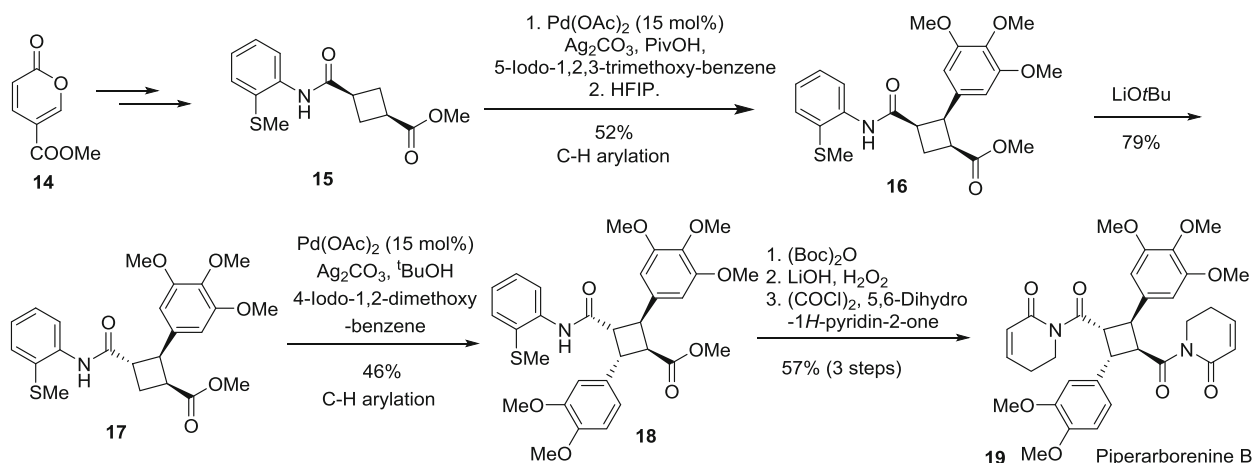
2.1b Synthesis of piperarborenine B: Baran laboratory has elegantly applied C-H activation that has culminated in the total synthesis of piperarborenine B **19** and piperarborenine D.¹² A strategy for the construction



Scheme 1. Stolz's Asymmetric total synthesis of (+)-dragmacidin F.



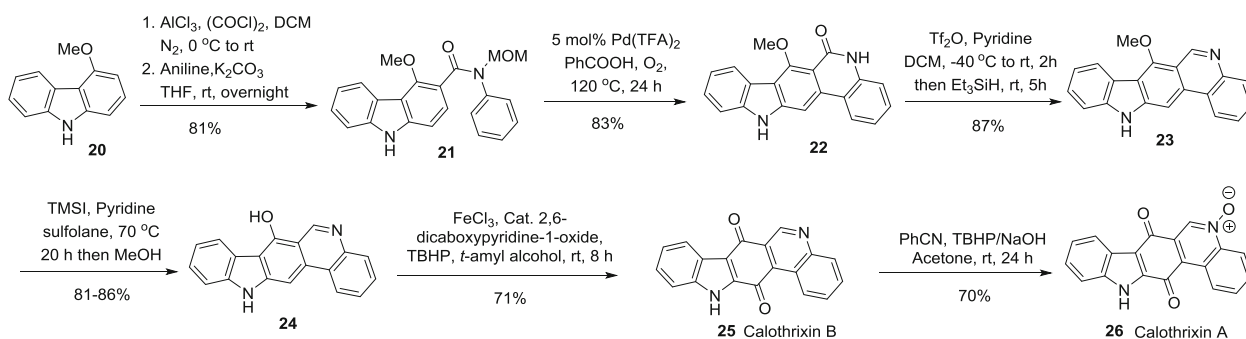
Scheme 2. Itami's total synthesis of dragmacidin D.



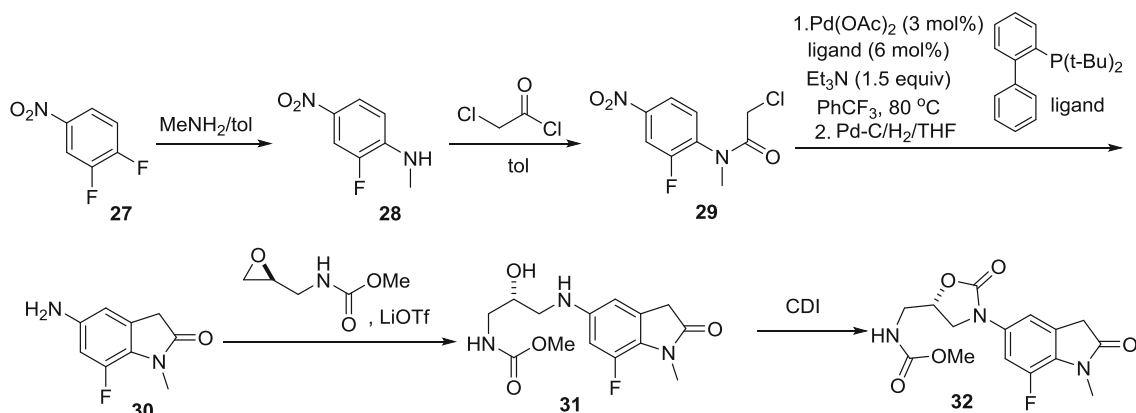
Scheme 3. Synthesis of Piperarborenes.

of unsymmetrical cyclobutanes using C–H functionalization logic by sequential, palladium catalyzed C–H activation followed by arylations with iodobenzene derivatives to afford mono- and di-aryl substituted cyclobutanes with

remarkable efficiency and stereochemical control is demonstrated (Scheme 3). These syntheses feature a new preparation of cis-cyclobutanedicarboxylates from commercially available coumalate starting material and the divergent approach



Scheme 4. Synthesis of Calothrixin A & B.



Scheme 5. Synthesis of Oxazolidinone anti-bacterial agent.

to the controlled *cis* or *trans* installation of the two distinct aryl rings found in the natural products is the first example of cyclobutane C–H arylation.

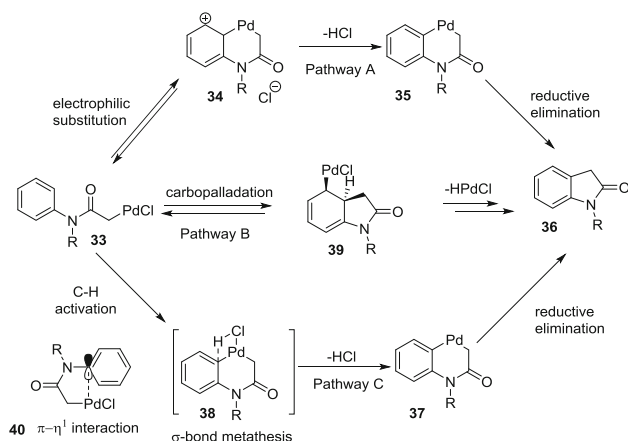
2.1c Synthesis of calothrixin A and B: The total synthesis of calothrixin A and B reported by Rajagopal Nagarajan features an intramolecular Pd-catalyzed cross coupling reaction via C–H activation (Scheme 4).¹³ Total synthesis of calothrixins have been reported by several groups by utilizing simple methods with good yields, however most of them comprise a greater number of steps.¹⁴ The C–H activation route has enabled the synthesis in reduced number of steps so that the overall yield has increased considerably and route has become more concise. The precursor **21** was synthesized in one pot by Friedel–Crafts acylation of **20** with oxalyl chloride in the presence of AlCl_3 in dry DCM followed by amidation with aniline. Pd-catalyzed intramolecular oxidative coupling of **21** in the presence of 5 mol% $\text{Pd}(\text{TFA})_2$ heated at 120°C for 24 h under an oxygen atmosphere in melted benzoic acid afforded the indolophenanthridinone **22** in 83% yield. Thereafter, **22** was subjected to chemoselective reduction using $\text{Tf}_2\text{O}/\text{Et}_3\text{SiH}$ to provide indolophenanthridine **23**, which was easily transformed into Calothrixin A **26** & B **25** in a couple of steps in a total of 5 steps over 35% overall yield.

2.1d Synthesis of oxazolidinone anti-bacterial agent: Michael Pamment and team at Pfizer Global R&D have

developed a kilogram scale synthesis of oxazolidinone anti-bacterial agent **32** following the palladium-catalyzed C–H activation strategy to build the key oxindole intermediate **30** (Scheme 5).¹⁵ The overall synthesis is a 6-step linear sequence and the C–H activation chemistry has been exploited in fourth stage of the synthesis. Authors found that the use of trifluorotoluene as solvent minimized the product decomposition and furnished the desired oxindole **32** in 75% yield with facile product isolation. This method was exploited to generate 4.9 kg of the oxindole **32** in 86% yield.

Synthesis of oxindole from chloroacetanilides was originally developed by Buchwald group.¹⁶ They have proposed three mechanistic pathways (Scheme 6). The first step is proposed to be oxidative addition of the chloroacetamide to the catalyst. This step is slow and rate determining. Pathway A involves electrophilic aromatic substitution to form a six-membered palladacycle which upon reductive elimination release the desired product with regeneration of $\text{Pd}(0)$ catalyst. Alternatively, the aromatic ring can undergo carbopalladation and subsequent HPdCl elimination generates the oxindole (pathway B). The third possibility is C–H activation which can either proceed by metathesis of C–H sigma bond or through the intermediacy of $\pi\eta^1$ interaction (pathway C).

2.1e Synthesis of SPT inhibitor: E. Jason Kiser and his team at Pfizer Inc. have developed a three-step, chromatography-free synthesis of oxyindole **45**, which is the



Scheme 6. Mechanistic consideration in the synthesis of oxazolidinone anti-bacterial.

key intermediate for the synthesis of a potential drug candidate **46** that has been proposed to elevate the level of HDL cholesterol by inhibition of serine palmitoyltransferase (SPT) enzyme, thus potentially useful in the treatment of heart diseases (Scheme 7).¹⁷ The original medicinal chemistry route for synthesizing the key intermediate **45** consists of a linear six-step synthetic process which was satisfactory for the preparation of small batches of **46**. However, for the kilo scale synthesis the team has developed a concise and scalable route by taking advantage of Buchwald's palladium-catalyzed C-H functionalization to cyclize a α -chloroacetanilide to form the five-membered ring. Intermediate **45** was synthesized twice on 5 kg scale and once on 10 kg scale in 76–84% yield following this chemistry.

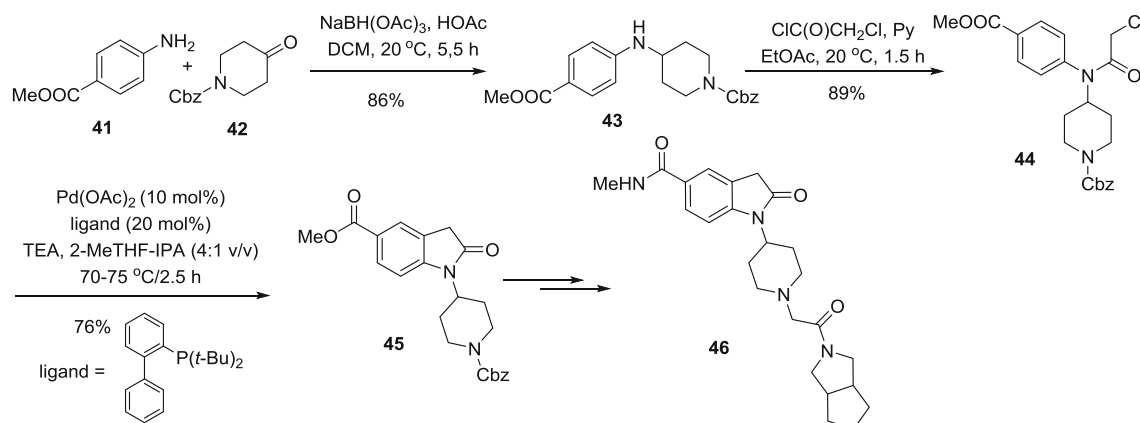
2.2 Rhodium catalyzed C-H activation

2.2a Synthesis of Lithospermic acid: First total synthesis of racemic heptamethyl lithospermate was reported by Jacobson in 1979.¹⁸ In this work, the synthesis was started with isovanillin, which was converted to racemic heptamethyl lithospermate by a sequence that largely involved pedestrian

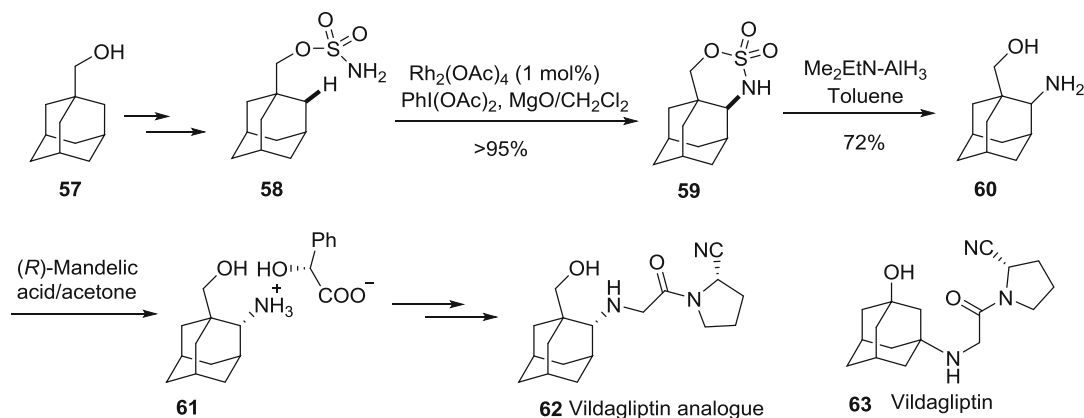
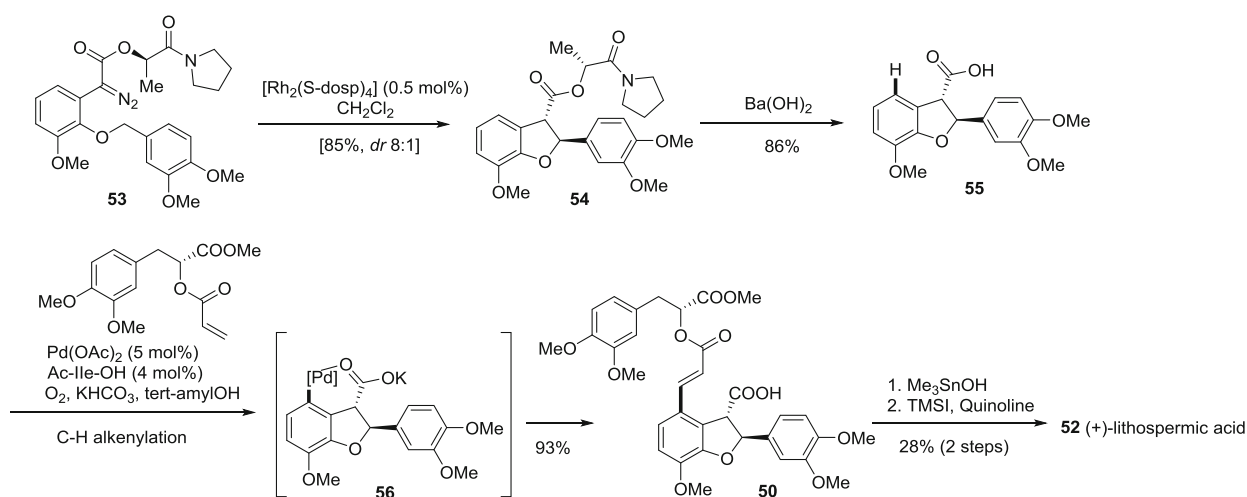
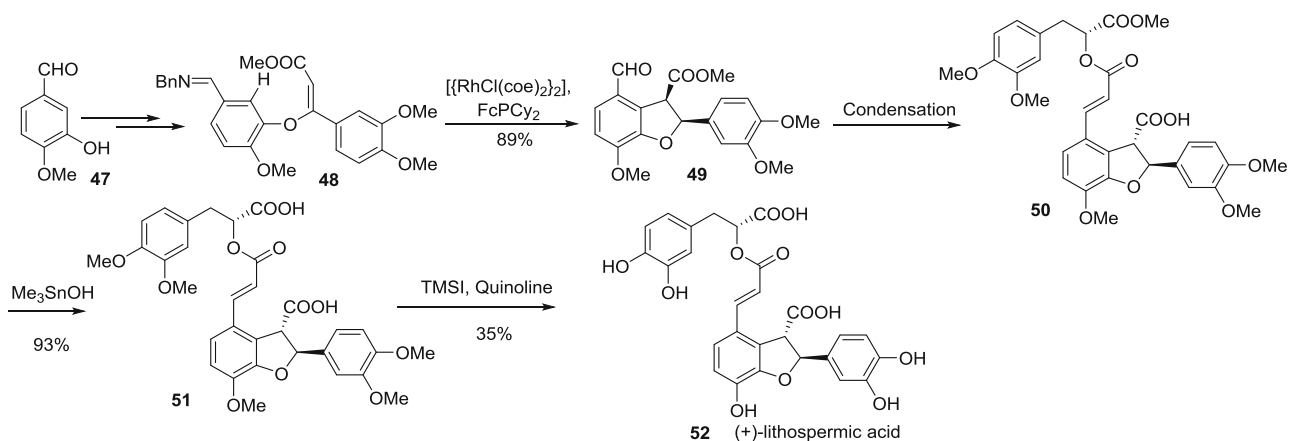
functional group transformations and condensation reactions for coupling of fragments. One of the pioneering work of C-H activation promoted carbon bond formation in the landmark synthesis of (+)-lithospermic acid **52** was reported by Bergman, Ellman and co-workers.¹⁹ In 2001, Ellman and co-workers have reported a rhodium-catalyzed intramolecular alkylation of aromatic imines tethered, through a mechanistic pathway that involve a directed C-H activation.²⁰ This methodology was later applied in an asymmetric setting with high level of enantio-control to access the benzofuran core of Lithospermic acid by C-H activation (Scheme 8). In a racemic system, the benzaldehyde derived benzylimine **48** was smoothly converted to benzofuran **49** in 89% yield as a single *cis* isomer. The optically active alkylation product **49** obtained (89% yield, 73% ee) was further enriched to 99% ee after recrystallization (56% overall yield). The side chain of (-)-lithospermic acid was attached onto aldehyde **49** through an analogous Knoevenagel condensation and the methyl ester bearing stereo center was also fortuitously epimerized under the reaction condition to obtain **50**. To complete the first total synthesis of (+)-lithospermic acid **52**, the final demethylation was ultimately achieved by TMSI-quinoline combination to fulfill this objective in 35% yield.

Through a highly ingenious approach, the Yu group have demonstrated a highly convergent total synthesis of (+)-lithospermic acid **52** by two successive C-H activation reactions as key steps.²¹ Rh-catalyzed carbene C-H insertion reaction utilizing Davies's catalyst was used to forge dihydrobenzofuran core **54**, and a late-stage intermolecular C-H olefination coupled the olefin unit with the dihydrobenzofuran core to construct the molecule in a highly convergent manner (Scheme 9). The directing group is a chiral non-racemic imine capable of intramolecular alkylation.

2.2b Synthesis of Vildagliptin analogues: Radim Hrdina *et al.*, have developed a straightforward way to prepare 1,2-disubstituted diamondoids by C-H bond amination reactions on a rigid tricyclic systems and applied this strategy to the synthesis of an enantiopure N-protected β -amino acid and new analogues of Vildagliptin.²² Traditionally, the

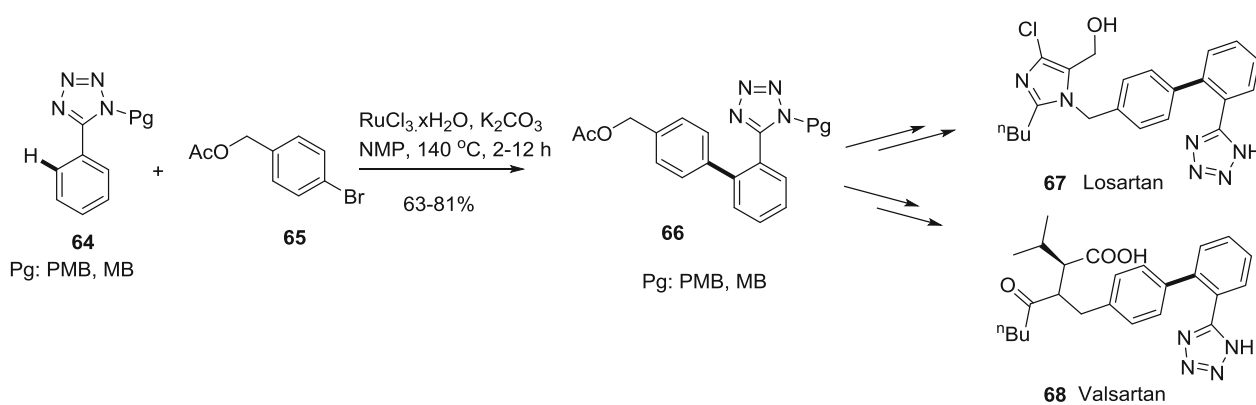


Scheme 7. Synthesis of SPT inhibitor.

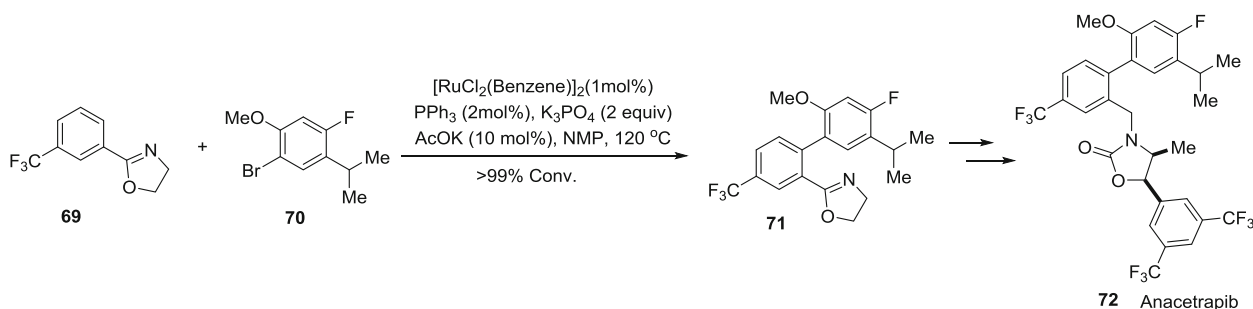


selective C–H functionalization of diamondoids have been achieved by undirected functionalization reactions, such as oxidation reactions, which mostly leads to tertiary products as the selectivity is based on the different C–H dissociation energies or thermodynamic stabilities of corresponding ions or radicals.²³ However, the C–H activation based approach

adopted by Radim Hridina laboratory ensured high reactivity of metal-bound nitrene species that would allow functionalization of un-activated rigid diamondoids and regioselectivity of nitrene insertions towards the formation of six-membered rings (Scheme 10). The synthesis of Vildagliptin analogue **62**, as new antidiabetic drug candidates (DPP-4 inhibitors)



Scheme 11. Synthesis of angiotensin II receptor blockers (ARBs).



Scheme 12. Synthesis of advanced intermediate of Anacetrapib.

has been achieved by intramolecular C–H functionalization using dirhodium-acetate-catalyzed (1 mol%) nitrene insertion reaction. This work is focused on C–H amination reactions of conformationally rigid tricyclic frameworks and presents the synthesis of two bioisosters of the antihyperglycemic agent DPP-4 inhibitor.

2.3 Ruthenium catalyzed C-H activation

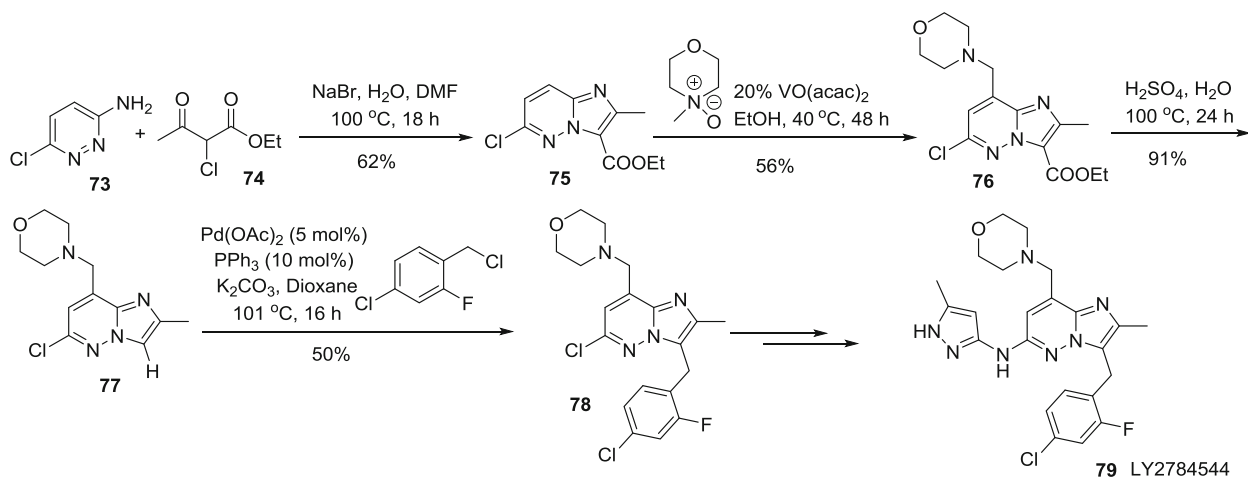
2.3a Synthesis of angiotensin II receptor blockers (ARBs): Masahiko Seki and Masaki Nagahama have developed an efficient catalytic system for C–H activation to functionalize aryltetrazoles that involves inexpensive $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and have successfully applied to the practical synthesis of angiotensin II receptor blockers (ARBs) Losartan **67** and Valsartan **68** (Scheme 11).^{24a} The previous synthetic approaches have critical drawbacks due to the need of stoichiometric amounts of expensive and/or hazardous organometallics such as Grignard reagents and boronic acids to install the fundamental biphenyltetrazole framework.²⁵ The robust catalytic system used for C–H activation route has been worked out that involves inexpensive $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and a specific amount of PPh_3 . The residual ruthenium that existed in the reaction mixture was thoroughly removed by treatment with properly selected metal scavengers. The new process afforded ready access to the important class of drugs in a highly atom-economical and sustainable manner. Lutz Auckermann have also similarly demonstrated C–H functionalizations of the aryltetrazoles to set the stage for

the preparation of various angiotensin II receptor blockers (ARBs) in a concise and atom-economical fashion.^{24b}

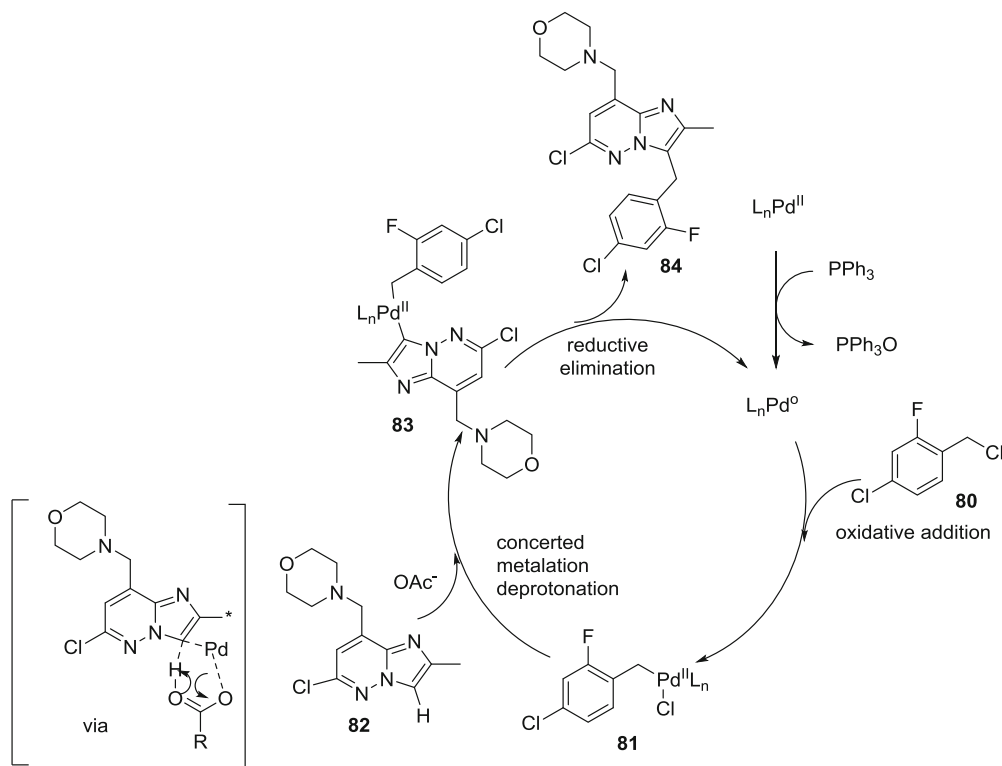
2.3b Synthesis of Anacetrapib: C–H biaryl coupling assisted by directing groups was applied to access the core structure **71** of anacetrapib **72** by Ouelett *et al.*, at Merck by using ruthenium catalyzed direct C–H arylation as the key step.²⁶ Lutz Auckermann inspired C–H arylation of oxazoline **69** with bromoanisole **70** under their robust ruthenium-based catalyst system was applied to obtain biaryl intermediate **71**, followed by reductive cleavage to afford the anacetrapib biaryl core.²⁷ Notably, this practical, scalable, and chromatography-free synthesis was successfully demonstrated on a kilogram scale (Scheme 12). The effect of low level impurity found in solvent is exploited to the high yielding arylation protocol demonstrated in multigram scale using carboxylate as the cocatalyst. Importantly, this C–H activation strategy was not only advantageous because of its economical and ecological benefits but also allowed streamlining the organic syntheses.

2.4 Vanadium catalyzed C-H activation

2.4a Synthesis of LY2784544: Researchers of Lilly Research Laboratories have reported an alternative synthetic route to a functionalized imidazopyridazine intermediate via sequential C–H bond functionalization for the synthesis of JAK2 inhibitor LY2784544 **79** that was undergoing clinical trials for the treatment of several myeloproliferative disorders.²⁸ The previously reported synthesis have several



Scheme 13. Synthesis of LY2784544.



Scheme 14. Mechanistic consideration in the synthesis of LY2784544.

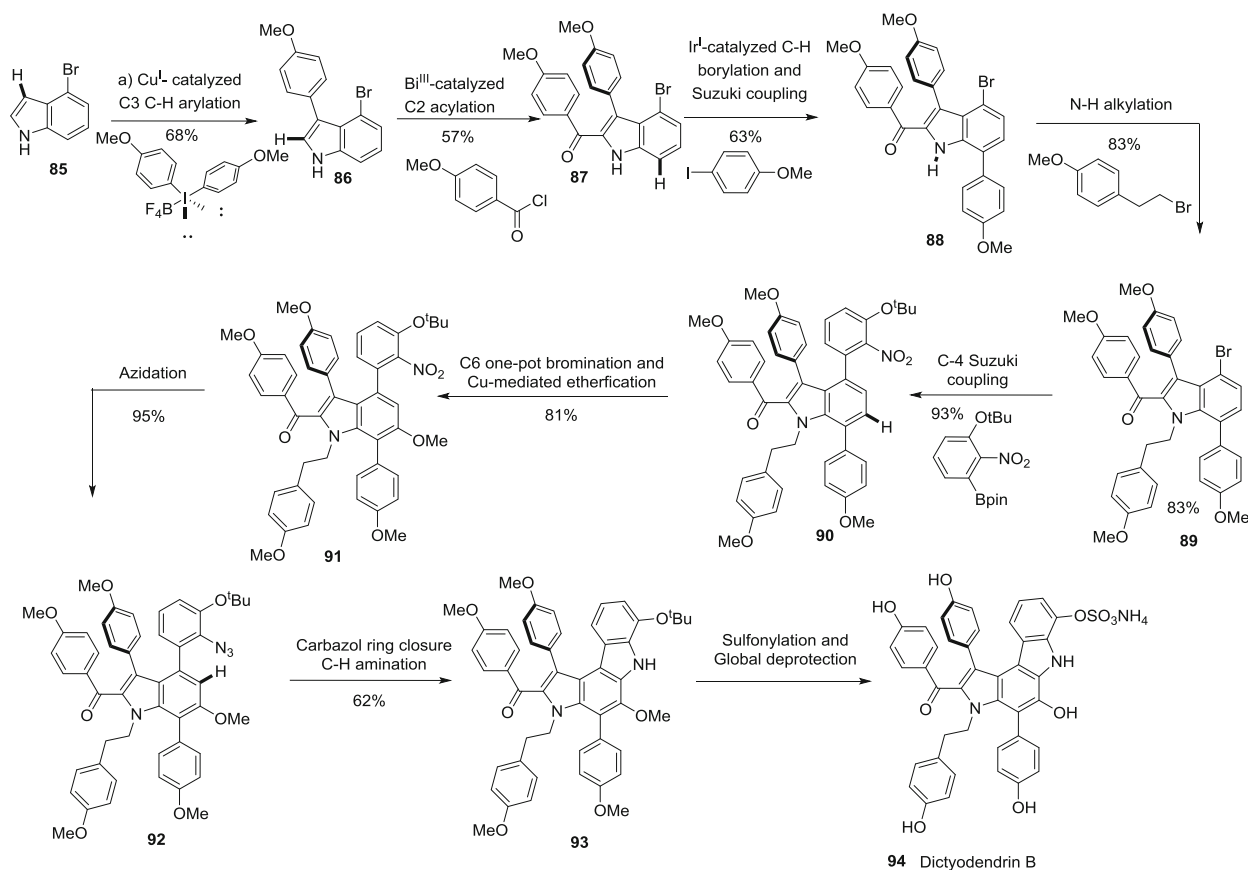
liabilities, including the use of amino acetal to form the pyridazine framework which was not readily available and usage trifluoroacetic acid (TFA) and triethylsilane liability from a waste disposal perspective, among others.²⁹ Key to the success of this alternative route is the use of two C-H functionalization reactions: a Pd-catalyzed direct benzylation reaction to functionalize a C-H bond with a substituted benzyl group and a V-catalyzed NMO addition reaction to install a benzylic morpholine moiety (Scheme 13). Thus team tasked to optimize the synthetic process developed a C-H activation driven synthetic route by successfully circumventing the major challenges associated with the previous route, namely

fluoride and silane waste incineration. Furthermore, using the route described in this report, the synthesis of the imidazopyridazine core is accomplished in a single step and avoided the use of the amino acetal which had required long lead times to secure (Scheme 14).²⁹

2.5 Various metal catalyzed C-H activation

2.5a Synthesis of dictyodendrin B:

The complex poly(hetero)aromatic architecture of marine natural alkaloid dictyohydrin has inspired a number of elegant total syntheses



Scheme 15. Synthesis of Dictyodendrin B.

from the groups of Fürstner, Iwoa and Ishibashi, Tokuyama and Jia having often lengthy chemical sequences.³⁰ However, Matthew J. Gaunt and his team have elegantly employed a sequential C-H functionalization strategy for the synthesis of structurally intriguing dictyodendrin B in concise synthetic approach.³¹ The total synthesis of dictyodendrin B **94** starting from a commercially available 4-bromoindole and involves six direct functionalization around the heteroarene core as part of a gram-scale strategy towards the natural product (Scheme 15). The inherent nucleophilicity of indole makes reactions through the C3 position an ideal starting point for copper-catalyzed C-H arylation using diaryliodonium salt. Inexpensive $\text{Cu}^{\text{I}}\text{Cl}$ (5 mol%) functioned effectively as the catalyst to combine 4-bromoindole **85** with bis(4-methoxyphenyl)iodonium tetrafluoroborate to afford **86** in 68% yield on 42 gram scale. Next, the intrinsic reactivity of indole for the C2 acylation was exploited and a bismuth(III) triflate catalyzed Friedel–Crafts type acylation afforded the 2,3-disubstituted indole product **87** as a single isomer in 57% yield. C7 substitution of Indole moiety **87** was achieved by utilizing the indole N-H motif to direct an iridium-catalyzed C-H borylation. With the indole N-H moiety having served its purpose for directing the C-H arylation, next N-alkylation was achieved by utilizing commercial 4-methoxyphenethyl bromide and K_2CO_3 to afford the desired N-alkylated product **89** in 83% yield. Thereafter, C4 arylation was achieved by Suzuki–Miyaura coupling of the C4 bromide and aryl boronic

ester using a mixture of $[\text{PdCl}_2(\text{dppf})]$ (5 mol%) and an aqueous solution of K_2CO_3 (2M) in dioxane at 90 °C to furnish the C4-arylated product **90** in 93% yield on a 1.5 gram scale. Electrophilic bromination at the C6 position of the indole was achieved with exclusive selectivity at room temperature using a slight excess of N-bromosuccinimide. Direct addition of a sodium methoxide solution in methanol (4M) and copper(I) iodide to the bromination reaction mixture led to the formation of the methyl ether, completing a two-step one-pot etherification process to obtain **91** in 81% yield on a 1.5 gram scale. The functional group transformation of nitro group into the azide was done by a two-step reduction/diazotization/azidation process in 95% yield on 1.5 gram scale to obtain **92**. This followed by C-H amination, presumably via the formation of nitrene intermediate, in super-heated dioxane at 180 °C in a continuous-flow process led to desired the carbazole product **93** in 62% yield. Finally, four-step deprotection and sulfonylation sequence afforded dictyodendrin B.

3. Conclusions

In summary, we have presented effective methods of C-H activation employed in the synthesis of medicinally relevant molecules like lithospermic acid, dragmacidin D, piperaborenine B, vildagliptin analogue, losartan,

valsartan, anacetrapib, dictyodendrin B, calothrixin A&B, oxazolidinone antibacterial, serinpalmitoyltransferase (SPT) enzyme inhibitor and LY2784544 (JAK2-V617F inhibitor) using transition metals which appeared in the literature since 2010.

Acknowledgements

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