Increasing molecular complexity in the synthesis has long been an ultimate goal of chemists as it resembles the Nature, wherein very complicated molecules such as palytoxin, maitotoxin and others could be synthesized, in creating multiple bonds, rings, and stereocenters in a single transformation. In this context, domino strategy is a powerful way to generate complex molecules in a fewer number of steps; a philosophy is used not only in basic research but also in the applied chemistry.

4.1 DIKHDA strategies in organic synthesis

When the pericyclic reaction, Diels–Alder or cycloaddition or sigmatropic or electrocyclic or retro-pericyclic or ene reaction, is coupled with itself or with other pericyclic or non-pericyclic reaction, leading to a sequence of two or more transformations, it leads to a variety of domino routes. Bioactive paracyclophanes, taxane, (+)-preussin, spinosyns etc. have effectively been synthesized via this route. The reaction can be performed under neutral or mild Lewis acidic condition. A combination of two types of cycloadditions, especially [4+2] and [4+2] is the most successive. An anionic reaction coupled with a pericyclic one also signifies as one of the widely used strategies. So the DKHDA approach stands first among three versatile anionic-pericyclic domino reactions like DKHDA reaction (1), domino Knoevenagel-ene reaction (2) and domino Knoevenagel-allylsilane cyclization (3), allowing highly diversified molecules to generate. Proceeding via in situ formed 1-oxa-1,3-butadiene from an aldehyde and a cyclic or heterocyclic or acyclic 1,3-dicarbonyl compound, it forms valuable dihydropyran ring via HDA reaction. Exceptionally it also leads to a domino/Knoevenagel-ene transformation.
A wide spectrum of aldehydes and 1,3-dicarbonyl compounds has been used in the strategy. Asymmetric versions are also in use to access natural products. DKHDA reaction begins with simple substrates, but ends with a highly complex molecule.\textsuperscript{15}

Two different approaches of the strategy, which are in use are given below:

1. Three–component reaction; which assembles 1,3-dicarbonyl, an aldehyde and a vinyl ether. Intermediate 1-oxabutadiene i.e Knoevenagel alkene undergoes an intermolecular HDA reaction with a suitable dienophile.

$$\text{RO} \quad \text{CHO} \quad \text{R}$$

2. Two–component reaction: Intermolecularly formed oxabutadiene undergoes intramolecular HDA reaction.

It proceeds \textit{via} an inverse electron demand Diels–Alder reaction that is governed by an overlap of diene LUMO with dienophile HOMO. EWG at 3\textsuperscript{rd} position of diene favors the transformation effectively due to lowering of diene’s LUMO energy. Any aldehyde like aromatic or hetero–aromatic, saturated or unsaturated aliphatic aldehydes can also be used. Similarly, any cyclic and acyclic 1,3-dicarbonyl units like Meldrum’s acid, barbituric acids, coumarins, 1,3-cycloalkanedione, $\beta$-ketoesters, and 1,3-diones can be treated as active methylene units. Further, phosphorus, nitrogen and sulfur analogues of these diketones have successfully been used. Hetero–analogues of 1,3-dicarbonyl
compounds such as 5-pyrazolones and isoxazolones can also be used as active methylene unit. Sometimes, domino Knoevenagel–ene process seldom becomes a main process or a side reaction to DKHDA reaction, depending upon the nature of substrates.\textsuperscript{16}

Prof. Tietze has widely investigated into the protocol. While, enol ethers are appropriate dienophiles, enamines more difficult to handle. A simple olefin is suitable, only if the Diels–Alder reaction takes place in an intramolecular mode. An excellent stereo–chemical control is possible. While aromatic or aliphatic $\alpha,\beta$–unsaturated aldehydes usually give \textit{cis}–fused cyclized product, simple aliphatic aldehydes the \textit{trans}–adduct.\textsuperscript{17} For the enantiopure products, chiral aldehydes, 1,3-dicarbonyl compounds as well as Lewis acids\textsuperscript{18} can be effectively used.

A wide range of solvents can be used in the transformation. Acetonitrile, dichloromethane and toluene are among the most appropriate ones. Alcohols and water are also suitable. Xylene in case of less reactive dienophile is more suitable.

![Figure 4.1 Four possible TS structures of intramolecular HDA reaction.](image)

Knoevenagel intermediate exist in either ($E$)– and a ($Z$)–configurations. An orientation of tethered dienophile leads to four possible transition structures; \textit{exo–E–anti} (1), \textit{endo–E–syn} (2), \textit{exo–Z–syn} (3) and \textit{endo–Z–anti} (4). Most favored among them decide stereochemical outcome of the reaction (Fig. 4.1).

Based on several experiments and calculations,\textsuperscript{19} the first and forth TS lead to a \textit{trans}– and the second and third to a \textit{cis}–annulated dihydropyran.
Further, in case of an aromatic aldehyde and aliphatic $\alpha,\beta$-unsaturated aldehydes, it favors an \textit{endo–E–syn} orientation giving \textit{cis–cycloadducts}. The normal aliphatic aldehydes \textit{via} favored \textit{exo–E–anti} orientation lead to \textit{trans} products along with a minor \textit{cis one}. The TS seems to be non–symmetric; so we assumed that the dienophile attacks the carbon at position–4 of oxabutadiene along a trajectory of about 109°. It causes planarity of the phenyl group to deviate \textit{via endo–E–syn} TS. In the latter case, steric interaction of the \textit{ortho–substituent} at the phenyl group, and the second carbonyl group are clearly diminished. High stereocontrol in all cases is clearly due to two substituents at terminal double bonds of the acceptor moiety which controls the conformation of the chain. We call this effect a sp$^2$ geminal effect,$^{20}$ which is due to the phenomenon of the 1,3-allylic strain.$^{21}$

Thus, the Knoevenagel reaction of 5 with the \textit{tert}-butylpyrazolone 6 gives exclusively (Z)–compound 7 which isomerizes at higher temperature to the (E)–compound 8 leading to the cycloadduct 9 \textit{via an endo–E–syn} TS. This mechanism was observed under irradiation, allows a $Z/E$-isomerization of 7/8, the domino reaction already takes place at 40 °C instead of 110 °C.$^{22}$

4.1.1 Natural products synthesis

4.1.1.1 Enantiomerically pure heterosteroids and homosteroids

Tietze, L. F. \textit{et al}.$^{23}$ described stereoselective \textit{trans–bonded} hetero–steroids 12 (\textit{de} >98 %) from an aldehyde 11 and cyclic 1,3-dioxo compound 10 or its analogs.
Asymmetric DKHDA reaction of a D–secoestrone derivative 13 with Meldrum’s acid 14 afforded corresponding bridged D–homoestrones 15 to other diketones also.24

4.1.1.2 Tetrahydrocannabinol and hexahydrocannabinol

Marihuana tetrahydrocannabinol ingredient and its hydrogenated products are well known psychoactive agents. Alkylidene-1,3-dicarbonyls 18 from citronellal 16 and 5-pentyl-1,3-cyclohexandione 17 in the presence of EDDA undergoes a cycloaddition in a highly stereoselective manner to tricycle 19 which aromatize to enantiopure hexahydrocannabinol 20.25

4.1.1.3 Deoxyloganin and secologanin

Monoterpene glycosides deoxyloganin and secologanin of iridoids and secoiridoids families respectively, are key intermediates in the biosynthesis of
monoterpenoid indole alkaloids; ipecacuanha, cinchona, and pyrroloquinoline. The key step in the synthesis of deoxyloganin 24 is condensation of Meldrum’s acid 14 and the aldehyde 22. Domino product 23 further transforms into deoxyloganin 24 via solvolysis in methanol, reduction with diisobutylaluminium hydride (DIBAH), acid–catalyzed elimination, and glycosidation.26

Secologanin aglycon ethyl ether 29 was obtained via a three–component reaction of monoprotected dialdehyde 25, trichlorooxobutanone 26, and enol ether 27 containing a sulfoxide group to give 28.27

4.1.1.4 Monoterpenoid indole alkaloids

Several alkaloids hirsutine 30, dihydro–corynantheine 31, dihydroantirhin28 32, corynanthe type alkaloid 33, emetine29 34 and tubulosine30 35 have been synthesized by this approach.
4.1.1.5 Natural product preethulia coumarin

Cravotto, G. et al. have accessed enol ether 45, 4-hydroxycoumarin 44, and \( \alpha \)-diketone 43, which gave cycloadduct 46 in 79% yields using catalyst Yb(OTf)\(_3\). Compound 46 could be transformed into the natural product preethulia coumarin 47.\(^ {31} \)
4.1.1.6 Meroterpenoid Guajadial

Guajadial 51 is a novel meroterpenoid that was isolated from the leaves of *Psidium guajava* (guava). Lee, V. *et al.* described its biomimetic synthesis from caryophyllene 48, benzaldehyde 49 and diformylphloroglucinol 50 via three-component coupling reaction in an aqueous media.

4.1.2 DKHDA strategy towards diversified heterocycles

Besides natural products, the approach afforded many diversified heterocycles. Various aspects like substrates, catalysts, reaction conditions, medicinal properties, industrial applications etc. have been covered in the new methodologies. Some recent reports are given below.

Moghaddam, F. M. *et al.* synthesized bi-functional starting aldehyde 52 with an unsaturated sultonate group in side chain, which gave novel thiopyrano indole-\(\delta\)-sultones 54 and 55 with indoline-2-thiones 53 in water via DKHDA reaction.
Balalaie, S. et al.\textsuperscript{34} reported Cul-ionic liquids as efficient reaction media for the synthesis of pyrano-annulated benzopyran derivatives.

\begin{equation}
\begin{align*}
\text{X} & \text{O} \text{CHO} + \text{O} \text{CHO} & \text{30 mol\% Cul} & \text{[Bmim]NO}_3 \\
56 & 57 & & 58
\end{align*}
\end{equation}

Antibacterial pyranoquinolinones 61 and 62 were prepared from quinolinone 60 with aldehyde 59 in EDDA.\textsuperscript{35}

\begin{equation}
\begin{align*}
\text{Ts-NCHO} + \text{NCHO} & \text{EDDA} & \text{Toluene}, \text{reflux, } 12 \text{ h} \\
59 & 60 & 61 & 62
\end{align*}
\end{equation}

Gallos, J. and Koumbis, A.\textsuperscript{36} used sugar derived \(\varepsilon,\varepsilon\)-unsaturated aldehydes 63 for synthesis of polyhydroxylated carbocycle-dihydropyran fused ring systems 64.

\begin{equation}
\begin{align*}
\text{D-ribose} & \text{BrO} & \text{EDDA} & \text{Na}_2\text{SO}_4, \text{CH}_3\text{CN} \\
\text{63} & \text{41} & 64 \\
\text{CH}_2\text{OBn} & \text{CH}_2\text{OBn}
\end{align*}
\end{equation}

Alonso, S. J. \textit{et al}.\textsuperscript{37} reported novel pyranonaphthquinones 67 & 68 based on their previous pharmacophore modeling studies, potential drugs that target human topoisomerase II catalytic inhibitors.

\begin{equation}
\begin{align*}
\text{H} & \text{OH} + \text{O} \text{CHO} & \text{EDDA} & \text{EtOH}, \text{reflux} \\
65 & 66 & 67 & 68
\end{align*}
\end{equation}
Tietze, L. F. et al. described a very short approach, using a three-component DKHDA reaction, to 2-alkoxy-6-methyl-5-nitro-3,4-dihydro-2H-pyran 72 obtained in 81–95%.

Using different lengths of a tether between aldehyde and dienophiles (in aromatic/heteroaromatic-based substrates), a broad variety of highly diversified heterocyclic compounds could be prepared. Reaction between 73 and 74 gave 75 containing a new 5,6-ring system, whereas reaction of 76 and 74 gave 77 with a 7,6-ring system.

Chiral 1,3-dicarbonyl compounds 78, 79 and oxathiolanes 80 have also been used to prepare enantiopure products. In addition, chiral mediators 81 have been employed with great success.

Yadav, J. S. et al. described O-propargylated sugar aldehyde 83 with 1,3-diketones; dimedone, cyclohexane-1,3-dione 82, to afford a novel class of carbohydrate analogues furochromene 84 via a DKHDA reaction in good yields.
Nagaiah, K. et al.\(^{43}\) described synthesis and antiproliferative activity of chromeno-annulated \textit{cis}-fused pyrano[3,4-\textit{c}]pyrans. 7-\textit{O}-prenyl derivatives of 8-formyl-2,3-disubstituted chromones 85 and 1,3-dicarbonyl/alogues active methylene unit 86 react to give desired products 87.

Bandyopadhyay, C. et al.\(^{44}\) reported \textit{N}-alkenyl-\textit{N}-arylamino-4-oxo-4\textit{H}-1-benzopyran-3-carbaldehyde 88 with dimedone 89 in pyridine in ethanol to assess polycyclic heterocycles 90 containing pyridine and chromon rings by one-pot method.

A new version of DKHDA strategy was described by Balalaie, S. et al.\(^{45}\) in the preparation of pyrano[3,4-\textit{c}]chromenes scaffolds. An aldehyde 91 gave new pyrano[3,4-\textit{c}]chromenes 93 with benzoylacetonitrile 92, in the presence of Cul and diammoniumhydrogen phosphate in good yields and high bond-forming efficiency.
Sarkar, A. *et al.* synthesized julolidine hybrid analogs \(96\) via DKHDA reaction of \(O\)-prenylated aldehyde \(94\) with 1,3-diketones \(95\).

Dehaen, W. *et al.* reported thiopyranopyrazolo–fused–pyrano pyrazoles \(99\) from pyrazolone–based aldehydes \(97\) and pyrazolones \(98\). They also attempted for several other heterocycles from pyrazole, pyrimidine, pyridine, indole and thiazole.\(^{47}\)

Moghaddam, F. M *et al.* synthesized polycyclic indole derivatives \(102\) from \(O\)-acylated salicylaldehydes \(100\) and dihydroindole-2-thiones \(101\) in water. Product yields were in the 65–95 % range with high regio- and stereoselectivity.

![Chemical structure](image1)

Lee, Y. R. *et al.* developed EDDA-catalyzed, efficient one-pot synthetic approach to benzopyranobenzopyrans 109 and naphthopyranobenzo-yps via a DKHDA reaction of resorcinol 107 or naphthols with O-allyl-ether-tethered salicylaldehydes 108 or naphthaldehyde. It allows a rapid access to polyheterocycles with stereochemically defined quaternary carbon centers.

![Chemical structure](image2)

Majumdar, K. C. *et al.* demonstrated an efficient and simple strategy for indole-annulated thiopyranobenzopyrans 112 and 113, in excellent yields from simple substrates 110 and 111. The reaction is highly stereoselective that lead to *cis*-annulated polyheterocycles.

![Chemical structure](image3)
Majumder, S. and Bhuyan, P. J.\textsuperscript{52} reported some novel complex thiopyranos[2,3-b]indoles \textbf{116} from simple thioindole \textbf{114} and 1,3-diketones \textbf{115} yielding products in the 62–75\% range in the presence of catalyst EDDA.

\begin{center}
\includegraphics[width=0.8\textwidth]{reaction1.png}
\end{center}

Reddy, B. V. \textit{et al.}\textsuperscript{53} reported angularly fused chromenes \textbf{119} from alkene–tethered chromene-3-aldehyde \textbf{117} and 1,3-cyclic diketones \textbf{118}.

\begin{center}
\includegraphics[width=0.8\textwidth]{reaction2.png}
\end{center}

\section*{4.2 TBA–HS, glycerol and ionic liquids in organic synthesis}

\subsection*{4.2.1 TBA–HS in organic synthesis}

To develop new methodologies that minimize the wastes generation, the PTC is often an alternative choice.\textsuperscript{54} As quaternary 'onium' salt such as ammonium, phosphonium, antimonium, and tertiary sulfonium salts, they are used in small quantity. Thermal decomposition of sodium trichloroacetate suspended in anhydrous chloroform in quaternary salt is useful reaction to generate reactive intermediate dichlorocarbene. Requiring no vigorous conditions, it offers fast reaction, even in anhydrous condition, and involves no tedious workup procedure. TBA–HS is an acid catalyst and has been widely used in the organic synthesis. Its use in DKHDA strategy is however very rare.

Acid–catalyzed DKHDA strategy is efficient synthetic route to complex heterocycles. Lewis acid particularly\textsuperscript{55} influences both the DA and HDA reactions in terms of reaction rate.\textsuperscript{56} Out of two reactions; anthracene with maleic anhydride at rt (1) and 1,4-benzoquinone and dimethyl fumarate in AlCl\textsubscript{3} (2), the increased rate of later (2) is due to lewis acid.\textsuperscript{57} Along with SnCl\textsubscript{4} which also promotes the reaction there are many other reports in the literature.\textsuperscript{58} Lewis acids such as ZnCl\textsubscript{2}, BF\textsubscript{3}, MeAlCl\textsubscript{2}, and Et\textsubscript{2}AlCl\textsuperscript{59} are common in HDA reaction.
The influence of acid can be rationalized by FMO theory. Normal DA reaction involves a dienophile–diene interaction. Decrease in HOMO–LUMO energy gap favors the reaction due to effective orbitals–overlap. In the process, coordination of Lewis acid towards carbonyl oxygen via lone pair electrons helps reduce LUMO–HOMO energy gap of aldehyde (Fig 4.2). Additionally with increased magnitude of carbonyl LUMO, it makes it more susceptible to the diene. Polarization as well changes the reaction pathway from a concerted non–synchronous mechanism to a stepwise mechanism. Substituents on reactants and reaction conditions also affect the mechanism.

![Figure 4.2 FMO diagram of HDA reaction in the presence and absence of a Lewis acid.](image)

**Figure 4.2** FMO diagram of HDA reaction in the presence and absence of a Lewis acid.

![Figure 4.3 The endo–selectivity is seen in the Lewis acid catalyzed HDA reaction as the solvated Lewis acid is exo, due to its size.](image)

**Figure 4.3** The *endo*–selectivity is seen in the Lewis acid catalyzed HDA reaction as the solvated Lewis acid is *exo*, due to its size.

The orientation of dienophile at TS decides the stereochemistry of products. The *endo*–selective is generally due to the preference of the Lewis acid being *exo* as a result of its size (Fig 4.3). In addition, the Lewis acid and the carbonyl R group are proposed to be trans to each other. Similarly, the uncatalyzed reaction of aldehydes and a diene demonstrate *endo*–selectivity for the carbonyl substituent.

Lewis acids are chosen based on experimental trial and error works. Kobayashi, S. *et al.* reported Lewis acids activity with aldehydes and imines.
states that strong acids don’t necessarily promote the reaction and that observed selectivities of aldehyde or aldimine depends upon nature of Lewis acid. Many metals like Eu, Ti, Yb, Cr, Zn, Co, Cu, Al, Sc, Li, etc., and its chiral auxiliaries are also used as Lewis acids.\textsuperscript{66} ILs are also employed as a both solvent and catalyst.\textsuperscript{67}

In view above, thus acid catalysts and their role in HDA strategy has been significant investigating area of research. TBA–HS has not been yet explored in DKHDA strategy although studied in many other reactions. The examples are given below.

TBA–HS\textsuperscript{68} was used in reaction of 2-phenylalkanenitriles \textbf{120} with 1,1- or \textit{cis}–dichloroethylene \textbf{121}, which gives ethynylated \textbf{122} in good yield.

\[
\begin{align*}
\text{PhCN} & \quad \text{CH}_2\text{CCl}_2 \\
\textbf{120} & \quad \textbf{121} \\
& \quad \begin{array}{c}
\text{50\%aq NaOH} \\
\text{TBA–HS}
\end{array} \\
\text{PhCN} & \quad \equiv \\
\textbf{122}
\end{align*}
\]

Carbamate \textbf{124}(5-methoxy N-acetyltrypamine–hormone produced and secreted in the pineal gland) is obtained from \textbf{123} with ethyl chloroformate in TBA–HS and NaOH in CH$_2$Cl$_2$.

\[
\begin{align*}
\text{MeO} & \quad \text{(CH$_2$)NHCOCH$_3$} \\
\textbf{123} & \quad \text{CICO$_2$Et} \\
\text{TBA–HS, NaOH} & \quad \begin{array}{c}
\text{MeO} \\
\text{(CH$_2$)NHCOCH$_3$} \\
\text{EtOOC}
\end{array} \\
\textbf{124}
\end{align*}
\]

Similarly, TBA–HS is used in alkylation,\textsuperscript{70} allylation,\textsuperscript{71} and sulfonylation.\textsuperscript{72} Also found that TBA–HS has been used to convert alkyl halides into azides. Under milder condition, heterocyclic chloroaldehyde \textbf{125} react with NaN$_3$ in DMSO to give azides \textbf{126} in higher yields.\textsuperscript{73}

\[
\begin{align*}
\text{CHO} & \\
\textbf{125} & \quad \begin{array}{c}
\text{NaN$_3$} \\
\text{TBA–HS}
\end{array} \\
\text{DMSO 20-70$^\circ$C} & \quad \begin{array}{c}
\text{CHO} \\
\text{N$_3$}
\end{array} \\
\textbf{126}
\end{align*}
\]

Recently, our research group reported a solvent–free, TBA–HS catalyzed DKHDA reaction of 2-alkenyloxy-acetophenones \textbf{127} with pyrazolones \textbf{128}, giving chromeno–fused pyrazoles \textbf{129}. Access to bioactive aminochroman–annulated heterocycles \textbf{130} from nitro analogous is useful application of this synthetic route.\textsuperscript{74}
One more report from our research laboratory that described TBA–HS mediated DKHDA appeared for synthesis of benzopyran–annulated pyrano[2,3-c]pyrazoles 133.\textsuperscript{75}

\[
\begin{align*}
\text{Ar} & \quad \text{N} \quad \text{N} \\
& \quad \text{CHO} \\
\text{CHO} & \quad \text{R} \\
\text{R} & \quad \text{R} \quad \text{N} \quad \text{N} \\
& \quad \text{Tea} \\
& \quad \text{Fe/HCl} \\
\end{align*}
\]

\[
\begin{align*}
R^1 & = \text{Ph; 4-ClPh; 2-ClPh; 3-ClPh; 2,5-Cl}_2\text{Ph; Ph; R}^2 = \text{Me, Ph} \\
& \quad \text{R}^1 \quad \text{R}^2 \\
\end{align*}
\]

4.2.2 Glycerol as a green solvent in organic synthesis

Solvents are useful in numerous processes such as medium in the organic synthesis, dissolving medium in the separation procedure, and diluters in the solution preparation. Traditionally, many non–polar organic solvents are in use. But due to environmental awareness, water and other highly polar solvents like ethylene glycol and formamide have emerged as effective medium, particularly, in the DA reaction.\textsuperscript{76} Thus, from environmental, economic, safety, handling, and products isolation point of view, the chemical, physical, and biological nature of the solvent plays a key role in the chemical process. Considering an impact of chemical processes on the environment, the search for innovative concepts that substitute volatile organic solvents has become a tremendous challenge in academia and industry.\textsuperscript{77} According to the twelve principles of green chemistry, a green solvent should meet numerous criteria such as low toxicity, non–flammability, non–mutagenicity, non–volatility and widespread availability among others. Moreover these green solvents have to be cheap and easy to handle and recycle.\textsuperscript{78}

Very recently glycerol (also known as 1,2,3-propanetriol or glycerin) has appeared as an alternative feed–stock source\textsuperscript{79} for green and sustainable organic
chemistry. As a byproduct of transesterification of triglyceride in the soap and biodiesel industries, glycerol has a very high boiling point and negligible vapor pressure, making it compatible with most organic and inorganic compounds, requiring no special handling or storage. Derivatives are also useful intermediates of pharmaceutical and food products. Like other polar organic solvents, glycerol not only dissolves inorganic salts, acids, and bases, as well as enzymes and transition metal complexes (TMCs), but also organic compounds that are poorly miscible in water, and is non-hazardous. Different hydrophobic solvents such as ethers and hydrocarbons which are immiscible in glycerol allow removal of reaction products simply by extraction. Distillation of products is also feasible due to the high boiling point of glycerol. In particular, the low toxicity of glycerol also allows the synthesis of pharmaceutically active ingredients in which the toxicity and residue of solvents are needed to be carefully controlled. Along with peculiar physical and chemical properties—such as polarity, low toxicity, biodegradability, glycerol with renewable feed stocks has prompted us to extend its use as a green solvent in DKHDA reaction. There are many known organic synthesis reported in this reaction medium. Useful references can be cited below.

Wolfson, A. and Dlugy, C. explored Palladium-catalyzed Heck coupling of halobenzenes 134 with various alkenes 135 and the Suzuki cross coupling of halobenzenes 134 with phenylboronic acid 136 in this medium.

\[
\begin{align*}
\text{Ph} - 
& R \quad 137 \\
& \text{Pd,Glycerol} \\
\text{Ph} - 
& X \quad 134 \\
& \text{Pd,Glycerol} \\
\text{Ph} - 
& \text{Ph} \quad 138 \\
& \text{Pd,Glycerol}
\end{align*}
\]

Wolfson, A. et al. also reported nucleophilic substitution of benzyl chloride 139 by potassium thiocyanate and the reduction of benzaldehyde 49 by sodium borohydride.

\[
\begin{align*}
\text{Ph} - 
& \text{Cl} \quad 139 \\
& \text{KSCN,Glycerol} \\
& \text{NCS} \quad 140
\end{align*}
\]
Jerome, F. et al\textsuperscript{82} demonstrated catalyst–free aza–Michael addition of amines 142 to $\alpha,\beta$-unsaturated carbonyl compounds 143.

The medium is also advantageous for electrophilic activation of aldehydes,\textsuperscript{83} wherein bis(indolyl)methane derivatives 147 could be accessed through a thermal reaction between 2-methylindole 146 and aldehydes 145, involving no acid catalyst.

2-Bromoketones 148 gave interesting thiazole derivatives 150 with thiourea/thioamide 149 in glycerol\textsuperscript{84}

Kumar, A. et al\textsuperscript{85} described a catalyst–free approach for C–H hydroarylation of \textit{in situ} generated ortho-quinone methide 154 from 4-hydroxycoumarins 151 and aldehydes 152, with electron rich arenes 153 (tertiary aryl amines) in glycerol.
Perin, G. et al.\textsuperscript{86} demonstrated efficient thioacetalization of aldehydes and ketones in glycerol, which combine carbonyl compounds 155 with 1,2-ethanethiol 156 and thiols 157, affording dithiolanes 158 and thioacetals 159 respectively.

Gu, Y. et al.\textsuperscript{87} used this medium in Diels–Alder reaction. Heating a mixture containing phenylhydrazines 160, $\beta$-ketoesters 161, paraformaldehyde 162, and styrenes 163 in glycerol at 110 °C gave pyrano[2,3-c]pyrazoles 164 in good yields.

Gu, Y. et al.\textsuperscript{88} also described a three–component intermolecular HDA reaction taking, together dimedone 89, formaldehyde 162 and styrene 165, in glycerol.

Perin, G. et al.\textsuperscript{89} obtained octahydroacridines 169 and 170 in good yields via one–pot HDA reaction of $(R)$–citronellal 167 with substituted arylamines 168 at 90 °C.
4.2.3 Ionic liquids in the organic synthesis

Rate enhancement, better yields and selectivity of a chemical reaction are key requirements of modern synthetic management.\textsuperscript{90} ILs, being best alternative to toxic and hazardous organic solvents (particularly chlorinated hydrocarbons) has received considerable attention in the synthesis.\textsuperscript{91} The green media has improved many synthetic routes;\textsuperscript{92} hence its demonstration is must and worth in the chemical synthesis.

4.2.3.1 ILs, their composition and properties

As low–melting salts (i.e. below 100 °C), ILs are electrolytes consisting of cationic and anionic species. Since their properties like melting point, viscosity, density and hydrophobicity can be modified with a particular end use, they are also known as designer solvents. Immiscibility with many organic solvents is useful polar alternative for two phase system. With thermal stability allowing a wide working temperature range, they have no vapor pressure, dissolving organic, inorganic and organometallic compounds. Significant impact on the reactivities and selectivities are due to their polar and non–coordinating properties. ILs are of two categories; simple salts and binary ILs. Example of former is [\text{EtNH}_3][\text{NO}_3] and of later is mixture of AlCl$_3$ and 1,3-dialkylimidazolium. Cations, in use, to build up ILs include ammonium, pyrrolidinium, phosphonium, sulfonium, and imidazolium. Anionic species include mononuclear [Cl$^-$, Br$^-$, NO$_3^-$, BF$_4^-$ etc.], bi– and polynuclear anions [Al$_2$Cl$_7^-$, Al$_3$Cl$_7^-$, Fe$_2$Cl$_7^-$ etc], which are sensitive to water. Sulfonamides are those ILs which contains both cationic and anionic centres in a single molecule.

Asymmetric cation confers ILs with lower melting.\textsuperscript{93} ILs may be hydrophilic and hydrophobic. Most tetra alkylammonium, alkylpyridinium, and 1,3-dialkylimidazolium ILs with perflorinated anions are hydrophobic.

4.2.3.2 Synthetic uses of ILs

Nature of ILs has great effect on the reaction. Acidic C(2) of imidazolium cation easily exchanges proton with base even in mild condition.\textsuperscript{94} Baylis–
Hillman reaction\textsuperscript{95} although 100\% atom economic in diazabicyclo[2.2.2]octane (DABCO), it takes more time. In [bmin]PF\textsubscript{6} however it is 33 times faster. Solubility of Knoevenagel adducts of malanonitrile in base KOH is drawback of [bmim][PF\textsubscript{6}]\textsuperscript{96}. Imidazolium ILs are thus suitable under basic condition for only few reactions.

\textbf{4.2.3.3 ILs used in chemical reactions}

Alkylation of isobutane by 2-butene in [bmim]Cl/AlCl\textsubscript{3} increases octane number of alkene produced. The reaction is more advantageous than the one in HF or H\textsubscript{2}SO\textsubscript{4}. Other examples are alkylation\textsuperscript{97} of benzene, indol and 2-napthol and active methylene units in C–C bond formation.

\[
\begin{align*}
\text{O} & \quad + \quad \text{RCH}_2\text{X} \quad \xrightarrow{\text{Et}_3\text{N}[\text{bpy}][\text{BF}_4]} \quad \text{60-70°C} \quad \text{RHC}_2\text{O} \\
14 & \quad 171 & \quad 172
\end{align*}
\]

More eco–friendly alkylation\textsuperscript{98} of methylene units is in palladium(0) by diphenylallyl acetate in [bmim]BF\textsubscript{4}.

Hydroformylation\textsuperscript{99} of higher olefins 173 competently soluble in ILs with PF\textsubscript{6}®, SbF\textsubscript{6}® and BF\textsubscript{4}® anions is industrially useful reaction.

\[
\begin{align*}
\text{CCl}_2\text{H}_2 \quad [\text{PtCl}_2(\text{PPh}_3)] & \quad \xrightarrow{[\text{bmim}][\text{Cl}][\text{SnCl}_2]} \quad \text{CHO} \\
173 & \quad + \quad 174 \\
\text{n: iso} = 19:1
\end{align*}
\]

The reaction rates and selectivity are enhanced more in [bmim]Cl–AlCl\textsubscript{3} than in conventional AlCl\textsubscript{3}\textsuperscript{100}. Chloroaluminates in Knoevenagel condensation have variable Lewis acidity.

\[
\begin{align*}
\text{R} & \quad \text{CHO} \quad \text{COOEt} \quad [\text{bmim}]\text{Cl} \times \text{AlCl}_3 \text{ or} \quad [\text{bpy}]\text{Cl} \times \text{AlCl}_3 \\
176 & \quad 177 & \quad 178
\end{align*}
\]

The Heck reaction\textsuperscript{101} of chlorobenzene with styrene in \textit{trans}-di(\textit{μ}-aceto) bis[\textit{o}-tollyphosphino]benzylidipalladium(II) in Bu\textsubscript{4}NBr is more economic than the one in expensive palladium catalyst.
Michel addition of acetylacetone 183 to methyl vinyl ketone 184 in Ni(acac)$_2$ in IL [bmim][BF$_4$] provides with excellent results in terms of activity, high selectivity and recyclable catalytic system.

Stereo–controlled Wittig reaction in [bmim]BF$_4^{102}$ involves no by–product (Ph$_3$PO) isolation. High yields of diaryl ethers from phenol, diaryl from aryl halide can be achieved in a base in [bmim][BF$_4$]–immobilized–CuCl than in DMF. ILs also promotes enzyme catalyzed reactions with other transformations. It includes Z–aspartame from carbobenzoxy–L–aspartate and L–phenylalanine methyl ester in catalyst thermolysin in [bmim][PF$_6$]. The usefulness of Diels–Alder$^{103}$ reaction lies in its high yield and high stereospecificity in ILs, and examples include [bmim][BF$_4$], [bmim][ClO$_4$], [bmim][CF$_3$SO$_3$], [bmim][NO$_3$] and [bmim][PF$_6$]. The reduction of aromatic and aliphatic aldehydes with trialkylborane generally requires higher temperature (150 ºC). But in [bmim][BF$_4$] and [bmim][PF$_6$] reaction rate enhances at low temperature. Other IL mediated reactions includes oxidation of aldehyde,$^{104}$ alcohol$^{105}$ and oximes,$^{106}$ oxidative carbonylation of amines,$^{107}$ Wacker type oxidation$^{108}$ and hydrogenation,$^{109}$ C–C bond forming Aldol reaction,$^{110}$ Suzuki,$^{111}$ Still,$^{112}$ and Negishi,$^{113}$ and Trost–Tsuji$^{114}$ type coupling reactions, Sakui,$^{115}$ Henry,$^{116}$ Stetter,$^{117}$ and Songashira$^{118}$ type reactions.

4.2.3.4 ILs used in HDA reaction

Fischer, T. et al.$^{119}$ reported Diels–Alder reaction between methyl acrylate 187 and cyclobutadiene 186 in a number of air and moisture stable ILs; [bmim][BF$_4$], [bmim][ClO$_4$], [bmim][CF$_3$SO$_3$], etc. with endo selectivity.
Recently, we\textsuperscript{121} reported some new angular benzopyran[3,4-c]pyranofused pyrazoles 196 from O-allylated/prenylated 2-hydroxyacetophenones 194 in ionic liquid cum–catalyst TEAA. The method is highly efficient, even in case of unactivated dieneophile too.

Another report from our laboratory\textsuperscript{122} also describes the application of TEAA in efficient synthesis of pyrano– and thiopyrano fused heterocycles 199 via DKHDA strategy.

Balalaie, S. \textit{et al.}\textsuperscript{123} performed DKHDA reaction of substrates 200 & 201 with unactivated dieneophile in catalyst zirconium oxide (NP)–[bmim][NO\textsubscript{3}].
4.3 Pyran–annulated heterocycles

Pyran is a six–membered oxygen containing heterocycle with two double bonds. It has four sp\(^2\) and one sp\(^3\) hybridized carbon making it a non–aromatic system.

Pyran–annulated heterocycles constitute an important class of compounds, found as important constituents of natural and synthetic products. They are well known antioxidant, anti–inflammatory, antiviral, antiallergic, hepatoprotective, anticarcinogenic, hypnotic, anthelmintic, insecticidal hepatoprotective, anticarcinogenic, anticoagulant and antifungal agents, in addition to HIV protease inhibitors.\(^{124}\) Naturally occurring compounds that include isoethuliacoumarin A, isoethuliacoumarin B, isoethuliacoumarin C, ethuliacoumarin A, ethuliacoumarin B, pterophyllin, calonone, isocalonone, (+) calanolide A, soulattroide and (+)-isofer–prenin,\(^{125}\) all possess a pyranocoumarin skeleton.

Compounds containing pyranone unit exist in plants, animals, marine organisms, bacteria and insects. They also involve in different biological processes like defense against other organisms, biosynthetic and intermediates, and as metabolites. They are also precursors to pharmacologically active compounds such as HIV protease inhibitors,\(^{126}\) antifungal,\(^{127}\) cardiotonics,\(^{128}\) anticonvulsants,\(^{129}\) antimicrobials,\(^{130}\) pheromones,\(^{131}\) natural pigments,\(^{132}\) antitumor agents,\(^{133}\) and plant growth regulators.\(^{134}\) Microbially derived 2-pyranones, from fungi of various genera, are found to display a wide range of cytotoxic, neurotoxic and phytotoxic properties.
Chapter 4

Figure 4.5 Naturally occurring compounds containing pyran

Palasz, A., synthesized pyrano[2,3-d]pyrimidines 206 & 207 via intermolecular HDA reaction of an aldehydes 203, barbituric acids 204 and ethyl vinyl ether 205.

Braun, A. E. et al., synthesized pyrano embelin derivatives 210 via DKHDA reaction of embelin 208 with paraformaldehyde and electron rich alkenes 209.

Intramolecular HDA reaction of 6-(4-alkenylxoymethylene)-2,4-cyclohexadien-1-ones 213—generated from salicylaldehyde derivatives 211 and unsaturated alcohols 212, afforded pyrano[3,2-c]benzopyrans 214.

Prajapati, D. and Gohain, M., investigated a new, simple and efficient synthesis of novel fused pyrimidines 217 via an inverse electron-demand HDA reaction. Dienophiles such as ethyl vinyl ether or dihydrofuran 216 were reacted.
with \textit{in situ} generated heterodiene $\alpha\beta$-ethylenic ketones 215 in the presence of 1 mol \% indium(III) trichloride.

\[
\text{215} \quad \text{+} \quad \text{216} \quad \xrightarrow{\text{InCl}_3} \quad \text{217}
\]

Lee, Y. R. and Hung, T. V.\textsuperscript{139} described synthesis of pyrano-fused tetrahydroquinoline 220 from $N,N$-dialkylated aminobenzaldehydes 218 and 1,3-diketones 219 in xylene using EDDA.

\[
\text{218} \quad \text{+} \quad \text{219} \quad \xrightarrow{\text{EDDA} \quad \text{Xylene}} \quad \text{220}
\]

Phenylsulfinyl- or phenylsulfonyl-2-propanone as well as phenylsulfonyl-acetophenone yielded corresponding Knoevenagel condensation products 221 with methyl-2-butenyloxy- and (E)-phenyl pro-penyloxybenzaldehyde that underwent intramolecular cycloaddition to major \textit{cis}-fused 2$H$-pyran derivatives 222. Generally, a \textit{cis}-diastereomer 222 or its mixture with \textit{trans}-223 was obtained.\textsuperscript{140}

\[
\text{221} \quad \xrightarrow{\text{PhS(O)}_n \quad \text{OR}^1 \quad \text{R}^2} \quad \text{222} \quad + \quad \text{223}
\]

Deb, M. L. and Bhuyan, P. J.\textsuperscript{141} synthesized pyrano annulated–pyrido[2,3-$d$]pyrimidines 226 \& 227 from 6-$N$-allyl-1,3-dimethyl-5-formyl uracils 224 and 1,3-diketones 225.
Nair, V. et al. reported *in situ* generated quinone 228 via Knoevenagel condensation of 4-hydroxycoumarin 44 and formaldehyde that underwent a facile Diels–Alder reaction with pentafulvenes 229 to afford novel pyranocoumarin derivatives 230 in good yield.\(^{142}\)

Our research group has also reported a solvent– and catalyst–free DKHDA reaction for pyrano–fused polyheterocycles from 231 and 232. Subsequent reduction of azo group afforded analogues amino frameworks 233.\(^{143}\)

Ghandi, M. et al.\(^{144}\) described catalyst–free and diastereoselective synthesis of novel dihydropyrano[3,2-\(c\)]chromen–annulated benzosultams 235 & 236 from \(N\)-(2-formylphenyl)-\(N\)-methyl- 2-phenylethenesulfonamides 234 and coumarin 44.
Baruah, B. and Bhuyan, P. J. described some complex pyrano[2,3-b]quinolines 239 from quinoline 237 and 1,3-dimethylbarbituric acid 238 using water.\textsuperscript{145}

Majumdar, K. C. \textit{et al.}\textsuperscript{146} described regioselective synthesis of chromeno [4′,3′:4,5]pyrano[3,2-c][1,8]naphthyridin-13-ones 242 via DKHDA reaction of 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1H)-one 241 with O-allylated/propargylated salicylaldehydes 240.

Raghunathan, R. \textit{et al.}\textsuperscript{147} reported pyranoquinoliones 245, 246 from 4-hydroxy-1,2-dihydro-2-quinolinones 243 and O-prenylated aromatic aldehydes 244 or aliphatic aldehyde citronellal \textit{via} an intramolecular HDA strategy. A high degree of chemoselectivity was achieved under a MWI condition.

4.4 Present work

Present \textbf{Chapter 4} of Part-II introduced to DKHDA strategies, TBA-HS, Glycerol and ionic liquids in organic synthesis, along with pyran-based heterocycles. Rest of the Part-II disseminates the synthesis and biological evaluation of pyran–annulated heterocycles in two \textit{Chapters 5} and \textit{6}. Both
intramolecular (Chapter 5) and intermolecular (Chapter 6) DKHDA approaches had been optimized and studied in three different conditions; TBA-HS under solvent–free environment—demonstrating pyrazolo—, benzopyrazolo and benzopyrano[2,3,4-kl] xanthenes, in glycerol—demonstrating pyrazolopyrano-fused thiochromeno[2,3-b] quinolines and in ionic liquid TEAA—demonstrating quinolyl— and indolylpyrano[2,3-c]pyrazoles. Biological screening tests were employed to determine in vitro antimicrobial, anti–tuberculosis and antioxidant activities.

References

18. (a) Tietze, L. F.; Saling, P. *Synlett* 1992, 281; (b) Tietze, L. F.; Saling, P. *Chirality* 1993, 5, 329.


92. (a) Ahluwalia, V. K.; Malhotra, S. *Environmental Science*, Ane Books, India, 2006, and the reference cited there in; (b) Ahluwalia, V. K. *Environmental Chemistry,


