SRI VENKATESWARA INTERNSHIP PROGRAM
FOR RESEARCH IN ACADEMICS
(SRI-VIPRA)

SRI-VIPRA

Project Report of 2023: SVP-2319

Deep eutectic solvents: Environment friendly media for Organic synthesis

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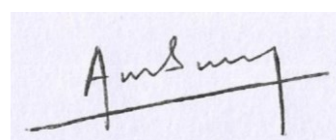
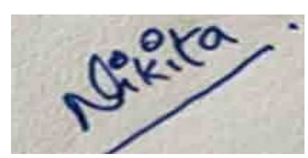
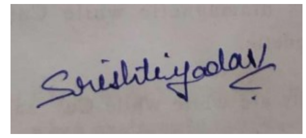
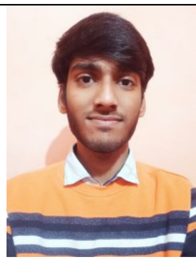
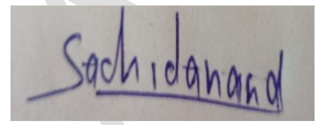
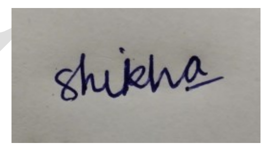
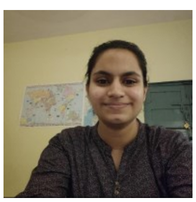
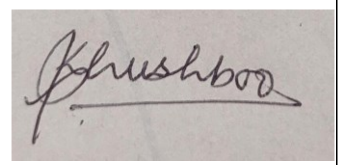
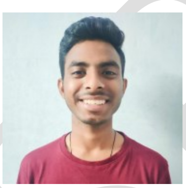
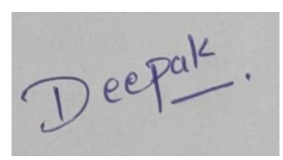
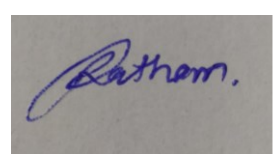
SRIVIPRA PROJECT 2023

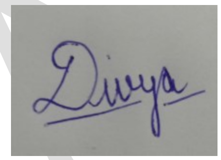
Title: Deep eutectic solvents: Environmental friendly media for Organic synthesis

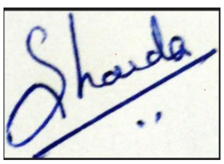
Name of Mentor: Prof. Sharda Pasricha **Name of Department:** Chemistry **Designation:**	**Photo** 

Table: List of students under the SRIVIPRA Project.

S.No.	Photo	Name of the student	Roll number	Course	Signature
1		Ann Sunny	1520039	B.Sc.(H) Chemistry	
2		Nikita Tuwani	1520048	B.Sc.(H) Chemistry	

3		Srishti Yadav	1520009	B.Sc.(H) Chemistry	
4		Sachidanand	1520063	B.Sc.(H) Chemistry	
5		Shikha	1520005	B.Sc.(H) Chemistry	
6		Khushboo Pilania	1521036	B.Sc. (H) Chemistry	
7		Deepak	1520017	B.Sc (H) Chemistry	
8		Pratham	1520035	B.Sc. (H) Chemistry	

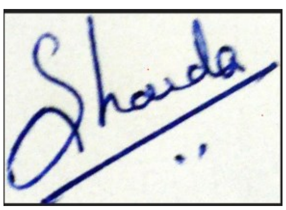
9		Harsh Pahuja	1522080	B.Sc. (H) Chemistry	
10		Divya Yadav	1520022	B.Sc. (H) Chemistry	



Signature of Mentor

CERTIFICATE OF ORIGINALITY

This is to certify that the aforementioned students from Sri Venkateswara College have participated in the summer project **SVP-2319** titled "**Deep eutectic solvents: Environment friendly media for Organic synthesis**". The participants have carried out the research project work under my guidance and supervision from 15 June, 2023 to 15th September 2023. The work carried out is original and carried out in an online/offline/hybrid mode.



Signature of Mentor

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Introduction

Solvents define fundamental features of chemical reactions and processes since they are important in the dissolution of reactants, catalysts, and reagents. Additionally, they aid in the purification and isolation of target chemicals, encourage mass and heat transmission, and have an impact on viscosity. Further, they can be deployed as catalysts in a number of reactions. Traditional solvents including toluene, acetonitrile, dimethyl formamide (DMF), etc. are currently discouraged due to their volatility and associated toxicity. Supercritical and gas-expanded fluids (SCFs), ionic liquids (ILs), biobased solvents, water, and fluorous solvents are just a few of the neoteric greener solvents that have garnered significant interest of the synthetic organic chemists. However, high toxicity and availability of fluorinated solvents, the procedural requirements for using SCFs, and the higher costs, toxicity, and tedious synthesis for ILs are some of the drawbacks that have shifted the focus towards biobased solvents. Deep eutectic solvents, a class of biobased solvents have caught the attention of chemists in the last decade as benign media and catalyst for organic reactions.

The synthesis of complex carbon frameworks that serve as vital intermediates in polymers, drugs, materials, natural products, and agrochemicals is made possible by the widespread use of C-C, C-N, C-S, C-O cross-coupling reactions, which are also hailed as useful toolboxes for the synthesis of unsubstituted molecules with well-defined stereochemistry.

In 2010, Suzuki, Heck and Negishi won the Nobel Prize, ushering in a new era of Pd-catalysts that have subsequently been crucial to cross-coupling reactions. Unique characteristics of Palladium (Pd) metal like moderate atomic size and partly occupied d-orbitals permit both electron pair acceptance and donation during catalyzed reactions as well as bestow excellent catalytic ability and reasonable stability to Pd based catalysts. There have also been reports of other coinage metals (such as Cu, Ag) and earth abundant, less toxic and low-cost transition metals-based catalysts such as Ni, Co, Ir, etc. for cross-coupling processes.

This project was aimed at exploring the synergy of Deep Eutectic Solvents, a class of biobased solvents, and transition metal catalysts for cross-coupling reactions.

Report

Deep eutectic solvents, a neoteric and designer task-specific, biobased solvents, surmised as “the organic reaction medium of the century”, have reverberated a new symphony throughout the present green millennium as eco-friendly substitutes for ionic liquids. DESs are eutectics usually prepared by mixing a hydrogen bond acceptor (HBA), for example, an inexpensive quaternary ammonium salts such as choline chloride (ChCl, included in the so-called vitamin B_4) produced on a scale of millions of tons per year, and a hydrogen bond donor (HBD) such as sugars, organic and amino acids, urea (most of them are from renewable resources) or glycerol (a waste product from biodiesel production). Thus, compared to other conventional solvents, DESs are recognized as nonflammable, thermally stable, biodegradable, relatively less toxic, non-volatile, and cheaper to produce. These solvents may play the role of an active catalyst/co-catalyst/reagent besides serving as the solvent for the reaction. Surprisingly, they play an important role in Nature, including solubility of animal metabolites, cryoprotection, dehydration and germination processes. Undoubtedly, eutectic mixtures are the missing pieces in Nature’s puzzle that significantly caught the attention of scientists in view of widespread possible applications. The advent of DES had a profound influence on scientific development, not only for being a new greener and recyclable medium but also for their ever-burgeoning applications in the fields of extraction, gas separation, analytical chemistry, renewable energy storage, biomass valorization, drug discovery and carriers, as well as in biotechnology and bioengineering. DESs are a modern generation of eutectic solvents that have started a new and exciting journey in the realms of the environmentally benign medium. **Figure 1** reaffirms the promise of finding DESs in almost every area of sciences and technologies in the near future.

Figure 1 Application of deep eutectic solvents in plethora of sciences and technologies

When employed for cross-coupling reactions, standard organic solvents have drawbacks such high toxicity, slow reaction rates, poor selectivity, average yields, non-recyclability, and narrow substrate range. Since cross-coupling reactions are associated with negative activation volumes and decreasing entropy owing to the conversion of two substrates to one molecule of the product, therefore the DESs with high-pressure cavities could be eminent candidates as solvent/catalyst/reagents for these reactions. Additional catalytic sites, increased stability, and recyclability in task-specific DESs further contributes to their rising popularity. With the evolution of the field, newer applications of DES are also coming into foray, their use as reagent is one such interesting domain. Therefore, use of DES is an incessantly improving practice in organic and biochemistry. The publication frequency on deep eutectic solvents in recent years is illustrated in Figure 2, with amazing growth.

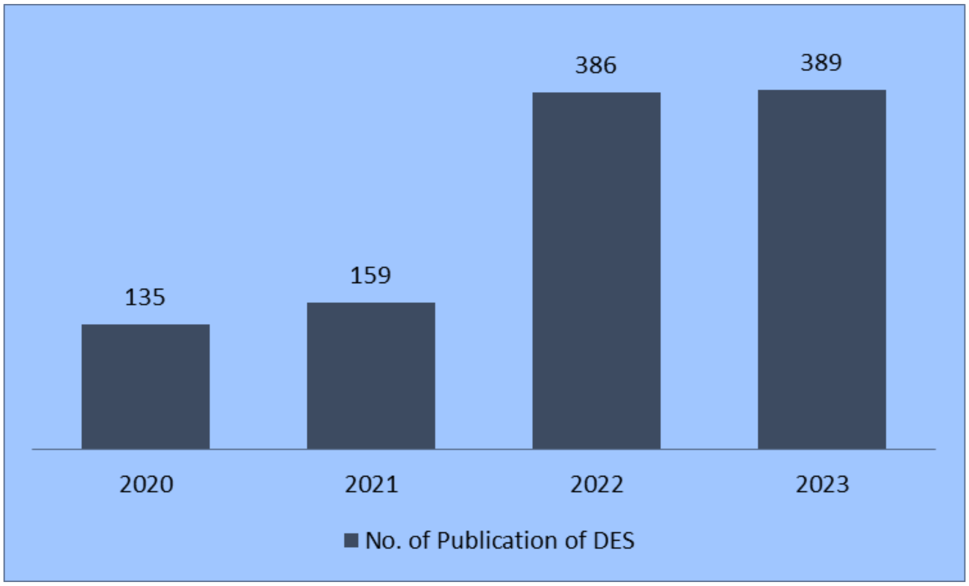

Figure 2 Frequency of publications regarding DESs from 2020 to 2023 (obtained from a search of the title, abstract, or keywords contained in Scopus)

The synergy of DES and transition metal catalysts for cross-coupling reactions was explored and some of the results are summarized in **Table 1**.

Table 1 Selective coupling reactions depicting DES and Transition Metal synergy

Reaction	HBA: HBD	TM Catalyst (Homogeneous/ Heterogeneous)	Product	Role of DES
Suzuki Miyaura coupling	ChCl: GLY 1:2	$Pd(OAc)_2$ (Homogeneous)	Benzodithiophenes	Solvent
	ChCl: Gly 1:2	$PdCl_2$ (Homogeneous)	3-Aryl thiophenes	Solvent
	PC:EG 1:10	XPhosPd (Homogeneous)	Benzo(2,3)(1,4)oxazepino(7,6-b) quinolines	Solvent
	PC:EG 1:1	$Pd(PPh_3)_4$ (Homogeneous)	3,4-Dihydroacridin-1(2H)-ones or 2-phenyl-3-(2-(4-phenylquinolin-2-yl) vinyl) quinolines	Solvent and catalyst
	PC: Gly 1:5	Fe_3O_4@PFC-Pd (0) (Heterogeneous)	Biphenyls	Solvent
	Ser:LA 1:5	Fe_3O_4@SBA-15@ZIF-8@Pd (Heterogeneous)	Biphenyls	Solvent
	ChCl: Gly 1:2	GO/Fe_3O_4@G_2/Co (Heterogeneous)	Biphenyls	Solvent
	ChCl:Urea 1:2	$Ni(cod)_2$ (Homogeneous)	2-Arylthiophenes	Solvent

Sonogashira coupling	PC:EG 1:10	XPhosPd (Homogeneous)	Benzo(2,3)(1,4)oxazepino(7,6-b) quinolines	Solvent
	ChCl:Gly 1:2	Pd/C (Heterogeneous)	Phenylacetylenes	Solvent
	PC:EG 1:5	Fe_3O_4@PFC-Pd (0) (Heterogeneous)	1,2-Diphenylacetylenes	Solvent
	DMAC: Gly 1:2	GO/Fe_3O_4@ Cellulose-Pd (Heterogeneous)	1,2-Diphenylacetylenes	Solvent
	ChCl: Gly 1:2	GO/Fe_3O_4@G_2/Co (Heterogeneous)	Phenylacetylenes	Solvent
Mizoroki-Heck coupling	ChCl: Gly 1:2	$Pd(OAc)_2$ (Homogeneous)	Tetrahydropyran (THP) and tetrahydrofuran (THF)	Solvent
	ChCl: Gly 1:2	$PdCl_2$ (Homogeneous)	2,5-Diarylthiophenes	Solvent
	ChCl: EG_2: DABCO 1:2:1	Pd@BUT-11 (Heterogenous)	Stilbenes	Solvent and catalyst
	ChCl: Gly 1:2	$Sn_{0.79}Ce_{0.20}Pd_{0.01}O_{2}-\delta$ (Heterogenous)	4-Hydroxystilbenes	Solvent
	DMAC: Gly 1:2	GO/Fe_3O_4@Cellulose-Pd (Heterogeneous)	Stilbenes and Cinnamates	Solvent
NEGISHI COUPLING REACTION	ChCl: Gly 1:2	$Pd[P(t\text{-}Bu)_3]_2$ (Homogeneous)	Arenes	Solvent
C-N Cross-coupling	ChCl: Water 2:1	CuI (Homogeneous)	Secondary/ tertiary amides	Solvent
Ullmann Type C–N Coupling	ChCl: Gly 1:2	CuI (Homogeneous)	Tertiary amines	Solvent
	ChCl: Gly 1:2	Fe_3O_4@L-Arginine-AC-Cu_2O (Heterogeneous)	Secondary amines	Solvent
C-O coupling reaction	ChCl: ROH 1:2	CuI or $CuCl_2$ (Homogeneous)	Aryl alkyl ethers	Solvent and Reagent
A^3 Coupling reaction	ChCl: Urea 1:2	CuCl (Homogeneous)	Propargylamines	Solvent
Glaser reaction	ChCl: Urea 1:2	CuI@g-C_3N_4/PEI (Heterogeneous)	1,3-Butadiynes	Solvent
	ChCl: EG: $Cu(OAc)_2$ 1:2:0.05	-	1,3-Butadiynes	Solvent and catalyst
Reductive coupling of olefins	ChCl: EG 1:2	$Fe(acac)_3$ (Homogeneous)	Poly substituted alkanes	Solvent and Catalyst

Conclusion

The results of the study clearly demonstrates that ChCl:Gly (1: 2) is possibly the most recurrently employed DES for cross-coupling reactions. Low toxicity and easy availability make glycerol a perfect contender along with ChCl to yield a model DES system for cross-coupling transformations. Further, transition metal-DES synergy was demonstrated to play a crucial role for green and sustainable synthesis of a plethora of complex organic molecules. It is believed that current study will help the chemists, material scientists, researchers and academicians working in pharmaceuticals, polymers, total synthesis of natural products and catalysis domain for the improved design and development of newer green media, reagents and catalysts for C–C, C–S, C–N, C–O cross-coupling reactions as well as the generation of other neoteric chemical linkages.

Future Plan

Having explored the synthetic utility of DES and transition metal catalysts for cross -coupling reactions, we plan to explore the utility of biologically important heterocycles using DES as media and catalysts.

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