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EFFICIENT AND SUSTAINABLE SYNTHESIS OF ARYL ETHER FROM TOSYLHYDRAZONES AND PHENOLS VIA SIMPLE AMINO ACID L-PROLINE CATALYSIS

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ABSTRACT
Aryl ethers are ubiquitous motifs in natural products and pharmaceutical compounds. They also serve as highly versatile scaffolds in synthetic organic chemistry. Traditionally, the synthesis of aryl ethers has often relied on transition-metal-catalysed reactions under harsh and potentially hazardous conditions. In contrast, this work introduces a novel, mild, and efficient strategy for synthesising aryl ethers through the reductive coupling of tosylhydrazones with phenols, utilising the readily available and environmentally benign amino acid L-proline as an organocatalyst. L-Proline is well known for its versatility in both asymmetric and non-asymmetric transformations, and in this reaction, its secondary amine and carboxylic acid functionalities act cooperatively to promote catalysis. This protocol provides a practical, metal-free alternative for aryl ether formation, demonstrating broad functional group tolerance and operational simplicity.
Keywords: L-Proline, Aryl Esters, Organobase Catalyst, Reductive Coupling, Tosylhydrazones.
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INTRODUCTION

The Robinson asymmetric annulation catalysed by (S)-proline, independently reported in the 1970s, represents a landmark in the field of organocatalysis and is now widely recognised as the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[1-3] Organocatalysts are particularly appealing for large-scale synthesis[4] because of their non-toxic nature, low cost, chemical stability and easy availability. They typically function under mild conditions, and immobilisation facilitates their straightforward recovery. Moreover, their metal-free character aligns closely with the principles of green chemistry.[5] L-Proline, in particular, has established itself as a highly versatile and efficient organocatalyst for a wide range of asymmetric transformations, including Aldol[6,7], Michael[8,9] and Mannich[10] reactions, as well as α-hydroxyamination, polymerisation, and multicomponent one-pot strategies. Simultaneously, transition-metal-mediated cross-coupling reactions[11-13] have revolutionised the synthesis of C-C and C-heteroatom bonds. Among these, C-O bond-forming reactions are especially significant for accessing biologically active diaryl ethers.[8,9] However, the use of traditional etherification reagents often suffers from drawbacks such as non-recyclability and environmental impact, necessitating greener alternatives. In this study, L-proline, a readily available and simple amino acid, is employed as a metal-free organocatalyst to promote the reductive coupling of aryl tosylhydrazones[14] with phenols, providing an efficient, sustainable, and practical synthetic route to aryl ethers, which are important scaffolds in pharmaceutical chemistry.[15,16]

EXPERIMENTAL

Material and Methods

All reagents and solvents employed in this study were of spectral grade. Melting points were determined in open capillary tubes and are reported uncorrected. All synthesised compounds were structurally characterised using GC–MS analysis.

Synthesis of Tosylhydrazones

A mixture of ketone or aldehyde (1equiv., 1.96 g) and p-toluenesulfonyl hydrazine (1 equiv., 3.72 g) in 50 mL of methanol was added to a 100 mL round-bottom flask and stirred at room temperature for 10 minutes.

The reaction mixture was subsequently heated to 70 °C and stirred until completion, as determined by thin-layer chromatography. Upon completion, the reaction mixture was cooled to room temperature, and the resulting solid was isolated by filtration and dried under vacuum for further analysis.

General Procedure for L-Proline-catalyzed Synthesis of Aryl Ether

L-Proline (1.15 g, 10 mmol) and tosylhydrazone (50 mg) were dissolved in ethanol (5 mL) and stirred at ambient temperature for 10 minutes. Phenol (16 mg) was added dropwise, and the reaction mixture was stirred at 80 °C for the optimized reaction period. The reaction progress was monitored by thin-layer chromatography. Upon completion, the reaction mixture was extracted with dichloromethane, dried and concentrated under reduced pressure. The crude product was purified by column chromatography and characterized by GC–MS, as NMR spectroscopy could not be performed due to the product's volatility and low boiling point.

RESULTS AND DISCUSSION

L-Proline was employed as a sustainable organocatalyst for the reductive coupling of tosylhydrazones with phenols to synthesise aryl ethers. A model reaction between tosylhydrazone (1a) and phenol (2a) was used to optimise reaction parameters. Screening various solvents under reflux revealed that ethanol was the most effective, affording a 96% yield of product (3a) at 80°C in 12 h, while chloroform and water gave poor conversions due to catalyst dispersion and solubility limitations. Protic solvents such as methanol and isopropanol also performed well (>90%), but ethanol provided a cleaner reaction profile with no detectable by-products. Catalyst loading studies (Table-1) established that 10 mol% L-proline was sufficient for full conversion, compared to the initial 50 mol%. Thus, ethanol was identified as the optimal medium, and a reaction time of 12 hrs. was found ideal for maximum yield.

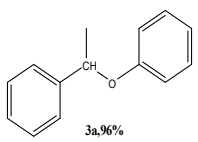
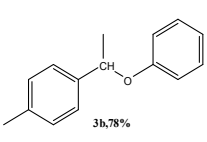
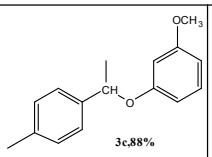
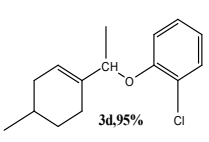
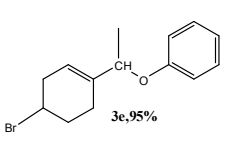
Table-1: Catalyst Load Optimisation for L-Proline Catalysed Etherification[a]

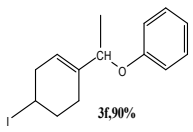
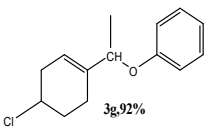
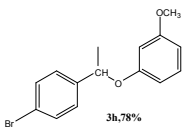
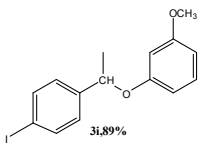
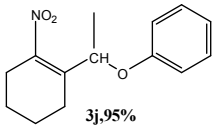
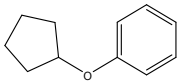
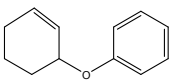
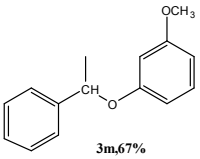
S. No.	Catalyst Load (in mmol)	Yield (%) [b]	S. No.	Catalyst Load (in mmol)	Yield (%) [b]
1	50	96	6	5	89
2	40	96	7	3	78
3	30	96	8	2	49
4	20	96	9	1	22
5	10	96	10	0	NR

[a]Reaction conditions: Tosylhydrazones (1a) (1 mmol) and phenol (1mmol) with L-Proline in a 5 mL of Ethanol at 80 °C for 24 hours. [b]All are isolated in yield.

The reaction proceeded efficiently at 80 °C, with no improvement in yield at higher temperatures and diminished efficiency at lower temperatures. L-Proline effectively catalysed the transformation without requiring additional additives or elevated temperatures. Optimisation confirmed highly selective aryl ether formation through reductive coupling, even when reactants were used in excess. Employing ethanol as the solvent and 10 mol% L-proline as the catalyst, the protocol was successfully extended to a range of tosylhydrazones and phenols, affording aryl ethers (3a-3m) in good to excellent yields, free from detectable impurities (Table-2). Both electron-donating and electron-withdrawing phenols exhibited excellent reactivity, while unsubstituted tosylhydrazones provided consistently good yields. In contrast, sterically hindered alkyl-substituted tosylhydrazones resulted in lower yields, likely due to solubility limitations (e.g., compounds 3g and 3b). Similarly, substituted phenols afforded moderate to good yields (e.g., compounds 3c, 3h, 3i, and 3m).

Table-2: L-Proline Catalysed Synthesis of Aryl Ether from Tosylhydrazones and Phenols

 3a,96%	 3b,78%	 3c,88%	 3d,95%	 3e,95%

 3f,90%	 3g,92%	 3h,78%	 3i,89%	 3j,95%
 3k,56%	 3l,65%	 3m,67%	[a] Reaction conditions: Tosylhydrazones (1 mmol) and phenols (1 mmol) with L-Proline (1 mmol) in a 5 mL of ethanol at 80 °C for 12 hours; [b] Gram scale, all are isolated yields.	

To assess the scalability of the developed protocol, the reaction was performed on a gram scale using tosylhydrazone (1a) and phenol (2a), affording aryl ether (3a) in 96% yield, comparable to the yield observed in the small-scale experiment (Table.2). The catalytic efficiency of L-Proline was further assessed through control experiments employing other organic bases, including triethylamine, TMEDA, and K_2CO_3, under identical reaction conditions (Table.3). These alternatives exhibited low reactivity and poor yields, likely due to the absence of a carboxylic acid functional group essential for effective catalysis. Even K_2CO_3, a commonly used base, failed to replicate L-proline's efficiency, confirming that its dual functionality secondary amine and carboxylic acid groups play a pivotal role in its superior catalytic activity.

Table-3: Control Experiment with Various other Catalysts[a]

S. No.	Catalysts	Yield (%) [b]
1	Triethyl amine	12
2	Di-isopropyl amine	05
3	Tetramethyl ethylene diamine	02
4	Pyridine	16
5	APTES	NR
6	K_2CO_3	68
7	L-Proline	96
8	Without catalyst	NR

[a]Reaction conditions: Tosylhydrazones (1a) (1 mmol) and phenol (1 mmol) with catalyst (10 mmol) in 5 mL of Ethanol at 80 °C for 24 hours. [b] All are isolated yields.

Table-4: Comparison of other Catalyst Used in the Etherification Reaction

Entry	Catalyst	Solvent	Catalyst load (%)	Temp. (˚C)	Time (hours)	Yield (%)	Ref.
1	K_2CO_3	1,4-Dioxane	3.5 eq	110	24	72	17
2	L-Proline	Ethanol	1.15 g	80	12	96	Present work

Table-4 provides a comparison of various base-catalyzed etherification strategies. In contrast to previously reported methods, the present organocatalytic protocol employing cost-effective and readily available L-proline offers a simpler and more efficient route for the synthesis of aryl ethers via tosylhydrazone-phenol coupling, delivering high yields under mild conditions.

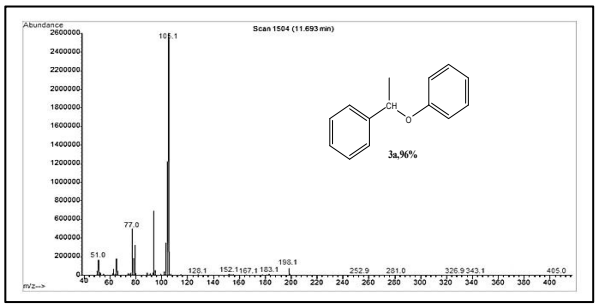


Fig.-1: GC-MS for (1-phenoxyethyl) Benzene (3a)

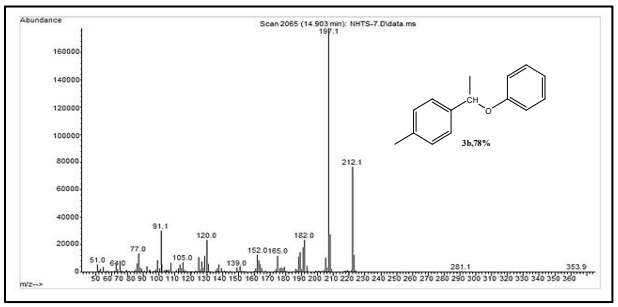


Fig.-2: GC-MS for 1-methyl-4-(1-phenoxyethyl) benzene (3b)

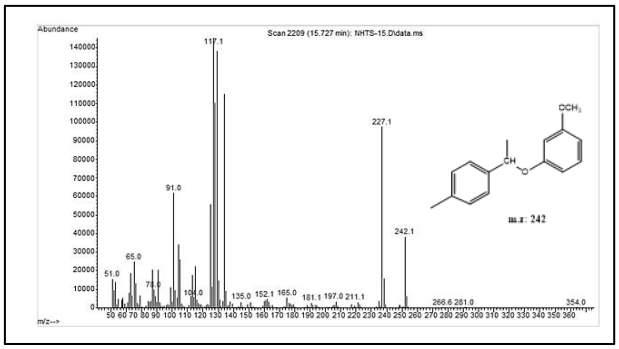


Fig.-3: GC-MS for 1-methoxy-3-(1-(p-tolyl)ethoxy) benzene (3c)

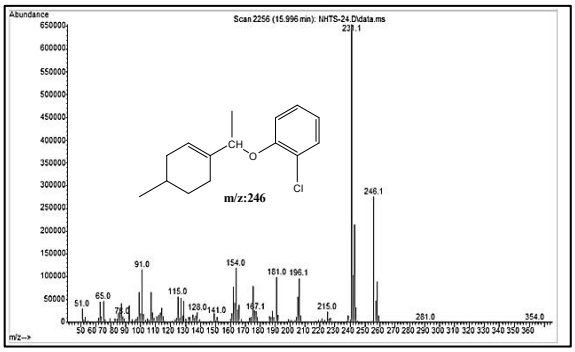


Fig.-4: GC-MS for 1-chloro-2-(1-(p-tolyl)ethoxy) benzene (3d)

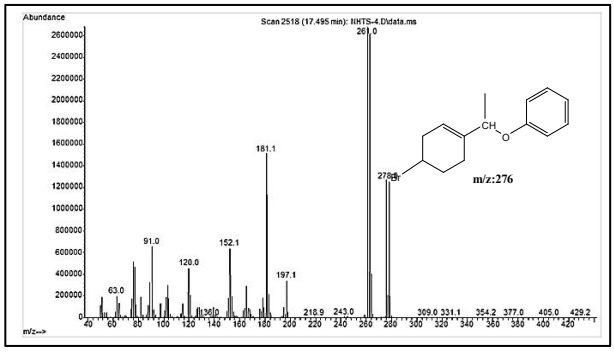


Fig.-5: GC-MS for 1-bromo-4-(1-phenoxyethyl) benzene (3e)

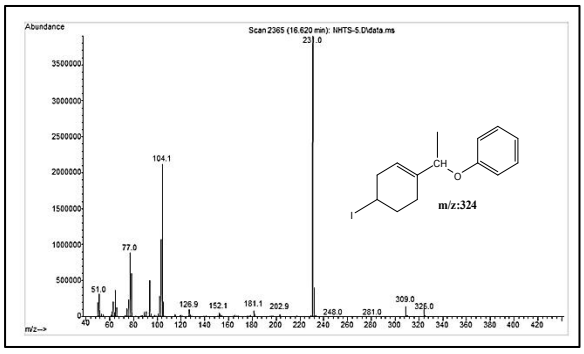


Fig.-6: GC-MS for 1-iodo-4-(1-phenoxyethyl) benzene (3f)

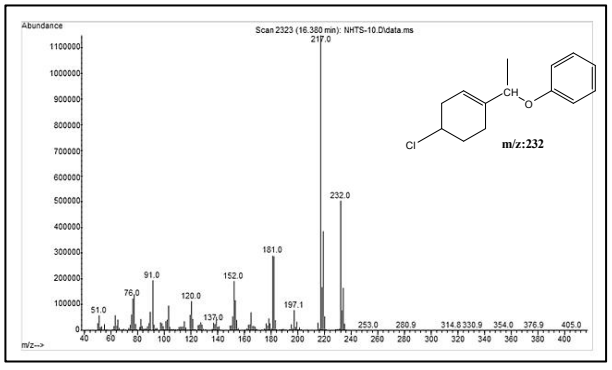


Fig.-7: GC-MS for 1-chloro-4-(1-phenoxyethyl) benzene (3g)

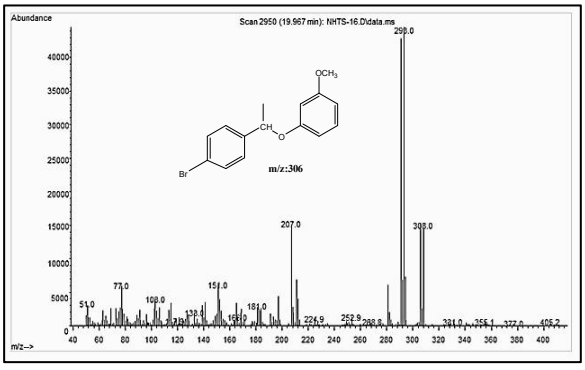


Fig.-8: GC-MS for 1-(1-(4-bromophenyl)ethoxy)-3-methoxybenzene (3h)

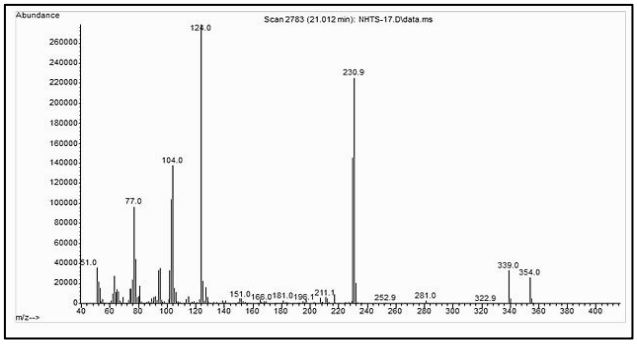


Fig.-9: GC-MS for 1-(1-(4-iodophenyl)ethoxy)-3-methoxybenzene (3i)

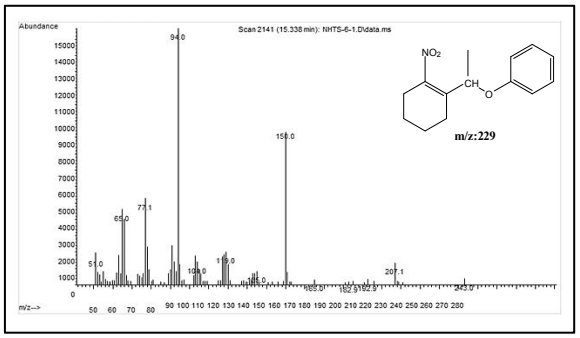


Fig.-10: GC-MS for 1-nitro-2-(1-phenoxyethyl)benzene (3j)

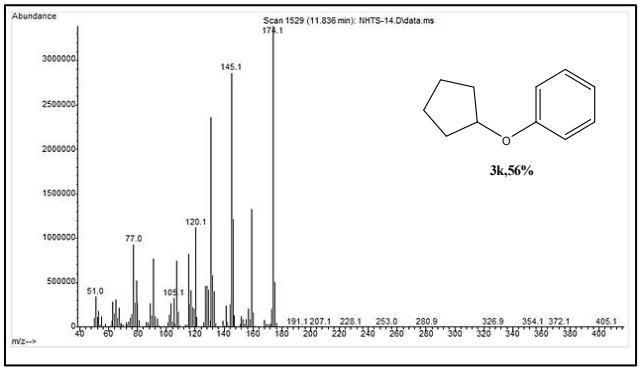


Fig.-11: GC-MS for (cyclopentyloxy)benzene (3k)

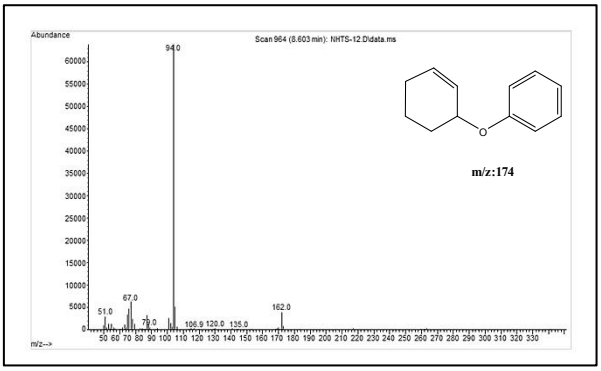


Fig.-12: GC-MS for (cyclohex-2-en-1-yloxy) benzene(3l)

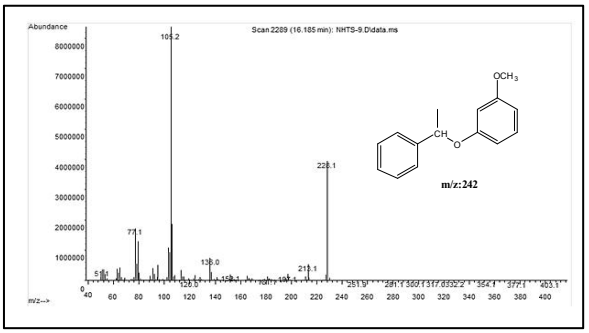


Fig.-13: GC-MS for 1-methoxy-3-((4-methylbenzyl)oxy) benzene (3m)

CONCLUSION

In conclusion, a sustainable and effective L-proline-catalysed a secondary amine functionalized organo-base, efficiently catalyzes the reductive coupling of tosylhydrazones with phenols to afford aryl ethers in good to excellent yields under mild, eco-friendly conditions. The process was successfully performed on a gram scale and shown acceptable substrate compatibility. The greater catalytic activity of L-proline in comparison to other widely used organic bases and inorganic bases was further shown by control studies. Therefore, by omitting transition-metal catalysts and severe reaction conditions, the current technology offers a straightforward, useful, and ecologically safe alternative for C-O bond synthesis.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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