A STUDY OF CHIRAL ENVIRONMENT INFLUENCE IN ORGANOCATALYTIC REACTIONS FOR ENHANCED EFFICIENCY

Varleen Kaur
Research Scholar
Department of Chemistry
NIILM University, Kaithal (Haryana)
varleen.kaur86@gmail.com

Dr. Ashish Narain Dubey
Professor
Department of Chemistry
NIILM University, Kaithal (Haryana)

ABSTRACT

In organic chemistry, chirality is crucial, especially when creating physiologically active compounds with enantiomers that have different effects. This work investigates the in situ synthesis of chiral oxazaborolidine catalysts using methyl iodide, tetrabutylammonium borohydride, and (1S,2R)-(-)-cis-1-amino-2-indanol. The asymmetric reduction of prochiral ketones to enantiopure alcohols, a crucial conversion in the chemical and pharmaceutical sectors, was carried out using these catalysts.

The results showed that because of the increased electrophilicity of the carbonyl carbon, which facilitates efficient transition states, electron-withdrawing substituents on acetophenone derivatives greatly improved enantioselectivity (up to 96% ee). Under moderate circumstances, the improved system produced good yields, demonstrating its usefulness and effectiveness.

This research positions organocatalysis as a sustainable substitute for metal-based systems by highlighting its benefits, which include low toxicity, stability, and environmental friendliness. These results highlight the promise of organocatalysis for scalable, effective, and selective asymmetric synthesis in industrial settings.

Keywords: Organocatalysis, Chirality, Enantiomeric Excess, Chiral Oxazaborolidine, Prochiral Ketones, Asymmetric Reduction

I.INTRODUCTION

A. Background of the Study

In the field of chemistry, organic chemistry has a central place and is essential to the production of complex molecules with a wide range of uses in many sectors (MacMillan, 2008). The development of medicines, agrochemicals, materials science, and several other scientific and commercial fields depends heavily on the synthesis of organic molecules, which are distinguished by their exceptional structural variety and functional adaptability. The regulated synthesis of organic molecules with asymmetry is one of the most exciting problems that organic chemists encounter. Underpinning the distinctive characteristics and biological activities shown by chiral compounds, chirality—the feature of asymmetry in molecules—has become a key idea in chemistry. When it comes to their interactions with biological systems, enantiomers—the mirror-image isomers of chiral compounds—can vary significantly (List et al., 2000). Because of this characteristic, it is crucial to precisely manage stereochemistry in organic synthesis, especially in the pharmaceutical sector where little modifications to a medication molecule's structure may result in significant differences in therapeutic effectiveness and safety. Asymmetric synthesis, often known as the synthesis of enantiomerically pure molecules, has long been a fundamental aspect of organic chemistry. However, achieving this level of accuracy is very difficult. In order to preferentially generate one enantiomer over the other, scientists must devise novel approaches and

techniques. Organocatalysts are useful in this situation.

According to MacMillan (2008), organocatalysts are an impressive class of catalysts made entirely of organic molecules. They are effective instruments for making asymmetric synthesis possible. Organocatalysts are superior than conventional metal-based catalysts in a number of ways. They facilitate the synthesis of sensitive molecules and reduce the possibility of undesirable side reactions by operating under moderate reaction conditions. Furthermore, they avoid adding metal residues to the finished product, which is very important in the pharmaceutical sector where purity is of the utmost importance.

B. Resolution of Racemic Mixtures

This method allows for the isolation of a single enantiomer from a racemic mixture. Using a chiral resolving agent—which has to be enantiomerically pure—is essential to this process. Through processes like crystallization, distillation, column chromatography, etc., the enantiomers are separated into two diastereomers with physically different characteristics. After then, the diastereomer is changed back into the enantiomer that was intended. If the resolving agent can be recycled after the transformation and the transformation is quantitative, this approach is effective (optically pure materials are potentially costly at large scale synthesis). This methodology's primary flaw is that, when just one enantiomer is sought, half of the material is often squandered, and the process's highest theoretical yield is only 50%. This approach is the most traditional manner of resolution procedures; other approaches, such as KR and DKR, are used nowadays and will be discussed.

C. Synthesis through Chiral Pool

The bioavailability of enantiopure chiral starting materials found in nature is the foundation of the second technique. This is sometimes called the "chiral pool" and is based on the use of chiral auxiliaries to add chirality to the products or syntheses that start with enantiopure chemicals. The simplest way to produce enantiopure compounds is most likely direct synthesis using chiral starting materials found in nature (as single enantiomers, such as sugars, amino acids, alkaloids, etc.). This tactic depends on the chiral information being conserved (without racemization) during the ensuing transformations. This approach is more effective if the structure of the desired chemical and the chiral starting material used are identical. This strategy's main disadvantage is that, in large-scale procedures, the cost of the starting material might be somewhat high.

D. Research Objectives

1. To develop a stable and efficient chiral organocatalyst for asymmetric reductions.
2. To evaluate the enantioselectivity of various acetophenone derivatives under optimized reaction conditions.
3. To explore the influence of electron-donating and electron-withdrawing substituents on enantioselectivity.

II.LITERATURE REVIEW

According to Sansinenea and Ortiz (2021), in order to reduce time and simplify the process of creating these natural chemicals, new approaches have been included into the whole syntheses of complicated natural products. We have

discussed the asymmetric synthesis of many natural products and physiologically active chemicals from the last decade to the present in this review. The key to producing the primary structure stereoselectively with the necessary stereochemistry is an asymmetric organocatalytic process. Even more impressive are the strong stereoselectivity of the organocatalytic cascade events and a potential approximation of the activation of the organocatalysts with substrates.

According to Larionov, Feringa, and Belokon (2021), asymmetric catalysis is one of the most significant advances in chemistry that occurred in the 20th century. This was recognized when Knowles, Noyori, and Sharpless were awarded the 2001 Nobel Prize in Chemistry for their creation of chiral metal catalysts for organic transformations. The catalysts' primary characteristics were the chiral ligand's vital function and the metal ions' makeup, which facilitated the substrates' catalytic transformations via direct coordination. Later, novel pathways for the synthesis of enantiopure molecules without the usage of metal ions were made possible by the advent of asymmetric organic catalysis. A different strategy for asymmetric catalysis has recently surfaced, one that depends on the ligands' own catalytic properties enhanced by coupling with metal ions. To put it another way, the ligands in these hybrid chiral catalysts activate the substrates rather than the metal ions. Through carefully planned and customized non-covalent interactions between the substrates and the ligand sphere of chiral metal complexes, activation and enantioselective control were achieved. Metal-centered chirality, which results from the spatial arrangement of achiral or chiral bi-/tridentate ligands around an octahedral metal center, increases the Brnsted acidity of the ligands. In these metal-templated catalysts, the metal either acted as a template (a purely structural role) or as the sole source of chirality. Despite its early stages, the area offers a promising blend of metal and organic catalysis and significant untapped potential to advance the boundaries of asymmetric catalysis. Here, we provide a summary of this new area of study, going into the fundamentals, uses, and viewpoints of chiral metal complexes that function as "organocatalysts in disguise." In asymmetric hydrogen bonding catalysis, phase-transfer catalysis, Brnsted acid/base catalysis, enamine catalysis, nucleophilic catalysis, photocatalysis, and bifunctional catalysis, it has been shown that these chiral metal complexes are effective and offer high stereoselective control. Furthermore, despite extremely low catalyst loadings, a large number of the catalysts have been shown to be highly effective. These hybrid systems are potential substitutes for metal-based and organocatalytic asymmetric transformations and provide several possibilities in the synthesis of chiral molecules.

These days, the discovery of novel enantioselective procedures is very important in chemistry since chiral molecules are important in biomedicine (mostly pharmaceuticals) and other disciplines like agrochemistry, animal feed, and flavorings (Ardevines, Marqués-López, & Herrera, 2021). Since the groundbreaking work of List and MacMillan in 2000, organocatalytic

techniques have emerged as a viable and effective substitute. These studies gave rise to the name "asymmetric organocatalysis" to describe this field of study, which has expanded rapidly in the last 20 years. Since then, several organic reactions and transformations have been discovered by the scientific community, all of which have shown exceptional reactivity and enantioselectivity. A few instances of tiny organic compounds and some natural products functioning as efficient catalysts may be found in the literature from older periods. New chemical architectures based on amines, thioureas, squaramides, cinchona alkaloids, quaternary ammonium salts, carbenes, guanidines, and phosphoric acids, among many others, have been created since the emergence of this kind of catalysis. In order to create compounds with high added value in an enantioselective manner, these organocatalysts have offered a wide variety of activation modes that provide privileged interactions between catalysts and substrates. Here, we provide a quick overview of this chemistry's history from our perspective, including our origins, the development of the discipline throughout the years, and the future.

According to Aukland and Benjamin's (2021) research, organocatalysis has made tremendous strides in the last two decades. With the help of hundreds of organizations and businesses worldwide, the field has grown from a few mechanistically vague niche reactions to one of chemistry's most active and inventive areas, offering a number of well defined general activation modes for selective catalysis. In commercial contexts, organocatalysis is increasingly becoming more popular, particularly for the synthesis of enantiomers, which are useful in fragrance chemistry, fine chemistry, pharmaceuticals, and crop protection. We will now examine some of the unique aspects of organocatalysis that we believe are very appealing and have contributed to this fruitful growth.

III.RESEARCH METHODOLOGY

The study employed (1S,2R)-(-)-cis-1-amino-2-indanol as a chiral catalyst, combined with tetrabutylammonium borohydride and methyl iodide to generate the chiral oxazaborolidine catalyst in situ. Various substituted acetophenones were subjected to asymmetric reduction, and reaction outcomes were analyzed using HPLC with chiral columns. The enantiomeric excess and yields were determined to assess the effectiveness of the catalyst system.

Experimental

General Procedure for Asymmetric Reduction of Ketonesusing (1*S*,2*R*)-(-)-*cis*-1-Amino-2-Indanol, Tetrabuty lammonium Boro hydride and MethylIodide

Tetrabutylammonium borohydride (25) (1 equiv.) and (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol(10 mol %) in THF (5 times) were taken in a three-neck RB flask. The contents werestirred at 25 -30^{0}C for about 10 min under nitrogen atmosphere. Methyl iodide (1 equiv.) was added using as yringe and the reaction mixture was stir red for about 30 min. Acetophenone derivative (1 equiv.) in THF (5 times) was added drop wisely for about 30min under nitrogen atmosphere. The reaction mixture was stirred till reaction completion. The

mixture was carefully quenched with HCl to get pH 5.0-6.0.The organic layer wasextracted with dichloromethane (10 times). The combined organic extract was washed with brine (3Times),dried over an hydro us sodium sulfate, and the solvent was evaporated to give the residue. The residue was purified on a silica gel column using hexane/ethyl acetate as eluent to furnish desired chirally pure alcohol**.** The procedure wasfollowed for different acetophenone derivatives (4a´-4k´) to get the reduced products (4a-4k).

a. Characterization Data

(1R)-1-phenylethan-1-ol(4a)

Colorlessoil;Yield:92%;^{1}HNMR(400MHz,$CDCl_3$):δ7.20–7.35(m,5H,ArH),4.85(q,1H,PhCHCH$_3$),2.18(brs,1H,OH),1.46(d,1H,CH$_3$);^{13}CNMR(100MHz,$CDCl_3$)δ146.0,128.7,127.7,125.6,70.6,25.3;MS(ESI)m/z:123$[M+H]^+$;$[\alpha]_D$: 43.9(*c*1.15, $CHCl_3$).

(1R)-1-(3,4-dichlorophenyl)ethan-1-ol (4b)

Paleyellowoil;Yield:93%;^{D}HNMR(400MHz,$CDCl_3$):δ7.44(d,1H,Ar-H),7.38(d,1H,Ar-H),7.16(dd,1H,Ar-H),4.82(q,1H,PhCHCH$_3$),2.36(brs,1H,OH),1.44 (d,3H,CH$_3$);CNMR(100MHz,$CDCl_3$,):δ146.0,132.5,131.1,130.4,127.5,124.8, 69.2,25.2;MS (ESI) m/z: 192 $[M+H]^+$; [α]: 35.9 (*c*1.05, CHCl).

(1R)-1-(4-methoxyphenyl)ethan-1-ol (4c)

Colorlessoil;Yield:88%;HNMR(400MHz,$CDCl_3$):δ7.30-7.24(m,2H,Ar-H),6.89-6.85(m,2H,Ar-H),4.83(q,1H,PhCHCH$_3$),3.79(s,3H,OCH$_3$),1.99(brs,1H, OH),1.46(d,3H,CH$_3$);CNMR(100MHz,$CDCl_3$):δ159.0,138.1,126.6,113.9, 69.9,55.3, 25.0;MS (ESI)m/z: 153 $[M+H]^+$;$[\alpha]_D$=49.5 (*c*1.20, CHCl).

(1R)-1-(2-bromophenyl)ethan-1-ol (4d)

Light yellow solid; Yield: 94 %; H NMR (400 MHz, $CDCl_3$): 7.58-7.55 (m, 1 H, Ar-H),7.50-7.48 (m, 1 H, Ar-H), 7.34-7.30 (m, 1 H, Ar-H), 7.13-7.08 (m, 1 H, Ar-H), 5.21 (q, 1H,PhCHCH$_3$),2.35(brs,1H,OH),1.46(d, 3H,CH$_3$);^{13}CNMR(100MHz,$CDCl_3$): 144.7, 132.7, 128.7, 127.8, 126.7, 121.7, 69.2,23.6;MS(ESI) m/z: 202$[M+H]^+$; $[\alpha]^{25}$= 54.2(*c*1.25, $CHCl_3$).

(1R)-1-(2-methoxyphenyl)ethan-1-ol (4e)

Colorlessoil;Yield:89%;HNMR(400MHz,$CDCl_3$):7.35-7.32(m,1H,Ar-H),7.25-7.21(m,1H,Ar-H),6.97-6.93(m,1H,Ar-H),6.87-6.85(m,1H,Ar-H),5.08(q,1H, PhCHCH$_3$),3.84(s,3H,OCH$_3$),2.77(brs,1H, OH),1.48(d,3H,CH$_3$);^{13}CNMR(100 MHz, $CDCl_3$) δ156.6, 133.7, 128.4,126.2, 120.9, 110.5, 66.5, 55.4,23.0;MS (ESI) m/z: 153$[M+H]^+$; $[\alpha]^{25}$= 28.2 (*c* 1.15, CHCl).

(1R)-1-(4-chlorophenyl)ethan-1-ol (4f)

Colorlessoil;Yield:93%;^{1}HNMR(400MHz,$CDCl_3$):δ7.32-7.25(m,4H,Ar-H),4.86(dq,1H,PhCHCH$_3$),1.96(brd,1H, OH),1.46(d,3H,CH$_3$);^{13}CNMR(100MHz, $CDCl_3$):δ144.3,133.1,128.6,126.8,69.7,25.2;MS(ESI)m/z:157$[M+H]^+$;$[\alpha]_D^{25}$= 44.5^{D}(*c*0.99, $CHCl_3$).

(1R)-1-(4-fluorophenyl)ethan-1-ol (4g)

Colorlessoil;Yield:92%;^{1}HNMR(400MHz, $CDCl_3$):7.33-7.30(m,2H,Ar-H),7.04-6.99(m,2H,Ar-H),4.85(q,1H,PhCHCH$_3$),2.16(brs,1H,OH),1.45(d,3H,CH$_3$); ^{13}CNMR(100MHz,$CDCl_3$)δ162.3,141.7,127.2,115.4,69.9,25.4;MS(ESI)m/z:

141[M+H]$^+$; [α]^{25}= 49.5(*c*0.98,CHCl).

(1R)-1-(3-methoxyphenyl)ethan-1-ol (4h)

Colorlessoil;Yield:90%;^{1}HNMR(400MHz, $CDCl_3$):δ 7.27-7.21 (m, 1H,Ar-H), 6.94-6.90 (m,2H,Ar-H),6.79(ddd,1H,Ar-H),4.84(q,1H,PhCHCH$_3$),3.79(s,3H,OCH$_3$),2.16(brs, 1H,OH),1.46(d,3H,CH$_3$);^{13}CNMR(100MHz,$CDCl_3$):δ159.8,147.6,129.5,117.7,112.9, 111.0, 70.3, 55.2,25.1;MS(ESI) m/z:153 [M+H]$^+$;[α]^{25}=38.2 (*c* 1.19, CHCl).

(1R)-1-(4-bromophenyl)ethan-1-ol (4i)

Pale yellow oil; Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.50 (m, 1 H, Ar-H),7.39-7.36 (m, 1 H, Ar-H), 7.27-7.24 (m, 1 H, Ar-H), 7.21-7.17 (m, 1 H, Ar-H), 4.82 (q, 1H, PhCHCH$_3$), 2.32 (br s, 1 H, OH), 1.45 (d, 3 H, CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ148.2,130.4,130.1,128.6,124.0,122.6,69.7,25.2;MS(ESI)m/z:202[M+H]$^+$;[α]^{25} =32.3 (*c*1.19, $CHCl_3$).

(1R)-1-(4-methylphenyl)ethan-1-ol (4j)

Colorlessoil;Yield:89%;^{1}HNMR(400MHz,$CDCl_3$):δ7.26-7.22(m,2H,Ar-H),7.16-7.11(m,2H,Ar-H),4.82(q,1H,PhCHCH$_3$),2.33(s,3H,CH$_3$),2.03(brs,1H, OH),1.46(d,3H,CH$_3$);^{13}CNMR(100MHz,$CDCl_3$):δ142.9,137.1,129.2,128.4, 125.4 , 70.2, 25.1, 21.1;MS (ESI) m/z: 137 [M+H]$^+$;[α]^{25}= 53.3 (*c*1.29, CHCl).

(1R)-1-(3-chlorophenyl)ethan-1-ol (4k)

Paleyellowoil;Yield:92%;^{1}HNMR(400MHz,$CDCl_3$):δ7.35(brs,1H,Ar-H),7.30-7.20(m,3H,Ar-H),4.84(dq,1H,PhCHCH$_3$),2.22(brd,1H, OH),1.45(d,3H,CH$_3$); ^{13}CNMR(100MHz,$CDCl_3$)δ148.0,134.6, 130.0,127.7,125.8,123.7,70.0,25.4;MS(ESI)m/z: 158 [M+H]$^+$;[α]$_D^{25}$=43.3 (*c*1.05, $CHCl_3$).

IV.CONCLUSION

The study emphasizes the remarkable potential of in situ generated chiral oxazaborolidine catalysts in achieving high enantioselectivity for the asymmetric reduction of prochiral ketones. The research showcased that employing (1S, 2R)-(-)-cis-1-amino-2-indanol as a chiral organocatalyst, along with tetrabutylammonium borohydride and methyl iodide, resulted in substantial enantiomeric excess, especially for substrates with electron-withdrawing groups. This highlights the critical influence of substituents on catalytic efficiency and stereoselectivity, providing insights into the design of optimized catalytic systems.

Moreover, the study underscores the eco-friendly and sustainable attributes of organocatalysis, presenting it as a robust alternative to metal-based catalysis. The practical advantages, including low toxicity, ease of handling, and stability under mild reaction conditions, make organocatalysis highly appealing for large-scale industrial applications, particularly in the pharmaceutical sector where product purity is paramount.

The exploration of diverse acetophenone derivatives further demonstrated the versatility and adaptability of the catalytic system, laying the groundwork for future studies to expand the substrate scope. Additionally, the findings encourage the development of cost-effective and scalable methodologies for asymmetric synthesis, aligning with the growing demand for greener and more sustainable chemical processes.

In conclusion, this work contributes significantly to the field of asymmetric catalysis by providing a detailed understanding of the structure-activity relationships governing enantioselective reductions. The outcomes not only advance fundamental knowledge but also pave the way for innovative applications in synthesizing chiral molecules with high precision and efficiency.

REFERENCES

1. Ardevines, S.; Marqués-López, E.; Herrera, R.P. Horizons in Asymmetric Organocatalysis: En Route to the Sustainability and New Applications. Catalysts 2022, 12, 101. https:// doi.org/10.3390/catal12010101

2. Aukland, M. & List, B. (2021). Organocatalysis emerging as a technology. Pure and Applied Chemistry, 93(12), 1371-1381.https://doi.org/10.1515/pac-2021-0501

3. Larionov, V. A., Feringa, B. L., & Belokon, Y. N. (2021). Enantioselective "organocatalysis in disguise" by the ligand sphere of chiral metal-templated complexes. Chemical Society Reviews, 50(17), 9715-9740.https://doi.org/10.1039/d0cs00806k

4. List, B., Lerner, R. A. & Barbas, C. F. III Proline-catalyzed direct asymmetric aldol reactions. J. Am. Chem. Soc. 122, 2395–2396 (2000)

5. MacMillan, D. W. C. The advent and development of organocatalysis. Nature 455, 304–308 (2008).

6. Sansinenea, Estibaliz & Ortiz, Aurelio. (2021). Asymmetric Organocatalytic Syntheses of Bioactive Compounds. Current Organic Synthesis. 19. 148-165. 10.2174/1570179418666210728145206.