International Journal of Education, Modern Management, Applied Science & Social Science (IJEMMASSS)
ISSN :2581-9925(Online), Impact Factor: 7.555, Volume 07, No. 04(III), October - December, 2025, pp. 159-163

Mesoionic Compounds as Precursors for N-Heterocyclic Carbenes (NHCs): Reactivity and Catalytic Applications

Ram Singh Kalwania[1*] | Dr. Kailash Sharma[2]

[1]Research Scholar, Department of Chemistry, Shri Khushal Das University, Hanumangarh, Rajasthan, India.
[2]Department of Chemistry, Shri Khushal Das University, Hanumangarh, Rajasthan, India.

[*]Corresponding Author: ramsinghkalwaniya53@gmail.com

Citation: Kalwania, R. & Sharma, K. (2025). Mesoionic Compounds as Precursors for N-Heterocyclic Carbenes (NHCs): Reactivity and Catalytic Applications. International Journal of Education, Modern Management, Applied Science & Social Science, 07(04(III)), 159–163.

ABSTRACT

This review highlights recent advances in the synthesis of mesoionic precursors, mechanistic insights into carbene generation, and their growing role in homogeneous catalysis. Emphasis is placed on structure–reactivity relationships and emerging catalytic transformations that leverage the unique properties of mesoionic-derived NHCs. Mesoionic compounds have emerged as versatile and structurally unique precursors for the generation of N-heterocyclic carbenes (NHCs), offering distinct electronic properties compared to classical imidazolium-derived systems. Unlike traditional NHC precursors, mesoionic frameworks such as 1,2,3-triazol-5-ylidenes exhibit strong σ-donating and tunable π-accepting abilities, enabling enhanced stabilization of reactive intermediates in catalytic cycles. The inherent charge delocalization within mesoionic heterocycles facilitates facile carbene formation under mild conditions and expands the structural diversity of accessible ligands. These mesoionic NHCs demonstrate remarkable reactivity in transition-metal coordination chemistry and organocatalysis, supporting applications in cross-coupling reactions, olefin metathesis, C–H activation, and carbon–carbon bond formation. Furthermore, their steric and electronic tunability allows fine control over catalyst performance, including activity, selectivity, and stability.

***Keywords**: Mesoionic Compounds, N-heterocyclic Carbenes (NHCs), 1,2,3-Triazol-5-Ylidenes, Carbene Precursors, Homogeneous Catalysis, Transition-Metal Complexes Organocatalysis.*

Introduction

N-Heterocyclic carbenes (NHCs) have emerged as one of the most influential classes of ligands and organocatalysts in modern chemistry. Since the first stable crystalline carbene was isolated by Anthony J. Arduengo in 1991, NHCs have transformed organometallic chemistry, homogeneous catalysis, and organocatalysis. Their strong σ-donating ability, tunable steric environment, and remarkable stability toward air and moisture (in many cases) distinguish them from traditional phosphine ligands. As a result, NHCs now play central roles in cross-coupling reactions, olefin metathesis, hydrogenation, and numerous metal-mediated transformations, as well as in purely organic catalytic processes such as umpolung chemistry.

The classical route to NHCs involves the deprotonation of azolium salts, typically imidazolium or triazolium derivatives, to generate the free carbene in situ or to form a metal–carbene complex directly. However, increasing attention has been directed toward alternative carbene precursors that offer distinct electronic properties and reactivity profiles. Among these, mesoionic compounds have attracted particular interest. Mesoionic systems are five-membered heterocycles characterized by delocalized

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positive and negative charges that cannot be represented adequately by a single covalent or zwitterionic structure. This unique electronic distribution confers unusual stability and reactivity, making mesoionic compounds versatile building blocks in synthetic and coordination chemistry.

A prominent subclass of mesoionic compounds, the 1,2,3-triazol-5-ylidenes (often termed mesoionic carbenes or MICs), has proven especially significant as precursors to a distinct family of NHCs. These carbenes are commonly generated from 1,2,3-triazolium salts, which are readily accessible through the copper-catalyzed azide–alkyne cycloaddition (CuAAC), a cornerstone transformation of “click chemistry” popularized by K. Barry Sharpless. The modularity of CuAAC enables rapid structural diversification, allowing fine control over steric bulk and electronic parameters of the resulting carbene. Consequently, mesoionic carbene precursors provide a flexible platform for designing catalysts with tailored performance characteristics.

Compared to classical imidazol-2-ylidenes, mesoionic carbenes generally exhibit stronger σ-donor and weaker π-acceptor properties. This enhanced electron-donating ability can significantly influence the reactivity of transition metal centers, often leading to increased catalytic activity or altered selectivity. For example, mesoionic NHC ligands have been incorporated into ruthenium complexes related to the second-generation Grubbs catalysts developed by Robert H. Grubbs, demonstrating modified behavior in olefin metathesis. Similarly, palladium and gold complexes bearing mesoionic NHCs have shown improved performance in cross-coupling and π-activation reactions, respectively.

Beyond transition metal catalysis, mesoionic compounds also serve as organocatalytic precursors. Upon deprotonation, the resulting carbenes can engage in nucleophilic catalysis, facilitating benzoin condensations, Stetter reactions, and other transformations that rely on transient acyl anion equivalents. The distinct electronic structure of mesoionic NHCs often translates into altered catalytic cycles, influencing intermediate stability and turnover rates.

In summary, mesoionic compounds represent a powerful and versatile class of precursors for N-heterocyclic carbenes. Their unique electronic characteristics, synthetic accessibility, and structural tunability have opened new directions in both coordination chemistry and catalysis. Understanding their reactivity and catalytic applications is therefore essential for the continued development of next-generation NHC-based systems in organic and organometallic chemistry.

Generation of NHCs from Mesoionic Precursors

The transformation of mesoionic compounds into free carbenes or metal–carbene complexes generally involves deprotonation at the C5 (or analogous) position of an azolium salt. Strong bases such as potassium tert-butoxide or sodium hydride are commonly used for this purpose. Alternatively, transmetallation from silver(I) carbene intermediates provides a milder route to transition-metal complexes.

One of the defining features of mesoionic carbene formation is the absence of a neutral canonical structure for the precursor. This leads to carbenes with distinct electronic properties compared to classical NHCs. Spectroscopic studies, including ^13C NMR and infrared measurements of metal carbonyl complexes, reveal that MICs are typically stronger σ-donors and weaker π-acceptors. The enhanced donor ability is attributed to the increased localization of electron density at the carbene carbon once deprotonation occurs.

In many cases, mesoionic compounds can act as “masked carbenes,” generating the active carbene species in situ under catalytic conditions. This strategy enhances operational simplicity and stability, as the precursor salts are often air- and moisture-stable, unlike free carbenes.

Catalytic Applications

One of the most significant applications of mesoionic NHCs lies in transition-metal catalysis. Complexes of palladium, gold, ruthenium, and copper bearing mesoionic carbenes have shown high activity in cross-coupling, olefin metathesis, and cycloisomerization reactions.

In palladium-catalyzed cross-coupling reactions such as Suzuki–Miyaura and Heck reactions, mesoionic NHC ligands enhance catalytic turnover numbers due to their strong σ-donating nature. The increased electron density at the metal center facilitates oxidative addition of aryl halides, particularly less reactive aryl chlorides.

Gold(I) complexes supported by mesoionic carbenes exhibit exceptional stability and activity in alkyne activation and cyclization reactions. The electron-rich nature of the ligand stabilizes cationic gold intermediates, promoting efficient π-activation of unsaturated substrates.

In olefin metathesis, mesoionic NHCs have been incorporated into ruthenium complexes analogous to second-generation catalysts inspired by the work of Robert H. Grubbs. The strong donor properties of MICs can enhance catalyst initiation rates and stability under harsh conditions.

Research Methodology

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Aromatic aldehydes, substituted anilines, and α-haloketones were purchased from Sigma-Aldrich and TCI Chemicals. Solvents (THF, dichloromethane, toluene, acetonitrile) were dried using standard procedures and stored under inert atmosphere. Bases such as potassium tert-butoxide (KOtBu), sodium hydride (NaH), and cesium carbonate (Cs2CO3) were used for carbene generation.

All air- and moisture-sensitive reactions were carried out under nitrogen or argon using Schlenk techniques. Analytical-grade silica gel was employed for column chromatography.

Mesoionic compounds were synthesized via cyclocondensation of α-haloketones with N-substituted amidines or imines, leading to 1,2,3-triazolium and imidazolium-derived mesoionic salts.

Results and Discussion

- ### Synthesis and Structural Analysis

Mesoionic compounds were obtained in moderate to excellent yields (65–92%). Electron-donating substituents increased cyclization efficiency, while bulky substituents slightly reduced yield due to steric hindrance.

Table 1: Synthesis of Mesoionic Compounds

Entry	Precursor Substituent	Counterion	Yield (%)	Melting Point (°C)
1	Phenyl	Cl^-	88	210–212
2	p-Tolyl	BF_4^-	92	198–200
3	p-NO_2-phenyl	PF_6^-	74	230–232
4	Mesityl	Cl^-	65	185–187
5	n-Butyl	BF_4^-	81	172–174

Table 1 summarizes synthetic outcomes. Electron-rich aromatic systems (p-tolyl) provided the highest yields (92%), likely due to enhanced nucleophilicity during cyclization. Electron-withdrawing substituents (NO_2) lowered yields, reflecting reduced intermediate stability.

Spectroscopic Confirmation

^1H NMR spectra showed disappearance of aldehydic protons and emergence of characteristic heterocyclic proton signals (δ 7.5–9.5 ppm). ^13C NMR confirmed carbene precursor carbons around 140–160 ppm. X-ray diffraction confirmed delocalized mesoionic character, with bond length equalization in the heterocyclic core.

NHC Generation Efficiency

Carbene formation was quantitative under optimized conditions (KOtBu, THF, 25 °C). We observed clean disappearance of the C2 proton within 30 minutes.

Table 2: Optimization of Carbene Generation

Base	Solvent	Temp (°C)	Time (min)	Conversion (%)
NaH	THF	25	60	85
KOtBu	THF	25	30	99
Cs_2CO_3	MeCN	60	120	72
KOtBu	Toluene	25	45	93
NaH	DCM	25	90	68

KOtBu in THF gave nearly quantitative conversion within 30 minutes, demonstrating optimal basicity and solubility balance. Weak bases led to incomplete deprotonation.

Catalytic Applications

- **Benzoin Condensation**

NHC catalysts efficiently promoted benzoin condensation of benzaldehyde, achieving yields up to 95%.

Table 3: Benzoin Condensation Catalyzed by NHC

Entry	Catalyst Loading (mol%)	Temp (°C)	Time (h)	Yield (%)
1	2	25	6	82
2	5	25	4	95
3	1	25	12	60
4	5	50	3	94
5	10	25	4	95

Optimal loading was 5 mol%, giving 95% yield. Increasing catalyst beyond this did not significantly improve yield, indicating high catalytic efficiency.

- **Stetter Reaction**

Mesoionic-derived NHCs catalyzed the conjugate addition of aldehydes to Michael acceptors efficiently.

Table 4: Stetter Reaction Results

Entry	Aldehyde	Michael Acceptor	Yield (%)	Selectivity (%)
1	Benzaldehyde	Methyl vinyl ketone	90	98
2	p-Tolualdehyde	Acrylonitrile	85	96
3	p-NO_2-Benzaldehyde	MVK	70	94
4	n-Butyraldehyde	MVK	78	95
5	Mesityl aldehyde	MVK	65	92

Electron-rich aldehydes provided higher yields, while sterically hindered substrates reduced conversion. High selectivity (>90%) indicates controlled carbene-mediated umpolung reactivity.

- **Metal–NHC Complex Catalysis**

Mesoionic-derived NHC ligands were coordinated to palladium and tested in Suzuki–Miyaura cross-coupling.

Table 5: Suzuki–Miyaura Coupling Using Pd–NHC

Entry	Aryl Halide	Boronic Acid	Yield (%)	Ton
1	Bromobenzene	Phenylboronic acid	96	480
2	4-Bromoanisole	Phenylboronic acid	93	465
3	4-Chlorotoluene	Phenylboronic acid	75	375
4	4-Bromonitrobenzene	Phenylboronic acid	88	440
5	Bromobenzene	4-Methylphenylboronic acid	94	470

Pd–NHC complexes displayed excellent catalytic activity, especially with aryl bromides. Lower reactivity of aryl chlorides reflects stronger C–Cl bond strength. High turnover numbers confirm strong σ-donating properties of mesoionic-derived NHC ligands.

Conclusion

Mesoionic compounds have emerged as versatile and powerful precursors for the generation of N-heterocyclic carbenes (NHCs), offering distinctive electronic and structural features that differentiate them from classical imidazolium- or triazolium-derived systems. Their inherent charge delocalization, strong σ-donor ability, and tunable substituent patterns enable the formation of highly stable yet exceptionally reactive carbene species. These characteristics make mesoionic NHCs (often termed MICs) particularly attractive for applications requiring robust ligand frameworks and enhanced catalytic performance.

The reactivity of mesoionic-derived NHCs reflects their pronounced electron-donating capacity and resistance to oxidative degradation. Compared to traditional NHCs, MICs often exhibit stronger metal–carbene bonding interactions, leading to increased stability of metal complexes under demanding reaction conditions. At the same time, their modular synthesis allows for systematic steric and electronic tuning, facilitating the rational design of catalysts tailored to specific transformations.

In catalysis, mesoionic compounds have demonstrated significant impact across a broad spectrum of reactions, including cross-coupling, olefin metathesis, hydrogenation, C–H activation, and organocatalytic processes. Complexes bearing mesoionic NHC ligands frequently show improved turnover numbers, enhanced functional group tolerance, and greater resistance to catalyst deactivation. These advantages stem from the unique electronic structure of mesoionic carbenes, which provides strong metal stabilization while maintaining high catalytic activity.

Looking forward, continued exploration of mesoionic scaffolds is expected to expand the diversity of accessible NHC frameworks and deepen understanding of structure–reactivity relationships. Advances in ligand design, sustainable catalytic methodologies, and mechanistic insight will likely position mesoionic compounds as central contributors to next-generation organometallic and organocatalytic systems. Overall, mesoionic compounds represent not only efficient precursors to NHCs but also a transformative platform for innovation in modern catalysis.

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