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Thiazol-2-ylidenes: Versatile N-Heterocyclic Carbene Ligands with Enhanced Electrophilicity for Transition-Metal-Catalysis

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Abstract. Over the last 20 years, N-heterocyclic carbenes (NHCs) have emerged as a dominant direction in ligand development in transition-metal-catalysis. In particular, strong σ -donation in combination with tunable steric environment make NHCs to be among the most common ligands used for C–C and C–heteroatom bond formation. Thus far, NHC ligand development has been almost exclusively limited to N-aryl-imidazolylikenes, such as IPr, prepared by deprotonation of symmetrical imidazolium salts. However, the molecular structure of imidazolylidene systems is constrained by the substitution with two nitrogen atoms, a limitation that prohibits the development of more active carbene

analogues. Herein, we report the first study on steric and electronic properties of thiazol-2-ylidenes. We demonstrate that the ring dissymmetry and enhanced π -electrophilicity result in a class of highly active carbene ligands for electrophilic cyclization reactions to form valuable oxazoline heterocycles. The evaluation of steric, electron-donating and π -accepting properties as well as structural characterization and coordination chemistry is presented. This mode of catalysis can be applied to late-stage drug functionalization to furnish attractive building blocks for medicinal chemistry. Considering the key role of N-heterocyclic ligands, we anticipate that N-aryl thiazol-2-ylidenes will be of broad interest as ligands in modern chemical synthesis.

Article. Since the first successful isolation in 1991¹ and the first use in catalysis in 1995,² N-heterocyclic carbenes (NHCs) have emerged as a powerful class of ligands in transition-metal-catalysis.^{3,4} The tremendous utility of NHCs hinges on strong σ -donation⁵ in combination with tunable steric environment,⁶ supercharging the catalytic activity of transition metals beyond other ligands. The most remarkable impact is in the development of Ru-catalyzed olefin metathesis⁷ and Pd-catalyzed cross-couplings,⁸ where the strong σ -donation and high stability of M–C(NHC) bond render NHCs superior to the more ubiquitous phosphine ligands. Thus far, NHC ligand development in transition-metal-catalysis has been almost exclusively limited to N-aryl-imidazolylienes **A**,^{4,8} such as IPr,⁹ prepared by deprotonation of symmetrical imidazolium salts (Figure 1). This is presumably due to enhanced electronic and steric stabilization of the carbene center by two nitrogen atoms as well as two N-Ar wingtip substituents, which render N-aryl-imidazolylienes more stable and easier to handle.¹⁰ The pioneering studies by Bertrand and co-workers established that cyclic carbene systems with a marked decrease of heteroatom stabilization, such as CAACs **B** (cyclic (alkyl)amino)carbenes),¹¹ are readily available, showing unique reactivity as supporting ligands in transition-metal-catalysis. More reactive and less stabilized systems, such as diamidocarbenes **C**,¹² mesoionic carbenes **D**¹³ and remote carbenes **E**,¹⁴ have been developed, each class showing varying degrees of heteroatom stabilization and distinctive promise in transition-metal-catalysis.¹⁵

Figure 1. Structures of classical NHCs (A), CAACs (B), diamidocarbenes (C), mesoionic carbenes (D) and remote carbenes (E) with different degree of stabilization. Energies calculated at B3LYP 6-311++g(d,p) level, R = Dipp.

In this context, N-aryl thiazol-2-ylidenes **F** are an intriguing class of N-heterocyclic carbenes (Figure 1). Following the isolation of a stable thiazol-2-ylidene by Arduengo in 1997,¹⁶ this class of ligands stayed dormant until 2008, when Grubbs demonstrated the unique reactivity of Ru-based thiazol-2-ylidene olefin metathesis catalysts.¹⁷ To our knowledge, this is the only application of N-aryl thiazol-2-ylidene ligands in transition-metal-catalysis reported to date.¹⁸ More recently, there has been a resurgence of organocatalyzed radical relays and decarboxylative couplings made possible through the

persistent radical stabilization by thiazol-2-ylidenes.¹⁹ In the meantime, studies by Boydston demonstrated organocatalyzed anodic oxidation of aldehydes through in situ generation of electroauxiliaries of thiazol-2-ylidenes,²⁰ while the first characterization of elusive Breslow intermediates from thiazol-2-ylidenes by spectroscopic and crystallographic methods has been reported.²¹

Biologically, thiazol-2-ylidenes are key intermediates in biochemical transformations of vitamin B1,²² including pyruvate decarboxylase, transketolase and dehydrogenase, a fact that spurred the interest in the burgeoning area of umpolung carbene reactivity.²³

Geometrically, replacement of one of the nitrogen atoms in imidazol-2-ylidene systems with sulfur in thiazol-2-ylidenes results in disrupting the symmetrical ring geometry of imidazolyliidenes.²⁴ At the same time, there is a strong electronic effect in decreasing stabilization of the carbene center through diminished π donation from sulfur.²⁵ Finally, the sulfur atom does not bear any wingtip substituents that in imidazolylidene systems often provide a significant contribution to the stabilization of the carbene center.^{4-8,24} These geometrical and electronic factors might explain why, with exception of the report by Grubbs,¹⁷ N-aryl thiazol-2-ylidenes have been unexplored as NHC ligands in transition-metal-catalysis.

In terms of electronics, the diminished π donation from sulfur due to unsymmetrical ring geometry and large sulfur radius is expected to result in more electrophilic carbenes than traditional imidazol-2-ylidene systems, while maintaining strong donor ability (Figure 1).²⁵

In terms of geometry, the effect of typical NHC ligands on M–C_(NHC) bond is defined as “umbrella” shaped, in contrast to cone shaped phosphines (Figure 1).⁶ The combination of a nitrogen atom with a quaternary carbon in CAACs renders these ligands as “wall-shaped” with regard to the M–C_(NHC) bond.¹¹ The steric properties of N-aryl thiazol-2-ylidenes render these ligands “half umbrella” shaped with the nitrogen N-wingtip oriented toward the M–C_(NHC) bond and lack of substitution on the sulfur atom.

As a part of our interest in NHC catalysis,²⁶ herein, we report the first study on steric and electronic properties of thiazol-2-ylidenes. Most importantly, we demonstrate that the ring dissymmetry and enhanced π -electrophilicity result in a class of highly active carbene ligands that supersede imidazol-2-

ylidenes. We present the evaluation of steric, electron-donating and π -accepting properties as well as structural characterization and coordination chemistry. Considering the key role of N-heterocyclic ligands, we envision that N-aryl thiazol-2-ylidenes will be of broad interest as ligands in chemical synthesis.

N-Aryl thiazol-2-ylidenes carbene precursors are readily available on multigram scale following the aforementioned protocols for organocatalytic transformations (see SI).¹⁹ Four N-aryl thiazol-2-ylidenes carbene precursors were selected as a starting point (Scheme 1). For the study, we chose structural sulfur analogues of IPr and IMes on 3-aryl-4,5-dimethylthiazol-2-ylidene framework; **^{Me}IPrS** and **^{Me}IMesS**. IPr ligand (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; N-Dipp, Dipp = 2,6-diisopropylphenyl) is by far the most common NHC ligand used in transition-metal-catalysis, while its smaller IMes (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, N-Mes, Mes = 2,4,6-trimethylphenyl) counterpart is often used for transformations requiring lower steric demand of the N-wingtip substituents. Furthermore, 3-aryl-4,5-cyclohexylthiazol-2-ylidene and 3-aryl-4,5-cycloheptylthiazol-2-ylidene, **⁶IPrS** and **⁷IPrS** were selected on the basis of the recent reports in organocatalytic transformations,¹⁹ where the fused cyclic ring on the backbone of N-aryl thiazol-2-ylidenes often provided advantageous stability of the system.

Scheme 1. Synthesis of Thiazol-2-ylidene Precursors^a

^aSee SI.

With access to N-aryl thiazol-2-ylidene precursors, we next prepared Ag(I) complexes [Ag(NHC)₂](ClO₄) **4a-4d** by the reaction with Ag₂O in CH₂Cl₂ (Scheme 2). Interestingly, complexes **4a-4c** ([Ag(**^{Me}IPrS**)₂](ClO₄) (**4a**), [Ag(**⁶IPrS**)₂](ClO₄) (**4b**) and [Ag(**⁷IPrS**)₂](ClO₄) (**4c**)) were found to be stable to air and moisture and could be fully characterized by X-ray crystallography (Figure 2, vide

infra). In contrast, the less sterically-hindered Ag(I) complex **4d** [Ag(^{Me}IMesS)₂](ClO₄) was found to be significantly less stable. This finding mirrors the study by Arduengo,¹⁶ who found that small N-wingtip substituents in thiazol-2-ylidene systems result in unstable carbenes. Unsurprisingly, the “half-umbrella” shape of N-aryl thiazol-2-ylidenes requires larger groups at the nitrogen atom for easy handling and isolation. Likewise, we found that the formation of bis-NHC–Ag(I) is needed to prevent decomposition of monomeric Ag(I)–NHCs in these thiazol-2-ylidene systems. From the outset, we were interested in Ag(I)–NHC complexes because of the untapped potential of Ag(I)–NHC complexes in catalysis as compared to other coinage metals.²⁷

Scheme 2. Synthesis of Ag(I) Complexes^a

^aConditions: Ag₂O (0.5 equiv), NaCl (2.0 equiv), CH₂Cl₂, 25 °C, 16 h, **4a**: 96%; **4b**: 95%; **4c**: 97%; **4d**: 90%.

Figure 2. X-ray crystal structure of Ag(I) complexes **4a–4c**. Two views: front (top); side (bottom). Hydrogen atoms and counterion have been omitted for clarity. Selected bond lengths [Å] and angles [°]: **4a**: Ag–C13, 2.082(3); Ag–C30, 2.086(3); N1–C13, 1.335(4); N2–C30, 1.337(4); S1–C13, 1.703(3); S2–C30, 1.697(3); C13–Ag–C30, 175.0(1). **4b**: Ag–C1, 2.075(4); Ag–C4, 2.078(4); N1–C1, 1.342(6); N2–C4, 1.331(6); S1–C1, 1.691(5); S2–C4, 1.693(6); C1–Ag–C4, 172.2(2). **4c**: Ag–C40, 2.087(2); Ag–

C39, 2.081(3); N1–C40, 1.339(3); N2–C39, 1.336(3); S1–C40, 1.699(4); S2–C39, 1.704(3); C40–Ag–C39, 175.5(1). **4a**: CCDC 2117719; **4b**: CCDC 2117722; **4c**: CCDC 2117721.

We next comprehensively evaluated steric and electronic properties of these N-aryl thiazol-2-ylidene ligands. As shown in Scheme 3, the linear copper(I) complex [Cu(^{Me}IPrS)Cl] (**5a**) was prepared after deprotonation with an excess of KO^t-Bu (2 equiv), while Rh(I) complexes, [Rh(⁶IPrS)(CO)₂Cl] (**6b**) and [Rh(⁷IPrS)(CO)₂Cl] (**6c**) were prepared by a two-step procedure via [Rh(NHC)(cod)Cl] and the reaction with carbon monoxide. We have also prepared the selenium adducts [Se(NHC)] (**5a–5d**) by adding the free carbene generated in situ to excess of selenium.

Scheme 3. Synthesis of Thiazol-2-ylidene Complexes^a

^aConditions: (a) CuCl (1.1 equiv), KO^t-Bu (1.0 equiv), THF, 25 °C, 16 h, 59%, **5a**, CCDC 2117739. (b) [Rh(cod)Cl]₂ (1.0 equiv), KO^t-Bu (2.0 equiv), THF, 23 °C, 8 h, then CO, CH₂Cl₂, 0 °C, 1 h, 95%, **6b**; 96%, **6c**. (c) Se (1.5 equiv), KO^t-Bu (1.2 equiv), THF, 25 °C, 12 h, 95%, **7a**; 96%, **7b**; 93%, **7c**; 93%, **7d**.

Cu(I)–NHC complex [Cu(^{Me}IPrS)Cl] (**5a**) was fully characterized by X-ray crystallography (Figure 3). Studies by Cavallo and co-workers demonstrated that catalytic pockets of M–NHCs are best described by the % buried volume (%V_{bur}) of model linear [M(NHC)Cl] complexes.²⁸ Complex [Cu(^{Me}IPrS)Cl] (**5a**) is linear (C(NHC)–Cu–Cl, 177.0°; C–Cu, 1.871 Å), making it a good model for evaluating %V_{bur} of N-aryl thiazol-2-ylidene ligands. Thus, the (%V_{bur}) of (**5a**) is 37.0%, which can be compared with the (%V_{bur}) of 47.6% determined for [Cu(IPr)Cl] (C–Cu–Cl, 176.7°; C–Cu, 1.881 Å).²⁹ A graphical representation of the steric mapping is shown in Figure 3B. Importantly, the X-ray crystallographic analysis revealed the (%V_{bur}) of 50.2%, 52.0%, 22.6%, 23.1% for each quadrant (Figure 3). The values can be compared with the (%V_{bur}) of 55.5%, 39.6%, 39.6%, 55.5% for each

quadrant of [Cu(**IPr**)Cl], revealing a “half-umbrella” steric arrangement of N-aryl thiazol-2-ylidene ligands.

Figure 3. (a) X-ray crystal structure of complex **5a**. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu–C1, 1.871(2); Cu–Cl, 2.0947(7); C1–N1, 1.338(2); C1–S1, 1.700(2); C6–N1, 1.460(3); N1–C3, 1.402(3); S1–C2, 1.723(2); C1–Cu–Cl, 176.98(7); N1–C1–S1, 107.3(1); C6–N1–C1, 121.3(2); C3–N1–C1, 117.0(2); C2–S1–C1, 94.5(1). (b) Topographical steric map of [Cu(^{Me}**IPrS**)Cl] (**5a**) showing % V_{bur} per quadrant. CCDC 2117739. Note dissymmetry of the ring.

The Tolman electronic parameter (TEP) has been determined from the CO stretching frequencies of [Rh(⁷**IPrS**)(CO)₂Cl] of $\nu_{sym} = 2078.0\text{ cm}^{-1}$ and $\nu_{asym} = 2001.4\text{ cm}^{-1}$ (CH₂Cl₂, 0.20 M), respectively. This corresponds to a TEP of 2051.9 cm^{-1} as a combined measure of the electronic properties of N-aryl thiazol-2-ylidene ligands.³⁰ These values can be compared with the classical imidazol-2-ylidene **IPr** (TEP of 2051.5 cm^{-1}) and a model cyclic (alkyl)amino)carbene CAAC^{Cy} (TEP of 2048.6 cm^{-1}),^{11a} indicating strong donor ability of N-aryl thiazol-2-ylidenes.

In the same vein, selenourea adducts allow to determine π -backbonding of NHC ligands from the ⁷⁷Se NMR spectra.³¹ As such, the δ_{se} values of 375.99 ppm for [Se(^{Me}**IPrS**)] and 374.88 ppm, 366.70 ppm, 329.96 for [Se(⁶**IPrS**)], [Se(⁷**IPrS**)], [Se(^{Me}**IMesS**)] (CDCl₃), respectively, indicate significantly better π -acceptance of N-aryl thiazol-2-ylidenes than imidazol-2-ylidene, **IPr** ($\delta_{se} = 90\text{ ppm}$), as expected from the sulfur substitution.

Moreover, one-bond CH J coupling constants from ¹³C satellites of the ¹H NMR spectrum give a good prediction of σ -donating properties of NHC ligands.³² The values of 218.70 Hz for ^{Me}**IPrS** and 218.34 Hz, 218.82 Hz, 219.36 Hz for ⁶**IPrS**, ⁷**IPrS**, and ^{Me}**IMesS** (HClO₄ salts, CDCl₃), respectively, are

consistent with N-aryl thiazol-2-ylidenes as strongly σ -donating NHC ligands, which can be compared with imidazol-2-ylidene IPr ($^1J_{\text{CH}} = 223.70$ Hz). However, at the same time, N-aryl thiazol-2-ylidenes are significantly more π -accepting and feature a distinct “half-umbrella” steric impact.

With structural and electronic characterization of N-aryl thiazol-2-ylidenes, we next evaluated the activity of Ag(I)–thiazol-2-ylidene complexes in catalysis (Table 1, and Schemes 4–5). As stated above, we selected Ag(I)–NHC complexes because Ag(I) complexes have been much less explored in catalysis than other group 11 metals²⁷ as well as to probe electrophilic π -activation of the ligands. Electrophilic *O*-cyclization of N-propargylic amides was selected as a model reaction due to the importance of the product oxazoline heterocycles in medicinal chemistry research.³³ As shown, the reaction proceeds under very mild conditions using bis-NHC–Ag(I) salts **4a-d** (5-10 mol%) in the presence of AcOH in CH₂Cl₂ at room temperature (Table 1, entries 1-8, see SI for details). AcOH is required as an additive (*vide infra*).³⁴ Likewise, no reaction takes place in the absence of N-aryl thiazol-2-ylidene Ag(I) complexes (Table 1, entries 9-10). Out of the complexes **4a-d**, the cycloheptyl complex [Ag(**7IPrS**)₂](ClO₄) showed the highest reactivity and was selected for scope studies. The loading could be further decreased to 1 mol% with excellent efficiency (>95%) (Table 1, entries 11-14). Most importantly, the use of classical imidazol-2-ylidene complexes [Ag(IPr)Cl] and [(Ag(IMes)Cl)] resulted in negligible reactivity (7-16%) (Table 1, entries 15-16), indicating superior reactivity of N-aryl thiazol-2-ylidenes. Additional studies to eliminate the effect of counterion further demonstrate the superior effect of N-aryl thiazol-2-ylidene Ag(I) complexes (see SI).³⁵

Table 1. Optimization of Ag–NHC-Catalyzed Cyclization of N-Propargylic Amides^a

Reaction scheme: N-propargylic amide **8** (N-(prop-1-yn-1-yl)benzamide) reacts with catalytic Ag–NHC under conditions to form oxazoline **9** (2-methyl-2,3-dihydro-4H-benzoxazole).

entry	catalyst	additive	mol%	yield (%)
1	4a	CH ₃ CO ₂ H	10	90
2	4b	CH ₃ CO ₂ H	10	95
3	4c	CH ₃ CO ₂ H	10	98

4	4d	CH ₃ CO ₂ H	10	96
5	4a	CH ₃ CO ₂ H	5	90
6	4b	CH ₃ CO ₂ H	5	93
7	4c	CH ₃ CO ₂ H	5	96
8	4d	CH ₃ CO ₂ H	5	91
9	-	CH ₃ CO ₂ H	-	-
10	4a–4d	-	10	-
11	4a	CH ₃ CO ₂ H	1	88
12	4b	CH ₃ CO ₂ H	1	85
13	4c	CH ₃ CO ₂ H	1	>95
14	4d	CH ₃ CO ₂ H	1	87
15	[Ag(IPr)Cl]	CH ₃ CO ₂ H	10	16
16	[Ag(IMes)Cl]	CH ₃ CO ₂ H	10	7

^aConditions: **8** (1.0 equiv), Ag–NHC ([Ag], 1-10 mol%), additive (1.0 equiv), CH₂Cl₂ (1.0 M), 25 °C, 8 h. See SI for details.

Having established the optimal conditions for electrophilic cyclization using N-aryl-thiazol-2-ylidene–Ag(I) complexes, next the scope was examined (Scheme 4).

As shown, the scope of the reaction is very broad and encompasses a variety of N-propargylic amides (Scheme 4). As such, aromatic amides with neutral (**9a**), electron-donating (**9b–9f**), electron-withdrawing (**9g–9n**) substituents at the para, ortho and meta positions could be successfully reacted to give diverse 2-aryl-2-oxazolines. Importantly, medically-relevant substituents, such as 3,4,5-trimethoxyphenyl (**9f**), nitro (**9g**), cyano (**9h**), trifluoromethyl (**9i–9j**) as well as halide functional handles that enable further derivatization (**9j–9n**) were well compatible with the reaction. Furthermore, π -conjugated substituents, such as naphthyl (**9o**) and cinnamyl (**9p**) furnished the products in high yields. Heterocyclic amides, such as 2-thienyl (**9q**) were well tolerated. Interestingly, highly selective mono-cyclization is possible using meta-substituted propargylic diamide (**9r**). Pleasingly, aliphatic amides with α -branching (**9s**) as well as 1° (**9t**, **9w**), 2° (**9v**), and 3° sterically-hindered aliphatic amides (**9u**) are

tolerated in this process despite the lack of $\text{Ar} \rightarrow \pi^*_{\text{C}=\text{O}}$ conjugation with the amide oxygen atom. Furthermore, substitution at the methylene carbon adjacent to the nitrogen to deliver 4-substituted oxazolines is also compatible (**9x-9aa**), increasing the overall synthetic utility of the process. Further, substitution of the alkyne is tolerated without loss in reaction efficiency (**9ab-9ad**), furnishing fully substituted oxazolines. The product **9ad** was crystalline and the structure was confirmed by x-ray crystallography, indicating (*Z*)-geometry of the double bond (*dr* > 98:2). This result is consistent with an anti-attack of the amide bond oxygen on the Ag(I)–NHC- π -activated alkyne (vide infra).

Scheme 4. Scope of Ag–NHC-Catalyzed Cyclization of N-Propargylic Amides^a

^aConditions: amide (1.0 equiv), catalyst **4c** ([Ag], 1 mol%), CH₃CO₂H (1.0 equiv), CH₂Cl₂ (1.0 M), 25 °C, 8 h. See SI for details, **9ad**: CCDC: 2125052.

Most crucially, the mild reaction conditions enabled by the N-aryl thiazol-2-ylidene ligands permit this mode of catalysis to be applied to late-stage functionalization to furnish attractive heterocyclic building blocks for medicinal chemistry and agrochemistry research (Scheme 5). Thus, electrophilic cyclization of propargylic amides from acifluorfen (**9af**, protoporphyrinogen oxidase inhibitor), piperonyllic acid (**9ag**, trans-cinnamate hydroxylase inhibitor), dicamba (**9ah**, broad spectrum herbicide), febuxostat (**9ai**, antigout) and probenecid (**9aj**, antihyperuricemic) delivered cyclization products in good to high yields without modification of the reaction conditions. This successful late-stage diversification highlights the mild conditions of the present protocol with tolerance to an array of sensitive functional groups (halides, cyano, nitro, sulfonamide, aryl ethers, S-heterocycles), demonstrating prospective impact on medicinal chemistry research.

Scheme 5. Late-Stage Functionalization in Ag–NHC-Catalyzed Cyclization of N-Propargylic Amides^a

^aConditions: amide (1.0 equiv), catalyst **4c** ([Ag], 1 mol%), CH₃CO₂H (1.0 equiv), CH₂Cl₂ (1.0 M), 25 °C, 8 h. See SI for details.

To gain insight into the reaction mechanism of this intriguing transformation, catalytic cycle was studied by DFT computations (Figure 4). Based on the previous work,³⁴ our calculation results show that the catalytic cycles for these processes are comprised of three key steps. In the first step, L₂Ag will give active catalyst **1'** in the presence of AcOH. The free energy of activation for this step is 20.1 kcal/mol for **TS1** (Figure 4). After formation of active catalyst **1**, the ligand exchange between AcO[−] and

amide **Re** would give intermediate **2** with a free energy release of -6.7 kcal/mol. In second step, **2'** would generate putative vinyl–silver intermediate **3'** by a 5-*exo-dig* cyclisation. The free energy of activation for **TS2** (*Z*) and **TS22** (*E*) is 12.7 and 19.6 kcal/mol, respectively. This calculation result for *Z/E* selectivity is fully consistent with the experiments results. The final step involves a 1,4-H shift that leads to the final product **P1**. First, two- and three-molecule HOAc-assisted 1,4-H shift (**TS31** and **TS32**) were calculated. The calculated activation free energy of **TS31** and **TS32** is high (27.4 and 24.5 kcal/mol, page S142, SI) to occur under the experimental conditions. Another possible pathway involves HOAc and ligand assisted 1,4-H shift. In this pathway, coordination of HOAc and ligand with **3'** would generate intermediate **4'** with a free energy release of -10.0 kcal/mol. The protodemetalation step would form the product **P1** and regenerate the silver catalyst and HOAc. This step is exergonic by -30.6 kcal/mol and the free energy barrier is 15.8 kcal/mol.

Figure 4. DFT-computed free energy profile of Ag–NHC catalyzed cyclization of N-propargylic amides. See SI for computational details.

To further evaluate the effect of nitrogen to sulfur replacement in N-aryl thiazol-2-ylidenes, HOMO and LUMO energy levels of carbenes ^{Me}**IPrS**, ⁶**IPrS**, ⁷**IPrS** and ^{Me}**IMesS** were determined at the

B3LYP 6-311++g(d,p) level (Figure 5 and SI). It is now recognized that the donating ability of carbenes is closely associated with the HOMO orbital, while the electron acceptance is associated with the LUMO orbital.^{5,11,30} Computation of frontier orbitals represents the most accurate evaluation of nucleophilicity (higher HOMO) and electrophilicity (lower LUMO) of NHC ligands,^{5,11,30} while the comparison must be available at the same level of theory.

The HOMO of **MeIPrS** (-6.07 eV, σ -bonding orbital) is comparable with **IPr** (-6.01 eV), which is a routine model for σ -donating NHCs. The HOMO of **⁶IPrS**, **⁷IPrS** and **MeIMesS** are -6.05 eV, -5.99 eV, -6.02 eV respectively, indicating that these N-aryl thiazol-2-ylidenes are similarly strongly nucleophilic as N-aryl-imidazol-2-ylidenes. Furthermore, the LUMO of **MeIPrS** (-0.66 eV, π -accepting orbital) is significantly lower than for the standard imidazol-2-ylidene ligands **IMes** (-0.33 eV), **IPr** (-0.48 eV) of the corresponding π -accepting orbitals. The LUMO of **⁶IPrS**, **⁷IPrS** and **MeIMesS** are -0.67 eV, -0.68 eV, -0.53 eV, respectively (**MeIMesS**, LUMO+1 due to required symmetry), indicating that N-aryl thiazol-2-ylidenes are significantly better π -acceptors than the standard imidazolylidene **IMes** and **IPr** ligands. In addition, the HOMO-1 (π -donating orbital) in the series of **MeIPrS**, **⁶IPrS**, **⁷IPrS** and **MeIMesS** is -6.57 eV, -6.49 eV, -6.44 eV, -6.51 eV, which is in the same range as for the π -donating orbital for the standard imidazolylidene **IMes** (-6.44 eV) and **IPr** (-6.55 eV) determined at the same level of theory. Overall, N-aryl thiazol-2-ylidenes can be characterized as π -accepting, σ -donating and sterically-distinct “half umbrella” shaped ligands that are well-poised for electrophilic catalysis.³⁶

Figure 5. HOMO and LUMO energy levels (eV) calculated at B3LYP 6-311++g(d,p). See SI for details.

Discussion. In conclusion, although N-heterocyclic carbenes represent a dominant direction in ligand development in the last 20 years, the majority of efforts in catalysis have been almost exclusively limited to N-aryl-imidazolylidenes, such as IPr. In this study, we reported the first study on steric and electronic properties of thiazol-2-ylidenes. We presented comprehensive evaluation of steric, electron-donating and π -accepting properties as well as structural characterization of Ag(I) and Cu(I) complexes of N-aryl thiazol-2-ylidenes. The ring dissymmetry and enhanced π -electrophilicity result in a class of highly active carbene ligands that supersede imidazol-2-ylidenes. We showed that this mode of catalysis can be applied to late-stage drug functionalization to furnish attractive building blocks for medicinal chemistry. The unique electronic properties in combination with steric differentiation in a “half umbrella” shape with the single nitrogen N-wingtip oriented toward the metal open a plethora of possibilities in the development of enhanced arsenal of thiazol-2-ylidene ligands of broad interest in chemical synthesis.

Methods

General procedure for the synthesis of Ag(I) Complexes. An oven-dried vial equipped with a stir bar was charged with N-Aryl thiazol-2-ylidenes carbene precursors (1.0 equiv), Ag₂O (typically, 0.5 equiv) and NaCl (typically, 2.0 equiv). The reaction mixture was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. DCM (typically, 0.04 M) was added and the reaction mixture was stirred away from light overnight at room temperature. The reaction mixture was filtered through Celite with DCM as eluent and concentrated under reduced pressure, and dried under high vacuum to afford silver(I) complex

General procedure for the cyclisation of propargylic amides. An oven-dried vial equipped with a stir bar was charged with propargylic amides (1.0 equiv), Ag catalyst **4c** (typically, 1.0 mol%). The reaction mixture was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Then AcOH (typically, 1.0 equiv) and DCM (typically, 1.0 M) was added

and the reaction mixture was stirred at room temperature for 8 h. The volatiles were removed in vacuo and the products were purified by column chromatography on silica gel (EtOAc/hexanes).

Data Availability

Experimental procedures, characterization data, computational details, cif files of **4a-4c**, **5a** and **9ad**, coordinates and energies are available within this article and its Supplementary Information. Data are also available from the corresponding author on request.

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Author contributions

J.Z., R.F. and M.S. conceived the concept and designed the experiments. T.L., X.L., A.L. X.L., Z.W., R.W. and Y.M. conducted the chemical reactions described in the manuscript. J.Z., R.F. and M.S. wrote the manuscript and all authors contributed to the reading and editing of the manuscript. T.L. compiled the Supplementary Information.

Additional information

Supplementary information is available in the online version of the paper. Reprints and permission information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to J.Z., R.F. and M.S.

Competing financial interests

The authors declare no competing financial interests.

Abstract

N-aryl thiazol-2-ylidenes

■ π -accepting ■ σ -donating

■ sterically-distinct

■ “half umbrella” shaped

Supplementary Files

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- [SupportingInformation.pdf](#)