Dalton Transactions



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View Article Online
View Journal | View Issue



Cite this: *Dalton Trans.*, 2025, **54**, 14659

Received 21st September 2025, Accepted 22nd September 2025 DOI: 10.1039/d5dt02258d

rsc.li/dalton



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The straightforward synthesis of new thiazolylidene gold complexes is described. Despite their decreased steric protection, these complexes demonstrate excellent stability and high catalytic activity in the HFIP-assisted cycloisomerization of propargylamides. The synthesis and catalytic activity of a novel, stable thiazolylidene gold alkoxide complex is also reported.

Over the past decades N-heterocyclic carbenes (NHCs) have emerged as highly valuable ligands in the fields of transition metal catalysis and organic synthesis. This has driven the development of diverse NHC architectures, each characterized by unique electronic and steric properties, that can act as supporting ligands or even organocatalysts. Tase in point are the now ubiquitous 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) NHCs, which can effectively stabilize and sterically protect the metal center and are accessible in large scales. The other architectures such as cyclic(alkyl)(amino) carbenes (CAACs) and triazolylidenes have also contributed to significant advancements.

Thiazolylidenes (more formally referred to as thiazol-2-ylidenes) are a class of N-heterocyclic carbenes generated by the deprotonation of thiazolium salts. This species was first proposed by Breslow in 1958 as the active form of thiamine (vitamin B₁) and subsequently isolated and unequivocally characterized by Arduengo in 1997. ^{12,13} Although thiazolylidenes are commonly used as *in situ* generated organocatalysts, ^{5,14} the development of catalytic systems based on thiazolylidene-supported metal complexes has remained relatively limited. ¹⁵ In 2008, *N*-aryl-thiazolylidene-Ru(II) complexes were shown as highly active catalysts in olefin metathesis reactions. ¹⁶ More recently, Szostak and coworkers have investigated the electronic and steric properties of these NHCs

and examined the catalytic activity of such silver complexes in the cycloisomerization of propargylamides.¹⁷

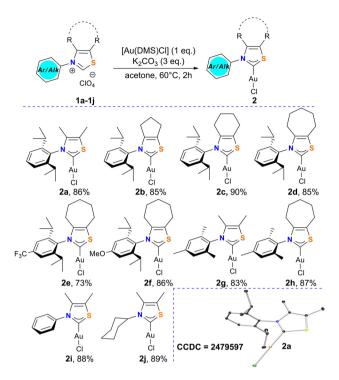
Their work highlights the increased reactivity of thiazolylidene–Ag(I) catalysts in electrophilic cyclization reactions compared to analogous imidazolylidene–Ag(I) catalysts. This was attributed to the increased π -acidity of thiazolylidenes relative to common imidazolylidenes, due to poor π -donation from the sulfur atom to the carbene center. Furthermore, the same research group designed new methodologies employing N-arylthiazolylidene–Cu(I) catalysts for the selective hydroboration of alkynes and Pd-free Sonogashira type reactions. 19,20

In the field of gold catalysis, limited examples of the synthesis and catalytic application of thiazolylidene–Au complexes have been reported, such as the A³ coupling protocol recently described by Guo and coworkers, 2¹ and the carbocyclization of acetylenic substrates and hydroalkoxylation of allenes study disclosed by Hilvert and coworkers. 2² In both cases, Au(1) complex pre-catalysts supported by thiazolylidene ligands were derived from thiamine and related analogues. Aiming to broaden the scope and applications of these organometallic compounds, we now disclose the straightforward synthesis of new Au(1) complexes featuring thiazolylidene ligands, along with the evaluation of their catalytic activity in the cycloisomerization of propargylamides.

For the preparation of the Au(I) complexes, we chose the thiazolium salt family introduced by Glorius and coworkers. ¹⁴ Widely-used *N*-substituents can be incorporated into the structure, such as *N*-Dipp (2,6-diisopropylphenyl) and *N*-Mes (2,4,6-trimethylphenyl), enabling the synthesis of sulfur-containing analogues of the ubiquitous imidazolylidene–Au(I) catalysts (*e.g.*, [Au(IPr)Cl], [Au(IMes)Cl]). Starting from various α-halogenated ketones, the size of the aliphatic backbone can be modulated to further tune the steric profile of the ligand, a factor shown to be important in optimizing catalyst performance and selectivity. ^{14,17,19,20,23} Notably, these salts can be readily prepared on a multigram scale. Utilizing the weak base route, we synthesized a series of new thiazolylidene–Au(I)–Cl complexes bearing various substitution patterns, without using inert conditions (Scheme 1). ^{24,25} Complexes 2a–2d featuring *N*-Dipp sub-

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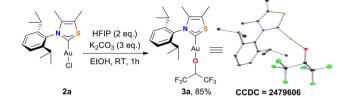


Scheme 1 Synthesis of the thiazolylidene-Au(ı)-Cl complexes. ORTEP-III diagram of the molecular structure of 2a showing 50% probability ellipsoids (H-atoms omitted for clarity).

stituents were isolated in high yields. The introduction of electron-donating or electron-withdrawing groups to the starting aniline enabled the synthesis of the trifluoromethylated complex 2e or the methoxylated complex 2f in 73% or 86% yield, respectively. The utilization of N-Mes-thiazolium salt precursors led to complexes 2g and 2h in high yields as well. Smaller substituents are also tolerated, furnishing complex 2i in 88% yield (N-Ph), and permits access to an alkyl cyclohexyl substituted congener (N-Cy) (2j, in 89% yield). These complexes proved to be air and moisture stable, despite their decreased steric protection. This contrasts with reported isolation of bench-stable thiazolylidene-Cu(I) and Ag(I) complexes, which has been limited to those containing bulky N-Dipp substituents. 17,19

Considering the growing interest in metal alkoxide complexes within NHC chemistry, where they serve as catalysts and versatile organometallic synthons, 26-28 we envisioned the synthesis of a thiazolylidene Au(I) complex bound to a hexafluoroisopropoxide anion. Using the weak base method, recently reported for the straightforward preparation of imidazolylidene-Au(1) fluoroalkoxides, we successfully extended its application to a thiazolylidene-Au(1) complex.²⁶ Using this simple protocol and 2a as starting reagent, we isolated complex 3a in 85% yield (Scheme 2). Brønsted-basic 3a remained stable to air and moisture, despite possessing a single exocyclic N-substituent, and, to the best of our knowledge, represents the first example of a thiazolylidene metal alkoxide complex.

Au(1) complexes 2a-2j and 3a were fully characterized spectroscopically and analytically. To unambiguously confirm



Scheme 2 Synthesis of thiazolylidene-Au(1) alkoxide 3a. ORTEP-III diagrams of the molecular structure of 3a showing 50% probability ellipsoids (H-atoms omitted for clarity).

atom connectivity, their identity was further confirmed by SC-XRD determination of their solid state molecular structures. They show monomeric linear 2-coordinate Au(I) complexes (carbene C-Au-X angles between 174.54(3) and 179.42 (13)°) with the only exception being 2g where the two Au(1) centres are proximal to each other by 3.1319(5) Å, typical of an aurophillic interaction in the solid state.²⁹ A plausible explanation for this exception are crystal packing effects, as the less sterically hindered analogue 2i shows no such interaction in the solid state. The Au-C(carbene) bond distances range between 1.964(5)-1.987(3) Å (see Table S4 in SI) and are like the one found in the Au(1)-Cl thiazolylidene complex reported by Hilvert (1.980(2) Å).22

Nevertheless, it must be noted that there is some variation in the crystallographically determined Au-C(carbene) distances with the shortest distances observed for the complexes featuring an odd-number cyclo-alkyl derivatized backbone and electron withdrawing Dipp substituents (e.g. 2e). The shortest Au-C(carbene) bond length of 1.952(2) Å is observed in 3a, where the chloride ligand has been substituted for an electron withdrawing hexafluoroisopropoxide ion. This is similar within the 3σ criterion with the distance of 1.961(9) Å found in (L = 3,4-dimethylthiazolylidene).³⁰ L-Au-C₆F₅ reductions in Au-C(carbene) bond lengths have been observed in other NHC-Au-OR complexes (R = aryl, fluoroalkyl) relative to their chloride-containing counterparts. 31-33

We next focused our attention on investigating the role of complexes 2a-2j as catalysts in the cycloisomerization of propargylamides (Table 1). Hexafluoroisopropanol (HFIP) was employed for its dual role as both the reaction solvent and catalyst activator. As we have previously demonstrated, HFIP activates the otherwise inert Au-Cl or M-amide (M = Cu, Ag) bond through hydrogen bonding, eliminating the need for additional activators such as silver, copper, and alkali metal borate salts. 32,34,35 Using 2a in 1 mol% loading led to product 5a in 59% yield after 1 hour at room temperature (Table 1, entry 1). Replacing the two backbone methyl substituents with a cyclopentyl (2b) or cyclohexyl (2c) ring resulted in decreased yields of 47% and 49%, respectively (Table 1, entries 2 and 3). On the other hand, employing complex 2d, bearing a cycloheptyl ring, afforded product 5a in 63% yield (Table 1, entry 4). The incorporation of a trifluoromethyl group on the Dipp N-substituent (para positioned) had minimal impact on catalyst performance (Table 1, entry 5), whereas the introduction

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Table 1 Catalyst screening and optimization

Entry ^a	[Au] (mol%)	Time (h)	5a ^b (%)
1	2a (1)	1	59
2	2b (1)	1	47
3	2c (1)	1	49
4	2d (1)	1	63
5	2e (1)	1	61
6	2f (1)	1	56
7	$2\mathbf{g}(1)$	1	36
8	2h (1)	1	38
9	2i (1)	1	43
10	2j (1)	1	35
11		1	_
12^c	2d (1)	1	_
13	[Au(IPr)Cl] (1)	1	27
14	2d (1)	4	86
15	2d (1.5)	4	96 (93)

^a Reaction conditions: 0.25 mmol of **4a**, 0.0025 mmol (1 mol%) or 0.00375 mmol (1.5 mol%) of catalyst, 0.250 mL of HFIP as solvent, under air. ^b Yields were determined by ¹H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parenthesis. ^c 0.250 mL of DCM as solvent.

of a methoxy group on the same position caused a slight decrease in yield (Table 1, entry 6). Complexes 2g, 2h, and 2i, featuring N-Mes and N-Ph substituents, led to lower yields (Table 1, entries 7-9). A similar trend was observed when the N-Cy complex 2j was used (Table 1, entry 10). As expected, the exclusion of catalyst completely inhibited cyclization (Table 1, entry 11). Likewise, complex 2d was completely inactive in DCM (Table 1, entry 12). Furthermore, the gold-standard imidazolylidene-based complex [Au(IPr)Cl] led to a lower reaction yield (27%) under identical conditions (Table 1, entry 13). This observation aligns with the trends reported by Szostak and coworkers in their study of thiazolylidene/imidazolylidene silver complexes.¹⁷ Using complex 2d and increasing the reaction time to 4 hours improved the yield to 86% (Table 1, entry 14). Compared to their thiazolylidene-Ag(1) counterparts, the catalytic efficiency of complexes 2a-2j exhibits greater sensitivity to the ligand's nature, while 2d delivers a similarly high reaction yield (86%), but within a shorter reaction time. 17 Nearly quantitative yield was achieved after adjusting the catalyst loading to 1.5 mol% (Table 1, entry 15).

With the optimized conditions in hand, we expanded our investigation into other propargylamide substrates (Scheme 3). Aryl propargylamides featuring *para* electron-withdrawing groups afforded oxazolines **5b-5h** in good to excellent yields (62–95%). Similarly, substrates bearing *para* electron-donating groups delivered products **5i** and **5j** in excellent yields (94% and 92%, respectively). *ortho* and *meta* substituted aryl propargylamides also proved effective substrates, furnishing products **5k-5n** in good to excellent yields (66–92%). π -Conjugated

Scheme 3 Substrate scope studies. ^a Reaction conditions: 0.25 mmol of 4, 0.00375 mmol (1.5 mol%) of 2d, 0.250 mL of HFIP as solvent, under air. Isolated yields. ^b 0.250 mL of TFE as solvent, 8 h. ^c 0.250 mL acetone/TFE (5/1) as solvent, 16 h. ^d Volatile compound. Solvent was removed using an argon flow. NMR yield. ^e 5 mol% of 2d, 16 h.

naphthyl and cinnamyl substrates readily participated in the transformation, as did a propargylamide featuring an alkyl tert-butyl substituent, leading to products 5o-5r in 79-99% yields. Furthermore, propargylamides with fully substituted nitrogen α-carbons proved suitable substrates, yielding oxazolines 5s-5u in 70-94% yields. Heterocyclic propargylamides were well tolerated, furnishing thiophenyl- and indolyl-substituted oxazolines 5v and 5w in 56% and 91% yield, respectively. Notably, a challenging nonterminal propargylamide proved to be a viable substrate, albeit requiring modified conditions (5 mol% 2d, 16 h) to achieve good conversion (62%, via ¹H-NMR analysis). In agreement with related works that examine the gold-catalyzed cyclization of nonterminal propargylamides, 36,37 two products were detected: the Z-oxazoline 5x originating from a 5-exo-dig cyclization as the major product in 54% yield, and the 1,3-oxazine 5x' resulting from a 6-endo-dig cyclization as the minor product in 8% yield. It is worth mentioning that in previous related studies the derivatization of nonterminal propargylamides using phosphineor imidazolylidene-based metal catalysts resulted in low yields

Table 2 Catalytic activity of complex 3a on the cycloisomerization of 4a to 5a

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Entry	[Au] (mol%)	Solvent	5 a ^b (%)
1	3a (1)	HFIP (1 M)	72
2^c	$[Au(IPr)(OCH(CF_3)_2)](1)$	HFIP (2 M)	41
3	3a (1)	DCM (1 M)	_

^a Reaction conditions: 0.25 mmol of 4a, 0.0025 mmol (1 mol%) of 3a, RT, 1 h, under air. ^b Yields were determined by ¹H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard. ^c Ref. 32

or no conversion, even under harsher conditions.^{34,35} Thus, the use of a thiazolylidene-based catalyst enables these challenging transformations. It should be noted that for substrates 5k, 5r, and 5w, trifluoroethanol (TFE) was used, in efforts to minimize the formation of significant amounts of the oxazole isomer observed in HFIP (>10%). The lower acidity of TFE effectively suppresses isomerization, thereby improving selectivity for the oxazoline products. Due to reduced catalyst activation in TFE,³⁴ reaction times were extended in these cases.

Complex 3a was also competent in the model reaction shown in Table 1 with 1 mol% loading, yielding 72% of oxazoline 5a in 1 hour (Table 2, entry 1). This complex demonstrated higher activity relative to the imidazolylidene-based analogue [Au(IPr)(OCH(CF₃)₂)] (Table 2, entry 2). When DCM was used, no product was detected (Table 2, entry 3), indicating that 3a is not a reactive intermediate, suggesting that the reaction most probably proceeds through the HFIP-assisted alkyne displacement of chloride pathway established in our previous study. 34

In conclusion, we have reported the straightforward preparation and characterization of a new family of air and moisture stable Au(1) complexes of the general type L–Au–X, (L = thiazolylidene ligand) of varying electronic and steric properties and X = Cl $^-$ or (CF $_3$) $_2$ CHO $^-$, under mild conditions and in high yields. Their catalytic potential was demonstrated in the HFIP or TFE assisted cycloisomerization of propargylamides, outperforming their imidazolylidene-based Au(1) congeners. The reaction proceeds efficiently and rapidly using low catalyst loadings at room temperature and without the need for inert conditions or dry solvents. A diverse array of substrates was successfully cyclized in good to excellent yields, including propargylamides bearing electron-rich and electron-poor aryl groups, π -conjugated systems, alkyl and heterocyclic substituents, as well as a challenging nonterminal propargylamide.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article are included in the supplementary information (SI). Supplementary information:

experimental details and copies of spectra. See DOI: https://doi.org/10.1039/d5dt02258d.

CCDC 2479597–2479607 for 2a-2j and 3a contain the supplementary crystallographic data for this paper. $^{38a-k}$

Acknowledgements

The research was supported by the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "1st Call for H.F. R.I. Research Projects to Support Faculty Members & Researchers and the Procurement of High-Cost Research Equipment" (Project Number: 16). Access to the SC-XRD diffractometer of the National and Kapodistrian University of Athens Core Facility is greatly appreciated. For work conducted in Ghent, the FWO (G0A6823N) is gratefully acknowledged for support.

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