Notes

Synthesis and Characterization of Gold(I) *N*-Heterocyclic Carbene Complexes Bearing Biologically Compatible Moieties

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*Summary: Two new gold(I) complexes bearing the bulky N-heterocyclic carbene IPr (IPr = bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) and respectively 2,3,4,6-tetra-O-acetyl-1-thio-β-D-pyranosatothiolato [(IPr)AuTgt (**1**)] and a saccharin ligand [(IPr)AuSac (**2**)] have been synthesized in good yield and are fully characterized by NMR spectroscopy and by inert-atmosphere MALDI-TOF. These complexes are well-behaved compounds analogous to gold drugs such as Auranofin and Solganol.*

Introduction

The use of gold salts in medicinal chemistry was first described in 2500 B.C.[1] In modern chemistry, the interest in these salts as potential pharmacophores emerged in 1890 with the discovery of $Au(CN)_2^-$ and its bacteriostatic properties.[2] Almost 40 years later, Forestier reported the first gold-based treatment against tuberculosis.[3] Today in vivo biochemistry of gold remains enigmatic, mainly due to a paucity of adequate models and an inadequate understanding of the reactivity of gold.[4] Moreover, as gold is not a metal naturally used in metabolism, it is believed that its chemistry in vivo differs from other transition metals such as iron and copper, which are carefully transported and stored by enzymatic processes.[5] The biochemistry of gold with D-penicillamine,[6] gluthadione,[7] thiomalic acid,[8] 2,3-dimercaptopropanol,[9] and albumin[10] has been studied. The reactivity of gold occurs though the thiolate function of these biological molecules and leads to the formation of gold(I) thiolates, also called chrysotherapy agents. These complexes are efficient against rheumatoid arthrisis and even HIV[11] and are commercialized under different trade names such as Myochrysine, Solganol, Krysolgan, and Allochrysine.[12] Other types of gold complexes used in medicinal chemistry are gold(I) mono- or bis-phosphines. They can bind to DNA via the guanine and cytosine bases[13] and act as antitumor agents against L1210 leukemia and M5076 reticulum cell sarcoma.[14] In 1972, Sutton synthesized a gold complex with a thiolate and a phosphine ligand: the 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-pyranosato-*S*-(triethylphosphine)gold(I) compound also known by the trade name Auranofin. It became one of the most promising gold complexes in medicinal chemistry,[15] with a great potency against rheumatoid arthritis and cancer cells such as P388 leukemia and B16.[16]

In 1991, Arduengo showed that free *N*-heterocyclic carbenes (NHCs) are stable enough species to be isolated,[17] sparking an ever-growing interest in their chemistry. Since then, these ligands have been used extensively to stabilize transition metal complexes.[18] Their unusual and tunable electronic and steric

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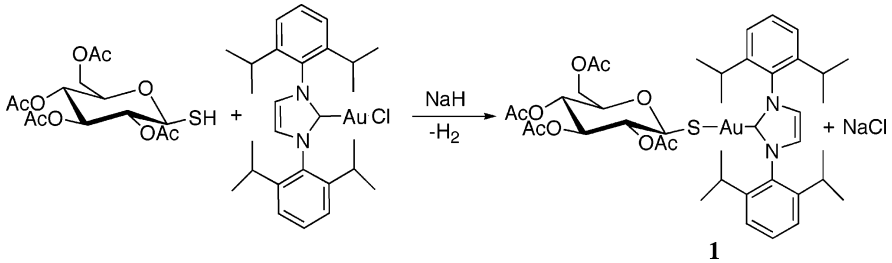
Scheme 1. Synthesis of (IPr)AuTgt (1)



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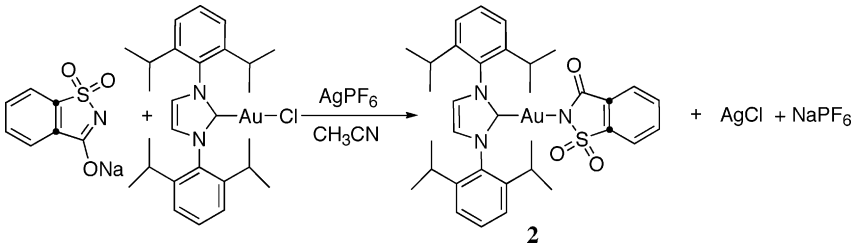
Scheme 2. Synthesis of (IPr)AuSac (2)



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properties have allowed for enhanced catalytic systems performance in palladium-catalyzed cross-coupling reactions,[19] olefin metathesis,[20] and copper-catalyzed hydrosilylation,[21] as the most prominent examples. Gold(I) NHCs have been known since 1989, and they can be neutral or cationic, with the respective formulas (NHC)AuX and $(NHC)_2AuX$.[22] They are now widely used as catalysts for organic transformations such as nucleophilic additions on alkynes.[23] Nevertheless their potential applications in pharmacology have only recently started to be examined, thanks to the work of Baker et al., who have reported the antitumor activity of a cationic gold(I) bis-carbene by a mitocondrial membrane permeabilization (MMP) mechanism[24] and even synthesized the first carbenic Auranofin mimics by substituting the phosphine ligand by different NHCs.[25]

In this Note, we report the synthesis of a new NHC Auranofin mimic using an alternative approach than that recently employed by Baker. We also report the synthesis of a carbenic gold(I) saccharin complex by using for the first time a cationic monoligated NHC gold(I) as reagent.[26] This unstable complex has usually been proposed as an intermediate in gold-catalyzed transformations.[27]

Results and Discussion

We first attempted to synthesize (IPr)AuTgt (**1**) (Tgt = 1-thio-β-D-glucose tetraacetate) by reacting directly the thiosugar with (IPr)AuCl[28] in refluxing dichloromethane (DCM). While the formation of HCl was expected to act as a driving force, no reaction was observed and the two starting materials were recovered. To enhance the nucleophilic behavior of the thiocarbohydrate, we generated the thiolate in situ using NaH. Addition of IPrAuCl permitted the bond formation between the electrophilic gold(I) and the nucleophilic thiolate. The overall reaction is favored by precipitation of sodium chloride (Scheme 1). After filtration over a plug of silica gel and evaporation of the DCM, the desired complex was obtained in a good yield and analytically pure form as an off-white, air-stable powder. It is interesting to note that reaction of the cationic $[(IPr)Au^+(MeCN)][PF_6^-]$, generated in situ from IPrAuCl and $AgPF_6$, with either the thiol or the thiolate failed, the NMR spectra indicating a decomposition pathway.

We first attempted to synthesize (IPr)AuSac (**2**) (Sac = saccharin) by directly reacting the sodium saccharin salt with (IPr)AuCl in DCM. While the formation of a gold−oxygen bond and the precipitation of NaCl were expected, no reaction was observed and the two starting materials were recovered. We attributed this lack of reactivity to the very poor affinity of gold for oxygen. To enhance the acidic character of the gold center, we generated the stable cationic $[(IPr)Au^+(MeCN)][PF_6^-]$ complex, by adding $AgPF_6$ in the presence of (IPr)AuCl. The addition of the saccharin salt allowed the slow formation of the desired complex with appearance of $NaPF_6$ as a white precipitate (Scheme 2). To increase the kinetics of the reaction, an excess of saccharin salt (2:1) was used. After filtration over a plug of silica gel and the evaporation of the volatiles, the desired complex was obtained in good yield and analytically pure form as an off-white air-stable powder.

In order to unambiguously characterize both complexes, NMR and X-ray diffraction studies were performed. A mass spectroscopy IA-MALDI-TOF study of both complexes was performed in order to study their stability in the gas phase.

The ^1H NMR resonances for the imidazole ring of both complexes appear as a singlet at 7.15 and 7.25 ppm, respectively.

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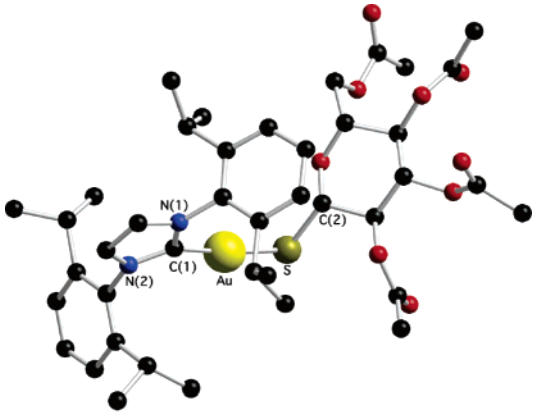

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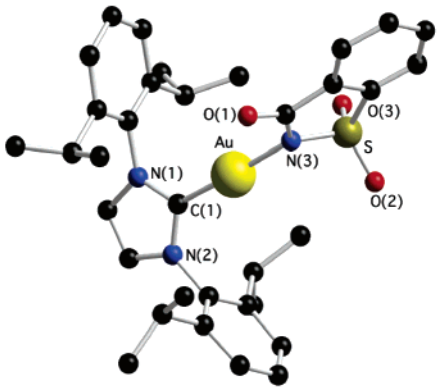

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Figure 1. Ball-and-stick representations of complexes (IPr)AuTgt (**1**) and (IPr)AuSac (**2**). Hydrogen atoms were omitted for clarity.

The same pattern as IPrAuCl is observed for the two diisopropylphenyl groups, indicating that neither sugar prevents the free rotation of the isopropyl groups by steric hindrance.[28] For (IPr)AuTgt (**1**), the signal of the thiolate proton at 2.24 ppm disappears, indicating the bond formation between gold and sulfur, while the four acetate groups appear as four well-defined singlets between 2.03 and 1.87 ppm. Moreover, all protons associated with the β-D-glucopyranose ring are shifted upfield and appear between 3.37 and 4.93 ppm.[25] For (IPr)AuSac (**2**), all aromatic protons are inequivalent. Two of these give well-defined doublets, shifted downfield, while the others give a broad multiplet overlapping the triplet from the aromatic protons assigned to the IPr moiety. The ^{13}C NMR spectra of both complexes exhibit a signal for their carbene carbon at 186.7 and 165.6 ppm, respectively. A good indication of the influence of the ligands, especially of their electronic effects, toward the gold(I) center can be correlated to the chemical shift of the carbene carbon signal.[29] A strong electron-donating ligand will trigger a downfield shift of the carbene carbon position. While the carbene carbon of (IPr)AuCl appears at 175.1 ppm,[28] it is obvious that both sugars for complexes **1** and **2** trigger two very different electronic environments around the gold(I) center. The sulfur appears to increase the electronic density at the gold(I) cation and appears to be strongly bound, as expected from its soft base character and its great affinity for gold. By comparing the carbene carbon signal of (IPr)AuSac (**2**) with the one reported for the cationic complex [(IPr)Au$^+$(MeCN)][PF$_6^-$],[26] we can confirm that nitrogen adds a small amount of electronic density on the gold(I) center and is probably weakly bound, as expected from its hard base character.

Scheme 3. Rearrangement of the Sugar upon Binding with the Gold Cation

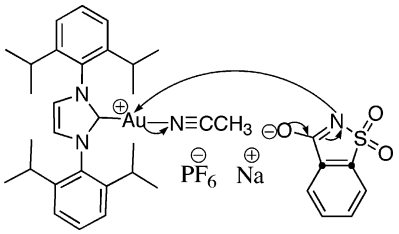

Table 1. Summary of MALDI Mass Spectrometric Data Obtained from Analysis of (IPr)AuTgt (1) and (IPr)AuSac (2) in Positive Ion Mode (the asterisk indicates the base peak in each spectrum)

	(IPr)AuTgt (**1**)		(IPr)AuSac (**2**)	
	m/z	assignment	*m/z*	assignment
molecular ion	948.3	not detected	767.3	not detected
agglomeration	1819.1	$[(IPr)_3Au_3S_2]^+$		
	1787.2*	$[(IPr)_3Au_3S]^+$		
	1564.4	$[(IPr)_2Au_2S(Tgt)\text{-}H]^+$		
	1532.5	$[(IPr)_2Au_2(Tgt)\text{-}H]^+$	1352.1	$[(IPr)_2Au_2(Sac)]^+$
	1266.3	$[(IPr)_2Au_2S_3]^+$		
	1202.8	$[(IPr)_2Au_2S]^+$		
fragments	847.1	$[H(IPr)_2Cl_2]^+$	847.1*	$[H(IPr)_2Cl_2]^+$
	787.1	[(IPr)Au(pyrene)]$^+$	787.1	[(IPr)Au(pyrene)]$^+$

Suitable crystals for X-ray diffraction were grown by slow diffusion of a mixture of DCM/heptane for (IPr)AuTgt (**1**) and (IPr)AuSac (**2**). In the solid state, both complexes (Figure 1) exhibit a two-coordinate gold(I) atom in a nearly linear environment with a C−Au−S bond angle of 173.49° and a C−Au−N bond angle of 177.09°. The respective Au−C(1) distances of 1.986(6) and 1.973(4) Å are in good agreement with previously reported structures of neutral and cationic Au(I)NHC.[25−29] The Au−S distance of 2.2873(16) Å for (IPr)-AuTgt (**1**) is close to the ones found in anionic thiolate gold complexes,[30] and the Au−N distance of 2.031(3) Å for (IPr)-AuSac (**2**) is similar to that found in complexes with nitrogen donor ligands.[31]

It is noteworthy that the gold(I) center binds the saccharin by the nitrogen due to the very poor affinity of gold for binding oxygen and triggers a rearrangement between both possible resonance forms of the saccharin salt, enabling the moiety binding reaction (Scheme 3). For both complexes, there is no noticeable *trans*-effect of the carbene moiety with respect to the sugar ligands. No aurophilic interactions are detected with a minimum Au···Au distance of 7.392 and 9.451 Å, respectively, between gold centers.[32]

We investigated the stability of both complexes in the gas phase by using the mass spectroscopy technique. Inert-atmosphere MALDI-TOF mass spectrometric analysis[33] of **1** and **2** was carried out using pyrene as a charge-transfer matrix (Table 1).

Analysis in negative ion mode revealed signals due to [CH$_3$COO]$^-$ for **1** (presumably arising from fragmentation of

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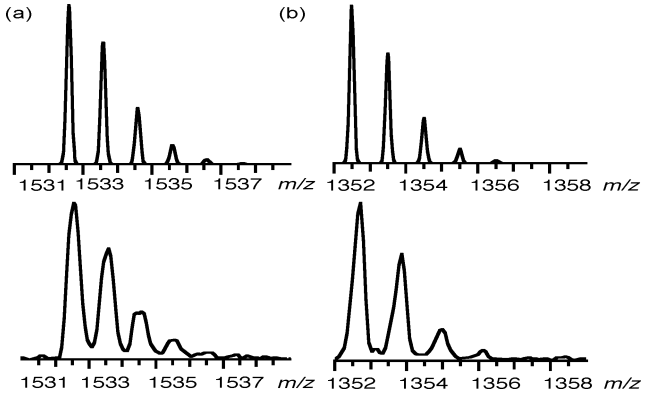

Figure 2. Inert-atmosphere MALDI-MS spectra (pyrene matrix) showing simulated (top) and observed (bottom) isotope patterns for (a) $[(IPr)_2Au_2(Tgt)\text{-}H]^+$ (**1a**) (observed *m*/*z* 1532.5, calculated *m*/*z* 1532.3) and (b) $[(IPr)_2Au_2(Sac)]^+$ (**2b**) (observed *m*/*z* 1352.1, calculated *m*/*z* 1352.3).

the thiolate ligand, Tgt), as well as signals for the $[Sac]^-$ ligand for **2**. In neither case could the intact molecular cations be observed in positive ion mode. Instead, prominent signals were present in each spectrum due to dinuclear Au complexes, resulting from agglomeration in the gas phase. Ample precedents exist for aggregation of coordinatively unsaturated ions via ion−molecule interactions in the gas phase.[34] Of particular interest are peaks assigned to $[(IPr)_2Au_2(Tgt)\text{-}H]^+$ (**1a**) and $[(IPr)_2Au_2(Sac)]^+$ (**2b**), respectively, on the basis of the match between their simulated and observed isotope patterns (Figure 2). The complexity of the patterns is due to the isotopic composition of the ligands, as gold is monoisotopic.

While numerous peaks for aggregated Au complexes are evident in the spectrum of **1**, including the peak for **1a**, **2b** is the sole agglomeration product observed in the spectrum for **2** (see Table 1 for a summary of mass spectrometric data). Additional signals at high *m*/*z* in the mass spectrum of **1** are due to aggregation products resulting from the cleavage of the sugar moiety from the thiolate ligand, rather than loss of the entire (Tgt) ligand. Prominent among these are signals for $[(IPr)_3Au_3S]^+$ (which is observed as the base peak) and $[(IPr)_2Au_2S]^+$. Retention of the sulfur donor, whether by rearrangement or by recapture following fragmentation, reflects the thiophilic nature of gold. It is worthy to note that for **2** there is no retention of nitrogen, emphasizing the low affinity of gold to bind nitrogen. The gold(I) cation, present in the ion fragments, remains bound to the IPr ligand, highlighting the very strong bond between gold and NHC ligands, responsible for the exceptional stability of the complex type. Present in the MALDI spectra for both **1** and **2** are peaks corresponding to $[H(IPr)_2Cl_2]^+$ (indeed, this signal is the base peak in the spectrum of **2**). Presumably this results from dimerization of the *N*-heterocyclic carbene, IPr, and the capture of chloride ions from residual AuCl and/or starting material. It should be noted that the relative intensity of ion peaks in the mass spectra does not necessarily correlate with abundance; the kinetic stability of the ion also plays a key role. The proportion of AuCl in the analyte itself is negligible, as judged from microanalysis. Also evident in the positive ion spectra are peaks due to $[(IPr)Au(pyrene)]^+$, which we attribute to scavenging of the coordinatively unsaturated $[(IPr)Au]^+$ by pyrene in the gas phase.

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Conclusion

We report the synthesis, in good yield, of two new neutral gold(I) complexes with ligands of biological interest. Generation of the nucleophilic thiolate or the electrophilic cationic gold(I) center has allowed the reactions to proceed smoothly and efficiently. Atom connectivity in the new complexes has been confirmed by NMR and XRD. IA-MALDI-TOF mass spectroscopy provides information as to the stability of **1** and **2** and decomposition routes accessible to compounds of this composition. Both complexes exhibit expected decomposition pathways in the gas phase in agreement with the chemistry of organogold complexes both in solution and in the solid state. Further NMR studies have emphasized the difference in electronic donation between the sugars toward the gold(I) center. The ability of these (and related congener) complexes to bind DNA and act as potential chemotherapeutic agents is currently under study.

Experimental Section

General Considerations. Complexes were synthesized using standard Schlenk techniques under an atmosphere of dry argon. Anhydrous solvents were either distilled from the appropriate drying agents or purchased from Aldrich and kept over molecular sieves. IA-MALDI-MS analyses were performed using a Bruker OmniFlex MALDI TOF mass spectrometer equipped with a nitrogen laser (337 nm) and interfaced to an MBraun Labmaster 130 glovebox. Data were collected in both positive and negative reflectron mode, with the accelerating voltage held at 20 kV for all experiments. Matrix (pyrene) and analyte solutions were prepared in acetontrile at concentrations of 20 and 1 mg/mL, respectively; samples were mixed in a matrix to analyte ratio of 20:1. Pyrene (99% purity) was used as received from Aldrich. Solvents for NMR spectroscopy were dried over molecular sieves. NMR spectra were collected on a 400 MHz Varian Gemini spectrometer. Elemental analyses were performed by Robertson Microlit Labs. (IPr)AuCl was synthesized following the literature procedure.[26]

Synthesis of (IPr)AuTgt (1). In a oven-dried Schlenk flask under argon, 1-thio-β-D-glucose tetraacetate (59 mg, 0.16 mmol, 1 equiv) was dissolved in 2 mL of DCM and the solution cooled at 0 °C with the aid of an ice bath. NaH (6 mg, 0.24 mmol, 1.5 equiv) was then added and allowed to react for 30 min, after which time (IPr)-AuCl (100 mg, 0.16 mmol) was added as a solid. The reaction was stirred overnight at room temperature. After filtration over a plug of silica gel and evaporation of volatiles, a white analytically pure powder was obtained (120 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, J = 8.0 Hz, 2H, C*H*-aromatic), 7.31 (m, 4H, C*H*-aromatic), 7.15 (s, *C*H-imidazole), 4.93 (t, J = 9.2 Hz, 1H, CH(C*H*)CH), 4.68 (t, J = 9.2 Hz, 1H, CH(C*H*)CH), 4.54 (d, J = 9.2 Hz, 1H, O(C*H*)S), 4.41 (t, J = 9.2 Hz, 1H, CH(C*H*)CH), 3.92 (m, 1H, CH(CH_2)O), 3.82 (m, 1H, CH(CH_2)O), 3.37 (m, 1H, CH_2-(C*H*)O, 2.63−2.55 (m, 4H, C*H*$(CH_3)_2$), 2.03 (s, 3H, OCH_3), 2.02 (s, 3H, OCH_3), 1.95 (s, 3H, OCH_3), 1.87 (s, 3H, OCH_3), 1.35 (m, 12H, CH (CH_3)$_2$), 1.22 (m, 12H, CH (CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7 (s, *C*-carbene), 171.2 (s, O*C*O), 170.6 (s, O*C*O), 169.8 (s, O*C*O), 169.4 (s, O*C*O), 146.1 (s, *C*H-aromatic), 146.0 (s, *C*H-aromatic), 134.4 (s, *C*H-aromatic), 130.9 (s, *C*H-aromatic), 124.4 (s, *C*H-aromatic), 124.3 (s, *C*H-aromatic), 123.1 (s, *C*H-imidazole), 82.8 (s, O(*C*H)S), 75.2 (s, CH(*C*H)CH), 74.4 (s, CH-(*C*H)CH), 69.7 (s, CH(*C*H)CH), 63.8 (s, CH(*C*H)CH), 29.0 (s, *C*H$(CH_3)_2$), 28.9 (s, *C*H$(CH_3)_2$), 24.6 (s, CH(*C*H_3)$_2$), 24.2 (s, CH-(*C*H_3)$_2$), 21.1 (s, OCH_3), 21.0 (s, OCH_3), 20.9 (s, OCH_3), 20.8 (s, OCH_3).). Anal. Calcd for $C_{41}H_{55}N_2O_9SAu$ (948.44): 51.92 C, 5.80 H, 2.95 N. Found: 51.74 C, 5.59 H, 2.67 N.

Synthesis of (IPr)AuSac (2). In an oven-dried Schlenk flask under argon, (IPr)AuCl (75 mg, 0.12 mmol, 1 equiv) was dissolved in 2 mL of acetonitrile. $AgPF_6$ (31 mg, 0.12 mmol, 1 equiv) was

added, and the solution was stirred for 30 s, with the rapid appearance of a precipitate (AgCl). Then the saccharin sodium salt (54 mg, 0.24 mmol, 2 equiv) was added, and the solution was stirred overnight at rt. Acetonitrile was removed under reduced pressure and replaced by cold DCM. The excess saccharin sodium and AgCl salts are not soluble in cold DCM; the solution was filtered over Celite, and the solids were discarded. Evaporation of the DCM gave a white powder (60 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, $J = 6.4$ Hz, 1H, C*H*-aromatic), 7.62 (d, $J = 6.8$ Hz, 1H, C*H*-aromatic), 7.52 (m, 4H, C*H*-aromatic), 7.32 (d, $J = 7.2$ Hz, 4H, C*H*-aromatic), 7.25 (s, 2H, *C*H-imidazole), 2.59 (sept, $J = 6.8$ Hz, 4H, C*H*$(CH_3)_2$), 1.42 (m, $J = 6.8$ Hz, 12H, CH(C*H*$_3)_2$), 1.25 (m, $J = 6.8$ Hz, 12H, CH(C*H*$_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2 (s, N*C*O), 165.6 (s, *C*-carbene), 145.9 (s, *C*H-aromatic), 142.0 (s, *C*H-aromatic), 133.9 (s, *C*H-aromatic), 132.8 (s, *C*H-aromatic), 132.7 (s, *C*H-aromatic), 132.1 (s, *C*H-aromatic), 131.1 (s, *C*H-aromatic), 124.5 (s, *C*H-imidazole), 124.1 (s, *C*H-aromatic), 123.5 (s, *C*H-aromatic), 120.2 (s, *C*H-aromatic), 29.2 (s, *C*H$(CH_3)_2$), 24.7 (s, CH(*C*H$_3)_2$), 24.3 (s, CH(*C*H$_3)_2$). Anal. Calcd for $C_{41}H_{55}N_2O_9SAu$ (948.44): 53.14 C, 5.21 H, 5.47 N. Found: 52.97 C, 5.30 H, 5.37 N.

Crystallographic information files (CIF) of complexes (IPr)AuTgt (**1**) and (IPr)AuSac (**2**) have been deposited with the CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K., and can be obtained on request free of charge, by quoting the publication citation and deposit numbers 615644 and 615645.

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Supporting Information Available: Crystallographic information files (CIF) of complexes (IPr)AuTgt (**1**) and (IPr)AuSac (**2**) and the IA-MALDI TOF spectra of the complexes are available free of charge via the Internet at http://pubs.acs.org.

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