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Rational Design of a Gold Carbene Precursor Complex for a Catalytic Cyclopropanation Reaction**

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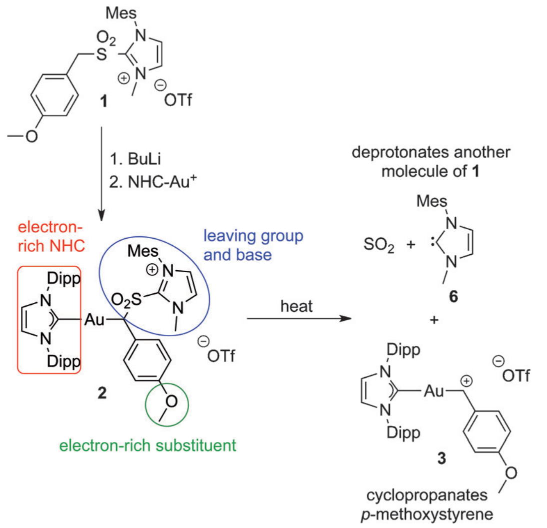
We report herein the rational design of an isolable gold carbene precursor complex and its reactivity in stoichiometric and catalytic cyclopropanation reactions. This work is another example of combined gas- and solution-phase studies for the rational discovery of new catalytic transformations.[1]

Cyclopropane motifs play a prominent role in chemistry and biology, as they are present in natural products and are found in biologically active compounds, such as pharmaceutical agents.[2] Cyclopropanes are interesting building blocks owing to their rigid structure and geometric similarities to olefins.[3] The challenging formation of highly strained cycloalkanes[4] can be accomplished using transition metals,[3,5] including gold-promoted carbon–carbon bond-forming reactions.[6] Most of these transformations presumably involve a gold carbene exhibiting carbocationic character.[7]

Our group has recently reported the first example of the mass spectrometric (ESI-MS/MS) detection of a cationic *N*-heterocyclic carbene (NHC) gold(I) benzylidene complex, generated from a phosphonium ylide.[8] Gas-phase characterization experiments have shown that these carbenes cyclopropanate electron-rich olefins.[8,9] This reactivity was not observed in solution under thermal conditions. This was attributed to a too-slow formation of gold benzylidene compared to other decay products, although the carbon–phosphorus bond was the first bond to break under collision-induced dissociation (CID) conditions in the gas phase.

Gai et al. have used sulfone-based compounds in nickel(II)-catalyzed cyclopropanation reactions. However, the procedure requires slow addition of methyllithium to the refluxing reaction mixture. This complicates the reaction setup and limits the scope to base-tolerant olefins. Furthermore, the exact mechanism of these transformations and the nature of the intermediates remain unresolved.[10] Other reports have shown that sulfone and structurally similar compounds are capable of ligating $Ph_3P{-}Au^I$ to give stable gold alkyl complexes.[11] The complexes were, however, unreactive in cyclopropanation.



Scheme 1. Design, synthesis, and fragmentation of gold carbene precursor **2**.

Based on these findings, we envisioned that appropriate modifications on the gold alkyl complex would give access to an isolable gold(I) carbene precursor complex **2** (Scheme 1), which would cyclopropanate olefins.[6a,12] The isolation of such a gold carbene precursor complex would not only allow for full characterization but also produce insights concerning the nature of gold carbenes and their cyclopropanation reaction mechanism.[7,13] Lastly, we sought to eliminate the need for addition of stoichiometric amounts of a strong base.

We reasoned that an electron-rich NHC ligand[14] and a methoxy substituent in the *para* position on the phenyl ring would stabilize the carbocationic gold carbene **3** and thus facilitate its formation. The SO_2-imidazolium moiety acts as a leaving group, which can dissociate to give SO_2 and imidazolylidene **6**. The latter, produced in situ, serves as a base to deprotonate another molecule of imidazolium sulfone salt **1** in the putative catalytic cycle (Scheme 2). Furthermore, the imidazolium moiety carries a charge, making it possible to manipulate the gold carbene precursor **2** not only in solution, but also in the gas phase. The presence of the SO_2 moiety is crucial as it: 1) acidifies the α-position in the imidazolium sulfone salt **1** owing to electronic stabilization; and 2) leaves the reaction as a gas that does not interfere with further steps.[15] The exact order of the C1–S1 and C2–S1 bond cleavage (Figure 1) is still unclear and could not be determined through gas- or solution-phase experiments. However, preliminary theoretical density functional theory (DFT) calculations suggest that either both bonds are cleaved

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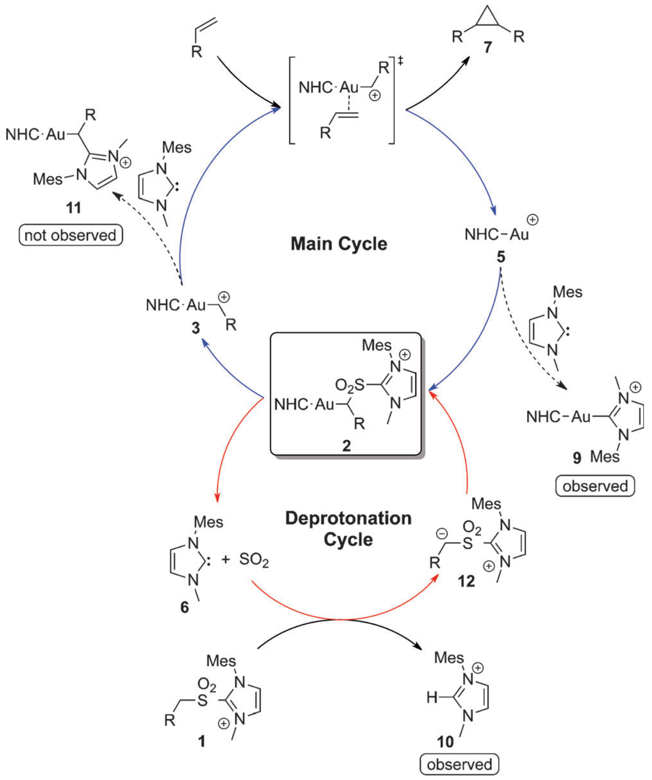


Scheme 2. Proposed catalytic cycle of gold carbene precursor **2** in the presence of imidazolium sulfone salt **1** and *p*-methoxystyrene. Triflate ions are omitted for clarity. R = 4-MeOC$_6$H$_4$, NHC = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

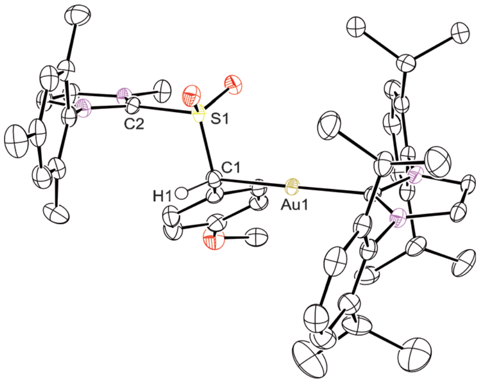


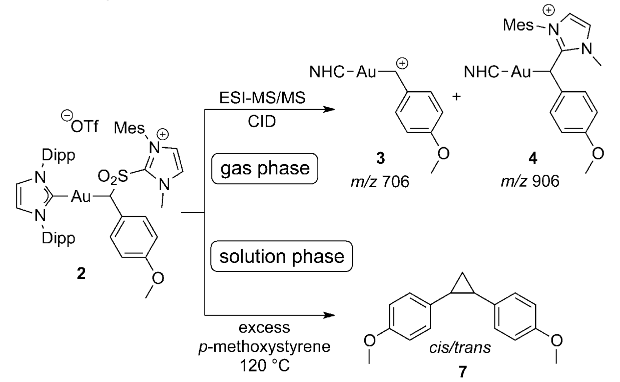
Figure 1. Structure of gold(I) carbene precursor **2** in the solid state. Ellipsoids are set at 50% probability for all heavy atoms except for Au (94% probability); hydrogen atoms (except H1) and the triflate ion are omitted for clarity.[16]

simultaneously or the C1–S1 bond dissociates first, followed by the dissociation of S1–C2.

The syntheses of imidazolium sulfone salt **1** and air-stable gold carbene precursor **2** (93% yield) were facile. The X-ray crystallographic structure of **2** (Figure 1) is consistent with reported structures of related complexes.[11]

For further characterization and confirmation of the formation of gold carbene **3**, precursor **2** was analyzed in the gas phase by means of electrospray ionization tandem mass spectrometry (ESI-MS/MS) on a Thermo-Finnigan TSQ Quantum instrument.[17] CID of **2** gave two signals, the first corresponding to gold carbene **3** (*m*/*z* 706),[8] generated by the loss of imidazolylidene **6** and SO$_2$. The second signal at *m*/*z* 906 appears to have been generated through the extrusion of SO$_2$ to give gold complex **4** (Table 1).[18] Such a rearrangement was not observed in solution but has previously been observed in the gas phase for organic sulfonamide compounds.[19]

Table 1: Chemical behavior of gold carbene precursor **2** in the gas and the solution phase.[a]



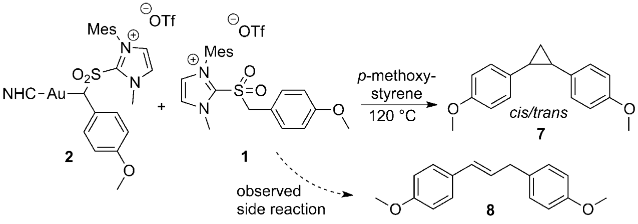
	solvent	*t* [h]	*T* [°C]	**7**	
				yield [%][b]	*cis*/*trans*
1	MeCN	3	120	99	5:1
2	THF	3	120	96	14:1
3	C_6H_5Cl	3	120	99	14:1
4	CH_2Cl_2	3	120	99	14:1
5	CH_2Cl_2	16	100	87	12:1
6	CH_2Cl_2	16	80	79	11:1
7	toluene	3	120	88	19:1
8	hexane	3	120	63	9:1

[a] Reactions were conducted in pressurizable glassware and in the presence of excess *p*-methoxystyrene. [b] Yields (by GC) relative to an internal standard.

Heating gold carbene precursor **2** to 120 °C in the presence of *p*-methoxystyrene gave the expected cyclopropane **7**[6a,12] in up to 99% yield (Table 1). The reaction did not exhibit strong solvent dependence and proceeded equally well in a range of solvents at 120 °C. The influence of the observed 5:1 to 19:1 *cis*/*trans* selectivity in cyclopropane formation warrants further studies, especially since a recently published article shows an opposite trend of selectivity.[6a] When a solution of **2** in the absence of *p*-methoxystyrene was heated to 120 °C, *p*-methoxybenzaldehyde along with other products was detected but no homocoupling product (stilbene) was observed.

The formation of cyclopropane **7** in solution is an indication that the desired gold carbene **3** was in fact generated. We then turned our attention to the development of a catalytic reaction (Scheme 2). The addition of gold carbene precursor **2** to a solution of imidazolium sulfone salt **1** and *p*-methoxystyrene gives the desired cyclopropanation product with up to 4.3 turnovers (Table 2), which is limited by a side reaction (see below).

Table 2: Gold-catalyzed cyclopropanation reaction and competitive decay of imidazolium sulfone salt **1**.[a]



	solvent	*t* [h]	**2**/**1**	conversion into **7** TON[b,c]	 conv. [%][d]	 *cis/trans*	**8**[e] [%]
1	CH_2Cl_2	1.7	1:6	2.7	29	8:1	37
2	CH_2Cl_2	1.7	1:14	4.0	22	7:1	36
3	CH_2Cl_2	3.0	1:22	4.3	16	7:1	50
4	CH_2Cl_2	1.7	1:112	2.6	1	6:1	49
5	THF	1.7	1:15	1.8	6	9:1	27
6	MeCN	1.7	1:12	1.6	6	6:1	5
7	C_6H_5Cl	2.7	1:7	1.7	9	13:1	40

[a] Reactions were conducted in pressurizable glassware and in the presence of excess *p*-methoxystyrene. [b] Yields that form the basis of the TON (by GC-FID) using internal standard. [c] TON: Turnover with respect to **2**. [d] Conversion of **1** into cyclopropane **7**. [e] Yields (by GC) of **8** relative to an internal standard with respect to **1**.

The catalytic cycle only tolerated a narrow range of solvents, CH_2Cl_2 being the solvent of choice (Table 2, entries 1–4). MeCN and THF are less suitable owing to the Lewis acidity of NHC–Au^I, which might lead to the deactivation of the gold cation. Nolan et al. have observed that gold(I) activates THF towards a cationic ring opening and subsequent polymerization.[20] Subjecting a reaction mixture after 1.7 h to ESI-MS/MS revealed complete consumption of **1** and precursor **2** along with nearly exclusive formation of **9** and **10**. This observation indicates that the rate-determining step is likely to be formation of gold carbene **3**, as complex **11**[11b] was not observed, while deprotonation of **1** followed by complexation to gold cation **5** is assumed to be rapid.

The above-mentioned side reaction, which occurs in the absence of NHC–Au^I, is the competitive decay of imidazolium sulfone salt **1** to form olefin **8** thereby limiting the turnover number. This reaction presumably proceeds by the heterolytic formation of an oxonium species, which is trapped by *p*-methoxystyrene, followed by deprotonation to form **8**.[21] Increasing the amount of **1** relative to gold carbene precursor **2** only increased the number of turnovers to a certain degree. This is most likely due to an irreversible trapping of imidazolylidene **6** by **5**, which removes the base needed for deprotonation in the catalytic cycle, as well as non-productive deprotonation of the carbocation leading to **8**, which we noted above. Control experiments indicate that cyclopropane **7** and olefin **8** do not undergo rearrangement in the presence of NHC–Au^I at 120 °C for 16 h. Under these conditions, a solution of NHC–Au^I in the presence of *p*-methoxystyrene and **1** gave only the olefin product **8**.

In conclusion, we have rationally designed a robust, isolable, and well-defined gold carbene precursor **2**, which is capable of effecting cyclopropanation of *p*-methoxystyrene in a range of different solvents at 120 °C. The addition of imidazolium sulfone salt **1** allows for a catalytic cyclopropanation reaction, which renders the addition of external base unnecessary, albeit with only modest turnover at present. The individual steps within the catalytic cycle were first probed in the gas phase, and then incorporated into the solution phase design. Further investigations concerning kinetics (to optimize turnover), as well as DFT calculations of the reaction, are underway.

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[1] a) P. Chen, *Angew. Chem.* **2003**, *115*, 2938–2954; *Angew. Chem. Int. Ed.* **2003**, *42*, 2832–2847; b) F. Coelho, M. N. Eberlin, *Angew. Chem.* **2011**, *123*, 5370–5372; *Angew. Chem. Int. Ed.* **2011**, *50*, 5261–5263; c) S. Maurizio, *Int. J. Mass Spectrom. Ion Processes* **1992**, *118–119*, 395–447.

[2] D. Y. K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642.

[3] H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.

[4] A. de Meijere, *Angew. Chem.* **1979**, *91*, 867–884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809–826.

[5] a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724; b) M. Brookhart, W. B. Studabaker, *Chem. Rev.* **1987**, *87*, 411–432.

[6] a) C. R. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955; b) S. Kramer, T. Skrydstrup, *Angew. Chem.* **2012**, *124*, 4759–4762; *Angew. Chem. Int. Ed.* **2012**, *51*, 4681–4684; c) J. F. Briones, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 11916–11919.

[7] a) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem.* **2009**, *121*, 2548–2551; *Angew. Chem. Int. Ed.* **2009**, *48*, 2510–2513; b) A. M. Echavarren, *Nat. Chem.* **2009**, *1*, 431–433; c) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482–486.

[8] A. Fedorov, M.-E. Moret, P. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 8880–8881.

[9] a) A. Fedorov, P. Chen, *Organometallics* **2009**, *28*, 1278–1281; b) A. Fedorov, L. Batiste, A. Bach, D. M. Birney, P. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 12162–12171; c) L. Batiste, A. Fedorov, P. Chen, *Chem. Commun.* **2010**, *46*, 3899–3901.

[10] Y. Gai, M. Julia, J.-N. Verpeaux, *Bull. Soc. Chim. Fr.* **1996**, *133*, 817–829.

[11] a) H.-J. Kneuper, K. Harms, G. Boche, *J. Organomet. Chem.* **1989**, *364*, 275–279; b) A. Fürstner, M. Alcarazo, R. Goddard, C. W. Lehmann, *Angew. Chem.* **2008**, *120*, 3254–3258; *Angew. Chem. Int. Ed.* **2008**, *47*, 3210–3214.

[12] a) E. s. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; b) H. Pellissier, *Tetrahedron* **2008**, *64*, 7041–7095.

[13] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019.

[14] W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, *134*, 5697–5705.

[15] Denk et al. have reported that some NHCs are capable of forming a stable NHC–SO_2 adduct. However, we reasoned that such an adduct is very unlikely to be stable at 120 °C, namely the temperature at which the cyclopropanation reactions in the

present study are conducted (see: M. K. Denk, K. Hatano, A. J. Lough, *Eur. J. Inorg. Chem.* **2003**, 224 – 231).

[16] For a summary of crystallographic data, see the Supporting Information. CCDC 928355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] For instrument setup and spectra, see the Supporting Information.

[18] For a more detailed discussion of the species at *m*/*z* 906, see the Supporting Information.

[19] a) M. Sun, W. Dai, D. Q. Liu, *J. Mass Spectrom.* **2008**, *43*, 383 – 393; b) N. Hu, P. Liu, K. Jiang, Y. Zhou, Y. Pan, *Rapid Commun. Mass Spectrom.* **2008**, *22*, 2715 – 2722.

[20] S. P. Nolan, P. De Frémont, *Vol. US 7767841(B1)*, C01F1/00; C07F1/12 ed., USA, **2008**.

[21] A reaction vessel charged with **1** and *p*-methoxystyrene in CH_2Cl_2 at 120 °C for 2 h yields olefin **8** in 36–48 % along with other polymerization products. A more detailed reaction mechanism is provided in the Supporting Information.