Carbene Chemistry

DOI: 10.1002/ange.200501056

A Gold Catalyst for Carbene-Transfer Reactions from Ethyl Diazoacetate**

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The use of transition-metal-based catalysts for the transfer of carbene units from diazo compounds constitutes a powerful tool in organic synthesis.[1] Several metals have been reported to mediate this transformation effectively, and the appropriate selection of ligands has permitted excellent selectivities. Highly chemo-, diastereo-, and/or enantioselective systems have been reported with rhodium-, copper-, or cobalt-containing catalysts. In fact, nearly all 12 elements of Groups 8–11 have been found to decompose diazo compounds and transfer a carbene unit to saturated or unsaturated organic substrates,[2] leading to the insertion or addition product, respectively (Scheme 1). Only one of these 12 elements remains unexplored in this chemistry: gold.[3] Although the other members of Group 11—copper and, to a lesser extent, silver—have been described to induce such transformations, conducting this type of catalytic reaction with gold remains a challenge. We therefore focused our attention on the development of a gold-based catalyst, as a result of our experience in the area of metal-catalyzed carbene transfer from ethyl diazoacetate (EDA).[4]

We recently reported the catalytic behavior of [(IPr)CuCl] (**1**, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) for the transfer of carbene from ethyl diazoacetate to olefins, amines, and alcohols to form cyclopropanes, amino acid derivatives, and ethers, respectively.[5] These promising results

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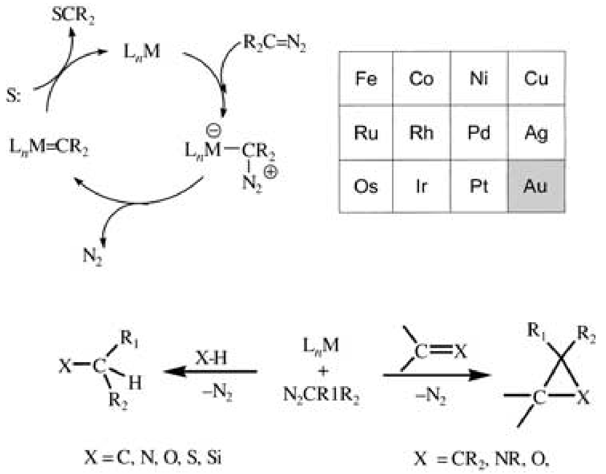
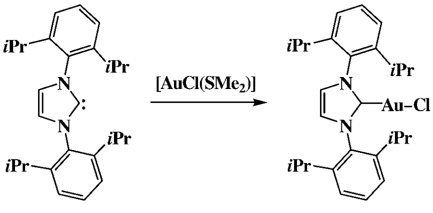
[**] We are grateful for financial support for this work (BQU2002–01114). We acknowledge the Universidad de Huelva (NMR Service), the MECD (M.R.F.), and the Ramon y Cajal Program (M.M.D.R.) as well as the National Science Foundation for work conducted at the University of New Orleans.

Supporting information for this article (general experimental procedures and product characterization data) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Top left: Catalytic cycle proposed for the metal-catalyzed decomposition of diazo compounds and subsequent carbene transfer to a saturated or unsaturated substrate (S:). Top right: Metals of Groups 8–11 that have been described to induce such a transformation; gold still remained unreported. Bottom: The most common examples of organic transformations using the methodology of carbene transfer from diazo compounds.

prompted us to examine the potential role of the gold analogue [(IPr)AuCl] (**2**), which was prepared from equimolar amounts of the IPr ligand and [AuCl(SMe$_2$)] [Eq. (1)].[6]



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(1)

This new compound was spectroscopically characterized, and its structure confirmed by X-ray diffraction studies (Figure 1). The gold(I) atom is two-coordinate in an essentially linear environment with C-Au-Cl bond angles close to 180°, an arrangement similar to that previously found for **1**.

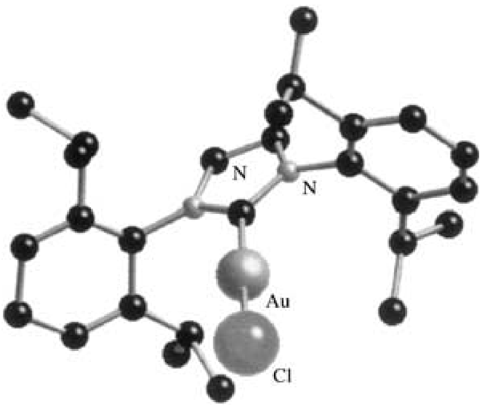
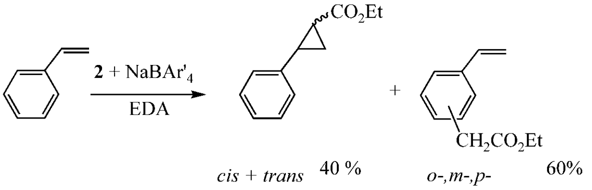


Figure 1. Ball-and-stick view of complex **2**; hydrogen atoms have been omitted for clarity.

Once prepared and characterized, complex **2** was employed as a catalyst for the cyclopropanation of styrene with ethyl diazoacetate, a well-known model reaction. Our previous work with the copper complex **1** suggested that the chloride ion had to be removed from the metal center prior to reaction with EDA.[5] We therefore employed a modified method in which the active catalytic species was generated in situ by using an equimolar mixture of **2** and the sodium salt of the non-coordinating anion tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr'$_4$). The use of a 2.5% catalyst loading (with respect to EDA) in neat styrene (1 mL) led to the consumption of EDA within a few minutes (see the Experimental Section). Analysis of the reaction mixture by GC and GCMS showed, besides the expected *cis*- and *trans*-cyclopropanes, three other products with the same molar mass, namely, the *o*, *m*, and *p* isomers of the styryl acetate shown in Equation (2). These additional products are formed



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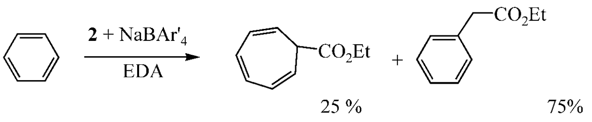

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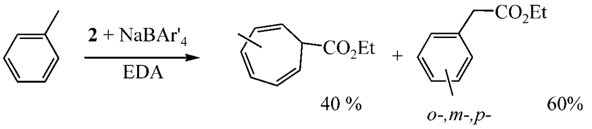


(4)

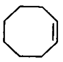
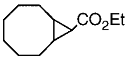
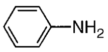
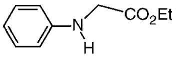
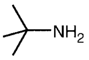
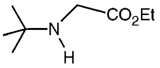
by the formal insertion of the :CHCO$_2$Et unit into the sp^2 C–H bond of the aromatic ring of the styrene. To the best of our knowledge, this type of intermolecular reaction is unprecedented.[7] All published reports have shown that the double bond of styrene is preferentially converted into the cyclopropane product in this reaction. A second, but nonetheless important feature of this gold catalyst is that no diethyl fumarate or maleate formed as a result of EDA coupling, even though the diazo compound was added to the reaction mixture in one portion.

To see whether this unexpected insertion reaction can be generalized, we examined two common aromatic substrates, benzene and toluene [Eqs. (3), (4); yields determined by NMR spectroscopy]. Previous reports have shown that the metal-catalyzed addition of EDA to these compounds results in the formation of cycloheptatriene rings as the major product.[4h,8] In the case of toluene, a few catalysts have also promoted insertion into the methyl C–H bond to provide the dihydrocinnamate derivative[4h,8,9] but there are no examples of insertion into the aromatic sp^2 C–H bond. In contrast, the use of **2** and NaBAr'$_4$ as the catalyst precursor for the reaction of EDA and benzene led to a mixture of the expected cycloheptatriene as well as ethyl phenylacetate [Eq. (3)], the latter formed by formal insertion into the aromatic C–H bond. Similar behavior was observed with toluene as the substrate [Eq. (4)]: The expansion products were observed along with the three isomers of ethyl tolylacetate. The identities of the new products are unambiguous, as their spectroscopic and chromatographic data are identical to those of commercial samples (see the Experimental Section).

No EDA-coupling products—that is, diethyl fumarate and maleate—were observed in the above transformations, highlighting the chemoselectivity of this catalytic system. Even allowing EDA to react with complex **2** at room temperature for several hours did not lead to any transformation of the initial diazo compound. Heating of the reaction mixture at 60 °C and 80 °C did not induce any Au-catalyzed EDA decomposition, therefore indicating the stability of the diazo compound in the presence of **2**, as was observed for the copper analogue **1**.[5]

We next screened several substrates to explore the range of activity for the gold system (Table 1). The use of *cis*-cyclooctene as the olefin provided the expected mixture of *exo*- and *endo*-cyclopropanes. The insertion of EDA into N–H and O–H bonds was also studied with amines and alcohols; in all cases the corresponding amino acid derivatives and ethers were obtained quantitatively. Again, no EDA coupling products were detected in the mixture at the end of the reaction.

Table 1: The addition or insertion of EDA catalyzed by **2** + NaBAr'$_4$.

Substrate	Product	Yield [%][a]
		> 99[b]
		> 99[b]
		> 99[b]
CH_3OH	$CH_3OCH_2CO_2Et$	> 99[c]
CH_3CH_2OH	$CH_3CH_2OCH_2CO_2Et$	> 99[c]

[a] No diethyl fumarate or maleate was detected in any experiment; see the Experimental Section for details. [b] Determined by NMR spectroscopy at the end of the reaction using an internal standard. [c] Determined by GC using an internal standard.

Kinetic experiments were performed using methanol as the substrate with complex **2** as the catalyst precursor both with and without the halide scavenger NaBAr'$_4$. First, the consumption of EDA was monitored in parallel experiments differing only in the presence or absence of NaBAr'$_4$. The two reactions lead to very similar decays that correspond to first-order behavior (Figure 2). Plots of ln[EDA] versus time provided k_{obs} values of 5.98×10^{-4} and $6.84 \times 10^{-4}\,s^{-1}$ for the experiments carried out in the absence and in the presence of the tetraarylborate anion, respectively; the latter reaction is slightly faster but of the same order of magnitude. Nearly identical values for k_{obs} were obtained from experiments in which the nitrogen evolution was measured (7.94×10^{-4} and $1.05 \times 10^{-3}\,s^{-1}$, respectively). These values compare well with those obtained from monitoring EDA consumption.

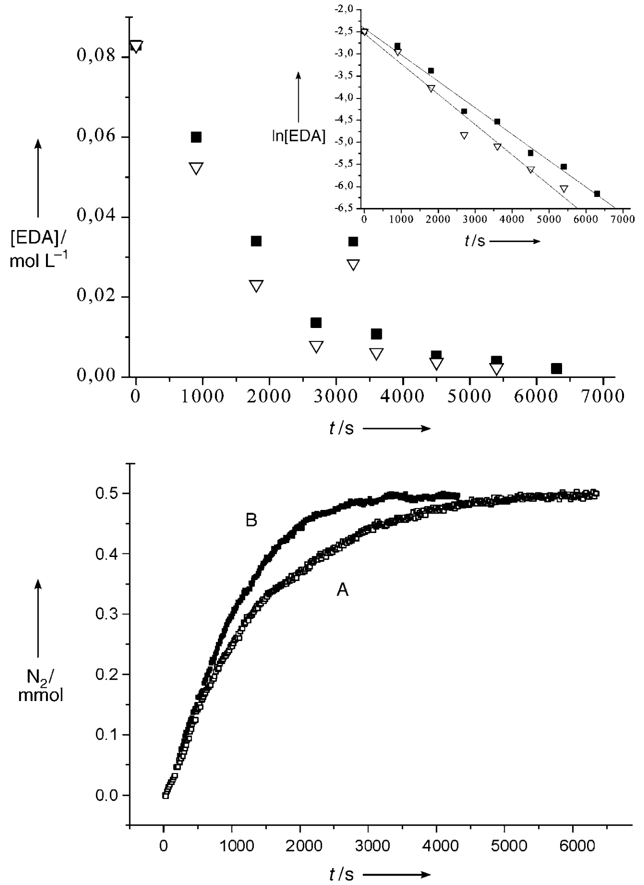
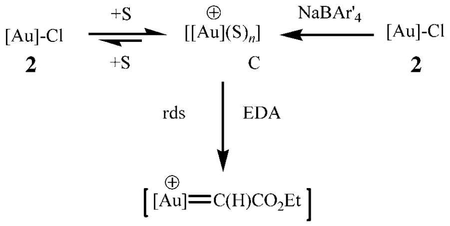


Figure 2. Top: Plot showing the consumption of EDA in the reaction of methanol and ethyl diazoacetate with **2** as catalyst in the absence (■) and presence of NaBAr'$_4$ (▽). Inset: Plot of ln[EDA] versus time t from which the following k_{obs} values were obtained: **2** as catalyst: $k_{obs} = 5.98 \times 10^{-4}\,s^{-1}$; **2** + NaBAr'$_4$ as catalyst: $k_{obs} = 6.84 \times 10^{-4}\,s^{-1}$. Bottom: Plot of nitrogen evolution under the same conditions. Exponential fitting provided the following values: $k_{obs} = 7.94 \times 10^{-4}$ (**2** as catalyst, A), $k_{obs} = 1.05 \times 10^{-3}\,s^{-1}$ (**2** + NaBAr'$_4$ as catalyst, B).

Scheme 2 illustrates a possible explanation for the experimental kinetic data. A cationic species **C**, probably containing coordinated methanol, is formed in both instances. The addition of NaBAr'$_4$ promotes the quantitative conversion of **2** into such a species; however, in the absence of NaBAr'$_4$, an equilibrium between the neutral **2** and the cationic **C** takes place. This also explains the slightly more sluggish reaction with **2** as catalyst since the amount of **C** is not equal to the



Scheme 2. Proposed mechanism for the generation of the catalytic species.

initial amount of **2**. In contrast, the use of the arylborate salt ensures that [**C**] = [**2**]$_{init}$. The catalytic cycle starts from **C**, and the rate-determining step is the formation of a metallocarbene intermediate, as commonly proposed for this type of transformation.[1]. The observation of very similar rate constants from the monitoring of nitrogen generation and EDA consumption is in line with the absence of fumarate and maleate products.

In conclusion, we have described the first example of a gold-based catalyst for the decomposition of ethyl diazoacetate and the subsequent transfer of the :CHCO$_2$Et unit to saturated and unsaturated substrates: Cyclopropanation of olefins as well as insertion into N−H and O−H bonds have been achieved. Even more interesting is the novel insertion of the carbene units into the C−H bonds of the aromatic ring of benzene, toluene, and styrene. Finally, this catalyst is very chemoselective, since no EDA coupling products are observed in any of the reactions studied.

Experimental Section

General: All reactions were carried out by using standard Schlenk techniques under an atmosphere of dry argon or in an MBraun glovebox containing dry argon or nitrogen. Anhydrous solvents were purchased from Aldrich and degassed prior to use. CD$_2$Cl$_2$ was either dried over CaH$_2$, or degassed with argon and dried over molecular sieves. The reagents (olefins, alcohols, amines) were also purchased from Aldrich and employed without further purification. IPr was synthesized by deprotonation of the imidazolium salt with base according to a literature procedure.[10] The immediate precursor, IPr·HCl, can be purchased from Strem Chemicals Inc. The ^{1}H and ^{13}C NMR spectra were collected on 400-MHz Varian Gemini and Varian Mercury spectrometers. The GC and GCMS were obtained in Varian 3800 and Saturn 2100 instruments, respectively. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

2: In a glove box a 100-mL Schenk flask was charged with IPr (686 mg, 1.8 mmol) and THF (35 mL), and then [AuCl(SMe$_2$)] (232 mg, 0.80 mmol) was added. The resulting solution was stirred at room temperature for 12 h. The solvent was removed under vacuum, and CH$_2$Cl$_2$ (5 mL) was added. The colorless solution was filtered, and hexane (10 mL) was added to the filtrate, resulting in precipitation of an off-white solid. The solid was washed with hexane (3 × 5 mL) and dried under vacuum. Yield: 770 mg (69 %). ^{1}H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 7.57$ (t, $J = 7.8$ Hz, 2 H; ArH), 7.35 (d, $J = 7.8$ Hz, 4 H; ArH), 7.24 (s, 2 H; Imid-H), 2.57 (septet, $J = 6.8$ Hz, 4 H; CH(CH$_3$)$_2$), 1.34 (d, $J = 6.8$ Hz, 12 H; CH(CH_3)$_2$), 1.23 ppm (d, $J = 6.8$ Hz, 12 H; CH(CH_3)$_2$); ^{13}C{^{1}H} NMR (125 MHz, CD$_2$Cl$_2$): $\delta = 175.09$ (C$_{carbene}$), 145.78 (C$_{Ar}$), 134.05 (C$_{Ar}$), 130.68 (C$_{Ar}$), 124.28 (C$_{Ar}$), 123.32 (C$_{imid}$), 28.79 (CH(CH$_3$)$_2$), 24.17 (CH(CH$_3$)$_2$), 23.74 ppm (CH(CH$_3$)$_2$); elemental analysis: calcd for C$_{27}$H$_{36}$N$_2$AuCl (621.69): C 52.11, H 5.79, N 4.50; found: C 51.70, H 5.61, N 4.38. Suitable crystals for crystallographic study were grown by slow evaporation of a saturated solution in acetone. CCDC-258274 (**2**) 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.

Catalytic experiments: The precatalyst **2** (0.025 mmol) was dissolved in neat substrate (1–3 mL), and NaBAr'$_4$[11] (1 equiv) was added to the solution. After 15 min of stirring, EDA (0.5 mmol) was added in one portion. After 1 h of additional stirring, the mixture was analyzed by GC and GCMS. The volatile components were then removed, and the residue analyzed by NMR spectroscopy to identify the products (see the Supporting Information). To establish the mass balance, an internal standard was employed.

Received: March 23, 2005
Revised: May 12, 2005

Keywords: C−H activation · carbenes · diazo compounds · gold · homogeneous catalysis

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