

Role of gold in a complex cascade reaction involving two electrocyclization steps

Jason G. Harrison · Dean J. Tantillo

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Abstract Quantum chemical computations (B3LYP/LACVP**) were applied to assess the impact of Au(I) complexation on activation barriers for sequential electrocyclization reactions (one a 1,2-dihydroazete ring-opening and another a pentadienyl cation ring-closure) proposed to occur during a complex reaction cascade that converts alkynes and imines to cyclopentenimines.

Keywords Catalysis · Cation · Gold · Electrocyclization · Nazarov

Introduction

Catalysis of organic transformations by gold complexes now plays a prominent role in the field of organic synthesis [1–16]. Nonetheless, it remains difficult to rationally design gold-promoted reactions ahead of experimentation. Quantum chemical calculations that quantify the energetic impact of gold complexation on barriers for organic reactions are extremely useful in this regard [17–23], and herein we describe the results of calculations aimed at assessing the impact of gold complexation on two types of electrocyclizations.

In 2009, Gonzalez and co-workers described the transformation of propargyl tosylates and *N*-tosylaldimines into cyclopent-2-enimines using Au(I) catalysts (e.g., Scheme 1, top) [24]. In addition, the authors were

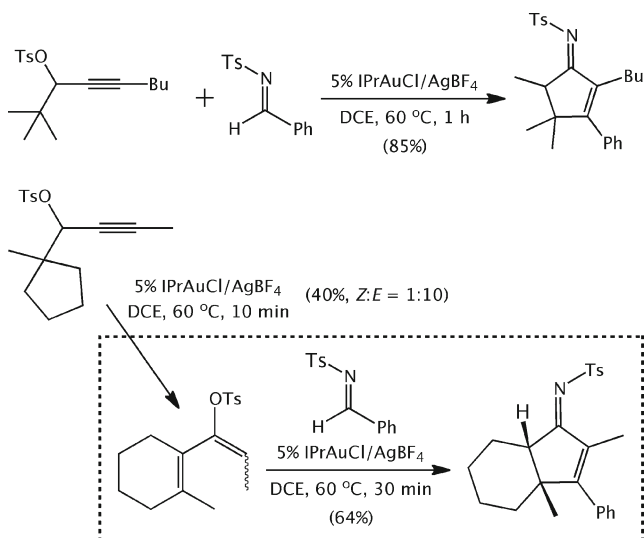
able to isolate the diene intermediate shown at the bottom of Scheme 1, and then convert it into a cyclopent-2-enimine product upon addition of more catalyst (Scheme 1, box). It was suggested that two different types of electrocyclization are involved in the transformation of such dienes into cyclopent-2-enimines: a 4-electron ring-opening of a 1,2-dihydroazete (Scheme 2, 5 → 6; shown for the model systems used in our calculations) [25, 26] and a 4-electron electrocyclization of a nitrogen-substituted pentadienyl cation (Scheme 2, 7 → 8; an analog of the Nazarov cyclization) [27–34]. We have examined both reaction steps using density functional theory calculations in order to assess the role played by the Au(I) catalyst in each transformation.

Methods

All calculations were performed with *Gaussian* [35]. Geometries were optimized without symmetry constraints using the hybrid Hartree-Fock/density functional theory (HF/DFT) B3LYP functional [36–39] with a split 6–31+G(d,p)-LANL2DZ basis set [40] unless otherwise specified (also known as LACVP**). This entails using LANL2DZ [41] as an effective core potential (ECP) for the Au atoms and treating all other atoms with the 6–31+G(d,p) Pople basis set [42]. This approach has been found to give good agreement with experimental data for a range of transition metal complexes [40], including those containing Au [17–23]. Solvent single point calculations were performed at the same level of theory in dichloroethane (DCE) using the CPCM model and UAKS radii [43–45]. The IPr ligand was approximated by a model system in which the aryl rings were replaced by methyl groups. All tosylate groups were approximated as a mesylates. All

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J. G. Harrison · D. J. Tantillo (✉)
Department of Chemistry, University of California–Davis,
One Shields Avenue,
Davis, CA 95616, USA
e-mail: tantillo@chem.ucdavis.edu



Scheme 1 Gold-catalyzed transformations from ref. [24] (IPr01,3-bis-(2,6-diisopropylphenyl)-imidazolyldene)

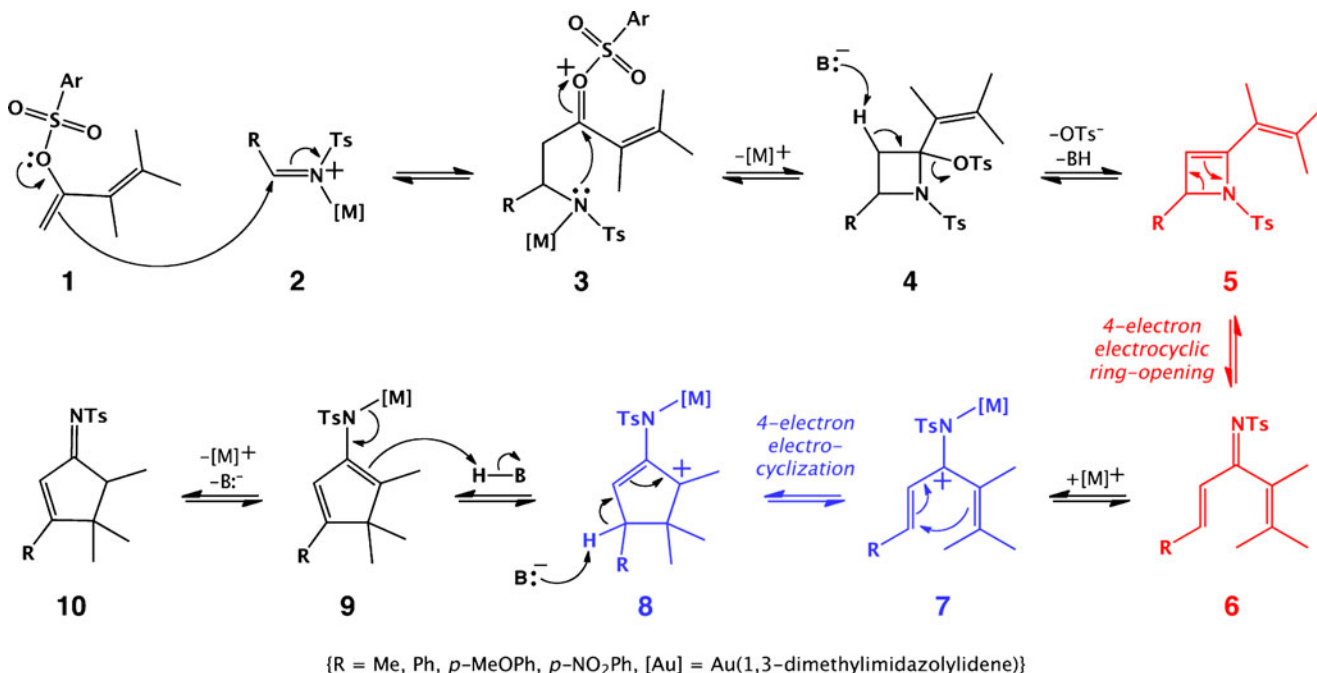
structures were characterized as transition state structures or minima by frequency analysis, and reported free energies (kcal mol^{-1}) include unscaled zero-point energy corrections at 298 K unless otherwise specified. Intrinsic reaction coordinate (IRC) calculations [46, 47] were also used to verify the identity of some transition state structures (see [Supporting information](#) for details). Several other methods were also surveyed, including the M06 and M06-2X [48, 49] functionals, in combination with the above basis sets and the SDD ECP and basis set as implemented in *Gaussian* [35]; the overall conclusions arrived at are the same when

results from these calculations are considered (see the [Supporting information](#) for details). Structural drawings were produced using *Ball&Stick* [50].

Results and discussion

Although it was not proposed that the Au(I) catalyst was directly involved in the ring-opening of 1,2-dihydroazete **5** [24], we wondered whether it might play an important role. Our calculations revealed that the barrier for ring-opening is, in fact, substantially decreased, by up to $\sim 12 \text{ kcal mol}^{-1}$ (Table 1), in the presence of Au (a representative reaction is shown in Fig. 1, left). This suggests that the Au–N interaction is more favorable in the transition state structure than in the reactant, strengthening as an enamine is transformed into an α,β -unsaturated imine (note that the Au–N distance decreases from 2.17 Å in the reactant to 2.12 Å in the transition state structure). It was also found that in the presence of dichloroethane (DCE) as solvent, barriers for ring-opening are decreased slightly, by up to $\sim 3 \text{ kcal mol}^{-1}$, without Au present, but changed less with Au present. These effects are much smaller than the effect of Au-complexation, however.

Substitution at the saturated carbon of the 1,2-dihydroazete (R, Scheme 2) was also examined. A strong preference for π -donating groups at this position was observed (Table 1), consistent with increased interaction of the substituent with the electron-deficient π -system that forms as the reaction proceeds.



Scheme 2 Proposed mechanism (after ref. [24])

Table 1 Gas phase free energy barriers (Tables of the corresponding enthalpy values can be found in the [Supporting information](#)) (values in DCE solvent in parentheses) for Au(I)-catalyzed and uncatalyzed 1,2-dihydroazete electrocyclic ring-opening (**5**-to-**6**) and subsequent

electrocyclization (**7**-to-**8**). All values are in kcal mol⁻¹ with respect to the energy of the productive conformer of the 1,2-dihydroazete (**5**) or imine (**7**) preceding the electrocyclic transition state structure (with or without Au⁺-2,3,-dimethylimidazolyldiene complexed)

Entry	R	Au catalyzed		Uncatalyzed	
		$\Delta G^\ddagger_{5\text{-to-}6}$	$\Delta G^\ddagger_{7\text{-to-}8}$	$\Delta G^\ddagger_{5\text{-to-}6}$	$\Delta G^\ddagger_{7\text{-to-}8}$
1	Me	16.7 (15.5)	26.6 (22.4)	26.9 (24.7)	37.4 (31.4)
2	Ph	7.4 (8.1)	27.4 (23.5)	18.8 (16.4)	38.4 (32.8)
3	<i>p</i> -MeOPh	4.9 (5.4)	28.5 (24.4)	16.9 (13.8)	38.5 (32.0)
4	<i>p</i> -NO ₂ Ph	10.7 (11.1)	27.5 (23.1)	22.3 (20.8)	38.9 (33.0)

Studies—experimental or theoretical—on 4-electron electrocyclizations of nitrogen-substituted pentadienyl cations are rare, especially those with nitrogens attached to the central carbon of the pentadienyl substructure [27–34]. The limited theoretical work on such systems suggests that appending a central NR₂ group to a pentadienyl cation should hinder cyclization, since this group would interact more strongly with the π -system of the reactant than with that of the transition state structure (or product) [27–34].

Consequently, we expected that complexation of the NSO₂R group by Au(I) would decrease its deleterious donating ability and consequently also the barrier for electrocyclization. Our computed barriers for electrocyclization (Table 1, **7**-to-**8**) are indeed consistent with this prediction and show that the magnitude of the barrier lowering is ~10 kcal mol⁻¹ (see [Supporting information](#) for details).

Inclusion of solvent was also found to decrease the activation energy, although again to a lesser extent than Au(I)

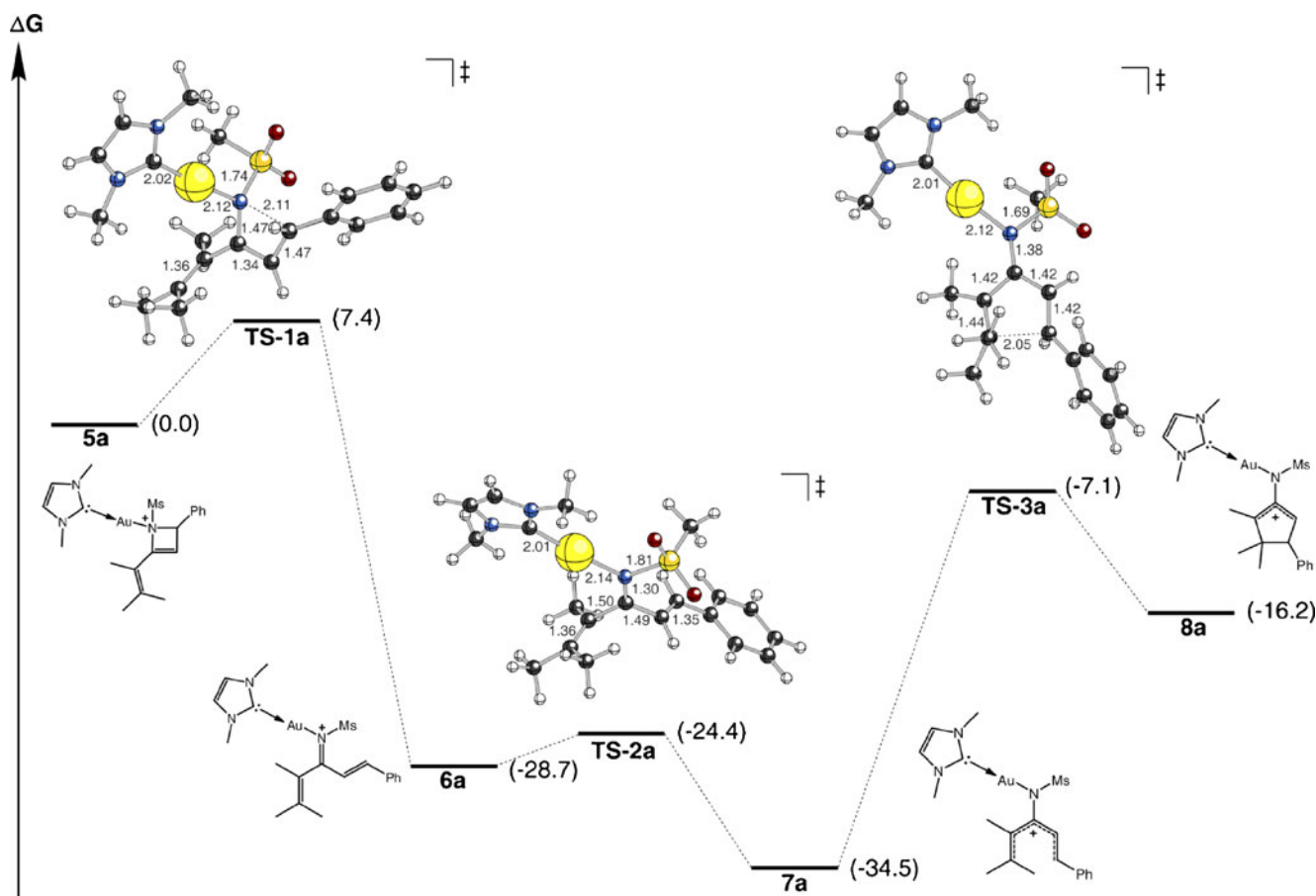


Fig. 1 Relative free energies (B3LYP/LACVP**; kcal mol⁻¹) for stationary points involved in the electrocyclic ring-opening of Au⁺-2,3,-dimethylimidazolyldiene-complexed **5** (R=Ph), a conformational

change to form the conformer of **7** that is productive for electrocyclization and electrocyclic ring-closure of **7** to **8** (R=Ph), along with geometries of transition state structures (selected distances in Å)

complexation (Table 1). As the cyclization proceeds, there is expected to be a net flow of positive charge to the nitrogen-substituted side of the molecule, increasing the overall dipole moment, and thereby facilitating interactions with the solvent (which is a more polar environment than the gas phase).

In contrast to the electrocyclic ring-opening (**5**→**6**), the electrocyclization (**7**→**8**) was found to be much less sensitive to substitution at the terminal position (R, Scheme 2; see Table 1). Aromatic π -donors, which are weaker donors than amino groups, increase the electrocyclization barrier only slightly.

Conclusions

Overall, our calculations indicate that Au(I) complexation can facilitate both electrocyclic ring-openings of 1,2-dihydroazetes and electrocyclizations of nitrogen-substituted penta-dienyl cations [51]. Consequently, we suggest that the Au(I) catalyst employed by Gonzalez and co-workers is likely involved throughout their cascade reaction (Schemes 1 and 2).

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