CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201203217

Reactivity of Stabilized Vinyl Diazo Derivatives toward Unsaturated Hydrocarbons: Regioselective Gold-Catalyzed Carbon–Carbon Bond Formation

José Barluenga,* Giacomo Lonzi, Miguel Tomás, and Luis A. López*[a]

The transition-metal-catalyzed decomposition of simple and unsaturated α-diazo carbonyl derivatives and the subsequent transfer of the carbene unit to saturated and unsaturated substrates is one of the most popular and powerful tools in organic synthesis.[1] In particular, the [2+1] cycloaddition of alkenes and alkynes is recognized as a straightforward and useful approach for the construction of three membered carbocycles. Extensive studies have led to the achievement of high levels of chemo-, diastereo-, and enantioselectivity by employing mostly complexes of copper and rhodium. In spite of the potential of gold catalysis in C–C bond formation,[2] the first example of gold-catalyzed carbene transfer from ethyl diazoacetate to unsaturated substrates was reported in 2005 by Nolan, Díaz-Requejo, Pérez et al.[3] After this seminal contribution, few gold-catalyzed transformations involving simple diazo substrates have been reported.[4] On the other hand, the synthetic potential of vinyl diazo derivatives has been well established, particularly in the cycloaddition area, and the reactivity of the carbene carbon versus the vinylogous carbon found to be dependent, at least in part, on the metal catalyst.[5]

Continuing with our interest in the development of new transition-metal-catalyzed transformations of stabilized vinyl diazo derivatives,[6] as well as in gold catalysis,[7] we herein report the first studies of the gold-catalyzed reaction of alkenyldiazo compounds and neutral alkenes[8] that results in the room temperature selective C–C coupling between the Csp^2(alkene) and the Cγ(alkenyldiazo) atoms. From a synthetic point of view, the alkenyl diazo compound behaves as a ethoxycarbonyl allyl cation in this process, allowing the regioselective preparation of γ-substituted, α,β-unsaturated carbonyl compounds (Figure 1).[9] This reactivity pattern contrasts with that observed when other common sources of alkenylgold carbenoids, such as propargylic esters or cyclopropenes, are used (2+1 cycloaddition).[10] Preliminary studies on the extension of this new gold-catalyzed carbon–carbon bond-forming process to alkynes and arenes are also reported.

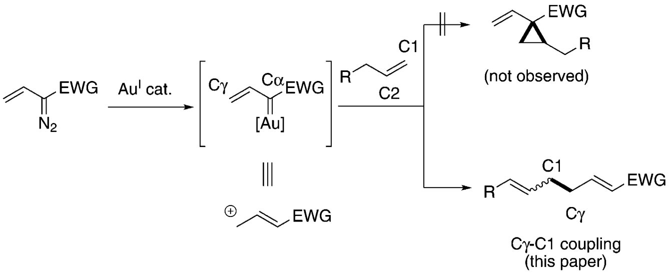
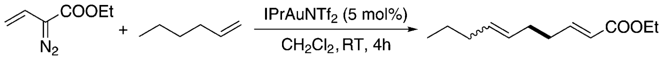


Figure 1. Regioselective preparation of γ-substituted, α,β-unsaturated carbonyl compounds.

For our exploratory studies, we investigated ethyl 2-diazobut-3-enoate (**1a**) and 1-hexene (**2a**, 4 equiv) as substrates and a series of gold catalysts (5 mol%) in dichloromethane at room temperature. To our delight, we found that the use of $IPrAuNTf_2$ gave (2*E*)-ethyl deca-2,6-dienoate **3a** in moderate yield (67%) as a nonseparable 1:1 mixture of 2*E*,6*E*/2*E*,6*Z* diastereoisomers (Scheme 1). This unprecedented process comprises two significant features: 1) in contrast to the results found in the reactions of alkenylgold carbenoids generated from other precursors,[10] neither cyclopropanes nor products resulting from an allylic C–H insertion reaction were detected, and 2) only the vinylogous position of the vinyldiazoacetate was involved in the reaction.[11]



1a **2a** **3a** (67%, *E*/*Z* 1:1)

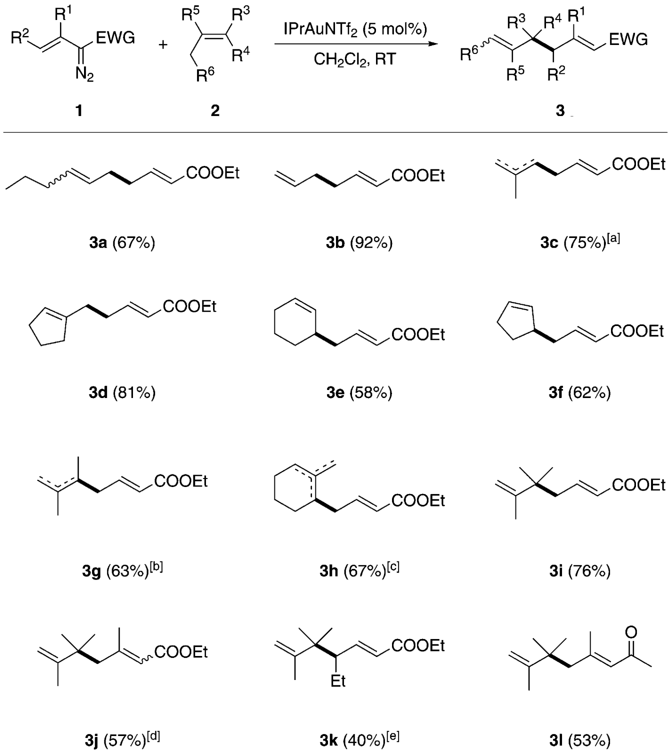
Scheme 1. Initial finding for the gold-catalyzed reaction of alkenyl diazoacetate **1a** and 1-hexene (**2a**).

On the basis of this promising result, we then focused on whether this reaction could be extended to a range of alkenes **2** and vinyldiazoacetates **1**. As depicted in Scheme 2, the process was found to tolerate a wide range of olefin substitution, including mono-, 1,1-di-, 1,2-di-, tri-, and even tetrasubstituted alkenes, affording the 2,6-diene derivatives **3** in moderate to high yields. Even simple petrochemical raw materials such as propylene (**2b**) and isobutylene (**2c**) were able to participate in this process, affording the coupling products **3b** and **3c**, respectively, in good yields. In general,

---

[a] Prof. J. Barluenga, G. Lonzi, Prof. M. Tomás, Dr. L. A. López
Instituto Universitario de Química Organometálica "Enrique Moles"
Universidad de Oviedo, c/Julián Clavería 8, 33007-Oviedo (Spain)
Fax: (+34) 989-510-3450
E-mail: barluenga@uniovi.es
lalg@uniovi.es

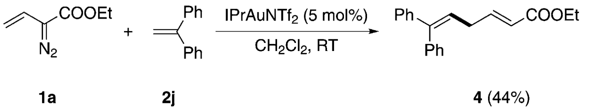
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203217.



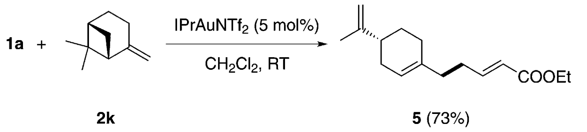
Scheme 2. Gold-catalyzed reaction of alkenyl diazoacetates **1** and alkenes **2**. Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), $IPrAuNTf_2$ (5 mol%), CH_2Cl_2 (0.1 M), RT. Values in parenthesis are the yields of the isolated products. [a] A 4:1 mixture of (*E*)-ethyl 6-methylhepta-2,6-dienoate and (*E*)-ethyl 6-methylhepta-2,5-dienoate was isolated. [b] A 4:1 mixture of (*E*)-ethyl 5,6-dimethylhepta-2,6-dienoate and (*E*)-ethyl 5,6-dimethylhepta-2,5-dienoate was isolated. [c] A 1.5:1:1 mixture of isomers was isolated. [d] A 1:1 mixture of *E* and *Z* isomers was isolated. [e] The product arising from a cyclopropanation reaction was also formed in 35% yield.

no products resulting from either [2+1] or [3+2] cycloaddition reactions were observed.[12] Moreover, in all cases, the alkene coupled to the diazo substrate with complete regioselectivity towards the less substituted alkene carbon atom. Interestingly, in most cases the reactions are highly diastereoselective, affording exclusively the *E* isomer at the C2 double bond. In relation to the structure of the diazo component **1**, some points are remarkable: 1) the reaction works well for substrates with alkyl substitution at the Cα atom (diazoacetate **1b**; R^1=Me, R^2=H), affording the expected product **3j** in moderate yield; 2) the presence of a substituent at the Cβ position (diazoacetate **1c**; R^1=H, R^2=Et) seems to exert a noticeable influence on the regiochemical outcome of the reaction as demonstrated by the formation of a 1:1 mixture of the expected product **3k** and the corresponding cyclopropane from the reaction with 2,3-dimethylbut-2-ene; 3) diazo derivatives in which the electron-withdrawing group (EWG) is an acetyl are also amenable to this coupling reaction, affording compound **3l** in moderate yield and with complete regio- and stereoselectivity. In general, the reaction showed a marked preference for the formation of the 2,6- rather than the 2,5-diene isomer.[13]

Other alkenes were tested to gain insight into the coupling reaction. Thus, we found that 1,1-diphenylethene (**2j**) reacts with vinyldiazoacetate **1a** under the standard conditions to afford (*E*)-ethyl 6,6-diphenylhexa-2,5-dienoate (**4**) in moderate yield after chromatographic purification, as well as minor amounts (<10%) of the cyclopropanation product [Eq. (1)]. On the other hand, in the case of β-pinene (**2k**), the corresponding coupling was accompanied by rearrangement, giving rise to the limonene derivative **5** [Eq. (2)].



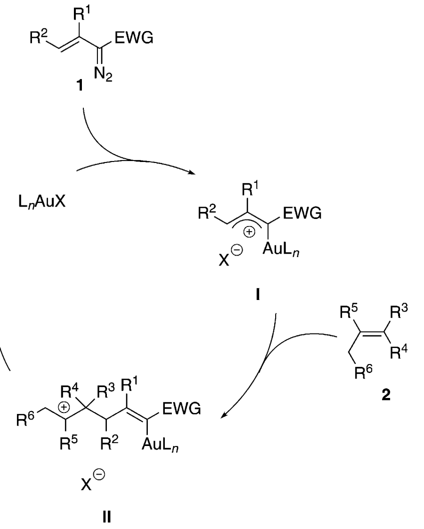
(1)



(2)

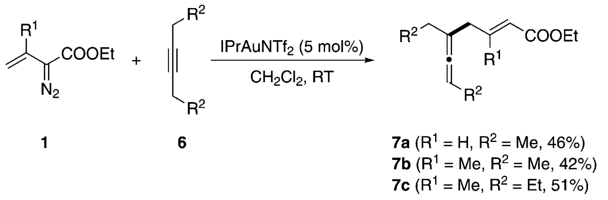
A mechanistic proposal that rationalizes the obtained results is given in Scheme 3. The initial reaction of the alkenyl diazo compound with the gold complex would afford the gold alkenylcarbenoid intermediate **I**, which can be described as an allyl gold cation.[14] Next, regioselective nucleophilic attack of the alkene to the C3 allyl cation would form the most stable carbocation intermediate **II**. Then, its deprotonation and protodemetalation would account for the formation of the products **3** and **4**. In the case of β-pinene, the initially formed tertiary carbocation would evolve through ring-opening of the cyclobutane unit followed by deprotonation/demetallation on the new carbocation to provide the observed cyclohexene derivative **5**.[15,16]

Our attention then turned towards determining whether closely related systems, such as alkynes, would be suitable substrates in this gold-catalyzed process. The preliminary ex-



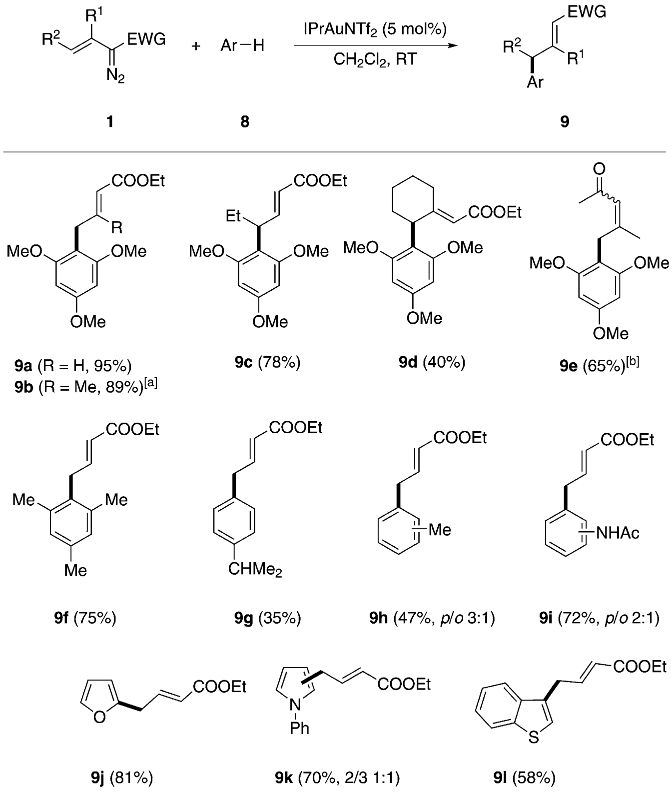
Scheme 3. Proposed mechanism for the gold-catalyzed reaction of alkenyl diazoacetates **1** and alkenes **2**.

periments for dialkylacetylenes, such as 3-hexyne (**6a**) and 4-octyne (**6b**), demonstrated that they behave in a similar way to alkenes when exposed to vinyldiazoacetates **1a** and **1b** under the same reaction conditions.[17] Thus, the synthetically useful allylallenes **7a–c** were isolated in moderate yield and with high regio- and *E*-stereoselectivity [Eq. (3)].



(3)

According to the mechanistic picture (see Scheme 3), we searched for other neutral nucleophiles that were amenable to C–C bond formation. As shown in Scheme 4, a number of activated arenes **8** were also prone to react at room temperature to afford the corresponding Friedel–Crafts products **9** (substituted 4-aryl-2-butenoate esters) with variable efficiency. First, the highly activated arene 1,3,5-trimethoxybenzene (**8a**) reacted under the standard conditions with unsubstituted and substituted alkenyldiazo derivatives **1**, providing the corresponding alkylated derivatives **9a–e** in moderate to excellent yields (40–95%) after chromatographic purification. The less-activated 1,3,5-trimethylbenzene (**8b**) provided the corresponding arylation product **9f** in 78% yield. On the other hand, arenes with a single alkyl activating group, such as cumene (**8c**) and toluene (**8d**), gave the expected products in rather low isolated yield (35 and 47%, respectively) as mixtures of the *ortho* and *para* isomers. Interestingly, it was found that the presence of the N–H functionality did not affect the course of the reaction.[17] Thus, the reaction of diazoacetate **1a** with acetanilide (**8e**) proceeded smoothly to provide **9i** as a 1:2 *ortho*/*para* mixture in 72% yield. This gold-catalyzed coupling reaction also proved to be amenable for electron-rich heteroarenes. Thus, the treatment of furan (**8f**), *N*-phenylpyrrol (**8g**), and benzo[*b*]thiophene (**8h**) with the diazo compound **1a** under the above reaction conditions afforded the compounds **9j–l** in good yield. Notably, *N*-phenylpyrrol underwent the reaction selectively at the electron-rich pyrrol moiety.[18]



Scheme 4. Gold-catalyzed reaction of alkenyl diazoacetates **1** and arenes **8**. Reaction conditions: **1** (0.5 mmol), **8** (2.0 mmol), IPrAuNTf$_2$ (5 mol%), CH$_2$Cl$_2$ (0.1 M), RT. Values in parenthesis are the yields of the isolated products. [a] A 1:1 mixture of *E* and *Z* isomers was isolated. [b] A 4:1 mixture of *Z* and *E* isomers was isolated.

In conclusion, we have discovered new reaction modes in the gold-catalyzed reaction of vinyldiazoacetates and unsaturated substrates and shown that the product outcomes differ significantly from those obtained using alternative sources of alkenylgold carbenoids. It is likely that the observed reactivity pattern relies on the formation of a highly electrophilic alkenylgold carbenoid, which may be involved in a carbocation-type mechanism. From a synthetic point of view, the process described represents a new C–C bond-formation reaction in which alkenes, alkynes, and arenes are active reagents for the Cγ-allylation, -allenylation, and -arylation, respectively, of alkenyldiazo substrates. Studies to increase the reaction scope further and to gain insight into the reaction mechanism are ongoing.

Experimental Section

Representative procedure (3i): IPrAuNTf$_2$ (21.6 mg, 0.025 mmol, 5 mol%) was added to a solution of vinyldiazoacetate (**1a**; 70 mg, 0.5 mmol) and 2,3-dimethylbut-2-ene (**2i**; 168 mg, 2.0 mmol, 4.0 equiv) in CH$_2$Cl$_2$ (5 mL). The mixture was stirred at room temperature until the disappearance of **1a** (monitored by TLC; 2 h). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO$_2$, *n*-hexane/EtOAc 50:1) to yield (*E*)-ethyl 5,5,6-trimethylhepta-2,6-dienoate (**3i**) (75 mg, 76%) as a pale yellow oil.

Acknowledgements

We are grateful to the Ministerio de Economía y Competitividad of Spain (MINECO) (Grant no. CTQ2010–20517-C02–01). G.L. thanks the MINECO and European Union (Fondo Social Europeo) for a predoctoral grant.

Keywords: alkenes · alkynes · arenes · diazo compounds · gold

---

[1] For selected reviews on the synthetic applications of diazocompounds, see: a) M. Regitz, G. Maas, *Diazo Compounds: Properties and Synthesis* Academic Press, London, **1986**, pp. 65–198; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; c) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; d) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; e) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577.

[2] For some representative reviews on gold catalysis, see: a) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448; b) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91; c) S. Gaillard, C. S. J. Cazin, S. P. Nolan, *Acc. Chem. Res.* **2012**, *45*, 778; d) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; f) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; g) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; h) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896.

[3] M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Angew. Chem.* **2005**, *117*, 5418; *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.

[4] a) J. F. Briones, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 11916; b) M. Delgado-Rebollo, A. Beltrán, A. Prieto, M. M. Díaz-Requejo, A. M. Echavarren, P. J. Pérez, *Eur. J. Inorg. Chem.* **2012**, 1380; c) P. J. Pérez, M. M. Díaz-Requejo, I. Rivilla, *Beilstein J. Org. Chem.* **2011**, *7*, 653; d) I. Rivilla, P. Gómez-Emeterio, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, *Organometallics* **2011**, *30*, 2855; e) A. Corma, M. Iglesias, F. X. Llabrés i Xamena, F. Sánchez, *Chem. Eur. J.* **2010**, *16*, 9789; f) A. Prieto, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, P. Pérez-Galán, N. Delpont, A. M. Echavarren, *Tetrahedron* **2009**, *65*, 1790; g) M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, *Chem. Commun.* **2009**, 5153; h) J. A. Flores, H. V. R. Dias, *Inorg. Chem.* **2008**, *47*, 4448; i) L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704; j) Z. Li, X. Ding, C. He, *J. Org. Chem.* **2006**, *71*, 5876; k) M. R. Fructos, P. de Frémont, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez, *Organometallics* **2006**, *25*, 2237.

[5] For a selection of contributions on carbenoid versus vinylogous reactivity in metal-stabilized vinylcarbenoids, see: a) D. Valette, Y. Lian, J. P. Haydek, K. I. Hardcastle, H. M. L. Davies, *Angew. Chem.* **2012**, *124*, 8764; *Angew. Chem. Int. Ed.* **2012**, *51*, 8636; b) D. Morton, A. R. Dick, D. Ghosh, H. M. L. Davies, *Chem. Commun.* **2012**, *48*, 5838; c) Y. Lian, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 1934;d) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457; e) Y. Lian, H. M. L. Davies, *Org. Lett.* **2010**, *12*, 924; f) Y. Sevryugina, B. Weaver, J. Hansen, J. Thompson, H. M. L. Davies, M. A. Petrukhina, *Organometallics* **2008**, *27*, 1750; g) H. M. L. Davies, B. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.* **1994**, *59*, 4535; h) H. M. L. Davies, E. Saikali, W. B. Young, *J. Org. Chem.* **1991**, *56*, 5696; i) H. M. L. Davies, E. Saikali, T. J. Clark, E. H. Chee, *Tetrahedron Lett.* **1990**, *31*, 6299.

[6] a) J. Barluenga, L. Riesgo, G. Lonzi, M. Tomás, L. A. López, *Chem. Eur. J.* **2012**, *18*, 9221; b) J. Barluenga, G. Lonzi, L. Riesgo, M. Tomás, L. A. López, *J. Am. Chem. Soc.* **2011**, *133*, 18138; c) J. Barluenga, G. Lonzi, L. Riesgo, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2010**, *132*, 13200; d) J. Barluenga, L. Riesgo, L. A. López, E. Rubio, M. Tomás, *Angew. Chem.* **2009**, *121*, 7705; *Angew. Chem. Int. Ed.* **2009**, *48*, 7569.

[7] For a recent contribution on this topic by our group, see: J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros, M. Tomás, *Angew. Chem.* **2011**, *123*, 2155; *Angew. Chem. Int. Ed.* **2011**, *50*, 2107.

[8] An example dealing with gold-catalyzed decomposition of vinyldiazo compounds, the [3+3] cyclization toward nitrosobenzenes, to provide quinolone oxides has just been reported, see: V. V. Pagar, A. M. Jadhav, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 20728; very recently, the same group reported the gold-catalyzed reaction of aromatic imines and alkenyldiazocarbonyl compounds, see: A. M. Jadhav, V. V. Pagar, R.-S. Liu, *Angew. Chem.* **2012**, *124*, 11979; *Angew. Chem. Int. Ed.* **2012**, *51*, 11809.

[9] The regioselective γ-alkylation of α,β-unsaturated carbonyl compounds represents a very challenging problem in synthetic organic chemistry. Thus, the reaction of an enolate anion of an α,β-unsaturated carbonyl compound with an alkylating agent affords an α-alkylation product as a major product.

[10] For a selection of methods for the catalytic generation of alkenylgold carbenoids and their use in the preparation of cyclopropane derivatives, see: a) F. Miege, C. Meyer, J. Cossy, *Chem. Eur. J.* **2012**, *18*, 7810; b) F. Miege, C. Meyer, J. Cossy, *Org. Lett.* **2010**, *12*, 4144; c) J. T. Bauer, M. S. Hadfield, A.-L. Lee, *Chem. Commun.* **2008**, 6405; d) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244; e) D. J. Gorin, P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 14480; f) M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002.

[11] From a different point of view, Davis et al. have developed the formal Cγ-allylation of rhodium-stabilized vinylcarbenoids with cyclic alkenes (cyclohexadiene and dihydronaphthalene frameworks), as well as allyl and vinyl ethers. However, they describe the reaction as occurring through insertion of the allyl C—H bond and a Cope rearrangement, see: J. H. Hansen, T. M. Gregg, S. R. Ovalles, Y. Lian, J. Autschbach, H. M. L. Davies, *J. Am. Chem. Soc.* **2011**, *133*, 5076; for a recent review on the synthetic applications and on the current mechanistic understanding of this process, see: H. M. L. Davies, Y. Lian, *Acc. Chem. Res.* **2012**, *45*, 923.

[12] On the contrary, the reaction of vinyldiazoacetate **1a** with styrene afforded ethyl 5-phenylcyclopent-1-enecarboxylate (65 % yield), resulting from a formal [3+2] cycloaddition reaction.

[13] For a similar behavior, see: R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773.

[14] The actual nature of alkenylgold carbenoids has, until recently, been a matter of discussion. Recent studies showed that the situation for a particular gold species depends largely on the substituents and the ancillary ligands ranging from gold-stabilized carbenes to allyl gold carbocations; for some interesting contributions on this topic, see: a) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232; b) G. Seidel, R. Mynott, A. Fürstner, *Angew. Chem.* **2009**, *121*, 2548; *Angew. Chem. Int. Ed.* **2009**, *48*, 2510; c) A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754; d) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard III, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482; e) R. B. Dateer, K. Pati, R.-S. Liu, *Chem. Commun.* **2012**, *48*, 7200; f) S. Bhunia, R.-S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16488; for recent reviews on the generation of dipolar species related to intermediate **I**, see: g) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462; h) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2011**, *7*, 1075.

[15] For a similar carbocationic rearrangement, see reference [13].

[16] It should be mentioned that, although the cationic mechanism depicted in Scheme 3 accounts well for the reported results, an alternative concerted mechanism, which is analogous to that reported by Davies et al. (reference [11]), in some related rhodium-catalyzed reactions cannot be strictly eliminated.

[17] The formation of compounds **7** can be explained by assuming a similar mechanism to that proposed for the reaction involving alkenes. In addition to compounds **7**, small amounts of cyclopentadiene derivatives resulting from a competing formal [3+2] cycloaddition reaction were also obtained as side products.

[18] For the addition of nitrogen nucleophiles to the vinylogous position of alkenyl carbenoids, see reference [5c].

[19] Unfortunately, non-activated arenes such as benzene or chlorobenzene remain unaltered under the standard reaction conditions.

Received: September 10, 2012