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Intermolecular Reaction of Internal Alkynes and Imines: Propargyl Tosylates as Key Partners in a Gold-Catalyzed [4 + 1] Unusual Cyclization Leading to Cyclopent-2-enimines

Samuel Suárez-Pantiga,[†] Eduardo Rubio,[†] Carmen Alvarez-Rúa,[‡] and José M. González*,[†]

Instituto Universitario de Química Organometálica "Enrique Moles"−Unidad Asociada al C.S.I.C. and Departamento de Química Orgánica e Inorgánica, and Servicio de Rayos X, Servicios Científico-Técnicos, Universidad de Oviedo, Julián Claveria, 8, 33006 Oviedo, Spain

jmgd@uniovi.es

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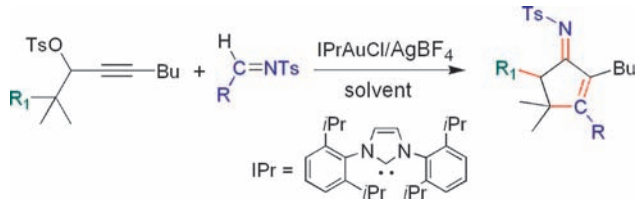
ABSTRACT



Propargyl tosylates react with *N*-tosylaldimines to afford cyclopent-2-enimines in a gold-catalyzed process that involves a deep reorganization of both substrates. The formal [4 + 1] cyclization is initiated by a 1,2-migration of the tosylate that eventually generates a substituted 1,3-diene. Subsequent interaction with the imine launches a series of reaction steps prior to a Nazarov-like cyclization to yield the final product.

The discovery of selective transformations associated with basic functionalities is at the core of advances in synthetic methodology. The reaction of internal alkynes with imines has been scarcely reported, but significant transformations have been described, among them, a vanadium-catalyzed reaction of propargyl alcohols with imines furnishing Mannich adducts[1] and an imidozirconocene-catalyzed carboamination of imines across alkynes.[2] Recent C−H activation-based processses dealing with those functionalities are also documented.[3] Also, reactions of imines, with internal alkynes and a third partner to furnish allyl amine derivatives, have been disclosed.[4] In general, these reactions take place through an initial formation of an azametallacycle implying the imine and the alkyne, which gives the product by catalytic activation of the third component. Besides, the PMP aldimine

[†] Instituto Universitario de Química Organometálica "Enrique Moles"−Unidad Asociada al C.S.I.C. and Departamento de Química Orgánica e Inorgánica.

[‡] Servicio de Rayos X.

(1) (a) Trost, B. M.; Chung, C. K. *J. Am. Chem. Soc.* **2006**, *128*, 10358. This result expands the scope of the oxovanadium-catalyzed aldol-type reaction. For early work on aldol-type products by vanadium-catalyzed addition of propargyl alcohol to aldehydes, see: (b) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230.

(2) Ruck, R. T.; Zuckerman, R. L.; Krska, S. W.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5372.

(3) Selected examples: (a) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (b) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

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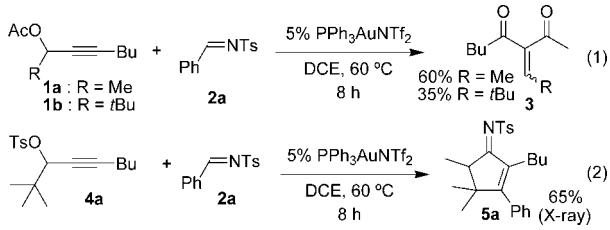
of benzaldehyde reacts as a dipolarophile with a 1,4-dipole arising from a gold-catalyzed rearrangement of 1-alkynyl-1-acetylcyclopropanes.[5]

Herein, a new catalytic transformation arising from the evolution of propargyl tosylates in the presence of different *N*-tosylaldimines and a gold-based catalyst is reported. The reaction promotes a moderate increase of molecular complexity from the precursors and results in a selective assembly of *N*-tosylimines derived from cyclopentenone scaffolds. The overall process has been studied in detail, and it is shown to comprise two well-defined cascade transformations that lead to the cyclic frame, namely, an initial rearrangement of the propargyl tosylate into a 2-tosyloxy-1,3-butadiene isomer and a subsequent assembly of the cyclic frame that goes through a multistep reaction sequence. Initial studies addressed the search for proper propargyl partners and that of efficient catalyst, with gold-based ones as an attractive choice due to their potential in the electrophilic activation of unsaturated carbon−carbon bonds.[6,7] Early studies with alkynyl acetates **1** led to the well-documented product of self-condensation **3** without participation of the imine **2** (Scheme 1, eq 1).[8]

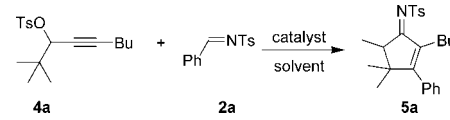
Scheme 1. Differential Behavior of Propargyl Acetates and Tosylates toward Gold-Catalyzed Reaction with *N*-Tosylaldimines



We then checked the impact that the type of propargyl ester being used might have over the reaction outcome as an option to unveil other transformations. Interestingly, while the use of phosphate esters gave no result at all, the switch from carboxylic acid esters to related tosylates allowed an alternative reaction path to occur and offered a simple way for broadening the reactivity of the propargylic fragment.[9] Thus, the reaction of imine **2a** with tosylate **4a** lead to the isolation of the cyclopent-2-enimine **5a** (see Scheme 1, eq 2, structure of **5a** was established by X-ray analysis). The formation of a cyclic structure, the ring size, a methyl migration, the loss of a molecule of *p*-toluenesulfonic acid, and the cleavage of the carbon−nitrogen imine bond are among the changes in going from the starting compounds to the product.

In this synthetic scenario, we investigated the conceivable usefulness of alternative metal catalysts for the electrophilic activation of alkynes. Moreover, a short screening for milder reaction conditions was also undertaken. Representative results are outlined in Table 1.

Table 1. Screening of Metal Complexes as Potential Catalysts



entry	catalyst[a] (5 mol %)	solvent	*T* (°C)	time (h)	yield[b] (%)
1	$Ph_3PAuNTf_2$	DCE[c]	60	8	65
2	$Au(DAVEPHOS)NTf_2$	DCE	60	8	13
3	$Au(JOHNPHOS)NTf_2$	DCE	60	8	43
4	**IPrAuCl/AgBF$_4$**	**DCE**	**60**	**1**	**85**
5	**IPrAuCl/AgBF$_4$**	**CH$_2$Cl$_2$**	**40**	**6**	**86**
6	IPrAuCl/AgBF$_4$	CH_2Cl_2	rt	20	60
7	$IPrAuNTf_2$	CH_2Cl_2	40	20	
8	$Ph_3PAuCl/AgBF_4$	CH_2Cl_2	40	8	51
9	$PtCl_2$[d]	DCE	80	14	68
10	IPrAuCl/$AgSbF_6$	CH_2Cl_2	40	6	83
11	$AuCl_3$	DCE	60	2	19
12	$Cu(MeCN)_4BF_4$[d]	DCE	80	48	
13	$AgBF_4$[d]	CH_2Cl_2	40	21	26
14	none	CH_2Cl_2	40	20	-

[a] See the Supporting Information for references and description of the catalysts structure and preparation. [b] Yield of isolated product after chromatographic purification. [c] DCE = 1,2-dichloroethane. [d] 7.5 mol %.

Although the reaction is feasible with metals such as Pt(II) (entry 9) or Ag(I) (entry 13), several gold(I) precatalysts gave

(4) Ni-catalyzed reactions with organoboron reagents: (a) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364. Iridium-catalyzed processes with hydrogen incorporation: (b) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. For an asymmetric version, see: (c) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Titanium-mediated processes with CO_2 fixation to afford α,β-unsaturated γ-lactams: (d) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912. Formally related synthesis of allylamines involving alkyne hydrozirconation, transmetallation to zinc and imine addition: (e) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. DABCO-mediated related three-component reactions: (f) Matsuya, Y.; Hayashi, K.; Wada, A.; Nemoto, H. *J. Org. Chem.* **2008**, *73*, 1987.

(5) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814.

(6) For recent reviews, see, for instance: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (f) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (g) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.

(7) Selected examples of gold-catalyzed intermolecular annulations: (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (b) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764. (c) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (d) Li, G.; Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 6944. (e) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244.

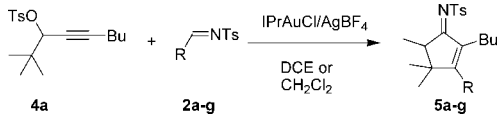
(8) (a) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414. (b) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2007**, *129*, 7772.

(9) Recent work on propargyl tosylates: (a) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. Revisions on the reactivity of propargyl esters: (b) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (c) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350. References not covered in these reviews: (d) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147. (e) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021. (f) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 1465. (g) Cordonnier, M. C.; Blanc, A.; Pale, P. *Org. Lett.* **2008**, *10*, 1569. (h) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718.

rise more efficiently to the desired transformation. Copper(I) fails to produce the target transformation, and gold(III) is quite inefficient for that purpose as it decomposes under the reaction conditions. The counteranion ultimately associated to the gold complex affects the reaction outcome; BF_4 and SbF_6 yield better results than NTf_2, probably because of the more coordinating ability of the latter that could hamper the reaction. This hypothesis is also consistent with the noticed absence of reaction when the process was assayed using acetonitrile rather than dichloromethane as solvent. Furthermore, the ligand present in the precatalyst and expected to remain attached to gold offers another resort to improve the reaction. Good results were obtained using a N-heterocycic carbene (NHC) ligand.[10] The best results were obtained using the combination IPrAuCl/$AgBF_4$ (entries 4−5)[11] that furnishes **5a** in better yield than a similar reaction using triphenylphosphine as ligand (see entries 5 and 8).[12]

Regarding the scope of the reaction, the transformation is versatile for a representative set of substituents at the imine carbon (Table 2). Thus, a variety of *N*-tosylimines could be employed in this cyclization event, including aryl groups other than phenyl (entries 2−5) and aliphatic ones (entries 6 and 7). The reaction is tolerant of both electron-rich (entries 2 and 4) and electron-deficient (entry 5) aromatic groups, though the former gave higher yields. Interestingly, the nature of the substituent at the imine nitrogen strongly affects the feasibility of the process. Thus, when imines derived from *N*-alkyl- or *N*-arylamines were employed rather than *N*-tosylimines, the formation of the related cyclopent-2-enimine derivatives of type **5** did not occur. No evidence could be gathered for a significant evolution of the starting compounds, probably speaking for a strong interaction of the imine with the metal and resulting in the catalyst deactivation.

Table 2. Screening for *N*-Tosylimines: Modification of the Substitution at the Imine Carbon Atom



4a **2a-g** **5a-g**

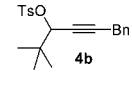
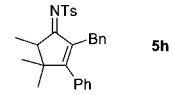
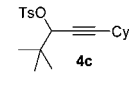
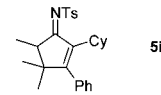
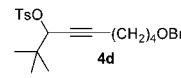
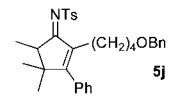
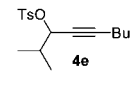
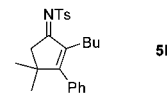
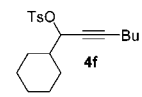
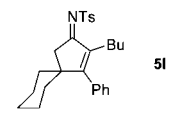
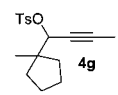
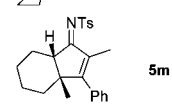
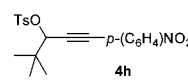
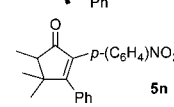
entry	R	*T* (°C)	time (h)	product	yield[a] (%)
1	Ph	40	6	**5a**	86
2	*p*-$CH_3(C_6H_4)$	40	6	**5b**	82
3	*p*-$Cl(C_6H_4)$	40	7	**5c**	64
4	*p*-$CH_3O(C_6H_4)$	40	4	**5d**	77
5	*p*-$NO_2(C_6H_4)$	60	3	**5e**	34
6	Cy	40	10	**5f**	70
7	*n*-C_7H_{15}	60	1	**5g**	59

[a] Yield of isolated product after chromatographic purification.

Studies aimed to prove the impact that the structure of the propargyl tosylate counterpart could have over the scope of the reaction were also conducted (Table 3).[13]

Preliminary results were obtained using as a model a compound with a bulky *tert*-butyl group next to the tosylate and modifying the substitution pattern at the other alkyne

Table 3. Screening of Propargyl Tosylates[a]

entry	alkyne	product	yield (%)
1	 **4b**	 **5h**	76
2	 **4c**	 **5i**	75
3	 **4d**	 **5j**	64
4	 **4e**	 **5k**	68
5	 **4f**	 **5l**	47
6	 **4g**	 **5m**	88
7	 **4h**	 **5n**	59[b]

[a] The reactions were run in DCE or CH_2Cl_2 at 40−70 °C during a 20 min−10 h period (for full details, see the Supporting Information) with imine **2a** in the presence of 5 mol % of IPrAuCl/$AgBF_4$. [b] After purification, only the ketone was isolated.

carbon atom. Far from the case of **4a**, with a linear alkyl group attached at that position, the reaction is compatible with other substitution patterns as benzyl or secondary alkyl groups and even with some functional group at either alkyl or aryl chains (entries 1−3 and 7). Moreover, the presence of the *tert*-butyl group is not compulsory to push the cyclization, which was proved compatible with secondary alkyl substituents at that position (entries 4 and 5). Several interesting structures were built including the spirane **5l** and the bicycle **5m** arising from a selective ring-expansion process.[14]

In order to get insight into the mechanism of the reaction, a clarifying result comes from the fact that the reaction of alkyne **4g** with the gold complex under the typical reaction conditions yields the diene **6** as a 10:1 mixture of isomers.[15]

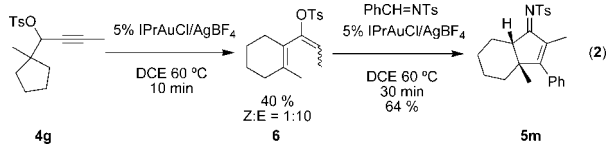
(10) Overall view on NHC in synthesis: (a) *N-Heterocyclic Carbenes in Synthesis*;Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2006. Recent work on determination of stereoelectronic parameters associated with NHC ligands, see: (b) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874. (c) Kelly, R. A., III.; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202.

(11) (a) De Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411. (b) De Fremont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045.

(12) Improved gold-catalyzed reactions are realized when switching from PPh_3 to the NHC IPr ligand; see, for instance: (a) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (b) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.

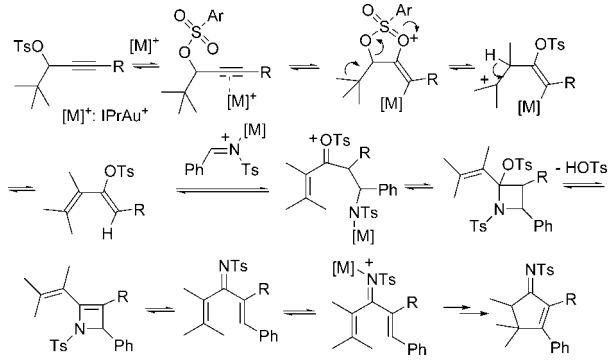
Subsequent addition of the imine **2a** and another charge of the catalytic system provides the cyclopentene imine **5m** in 64% yield (Scheme 2).

Scheme 2. Stepwise Elaboration of Cyclopent-2-Enenone Schiff Base Derivatives



The successful assembly of the cyclopent-2-enimine scaffold in the above-depicted stepwise process provides compelling support to the involvement of related 2-tosyloxy-1,3-butadienes in the one-pot approach previously described that ultimately affords the same cyclic products. Thus, a reasonable mechanistic proposal that accounts for the overall reaction described from propargyl tosylates with *N*-tosylimines is outlined in Scheme 3 and involves a nicely orchestrated combination of catalyzed reactions to gain access to those elaborated cycles from readily available precursors.

Scheme 3. Proposed Mechanism: Main Steps Involved in the One-Pot Approach



Upon coordination of the catalyst to the alkyne, an initial isomerization of the propargyl tosylate occurs that leads to a diene similar to **6**. The isomerization process comprises a 1,2-tosyl rearrangement inducing a vicinal alkyl migration[16] and a further elimination step that enables the protonation of the carbon−gold bond affording the 1,3-diene skeleton.[17] Then, the intermediate 1,3-diene adds to the activated imine[18] to form a strained azetine that, through an electrocyclic ring opening in a formal metathesis process, opens up to a 1,4-pentadiene.[19] Again, the gold complex can activate this intermediate to a "Nazarov-like" ring closure to the final product.[20] Also of interest, this fomal [4 + 1] annulation mode expands the set of known reaction patterns for dienes and imines, among them well established [4 + 2] cyclizations or interesting vinylogous Mannich reactions.[21] In short, a new gold-catalyzed reaction cascade involving propargyl derivatives and aldimines has been disclosed. The product resulting from the overall transformation represents an unprecedented coupling mode for these two partners. Furthermore, the role of the 2-tosyloxy-1,3-butadiene scaffold as intermediate for this process has been elucidated. A subsequent reaction with the imine gave access to the final cyclic compound through another selective combination of steps, among them a well-documented Nazarov cyclization. Further studies on the usefulness of the 1,2-shift of tosyl group upon metal-catalyzed alkyne activation are in progress.

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Supporting Information Available: Experimental details, X-ray data for **5a** and **5i**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The consumption of the propargyl tosylate was noticed for all of the reactions depicted in Tables 2 and 3, with the exception of **5c** (21% of **4a** was recovered; extended reaction times did not improve the yield). As a rule, NMR inspection of the reaction crude revealed conversion of starting materials into the corresponding product **5** as the only noticeable major reaction path. The standard column chromatographic purification process was difficult, and partial hydrolysis of compounds **5** occurs to give the related ketone easily, as noticed previously in the obtention of related unsaturated imines; see: Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777. This fact accounts for the moderate isolated yields obtained for some of the unsaturated imines reported.

(14) To date, under the standard conditions, primary substituents at that position fail to yield a clean transformation producing related cycles.

(15) For related intramolecular gold-catalyzed diene formation, see: (a) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585. (b) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985. (c) Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740.

(16) For 1,2-alkyl migration in π-acid catalyzed reactions: (a) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514. For ligand effects on migration of propargyl esters, see: (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. For a recent example of substrate design to facilitate 1,2-shifts in activation of propargyl alcohol derivatives, see: (c) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598.

(17) The rearrangement shows the chemoselectivity of [1,2]-shifts with or without the occurrence of electron sextets. Bruckner, R. *Advanced Organic Chemistry*; Hartcourt/Academic: San Diego, 2002; pp 438−466.

(18) NMR monitoring of the reaction showed a deshielding of the imine proton upon mixing equimolecular amounts of the reagents providing evidence for the formation of an imine−gold complex. A gold(III)-catalyzed addition of arenes to imines has been reported in Luo, Y.; Li, C.-J. *Chem. Commun.* **2004**, 1930. An alternative pathway involving straightforward addition of the C−Au σ-bond in the complex with the diene—prior to its protonation—cannot be rigorously ruled out at present.

(19) One of the reviewers suggested that the formation of the azetine is a high energy pathway and proposed a plausible alternative that involves the elimination of $TsNH_2$ to form a pentadienone with Ts attached to the carbonyl oxygen and further exchange of TsOH by $TsNH_2$.

(20) A carbonyl metathesis followed by a Nazarov cyclization has been invoked in: (a) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137. For alkyne carbonyl metathesis, see: (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259. Recent studies on the Nazarov cylization: (c) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379. (d) Cavalli, A.; Pacetti, A.; Recanatini, M.; Prandi, C.; Scarpi, D.; Occhiato, E. G. *Chem.—Eur. J.* **2008**, *14*, 9292. (e) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073. Metal-catalyzed asymmetric approaches: (f) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 954. (g) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315.

(21) (a) Giera, D. S.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259. (b) Salvador González, A.; Gómez Arrayás, R.; Rodríguez Rivero, M.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335.