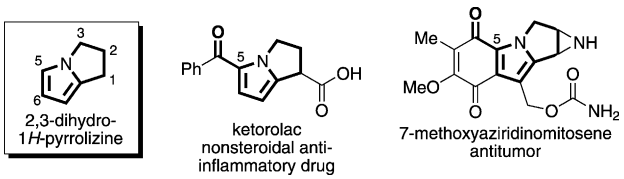
Gold Catalysis

DOI: 10.1002/anie.201203678

Gold-Catalyzed One-Step Construction of 2,3-Dihydro-1*H*-Pyrrolizines with an Electron-Withdrawing group in the 5-position: A Formal Synthesis of 7-Methoxymitosene**

*Ze-Yi Yan, Yuanjing Xiao, and Liming Zhang**

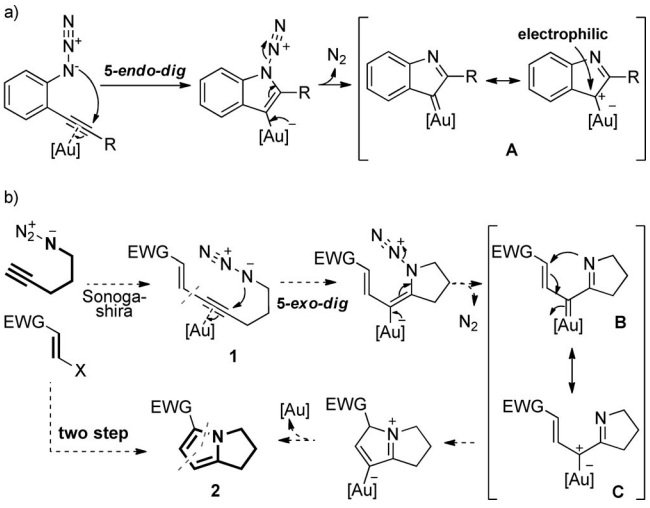
2,3-Dihydro-1*H*-pyrrolizines form an important class of bicyclic pyrroles. Among the many bioactive compounds containing this structural motif are ketorolac, a nonsteroidal anti-inflammatory drug, and 7-methoxyaziridinomitosene, a mitosene that is more stable than mitomycin C but possesses similar antitumor activities[1] (Scheme 1). Notably, both of



Scheme 1. 2,3-Dihydro-1*H*-pyrrolizine, and bioactive compounds containing a common motif that consists of this structure with an additional electron-withdrawing group at its 5-position.

these compounds, as well many others,[2] contain an electron-withdrawing group (EWG) at the 5-position of the dihydropyrrolizine. Synthesis of this biologically important structural motif from easy-to-assemble linear substrates in one step would offer desirable synthetic convergence and flexibility and perhaps improve overall efficiency, but to the best of our knowledge there is only one example of such a synthesis and this has limited scope.[3] Herein, we report a generally applicable and efficient gold catalysis[4] that addresses this need; moreover, this chemistry features the use of azides as nitrene precursors, and electrocyclizations of destabilized 1-azapentadienium intermediates.[5]

In line with our previous work[6] on the generation of α-oxo gold carbenes by alkyne oxidation,[7] we have recently reported results pertaining to the generation of their nitrogen counterparts, that is, α-imino gold carbenes, by either intra-[8] or intermolecular[9] delivery of a nitrene precursor to a C–C triple bond.[10] In the intramolecular case,[8] an azido group[11] was employed in the same capacity as a nucleophilic oxidant such as sulfoxide,[6a,7a] but to deliver a nitrene instead to the tethered alkyne in a 5-*endo-dig* cyclization manner,[12] thus yielding a reactive gold carbene (**A**; Scheme 2a) that possesses umpolung reactivity at the normally nucleophilic 3-position of the indole. As azido groups can be easily installed, the strategy of accessing a reactive α-imino gold carbene using the combination of alkyne and azide is very appealing. However, in the context of gold catalysis, only the 5-*endo-dig* cyclization of an azido group, acting as a nitrene precursor, with an alkyne has so far been reported. We reasoned that a 5-*exo-dig* cyclization would become feasible if an electron-deficient C–C double bond were to be attached to the distal end of the alkyne (Scheme 2b) because: a) this group could electronically bias the C-C triple bond so that the alternative 6-*endo-dig* cyclization could be minimized;[13] b) upon generation of the gold carbene intermediate **B,** a 4π electrocyclic ring closure might occur to eventually afford the 2,3-dihydro-1*H*-pyrrolizine **2** with a desired electron-withdrawing group at its 5-position. Notably, due to the weak back-bonding capacity of gold,[14] a mesomeric form of **B** of significant contribution is the 1-azapentadienium **C**,[5] which is a conjugated cation[15] doubly destabilized by the imine moiety and the EWG group. Since the enynyl azide **1** can be assembled easily, for example, by the Sonogashira reaction, this strategy would provide a convergent, two-step approach to the biologically important 2,3-dihydro-1*H*-pyrrolizines with EWGs at the 5-position.



Scheme 2. Azide as intramolecular nitrene precursor in gold catalysis: our previous study and a new strategy.

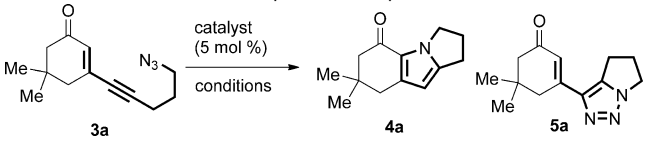
[*] Dr. Z.-Y. Yan, Dr. Y. Xiao, Prof. Dr. L. Zhang
Department of Chemistry and Biochemistry
University of California, Santa Barbara, CA (USA)
E-mail: zhang@chem.ucsb.edu
Homepage: http://www.chem.ucsb.edu/~zhang/index.html

[**] The authors thank NSF (CAREER CHE-0969157) and the China Scholarship Council (Z.-Y.Y. and Y.X.) for generous financial support and Sigma–Aldrich for the generous donation of [BrettPhosAuNTf$_2$].

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201203678.

We surmised that a ketone carbonyl group would be a suitable electron-withdrawing group and, furthermore, that having a cyclohexenone ring as the electron-deficient alkene component would offer a product with the pyrrolo[1,2-*a*]indole skeleton of mitosenes. Hence, cyclohexenone **3a** was chosen as the substrate for reaction development and optimization (Table 1). **3a** was readily prepared in 86% yield by a Sonogashira coupling between 5-azidopent-1-yne and 5,5-dimethyl-3-iodocyclohex-2-en-1-one. Much to our delight, the anticipated reaction indeed occurred with $[(Ph_3P)AuNTf_2]$ as the catalyst[16] and in 1,2-dichloroethane (DCE), and the expected cyclohexenone-fused 2,3-dihydro-1*H*-pyrrolizine **4a** was formed in 22% yield (Table 1, entry 1). Despite the sluggishness of the reaction, we were encouraged by the rather high yield (81%) based on the reaction conversion. To speed up the reaction, we first tried a range of other catalysts (Table 1, entries 2–5); the catalysts based on bulky biphenylphosphine ligands (e.g., *t*BuXPhos and BrettPhos)[17] led to better yields and higher conversions at ambient temperature (Table 1, entries 4 and 5). Further increase of the phosphine ligand size (e.g., Me_4*t*BuXPhos),[18] however, led to a much lower conversion (Table 1, entry 6). Although heating the reaction at 80°C was not very helpful when $[t$BuXPhosAuNTf$_2]$ was used (Table 1, entry 7), at the same elevated temperature, the yield was improved with $[$BrettPhosAuNTf$_2]$[17b] as the catalyst, and **4a** was formed in a satisfactory 69% yield, as determined by NMR spectroscopy (Table 1, entry 8). Screening the reaction solvents revealed that toluene was better than DCE, and the yield was improved to 96% (Table 1, entry 9). In comparison, $[(Ph_3P)AuNTf_2]$ was a lot inferior under the same reaction conditions (Table 1, entry 10), and neither $KAuCl_4$ (Table 1, entry 11) nor $PtCl_2$ (Table 1, entry 12) were effective for this transformation.

Table 1: Initial reaction development and optimization.[a]



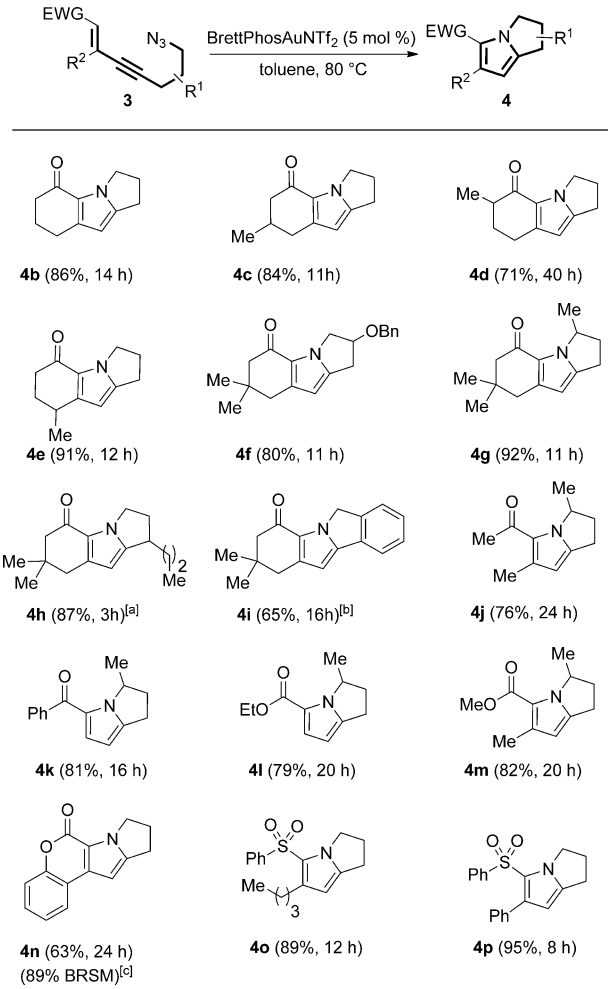
Entry	Catalyst	Conditions	*t* [h]	**4a** [%][b]	**5a** [%][b]	conv. [%][b]
1	$[(Ph_3P)AuNTf_2]$	$(ClCH_2)_2$, RT	28	22	–	27
2	$[IPrAuNTf_2]$	$(ClCH_2)_2$, RT	28	29	–	41
3	$[(4\text{-}CF_3C_4H_4)_3PAuNTf_2]$	$(ClCH_2)_2$, RT	28	30	–	37
4	$[t$BuXPhosAuNTf$_2]$	$(ClCH_2)_2$, RT	28	50	–	69
5	$[$BrettPhosAuNTf$_2]$	$(ClCH_2)_2$, RT	28	53	–	64
6	$[Me_4t$BuXPhosAuNTf$_2]$	$(ClCH_2)_2$, RT	32	26	–	32
7	$[t$BuXPhosAuNTf$_2]$	$(ClCH_2)_2$, 80°C	17	51	9	84
8	$[$BrettPhosAuNTf$_2]$	$(ClCH_2)_2$, 80°C	17	69[c]	3[c]	96[c]
9	$[$BrettPhosAuNTf$_2]$	toluene, 80°C	6	96[d]	–	100
10	$[(Ph_3P)AuNTf_2]$	toluene, 80°C	18	37	15	74
11	$KAuCl_4$	toluene, 80°C	19	3	14	45
12	$PtCl_2$	toluene, 80°C, CO	18	11	13	49
13	-	toluene, 80°C	18	0	17	33
14	$HNTf_2$ (5 mol%)	toluene, 80°C	18	–	56	82
15[e]	$[$BrettPhosAuNTf$_2]$	toluene, 80°C	8	30	15[f]	49

[a] [**3a**] = 0.05 M. [b] Estimated by ^{1}H NMR spectroscopy using dibromomethane as the internal reference. [c] 84%/2%/99% with base-washed DCE. [d] Yield of the isolated product. [e] 10 mol% of **5a** was added to the reaction. [f] The amount formed during the reaction. Tf = trifluoromethanesulfonyl.

A major side reaction of this alkynyl azide substrate was the Huisgen 1,3-dipolar cycloaddition.[19] When neat **3a** was stored over 6 days in the refrigerator, tiny amounts of polar impurities were formed, and upon inspection of the ^{1}H NMR spectrum, we attributed their formations mainly to intermolecular Huisgen reactions. In solution reactions at elevated temperatures (Table 1, entries 7–12), the triazole **5a**, formed by the intramolecular cycloaddition, was detected in up to 14% yield (Table 1, entry 11). In the absence of any catalyst (Table 1, entry 13), however, **5a** was formed in a higher 17% yield upon heating the reaction for a similar duration, thus suggesting that this side reaction is most likely not catalyzed by the gold catalysts but instead promoted by heating. Interestingly, $HNTf_2$ also promoted the formation of **5a** but did not promote the formation of **4a** at all (Table 1, entry 14). We also observed that the addition of 10 mol% of **5a** to the reaction mixture slowed the reaction rate substantially (Table 1, entry 15); this result is consistent with the fact that the basic triazole **5a** could deactivate the $[$BrettPhosAuNTf$_2]$ catalyst by coordination to the gold center.[20]

With the optimal conditions found (Table 1, entry 9) the reaction scope was then examined (Scheme 3). To avoid catalyst deactivation by the triazole impurities, all the substrates were used straight after column purification. At first, we focused on substrates deviating from **3a** at the cyclohexenone ring. To our delight, the substrate having no methyl group and those with one methyl group at various positions all gave the tricyclic pyrrole products (**4b**–**4e**) in mostly good yields. Substituents α or β to the azido group were readily tolerated, and the reaction yields were good to excellent (**4f** and **4g**). In the case of a γ-*n*-propyl group, the intramolecular Huisgen cycloaddition was surprisingly facile. The corresponding triazole **5h** was formed in 32% yield together with the desired 2,3-dihydro-1*H*-pyrrolizine **4h** (55% yield), even though the catalyst loading was 10 mol% and the reaction time was 26 h. To our delight, the reaction was dramatically improved when 15% of the catalyst was used (Scheme 3, **4h**). Notably, the reaction time was only 3 h. This result is consistent with our previous observation that the triazole side product hampers the gold catalysis, and suggests that the gold catalysis is initially fast but then slows down dramatically as the amount of the triazole builds up. The linker can also be fused to a benzene ring, although 10% of the catalyst was needed to obtain a decent yield of **4i** because of the competing Huisgen cycloaddition. The cyclohexenone moiety could be replaced by other linear electron-deficient alkenes. For example, pent-3-en-2-one can be used to deliver the dihydropyrrolizine **4j** in 76% yield, where an acetyl group is installed at the 5-position. Similarly, a benzoyl group was readily incorporated at the 5-position, and the product **4k** was formed in 81% yield. Interestingly, **4k** is the decarboxylated ketorolac.

As well as using ketones as the electron-withdrawing groups, esters including a lactone could similarly control the regioselectivity of the initial cyclization, and the yields were

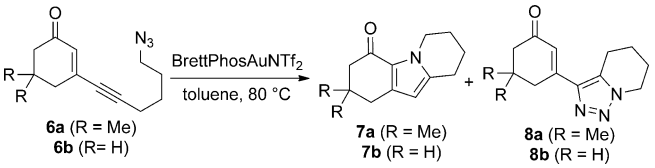


Scheme 3. Studies in the scope of the reaction. The reactions were run in a vial without exclusion of air and moisture. Unless otherwise noted, the amount of the triazole side product was typically less than 5%. [**3**] = 0.1 M. The yield of the isolated products are reported. [a] 15% catalyst. [b] 10% of gold catalyst, and 28% of the corresponding triazole was isolated. [c] [Cy-JohnPhosAuNTf$_2$] as the catalyst.

mostly good (Scheme 3, **4l**–**4n**). The synthesis of **4n** did not go to completion, but the yields based on conversion were high. By inspecting the yields for products **4j**–**4m** it can be seen that having $R^2 = H$ does not seem to affect the reaction. To our delight, benzenesulfonyl group also turned out to be an excellent EWG for this reaction; in both examples, the expected dihydropyrrolizine products (**4o** and **4p**) were formed smoothly and in high yields.

Our initial attempt to extend the chemistry to the substrate azidoenynone **6a**, which possesses a four-carbon linker between the C–C triple bond and the azido group resulted in a low yield of the expected tetrahydroindolizine **7a** (Table 2, entry 1). Instead, the triazole **8a** was formed in 74% yield, as determined by ^{1}H NMR spectroscopy. This Huisgen side reaction proceeded nearly quantitatively in the absence of any gold catalyst either upon heating over an extended time (Table 2, entry 2) or in just 2 minutes when HNTf$_2$ (1.1 equiv) was added (Table 2, entry 3). This dramatic rate acceleration resulting from the addition of a strong acid was

Table 2: Extension of the reaction to the formation of tetrahydroindolizine.[a]



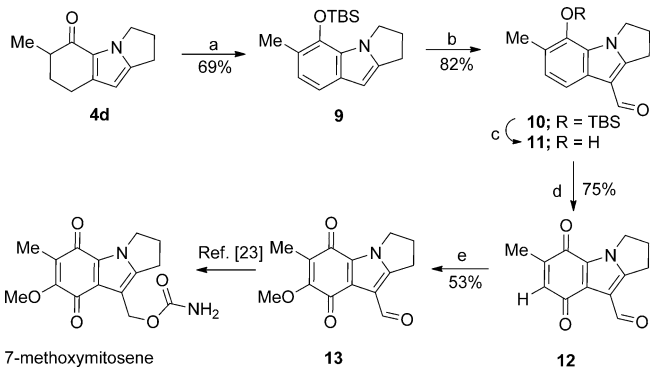
Entry	Substrate	Catalyst loading	*t*	**7** (Yield [%])	**8** (Yield [%])
1	**6a**	5%	19 h	**7a** (26)	**8a** (74)
2	**6a**	0	28 h	**7a** (0)	**8a** (95)
3	**6a**	0[b]	2 min	**7a** (0)	**8a** (96)
4	**6a**	10%	10 h	**7a** (89/83[c])	**8a** (11)
5	**6a**	15%	2 h	**7a** (94[c])	**8a** (< 2)
6	**6b**	15%	2.5 h	**7b** (91[c])	**8b** (< 2)

[a] The reactions were run in vial without exclusion of air and moisture; [**6**] = 0.2 M. [b] HNTf$_2$(1.1 equiv). [c] Yield of the isolated product.

much to our suprise. When the catalyst amount was increased to 10 mol%, the desired tetrahydroindolizine **7a** was isolated in 83% yield, whereas the triazole **8a** was formed in only 11% (Table 2, entry 4). The reaction can be further improved by using 15 mol% of the catalyst (Table 2, entry 5). This trend is consistent with our previous observation with **4h**. These optimized reaction conditions (Table 2, entry 5), when applied to the substrate **6b**, gave the corresponding tetrahydroindolizine **7b** in an equally excellent yield (Table 2, entry 6).

The ready access to the tricyclic pyrrolo[1,2-*a*]indole skeleton of mitosenes through this chemistry offers a new synthetic route to these biologically interesting compounds. 7-methoxymitosene was chosen as a target, and its synthesis commenced from **4d**.[21] After much experimentation, we realized a one-step oxidative aromatization of its cyclohexenone ring by using a combination of TBSCl (3 equiv), AgNTf$_2$ (3 equiv), and Et$_3$N in CH$_2$Cl$_2$. As the reaction was run under dry air, oxygen was most likely the oxidant, which is different from the known protocols where a metal oxidant such as MnO$_2$[22] was needed. The resulting tricyclic indole **9** was then subjected to a regioselective Vilsmeier–Haack reaction, delivering the aldehyde **10** in 82% yield. After desilylation, phenol **11** was efficiently oxidized into the indoloquinone **12** using oxygen as the oxidant and salcomine as the catalyst. The requisite 7-methoxy group (mitosene numbering) in **13** was then installed in one step by treating **12** with a solution of I$_2$ and KOH in MeOH. As **13** has been previously converted into 7-methoxymitosene in a three-step sequence,[23] this route constitutes a formal synthesis of the 7-methoxymitosene (Scheme 4).

In summary, we have developed a gold-catalyzed synthesis of 2,3-dihydro-1*H*-pyrrolizines having electron-withdrawing groups in the 5-postion, from linear azidoenynes. As the substrates can be easily assembled by the Sonogashira reaction, this reaction constitutes a two-step, convergent approach to this subclass of dihydropyrrolizines of proven medical importance. Mechanistically, the azido group acts as a nitrene precursor, and in the presence of a gold catalyst, the C–C triple bond is transformed highly regioselectively into an α-imino gold carbene. This intermediate, which is mesomeric



Scheme 4. A formal synthesis of 7-methoxymitosene. Reagents and conditions: a) TBSCl (3 equiv), $AgNTf_2$ (3 equiv), Et_3N (4 equiv), molecular sieves (4 Å), RT, dry air, 69%. b) $(COCl)_2$ (1.2 equiv), DMF, 0°C, 82%. c) LiOH (3 equiv), DMF, RT, 12 h, quantitative. d) Salcomine (10 mol%), O_2, DMF, RT, 75%. e) I_2 (4 equiv), KOH (8 equiv), MeOH.

to a destabilized 1-azapentadienium ion, undergoes apparent electrocyclic ring closure to deliver the pyrrole ring. The synthetic utility of this chemistry is demonstrated in a formal synthesis of 7-methoxymitosene.

Experimental Section

General procedure for the gold-catalyzed synthesis of dihydropyrrolizine: [BrettPhosAuNTf$_2$] (5.1 mg, 0.005 mmol) was added to a solution of freshly prepared azidoalklyne **3** (0.10 mmol) in toluene (1.0 mL) at room temperature. The reaction mixture in a vial was stirred at 80°C, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel flash chromatography (eluant: ethyl actate/hexanes) to afford the desired dihydropyrrolizine product.

Received: May 11, 2012
Published online: July 29, 2012

Keywords: carbene · gold · homogeneous catalysis · mitosene · nitrene

[1] a) E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double, M. C. Bibby, *J. Med. Chem.* **1989**, *32*, 1612; b) B. S. Iyengar, W. A. Remers, W. T. Bradner, *J. Med. Chem.* **1986**, *29*, 1864; c) B. S. Iyengar, R. T. Dorr, W. A. Remers, *J. Med. Chem.* **1991**, *34*, 1947; d) V.-S. Li, D. Choi, M.-s. Tang, H. Kohn, *J. Am. Chem. Soc.* **1996**, *118*, 3765.

[2] a) J. M. Muchowski, S. H. Unger, J. Ackrell, P. Cheung, J. Cook, P. Gallegra, O. Halpern, R. Koehler, A. F. Kluge, *J. Med. Chem.* **1985**, *28*, 1037; b) G. Dannhardt, W. Kiefer, *Arch. Pharm.* **1994**, *327*, 509; c) S. E. Abbas, F. M. Awadallah, N. A. Ibrahim, A. M. Gouda, *Eur. J. Med. Chem.* **2010**, *45*, 482.

[3] X. Huang, S. Zhu, R. Shen, *Adv. Synth. Catal.* **2009**, *351*, 3118.

[4] For early leading reviews, please see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.

[5] D. Alickmann, R. Fröhlich, A. H. Maulitz, E.-U. Würthwein, *Eur. J. Org. Chem.* **2002**, 1523.

[6] For our early works, see: a) G. Li, L. Zhang, *Angew. Chem.* **2007**, *119*, 5248; *Angew. Chem. Int. Ed.* **2007**, *46*, 5156; b) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550; c) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258.

[7] For selected examples, see: a) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160; b) G.-Y. Lin, C.-W. Li, S.-H. Hung, R.-S. Liu, *Org. Lett.* **2008**, *10*, 5059; c) A. S. Hashmi, M. Bührle, R. Salathé, J. Bats, *Adv. Synth. Catal.* **2008**, *350*, 2059; d) P. W. Davies, S. J. C. Albrecht, *Angew. Chem.* **2009**, *121*, 8522; *Angew. Chem. Int. Ed.* **2009**, *48*, 8372; e) H. S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J. E. Lee, S. S. Lee, S. Shin, *Angew. Chem.* **2010**, *122*, 1655; *Angew. Chem. Int. Ed.* **2010**, *49*, 1611; f) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15372; g) S. Bhunia, S. Ghorpade, D. B. Huple, R.-S. Liu, *Angew. Chem.* **2012**, *124*, 2993; *Angew. Chem. Int. Ed.* **2012**, *51*, 2939.

[8] B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem.* **2011**, *123*, 8508; *Angew. Chem. Int. Ed.* **2011**, *50*, 8358.

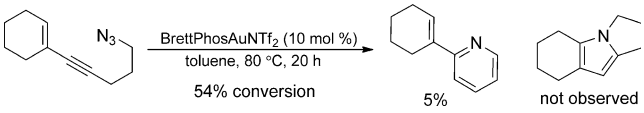
[9] C. Li, L. Zhang, *Org. Lett.* **2011**, *13*, 1738.

[10] P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem.* **2011**, *123*, 9093; *Angew. Chem. Int. Ed.* **2011**, *50*, 8931.

[11] a) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260; b) K. Hiroya, S. Matsumoto, M. Ashikawa, K. Ogiwara, T. Sakamoto, *Org. Lett.* **2006**, *8*, 5349.

[12] A. Wetzel, F. Gagosz, *Angew. Chem.* **2011**, *123*, 7492; *Angew. Chem. Int. Ed.* **2011**, *50*, 7354.

[13] For the enyne shown below, which lacks an EWG group, on the alkene, the gold catalysis led to a low yield of the pyridine product, the formation of which is attributed to an initial *6-endo-dig* cyclization. The expected tricyclic pyrrole was not detected.



[14] a) A. Fürstner, L. Morency, *Angew. Chem.* **2008**, *120*, 5108; *Angew. Chem. Int. Ed.* **2008**, *47*, 5030; b) W. He, L. Xie, Y. Xu, J. Xiang, L. Zhang, *Org. Biomol. Chem.* **2012**, *10*, 3168.

[15] X. Creary, *Chem. Rev.* **1991**, *91*, 1625.

[16] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133.

[17] a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552; b) L. Ye, W. He, L. Zhang, *Angew. Chem.* **2011**, *123*, 3294; *Angew. Chem. Int. Ed.* **2011**, *50*, 3236.

[18] a) Y. Wang, K. Ji, S. Lan, L. Zhang, *Angew. Chem.* **2012**, *124*, 1951; *Angew. Chem. Int. Ed.* **2012**, *51*, 1915; b) F. Barabé, P. Levesque, I. Korobkov, L. Barriault, *Org. Lett.* **2011**, *13*, 5580; c) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 4427; *Angew. Chem. Int. Ed.* **2006**, *45*, 4321; d) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146.

[19] R. Huisgen, *Proc. Chem. Soc.* **1961**, 357.

[20] a) D. Wang, L. N. S. Gautam, C. Bollinger, A. Harris, M. Li, X. Shi, *Org. Lett.* **2011**, *13*, 2618; b) D. Wang, Y. Zhang, A. Harris, L. N. S. Gautam, Y. Chen, X. Shi, *Adv. Synth. Catal.* **2011**, *353*, 2584; c) H. Duan, S. Sengupta, J. L. Petersen, N. G. Akhmedov, X. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 12100.

[21] This compound was prepared in 68% yield on a 0.6 g scale.

[22] a) R. B. Boers, P. Gast, A. J. Hoff, G. H. J. M. De, J. Lugtenburg, *Eur. J. Org. Chem.* **2002**, 189; b) A. van der Klei, R. L. P. de Jong, J. Lugtenburg, A. G. M. Tielens, *Eur. J. Org. Chem.* **2002**, 3015.

[23] G. R. Allen, J. F. Poletto, M. J. Weiss, *J. Org. Chem.* **1965**, *30*, 2897.

