Homogeneous Gold Catalysis

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# Gold-Catalyzed Transformation of 2-Alkynyl Arylazides: Efficient Access to the Valuable Pseudoindoxyl and Indolyl Frameworks**

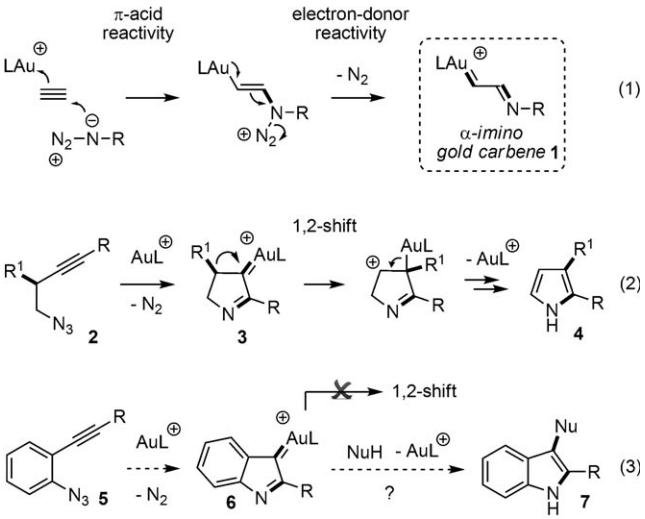
*Alexander Wetzel and Fabien Gagosz**

Gold catalysis has recently emerged as a "convenient tool for generating molecular complexity"[1] and diversity.[2] The majority of the synthetic chemistry that has been developed in this field is intimately linked to the π Lewis acidic property of electrophilic gold species.[3] These catalysts have indeed proven to be particularly useful for the activation of π systems, such as alkynes or allenes, towards the addition of various nucleophiles. In addition to this acidic character, gold can also act as an electron donor thus stabilizing the intermediate cationic species and favoring reaction pathways that are not accessible with other Lewis acids.[4] This π acid/electron donor dual reactivity is highlighted, for instance, in the gold(I)-catalyzed reaction of an alkyne with an azide [Scheme 1, Eq. (1)], where an α-imino gold carbene **1** can be generated by a sequence of nucleophlic azide addition followed by gold-assisted expulsion of $N_2$.

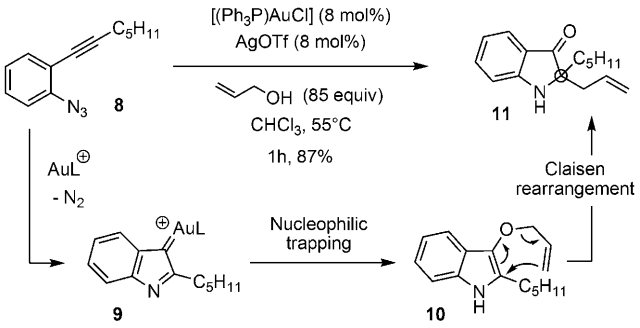
This reactivity pattern was exploited by Toste and co-workers in the design of a gold(I)-catalyzed intramolecular acetylenic Schmidt reaction, which converts an homopropargylazide **2** into a pyrrole **4** [Scheme 1, Eq. (2)].[5,6] In this transformation, the key intermediate α-imino gold carbene **3** undergoes a 1,2-hydride, 1,2-alkyl, or 1,2-aryl shift that ultimately furnishes compound **4**. Surprisingly, following this seminal study, little work was done to further exploit this reaction. A single example, in which intermediate **3** was oxidized to the corresponding ketone by diphenyl sulfoxide, was later reported by Toste and co-workers.[7] Although efficient, this oxidative process was, however, in competition with the 1,2-shift initially reported. In this context and in relation with our continuous interest in gold catalysis,[8] we were curious about how the α-imino gold carbene could evolve if the 1,2-shift reaction pathway was impossible. We surmized that a 2-alkynyl arylazide **5** might be a suitable substrate to answer this question and were particulary interested by the possibility of trapping the corresponding α-imino gold carbene **6** by a nucleophile [Scheme 1, Eq. (3)]. This trapping would not only increase the complexity of the transformation but might also lead to the formation of functionalized indoles of type **7**, which are privileged structures in medicinal chemistry.[9]

To validate our hypothesis, model substrate **8** was treated with 8 mol% of the gold catalyst [$(Ph_3P)$AuOTf] in chloroform and in the presence of a large excess of allylic alcohol (85 equiv; Scheme 2). Although no conversion of **8** could be observed at room temperature, a rapid (1 h) and clean transformation took place when the temperature was raised to 55 °C. However, the expected 3-allyloxyindole **10** that would result from the nucleophilic trapping of the α-imino gold carbene **9** by allyl alcohol could not be isolated. Indolin-3-one **11** was obtained instead in a good 87% yield probably as a result of a Claisen rearrangement, which proceeds from the desired 3-allyloxyindole **10**.[10–12]

This rapid and efficient formation of **11** is remarkable since it formally corresponds to an amino-oxy-allylation of




***Scheme 1.*** Synthetic design for the trapping of α-imino gold carbene. $R^1$ = H, alkyl, aryl.




***Scheme 2.*** First attempt of trapping with allylic alcohol.

[*] Dr. A. Wetzel, Dr. F. Gagosz
Département de Chimie, UMR 7652 CNRS
Ecole Polytechnique, 91128 Palaiseau (France)
E-mail: gagosz@dcso.polytechnique.fr

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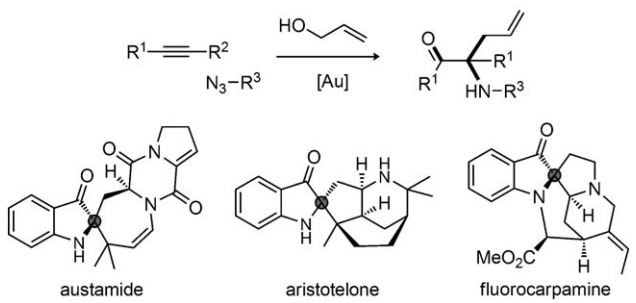
the alkyne moiety in **8** with the additional formation of a new quaternary carbon center (Scheme 3). Moreover, it is of potential synthetic interest since the 2,2-disubstituted indolin-3-one core is present not only in the structure of several biologically active compounds,[13] but also in that of a variety

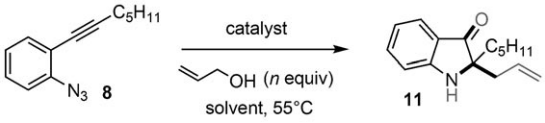


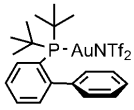
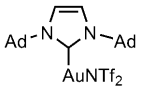

***Scheme 3.*** Amino-oxy-allylation principle and examples of pseudo-indoxyl alkaloids.

of natural products such as the pseudoindoxyl alkaloids austamide, aristotelone, and fluorocarpamine (Scheme 3).[14]

We therefore decided to study this unprecedented transformation and first focused our attention on the optimization of the reaction conditions (Table 1). An initial screening of different gold catalysts (8 mol%) showed that the phosphine gold complexes [$(Ph_3P)AuNTf_2$][15] and [(JohnPhos)$AuNTf_2$] **12**[16] were also suitable for this transformation, although the reaction times were slightly increased in these cases (Table 1, entries 2 and 3). The best result in terms of efficiency and reaction rate was obtained with the NHC-gold complex

***Table 1:*** Optimization of the catalytic system.



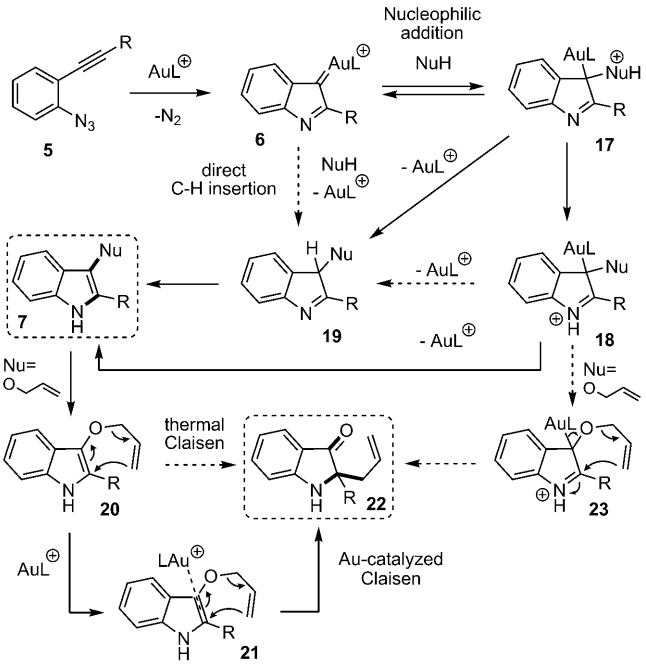

| Entry | Catalyst | Cat. [mol%] | *n* | Solvent | *t* [h] | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1 | [$(Ph_3P)AuCl$], AgOTf | 8, 8 | 85 | $CHCl_3$ | 1 | 87 |
| 2 | $(Ph_3P)AuNTf_2$ | 8 | 85 | $CHCl_3$ | 1.5 | 72 |
| 3 |  | 8 | 85 | $CHCl_3$ | 2 | 89 |
| 4 |  | 8 | 85 | $CHCl_3$ | 0.75 | 96 |
| 5 | **13** | 2 | 85 | $CHCl_3$ | 19.5 | 33 |
| 6 | **13** | 2 | 85 | $(CH_2Cl)_2$ | 10 | 54 |
| 7 | **13** | 4 | 85 | $(CH_2Cl)_2$ | 4 | 94 |
| 8 | **13** | 4 | 10 | $(CH_2Cl)_2$ | 4 | 96 |
| 9 | **13** | 4 | 2 | $(CCl)_2$ | 8 | 32 |
| 10 | $AgNTf_2$ | 4 | 10 | $(CH_2Cl)_2$ | 3 | –[b] |
| 11 | $HNTf_2$ | 4 | 10 | $(CH_2Cl)_2$ | 3 | –[b] |
| 12[c] | – | – | 10 | $(CH_2Cl)_2$ | 3 | –[b] |

[a] Yield of the isolated product. [b] No reaction was observed. [c] No catalyst was used. Tf = trifluoromethanesulfonyl.

[(IAd)$AuNTf_2$] **13**[17] (45 min, 96%; Table 1, entry 4). We next optimized the catalyst loading and the number of equivalents of allyl alcohol (Table 1, entries 5–9). We finally found that indolin-3-one **11** could be obtained in an excellent 96% yield by treating **8** with 4 mol% of **13** and 10 equiv of allyl alcohol in 1,2-dichloroethane at 55°C for 4 h (Table 1, entry 8). It should be noted that neither the silver salt $AgNTf_2$, nor the Brønsted acid $HNTf_2$ was a suitable catalyst for this transformation (Table 1, entries 10 and 11). Also, the reaction could not be performed under simple thermal reaction conditions (Table 1, entry 12).

With a set of optimized reaction conditions to hand (Table 1, entry 8), we then explored the scope of the reaction. We first focused our attention on the variation of the allylic alcohol and the substitution on the aryl moiety. As seen from the results compiled in Table 2, a series of indolin-3-ones **15a–i** could be obtained in good to excellent yields (65–92%), by reacting a series of aryl azides **8** and **14a–i** with a range of allylic alcohols for 1–24 h. An additional asymmetric center could be generated when allylic alcohols substituted at the C3-position were used as the nucleophiles (Table 2, entries 1–3, 5, and 6). There was, however, only moderate or no diastereoselectivity in these cases. Remarkably, it was even possible to produce indolin-3-ones possessing two vicinal quaternary centers under mild reaction conditions and without loss of efficiency (Table 2, entries 4, 5, 8, and 9).[11] This transformation would be of special interest for the synthesis of austamide and aristotelone, both of which have such a substitution pattern (see Scheme 3). Finally, the reaction could also be performed with substrates possessing a range of substituents with differing electronic natures on the aromatic ring (Cl, OMe, $CF_3$, ester; Table 2, entries 6–9).

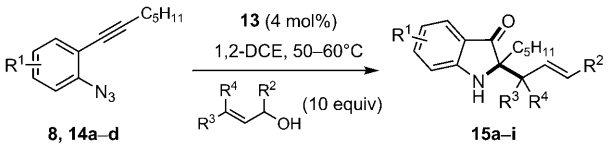
We also attempted to react azide **8** with a range of other nucleophiles that would not be suitable for the Claisen



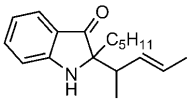
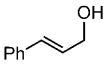
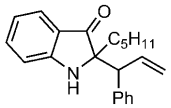
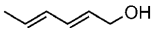
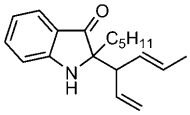
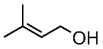
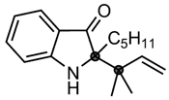
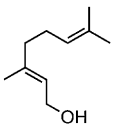
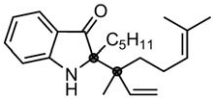
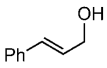
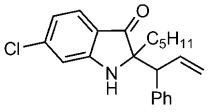
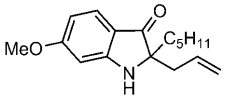
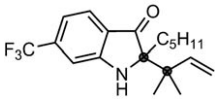
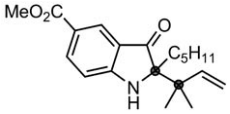

***Scheme 4.*** Mechanistic proposal.

***Table 2:*** Substrate scope.




**8, 14a–d** **15a–i**

| Entry | Substrate | NuH | *t* [h] | Product | | d.r.[b] | Yield [%][a] |
|---|---|---|---|---|---|---|---|
| 1 | **8** $R^1$ = H |  | 1 |  | **15a** | 3:1 | 92 |
| 2 | **8** $R^1$ = H |  | 1.5 |  | **15b** | 4:1 | 81 |
| 3 | **8** $R^1$ = H |  | 2 |  | **15c** | 3:1 | 76 |
| 4 | **8** $R^1$ = H |  | 1.5 |  | **15d** | - | 79 |
| 5 | **8** $R^1$ = H |  | 12 |  | **15e** | 9:1 | 59 |
| 6 | **14a** $R^1$ = 3-Cl |  | 2 |  | **15f** | 4:1 | 79 |
| 7 | **14b** $R^1$ = 3-OMe |  | 24 |  | **15g** | – | 79 |
| 8 | **14c** $R^1$ = 3-$CF_3$ |  | 16 |  | **15h** | – | 65 |
| 9 | **14d** $R^1$ = 4-$CO_2$Me |  | 1.5 |  | **15i** | – | 91 |

[a] Isolated yield. [b] Determined by $^1$H NMR spectroscopy. 1,2-DCE = 1,2-dichloroethane.

rearrangement (Table 3). The reaction could be performed with a primary and a secondary alcohol, as exemplified by the efficient formation of the 3-alkoxyindoles **16a** and **16b** (99% and 80%; Table 3, entries 1 and 2). Surprisingly, the poorly nucleophilic *tert*-butanol could also be used in this transformation (Table 3, entry 3) and the corresponding 3-*tert*-butoxyindole **16c** was obtained in a moderate 41% yield. Water also proved to be a good nucleophilic partner, as attested by the efficient formation of indolin-3-one **16d** (Table 3, entry 4). The use of phenol did not result in the formation of the corresponding 3-phenoxyindole. 3-Arylindole **16e** was obtained instead in 69% yield as the result of a Friedel–Crafts reaction (Table 3, entry 5).[18] A similar reactivity was observed when the reaction was performed with 2,6-dimethylaniline (Table 3, entry 6).

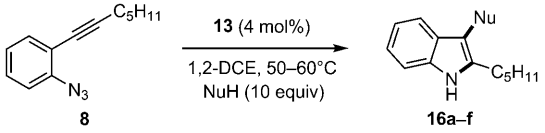
A mechanistic proposal for the formation of indole **7** and indolin-3-one **22** from azide **5** is presented in Scheme 4. The activation of the alkyne moiety in **5** by the gold(I) complex could lead, after extrusion of $N_2$, to the formation of an intermediate α-imino gold carbene **6**. This species could undergo a subsequent nucleophilic addition that would furnish **17**. Indole **7** could then be produced from **19** either via iminium **18** by a prototropy/demetalation sequence or via **19** by a protodemetalation/tautomerization sequence.[19] Alternatively, intermediate **19** might be produced by a direct insertion of the gold-carbene **6** into the Nu–H bond.[20] However, this carbenoid reactivity seems to be less probable since no cyclopropanation product could be formed when an alkene was used as a trapping agent.[21,22] The formation of indolin-3-one **22**, which was observed when an allylic alcohol was used as the nucleophile, can be rationalized by a Claisen rearrangement of **20**.[23,24] This transformation could be thermally induced, or more probably gold catalyzed (via gold complex **21**) given the mildness of the reaction conditions under which the transformation is performed (50–60°C). Indolin-3-one **22** could alternatively be formed from iminum **18** via intermediate **23**.

To futher highlight the synthetic potential of this new gold-catalyzed transformation and its usefulness for the rapid and efficient production of a range of heterocyclic compounds, a series of aryl azides, possessing various substituents at the alkyne terminus, were converted under the optimized reaction conditions (Table 1, entry 8) into either 3-substituted indoles or indolin-3-ones in the presence of various nucleophiles. The collection of examples presented in Scheme 5 reflect the diversity of products that can be produced and the tolerance for a variety of common functional groups (halogen, ester, et0her, amide, imide, alkene, azole) present either on the aromatic ring, on the alkyne substituent, or on the nucleophile.[25]

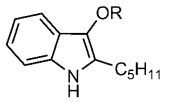
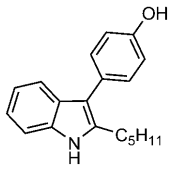
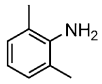
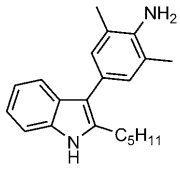
In conclusion, we have developed a new gold(I)-catalyzed reaction that converts 2-alkynyl arylazides into indolin-3-ones and 3-substituted indoles. The reaction, which is performed

***Table 3:*** Formation of 3-substituted indoles.

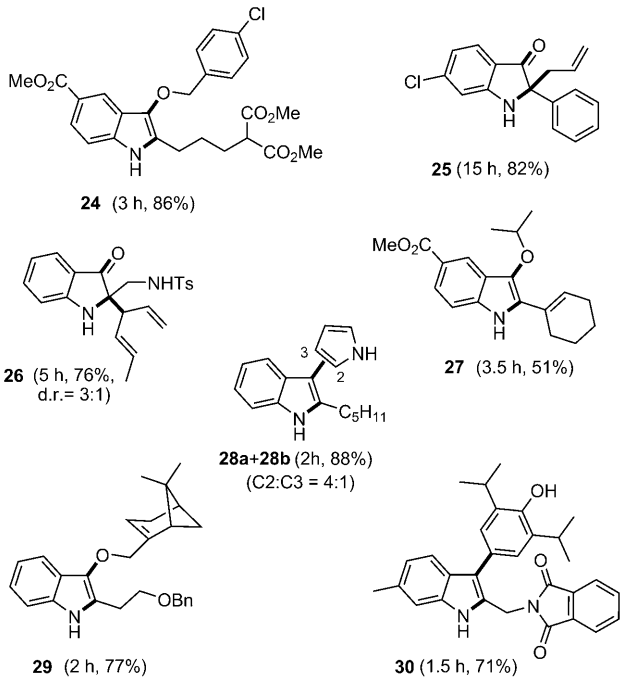



**8** **16a–f**

| Entry | NuH | *t* [h] | Product | | Yield [%][a] |
|---|---|---|---|---|---|
| | ROH | | | | |
| 1 | EtOH | 1 |  | **16a** | 99 |
| 2 |  | 2 | | **16b** | 80 |
| 3 | *t*BuOH | 6 | | **16c** | 41 |
| 4 | $H_2O$ | 2 | | **16d** | 89[b] |
| | ArOH | | | | |
| 5 |  | 2 |  | **16e** | 69 |
| 6 |  | 24 |  | **16f** | 66[c] |

[a] Yield of the isolated product. [b] Compound **16d** was isolated as the 3-oxindole structure. [c] Conversion: 77%.

under mild reaction conditions, is generally rapid, efficient, and tolerates the presence of various functional groups. The intermediate α-imino gold carbene could be trapped by various oxygen and carbon nucleophiles to furnish heterocyclic motifs that are frequently found in the structure of biologically active compounds or natural products. The possibility of producing indolin-3-ones possessing two vicinal asymmetric quaternary carbon centers is also noteworthy given its potential applicability to the synthesis of pseudoindoxyl alkaloids. Further studies on this new process and its application to the synthesis of natural products are in progress.




***Scheme 5.*** Generation of molecular diversity. Bn = benzyl, Ts = *p*-toluenesulfonyl.

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**Keywords:** azides · Claisen rearrangement · gold · homogeneous catalysis · nitrogen heterocycles

[1] A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208.
[2] E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333.
[3] For recent selected reviews on Au catalysis, see: a) V. Michelet, P. Y. Toullec, J. P. Genêt, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268; b) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; d) Z. Li, C. Brower, C. He, *Chem. Rev.* **2008**, *108*, 3239; e) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; f) D. J. Gorin, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; g) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; h) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410.
[4] a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; b) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482.
[5] D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260.
[6] For related studies on the reaction of homopropargyl azide with $PtCl_4$, see: a) K. Hiroya, S. Matsumoto, M. Ashikawa, K. Ogiwara, T. Sakamoto, *Org. Lett.* **2006**, *8*, 3181; b) Y. Xia, G. Huang, *J. Org. Chem.* **2010**, *75*, 7842; for other uses of azide derivatives in gold catalysis, see: c) Z. Huo, Y. Yamamoto, *Tetrahedron Lett.* **2009**, *50*, 3651; d) Z. Huo, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2010**, *75*, 1266; e) Y. Sawama, Y. Sawama, N. Krause, *Org. Lett.* **2009**, *11*, 5034; for a recent study involving the generation of related α-imino gold carbenes, see: f) C. Li, L. Zhang, *Org. Lett.* **2011**, *13*, 1738.
[7] A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838.
[8] For recent gold-catalyzed transformations developed in our group, see: a) B. Bolte, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 7294; b) Y. Odabachian, I. Dias-Jurberg, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 3543; c) C. Gronnier, Y. Odabachian, F. Gagosz, *Chem. Commun.* **2011**, *47*, 218; d) B. Bolte, F. Gagosz, *J. Am. Chem. Soc.* **2011**, *133*, 7696.
[9] For a recent review on the functionalization of indoles, see: a) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; for a review on the use of organic azides, see: b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188; for very recent example of a rhodium(II)-catalyzed conversion of arylazide derivatives into indoles, see: c) B. J. Stokes, S. Liu, T. G. Driver, *J. Am. Chem. Soc.* **2011**, *133*, 4702; d) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem.* **2011**, *123*, 1740; *Angew. Chem. Int. Ed.* **2011**, *50*, 1702.
[10] No example of such a Claisen rearrangement has been reported in the literature.

  

[11] For a review on the Claisen rearrangement, see: A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939.
[12] For other selected examples of gold-catalyzed Claisen rearrangements, see: a) F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181; b) A. Saito, T. Konishi, Y. Hanzawa, *Org. Lett.* **2009**, *12*, 372; c) B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605; d) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978; e) M.-C. P. Yeh, H.-F. Pai, C.-Y. Hsiow, Y.-R. Wang, *Organometallics* **2009**, *29*, 160.
[13] For selected examples, see: a) M. Kawada, H. Sugihara, I. Mikami, K. Kawai, S. Kuzuna, S. Noguchi, Y. Sanno, *Chem. Pharm. Bull.* **1981**, *29*, 1912; b) A. Asai, S. Nagamura, E. Kobajashi, K. Gomi, H. Saito, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1215; c) H. Fujii, R. Ogawa, K. Ohata, T. Nemoto, M. Nakajima, K. Hasebe, H. Mochizuki, H. Nagase, *Bioorg. Med. Chem. Lett.* **2009**, *17*, 5983.
[14] For austamide, see: a) P. S. Steyn, *Tetrahedron* **1971**, *12*, 3331; for aristotelone, see: b) V. Zabel, W. H. Watson, M. Bittner, M. Silva, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2842; for fluorocarpamine, see: c) H. Takayama, M. Kurihara, S. Subhadhirasakul, M. Kitajima, N. Aimi, S. Sakai, *Heterocycles* **1996**, *42*, 87.
[15] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133.
[16] A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614.
[17] L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704.
[18] Compound **16e** was isolated with a small amount of the *ortho*-substituted phenol regioisomer (9:1 ratio; see the Supporting Information for more details). For other selected examples of gold-catalyzed Friedel–Crafts reactions, see: a) C. H. M. Amijs, C. Ferrer, A. M. Echavarren, *Chem. Commun.* **2007**, 698; b) P. Y. Toullec, E. Genin, L. Leseurre, J. P. Genêt, V. Michelet, *Angew. Chem.* **2006**, *118*, 7587; *Angew. Chem. Int. Ed.* **2006**, *45*, 7427.
[19] Intermediate **19** could also be produced from iminium **18**.
[20] For examples of gold-carbene insertions into O–H, N–H, and C–H bonds, see: 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.
[21] No cyclopropanation products were formed when **8** was treated with 8 mol% of gold complex **13** and 10 equiv of styrene.
[22] The carbene reactivity is not supported by the selectivity observed in the formation of the 3-arylated indoles **16e–g** (Table 3, entries 5 and 6).
[23] The moderate selectivity observed in the Claisen products is possibly due to steric effects that do not favor a chairlike over a boatlike transition-state intermediate.
[24] When the reaction of azide **8** with allylic alcohol was monitored by $^1$H NMR spectroscopy ($CDCl_3$ as solvent), the postulated 3-allyloxyindole intermediate **10** could not be observed. This result tends to support a reaction pathway involving a rapid Claisen rearrangement via gold complex **21** or a reaction pathway involving the iminium species **23**.
[25] The use of the sterically congested nucleophile (−)-myrtenol did not result in the Claisen rearrangement, and only compound **29** could be obtained.

  