Subscriber access provided by American Chemical Society

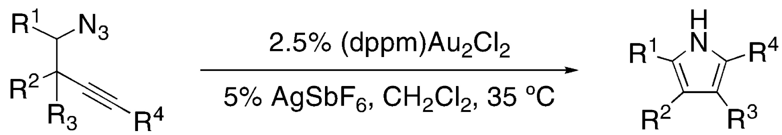
Communication

Gold(I)-Catalyzed Intramolecular Acetylenic Schmidt Reaction

David J. Gorin, Nicole R. Davis, and F. Dean Toste

J. Am. Chem. Soc., **2005**, 127 (32), 11260-11261• DOI: 10.1021/ja053804t • Publication Date (Web): 23 July 2005

Downloaded from http://pubs.acs.org on March 25, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 48 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

High quality. High impact.

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Published on Web 07/23/2005

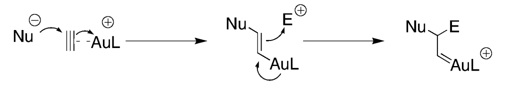
Gold(I)-Catalyzed Intramolecular Acetylenic Schmidt Reaction

David J. Gorin, Nicole R. Davis, and F. Dean Toste*

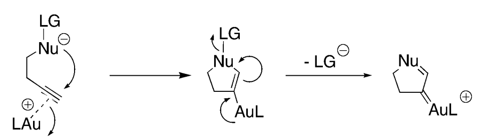
Department of Chemistry, University of California, Berkeley, California 94720

Received June 10, 2005; E-mail: fdtoste@berkeley.edu

Gold(I) complexes have seen increased utility as catalysts for the activation of alkynes toward addition by a variety of nucleophiles.[1,2] Recently, we proposed that back-bonding from gold into an electron-deficient intermediate may play a role in mediating the formation of bicyclo-[3.1.0]-hexene products from 1,5-enynes.[1d] This metal carbenoid-like behavior (eq 1) has been proposed in other transformations,[3] although chirality transfer in the course of a gold(I)-catalyzed Rautenstrauch rearrangement suggests that full carbene character is not present in all cases.[4] On the basis of these results, we sought to extend the reactivity of gold beyond the paradigm of electrophilic activation and further develop reactions around the mechanistic hypothesis wherein gold serves both as a π-acid and as an electron donor. We envisioned exploiting this reactivity by gold(I)-promoted addition of a leaving-group-bearing nucleophile to an acetylene with subsequent gold(I)-assisted loss of the leaving group (eq 2).



(1)

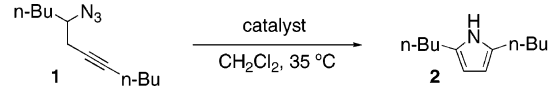


(2)

We hypothesized that this reactivity could be employed in modification of the Schmidt reaction[5] wherein alkyl azides serve as nucleophiles toward gold(I)-activated alkynes with subsequent gold(I)-aided expulsion of dinitrogen. To this end, treatment of homopropargyl azide **1** with 5 mol % of $Ph_3PAuCl/AgSbF_6$ in dichloromethane produced 2,5-dibutylpyrrole **2** in 72% yield (Table 1). While modification of the triarylphosphine ligand resulted in a deterioration in the yield of **2** (entries 2 and 3), bidentate phosphine digold(I)[6] complexes proved to be optimal catalysts for the cyclization (entries 4 and 5). In sharp contrast, other group 11 metal complexes[7] were not viable catalysts for this transformation (entries 6−8).

We were pleased to find that the gold(I)-catalyzed Schmidt reaction allowed for the preparation of pyrroles with a variety of substitution patterns (Table 2). Primary (entries 2 and 5−8) and secondary azides both participated in the gold(I)-catalyzed cyclization, allowing for introduction of C2 substituents. Additionally, gold(I)-catalyzed reaction of azide **7** substituted at the propargyl position produced trisubstituted pyrrole **8** in 73% yield (entry 4). The reaction tolerated substitution of the alkyne with both alkyl and aryl groups. Notably, substitution of the latter with electron-donating (entry 6) or electron-withdrawing (entry 7) substituents did not affect the course of the reaction. Additionally, azide **13**, containing a 1,5-enyne moiety, chemoselectively underwent the acetylenic Schmidt reaction at the expense of the cycloisomerization, albeit in slightly diminished yield (27% recovered **13**) (entry 10).

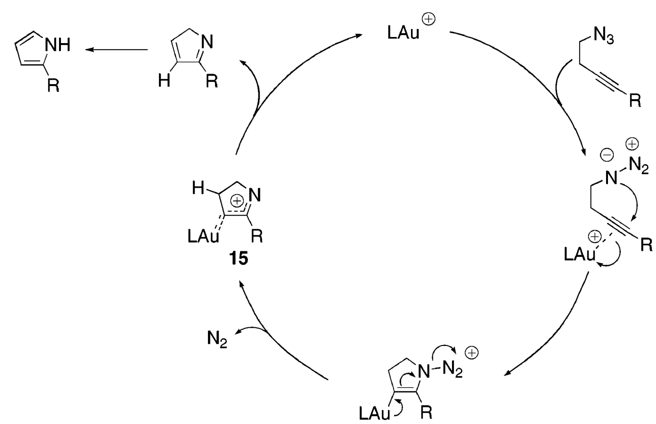
Table 1. Catalyst Optimization



entry	catalyst	% azide (**1**)[a]	% pyrrole (**2**)[a]
1	5% PPh_3AuCl, 5% $AgSbF_6$	9	72
2	5% $(4\text{-MeO-}C_6H_4)_3PAuCl$, 5% $AgSbF_6$	23	58
3	5% $(4\text{-CF}_3\text{-}C_6H_4)_3PAuCl$, 5% $AgSbF_6$	42	51
4	2.5% $(dppm)Au_2Cl_2$, 5% $AgSbF_6$	0	93
5	2.5% $(dppp)Au_2Cl_2$, 5% $AgSbF_6$	0	86
6	5% $AuCl_3$	>95	0
7	5% CuI	>95	0
8	5% $AgSbF_6$	>95	trace

[a] Conversion by ^1H NMR against an internal standard (1,2,3-trimethoxybenzene).

Scheme 1. Mechanistic Hypothesis

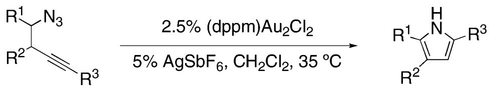


A mechanistic hypothesis involving gold(I)-induced activation of the alkyne toward addition by the proximal nitrogen of the azide is detailed in Scheme 1. Subsequent loss of dinitrogen produces cationic intermediate **15**,[8] which is stabilized by electron donation from gold(I). A formal 1,2-shift[9] regenerates the cationic gold(I) catalyst and produces a 2H-pyrrole that tautomerizes to the 1H-pyrrole product. While a mechanism involving generation of a nitrene-like intermediate[10] cannot be fully excluded, the observation that nonhomopropargylic alkyl azides are unreactive under the reaction conditions disfavors a mechanism initiated by gold(I)-promoted decomposition of the azide.

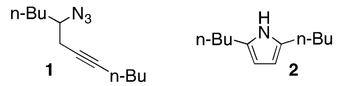
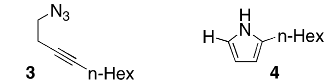
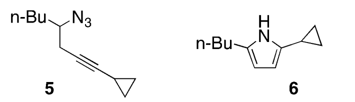
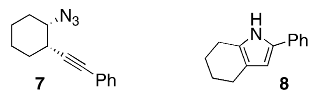
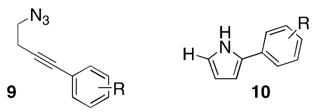
On the basis of this proposed mechanism, we envisioned taking advantage of intermediate **15** to prepare 2,3-substituted pyrroles by replacing the migrating hydrogen with alternative migrating groups. To this end, gold(I)-catalyzed rearrangement of cyclobutyl azide **16a** afforded trisubstituted pyrrole **17a** in 80% yield (eq 3). This cyclization−ring expansion strategy also allowed for the synthesis of tetrasubstituted pyrrole **17b** in 84% yield. These tandem

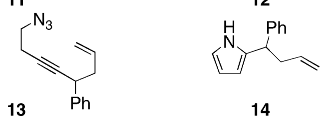
10.1021/ja053804t CCC: $30.25 © 2005 American Chemical Society

Table 2. Au(I)-Catalyzed Acetylenic Schmidt Reaction[a]



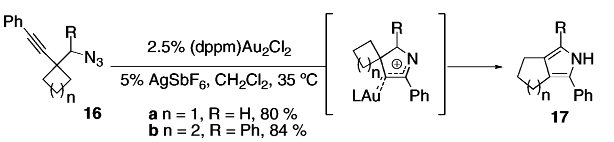
Entry	Azide	Pyrrole		Isolated Yield
1	1	2		82
2	3	4		76
3	5	6		78
4	7	8		73
5	9	10	**a** R = H	68
6			**b** R = 2-OMe	88
7			**c** R = 3-CF_3	93
8			**d** R = 4-I	87
9	11	12		61
10	13	14		41

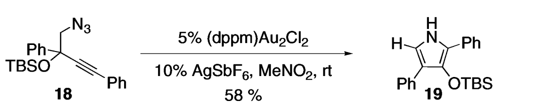


[a] Conditions: 2.5 mol % of (dppm)Au_2Cl_2, 5 mol % of $AgSbF_6$, 0.05 M CH_2Cl_2 at 35 °C for 20−40 min.

Scheme 2. Tandem Cyclization−Ring Expansion



(3)



(4)

addition−migration reactions are not limited to carbocyclic substrates. For example, TBS ether **18** underwent selective gold(I)-catalyzed cyclization−migration of the siloxy group to furnish pyrrole **19** (eq 4).

In summary, we have developed a gold(I)-catalyzed acetylenic Schmidt reaction of homopropargyl azides for the synthesis of multiply substituted pyrroles.[11] The reaction is characterized by mild conditions and simple preparation of the catalyst and allows for regiospecific substitution at each position of the pyrrole ring. A mechanism in which gold(I) serves both to activate the alkyne toward nucleophilic addition and also to donate electron density back into an electron-deficient π-system is proposed. The development of reactions that take advantage of this dual behavior of gold(I) complexes is ongoing in our laboratories and will be reported in due course.

Acknowledgment. We gratefully acknowledge the University of California, Berkeley, NIHGMS (R01 GM073932-01), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, and Eli Lilly & Co. for financial support.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (c) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (d) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (e) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (f) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (g) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (h) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (i) Nevado, C.; Echavarren, A. M. *Chem.*−*Eur. J.* **2005**, *11*, 3155. (j) For an excellent review of homogeneous gold-catalyzed reactions see: Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51.

(2) (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (c) Mizushima, E.; Sato, K.; Hayashi T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563.

(3) (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (c) Mainetti, E.; Mouriés, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132. (d) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260. (e) Martin-Matute, B.; Nevado, C.; Cardena, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. (f) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505. (g) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriés, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (h) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. (i) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (j) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793.

(4) Shi, X.; Gorin, D. J.; Toste F. D. *J. Am. Chem. Soc.* **2005**, *127,* 5802.

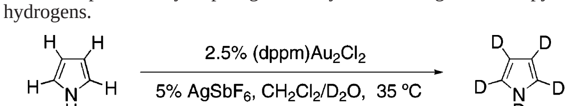
(5) For intramolecular Schmidt reaction of ketones and alkyl azides, see: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10499. For intramolecular Schmidt reaction of carbocations and alkyl azides, see: (c) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183. For Hg(II)-promoted reaction of alkyl azides with alkenes, see: (d) Pearson, W. H.; Hutta, D. A.; Fang, W. *J. Org. Chem.* **2000**, *65*, 8326. See also: (e) Molina, P.; Alcántara, J.; Kópez-Leonardo, C. *Synlett* **1995**, 363.

(6) (a) Brandys, M.-C.; Jennings, M. C.; Puddephat, R. J. *Dalton* **2000**, 4601. (b) Schmidbaur, H.; Wohlleben, A.; Wagner, F.; Orama, O.; Huttner, G. *Chem. Ber.* **1977**, *110*, 1748.

(7) Cu(I)-complexes are excellent catalysts for the [3 + 2]-cycloaddition of organic azides with terminal alkynes. See: Himo, F.; Loveli, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J Am. Chem. Soc.* **2005**, *127*, 210.

(8) Attempts to intercept this intermediate by intermolecular addition of styrene were unsuccessful, producing only the pyrrole product.

(9) Attempts to observe this 1,2-shift using deuterium-labeled propargyl azides were complicated by rapid gold-catalyzed exchange of the pyrrole hydrogens.



(10) For the generation of metal−imido (nitrene) complexes from reaction with organic azides, see: Nugent, W. A.; Mayer, J. M. *Metal*−*Ligand Multiple Bonds*; Wiley: New York, 1988.

(11) For some recent examples of metal-catalyzed pyrrole synthesis, see: (a) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, ASAP. (b) Siriwardana, A. I.; Kathriarchchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (c) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (d) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957. (e) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853. (f) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (g) Takaya, H.; Kojima, S.; Murahashi, S. *Org. Lett.* **2001**, *3*, 421.

JA053804T