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The Au(I)-Catalyzed Intramolecular Hydroarylation of Terminal Alkynes Under Mild Conditions: Application to the Synthesis of 2*H*-Chromenes, Coumarins, Benzofurans, and Dihydroquinolines

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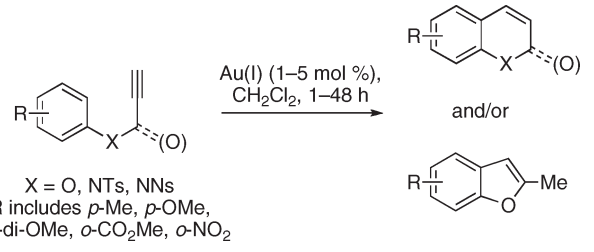
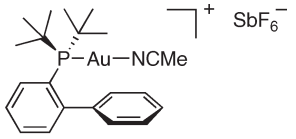


Operationally simple Au(I)-catalyzed intramolecular hydroarylation (IMHA) reactions of terminal alkynes that proceed in high yield and under very mild conditions are described. These processes involve low catalyst loadings, mild reaction temperatures, and short reaction times, require no cocatalysts or additives, and allow for the generation of a number of important heterocyclic motifs from readily accessible starting materials.

Cationic gold complexes are rapidly emerging as excellent catalysts for facilitating the assembly of a variety of carbon−carbon and carbon−heteroatom bonds with the result that powerful new methodologies based upon such processes are now being reported with increasing frequency.[1] Such complexes can be particularly effective in selectively activating alkynes toward nucleophilic addition and numerous reactions employing this strategy have been disclosed recently.[2] The majority of such processes require a cocatalyst, usually in the form of a silver salt, to activate the Au(I) species that is used. However, these silver salts are often hygroscopic, difficult to weigh accurately, and frequently result in an acidic reaction medium. Furthermore, the presence of a silver cocatalyst can promote unwanted side reactions.[3] Accordingly, a single-component Au(I) species that can activate alkynes toward nucleophilic attack offers numerous advantages over the conventional Au−Ag cocatalyst systems.

Recently, Echavarren and co-workers reported the synthesis of the stable Au(I) complex **1** possessing a weakly coordinating acetonitrile ligand that can, in the absence of silver and upon addition of a suitable substrate, be replaced by alkyne functionalities.[4] As a result this complex, which is able to be handled under standard benchtop conditions, has proven effective in catalyzing the cyclization of both enynes[2g,5a] and indole-tethered alkynes.[5b]



1

Our recent discovery of a highly efficient cascade reaction[6] that is catalyzed by complex **1** prompted us to investigate the capacity of this species to effect the intramolecular hydroarylation (IMHA) of alkynes. The latter process involves the formal addition of an arene unit and a hydrogen across the sp-hybridized carbons of a tethered alkyne.[7] While metals such as Pd,[8] Ru,[9] Ga,[10] Pt,[11] and Hg[12] as well as Tf_2NH[13] are

(1) Recent reviews: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Hashmi, A. S. K. *Nature* **2007**, *449*, 292. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (h) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (i) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(2) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (d) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (e) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (f) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (g) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

(3) (a) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155. (b) Curtis, N. R.; Prodger, J. C.; Rassias, G.; Walker, A. J. *Tetrahedron Lett.* **2008**, *49*, 6279.

(4) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(5) (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (b) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

(6) Banwell, M. G.; Sharp. P. P. Unpublished results.

(7) Reviews: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (c) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111. For examples of the Au(I)-catalyzed IMHA reactions, see: (e) Reetz, M.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (f) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669.

(8) (a) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.

(9) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913.

(10) (a) Inoue, H.; Chatani, N.; Muari, S. *J. Org. Chem.* **2002**, *67*, 1414. (b) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 7577.

(11) (a) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (b) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112. (c) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556. (d) Pastine, S, J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (e) Pastine, S, J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859.

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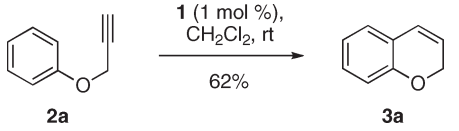
known to promote the IMHA reactions of alkynes, $AuCl_3$ is not effective[11d] in this regard. Among the isolated examples of Au(I)-catalyzed IMHA reactions of alkynes that have been reported, almost all require the use of a cocatalyst such as a Ag(I) salt or HBF_4.[3] We speculated that the now commercially available catalyst **1** would be ideal for effecting the IMHA reactions of a broad range of alkynes under mild conditions. As revealed herein, this has proved to be the case and allowed us to establish particularly convenient methods for the preparation of various 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines.

In a preliminary experiment designed to test our hypothesis, a dichloromethane solution of readily available phenyl propargyl ether (**2a**) maintained at ambient temperatures was treated with 1 mol % of complex **1**. Pleasingly, after 1 h the expected product, 2*H*-chromene (**3a**), was generated in 62% yield (Scheme 1).[14] Accordingly, we immediately sought

SCHEME 1. Au(I)-Catalyzed IMHA Reaction of Phenyl Propargyl Ether (2a)



to establish the scope and generality of this type of process. To that end a range of readily accessible aryl propargyl ethers was prepared and then subjected to the same reaction conditions. The outcomes of such studies are shown in Table 1, which reveals that the IMHA reactions effected by catalytic quantities of complex **1** are both broad in scope and highly efficient, even in instances where the arene ring incorporates electron-withdrawing groups (entries 3, 5, and 6). In cases involving nonsymmetrically substituted arene rings (entries 4 and 8) the cyclization reactions proceed regioselectively. Furthermore, when the ether tether was replaced with an ester linkage, as in the case of substrates **2k** and **2l** (entries 10 and 11, respectively), the corresponding coumarin-derived products **3k** and **3l** were obtained in good yield.

Benzofurans (**4**) were generated as coproducts (or as the only product) in a number of instances (entries 4, 5, 6, 8, and 9). Prior to the present study, the formation of benzofurans (**4**) from aryl propargyl ethers (**3**) had only been observed under much more forcing conditions (>200 °C, refluxing diethylaniline).[15] The formation of such coproducts in the present work may well involve fragmentation of the aurylated species **5**, a likely late-stage intermediate associated with the formation of the 2*H*-chromenes **3**, to give the allene **6** (Scheme 2), which engages in a 5-exo-dig cyclization reaction to give the observed product **4**.[16] This proposal is

SCHEME 2. Possible Pathway for the Formation of Benzofurans 4 from Substrates 3

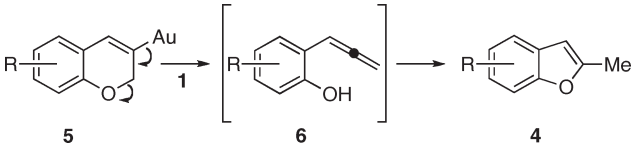


TABLE 1. Outcomes of Au(I)-Catalyzed IMHA Reactions of Certain Aryl Propargyl Ethers, Aryl Propargylates, and Aryl Propargyl Amine Derivatives

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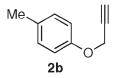
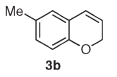
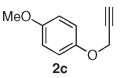
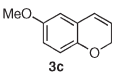
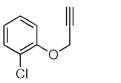
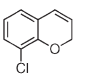
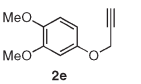
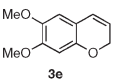
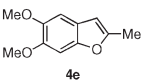
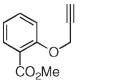
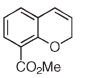
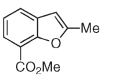
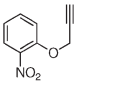
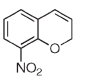
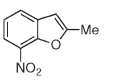
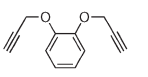
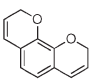
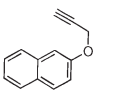
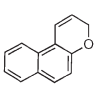
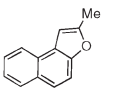
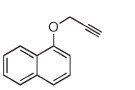
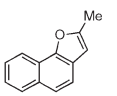
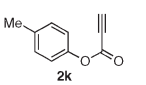
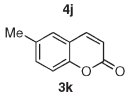
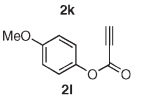
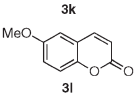
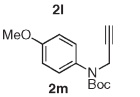
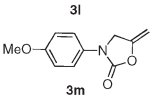
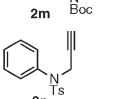
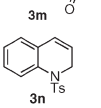
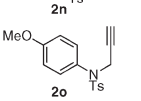
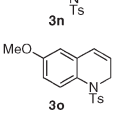
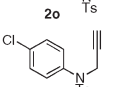
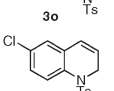
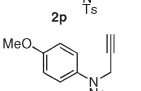
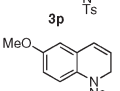
1	 2b	 3b		66
2	 2c	 3c		73
3	 2d	 3d		90
4	 2e	 3e	 4e	40 (**3e**) 13 (**4e**)
5	 2f	 3f	 4f	17 (**3f**) 80 (**4f**)
6	 2g	 3g	 4g	39 (**3g**) 39 (**4g**)
7	 2h	 3h		62
8	 2i	 3i	 4i	41 (**3i**) 31 (**4i**)
9	 2j	 4j		58
10	 2k	 3k		60
11	 2l	 3l		94
12	 2m	 3m		71
13	 2n	 3n		81
14	 2o	 3o		79
15	 2p	 3p		52
16	 2q	 3q		75

[a]The substrates were readily prepared by conventional methods (see the SI). [b]Conditions used for effecting the IMHA reactions shown are given in the Experimental Section and/or the SI. [c]All yields cited are of isolated and chromatographically purified materials.

(12) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563.

(13) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

(14) See the Supporting Information for experimental details.

consistent with that of Echavarren,[5b] who has invoked related processes to account for the formation of 2-allenyl indoles from certain *N*-propargyl tryptophans in the presence of complex **1**.[5b]

When aryl propargyl amines are used as substrates for the IMHA reactions, the third group attached to nitrogen has a significant impact on the nature of the observed product. Thus, subjection of the *N*-Boc protected compound **2m** (entry 12) to the same reaction conditions as used earlier afforded oxazolidinone **3m**[17] in 71% yield and as the exclusive product of reaction. In contrast, replacement of the Boc group on nitrogen with a tosyl residue provided substrates that readily cyclized to the corresponding dihydroquinolines (see entries 13 and 14). Substrate **2p**, possessing an electron-withdrawing chloro-substituent on the aromatic ring, cyclized as expected to afford the corresponding dihydroquinoline derivative **3p** in 52% yield (entry 15). Compound **2q**, bearing a more easliy removed 2-nitrobenzenesulfonyl (Ns) nitrogen protecting group,[18] also reacted in the presence of complex **1** to give the corresponding dihydroquinoline derivative **3q** in good yield (75%, entry 16).

The protocols reported here provide an operationally simple method for effecting IMHA reactions that proceed under exceptionally mild conditions and in a time-efficient manner. A number of important heterocyclic motifs including 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines can thus be formed expeditiously from readily accessible starting materials.

Experimental Section

Compound 3a. A magnetically stirred solution of aryl propargyl ether (**2a**)[19] (40 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) maintained at 18 °C was treated with (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**1**) (2.4 mg, 1 mol %). The resulting solution was stirred at 18 °C for 1 h then concentrated under reduced pressure and the ensuing yellow oil was subjected to flash column chromatography[20] (silica gel, hexane) to give, after concentration of the appropriate fractions (R_f 0.3 in 1:49 v/v ethyl acetate/hexane), chromene **3a**[21] (25 mg, 62%) as a clear, colorless oil. ^{1}H NMR (300 MHz) δ 7.13−7.08 (1H, m), 6.96−6.95 (1H, d, J = 7.2 Hz), 6.89−6.84 (1H, m), 6.78 (1H, d, J = 7.8 Hz), 6.43 (1H, d, J = 9.9 Hz), 5.80−5.74 (1H, m), 4.83 (2H, broad s); ^{13}C NMR (75 MHz) δ 154.0, 129.1, 126.5, 124.5, 122.3, 121.9, 121.3, 115.7, 65.5; IR ν_{max} (NaCl) 1640, 1608, 1488, 1458, 1229, 1201, 1117, 1043, 941, 756 cm^{-1}; MS (EI, 70 eV) m/z 132 ($M^{+\bullet}$, 96%), 131 (100), 103 (56), 77 (61), 51 (78); HRMS m/z calcd for C_9H_8O $M^{+\bullet}$ 132.0575, found 132.0572.

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Supporting Information Available: Detailed procedures and full characterization data for all new compounds and ^{1}H and ^{13}C NMR spectra for compounds **2g**, **2p**, **2q**, **3a**−**i**, **3k**−**q**, **4e**−**g**, **4i**, and **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148. (b) Ishikawa, T.; Nagai, K.; Ohkubo, N.; Ishii, H. *Heterocycles* **1994**, *39*, 371.

(16) We thank a referee for useful suggestions regarding the reaction pathway proposed in Scheme 2.

(17) Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

(18) (a) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. (b) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.

(19) Pal, M.; Parasuraman, K.; Yeleswarapu, K. R. *Org. Lett.* **2003**, *5*, 349.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(21) Varela, J. A.; González-Roríguez, C.; Rubín, S. G.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9576.