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# Sequential Rhodium-, Silver-, and Gold-Catalyzed Synthesis of Fused Dihydrofurans

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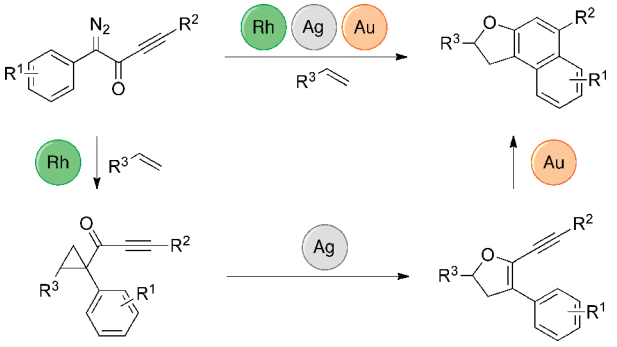
## ABSTRACT




**A triple cascade process was developed for the rapid synthesis of polycyclic benzo-fused dihydrofurans. The first step is a rhodium-catalyzed cyclopropanation of α-aryldiazoketones with alkenes. This is followed by a silver-catalyzed ring expansion to dihydrofurans, which then undergo a gold-catalyzed cyclization to form benzo-fused dihydrofurans.**

A feature of the metal-catalyzed reactions of diazo compounds is the formation of highly energetic metal-carbenoid intermediates under very mild reaction conditions. The resulting carbenoid reactions often generate strained or reactive products, capable of undergoing further transformations.[1,2] Our group has developed a variety of cascade reactions using carbenoid intermediates, such as ylide formation/[3 + 2] cycloaddition,[3] ylide formation/[2,3] sigmatropic rearrangement,[4] and cyclopropanation/Cope rearrangement.[5] An alternative way of achieving a cascade sequence is to conduct a further metal-catalyzed transformation through multicatalytic processes.[6] We have been interested in developing synthetic sequences that combine the rhodium-catalyzed reactions with other complementary metal-catalyzed reactions with orthogonal reactivity.[7] In this paper we describe a triple cascade sequence that involves sequential rhodium-, silver-, and gold-catalyzed reactions.

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(1) For reviews: (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (b) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072. (c) Padwa, A. *J. Org. Chem.* **2009**, *74*, 6421. (d) Davies, H. M. L.; Beckwith, R. E. *Chem. Rev.* **2003**, *103*, 2861. (e) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.

(2) For recent examples: (a) Jiang, J.; Xu, H.; Xi, J.; Ren, B.; Lv, F.; Guo, X.; Jiang, L.; Zhang, Z.; Hu, W. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (b) Zhu, Y.; Zhai, C.; Yang, L.; Hu, W. *Eur. J. Org. Chem.* **2011**, 1113. (c) Hu, W.; Xu, X.; Zhou, J.; Liu, W.; Huang, H.; Hu, J.; Yang, L.; Gong, L. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (d) Liu, Y.; Bakshi, K.; Zavalij, P.; Doyle, M. P. *Org. Lett.* **2010**, *12*, 4304. (e) England, D. B.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 2792.

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(4) Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396.

(5) For examples: (a) Schwartz, B. D.; Denton, J. R.; Lian, Y.; Davies, H. M. L.; Williams, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 8329. (b) Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573. (c) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312. (d) Davies, H. M. L.; Loe, Ø.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561.

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(7) (a) Deng, L.; Giessert, A. J.; Gerlitz, O. O.; Dai, X.; Diver, S. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2005**, *127*, 1342. (b) Ni, A.; France, J. E.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5594.

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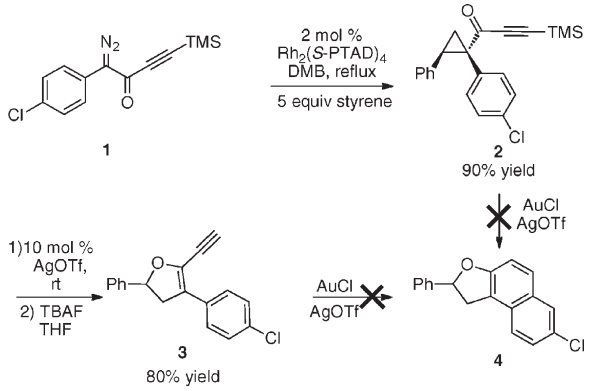
In recent years, homogeneous gold-catalyzed reactions have developed rapidly.[8] One class of gold-catalyzed reactions is the cycloisomerization of alkynyl cyclopropane derivatives.[9] Recently, we explored the rhodium-catalyzed asymmetric cyclopropanation chemistry of α-aryldiazoketones.[10] During the course of the optimization studies of this chemistry, we discovered that alkynyl-substituted diazo compounds were the optimum substrates for high asymmetric induction. As the resulting products have multiple reactive sites, such as the cyclopropyl ketone and the alkyne functionality, we considered that they would be ideal substrates for multiple metal-catalyzed cascade processes.

**Scheme 1.** Initial Study of the Gold-Catalyzed Cycloaddition Reaction

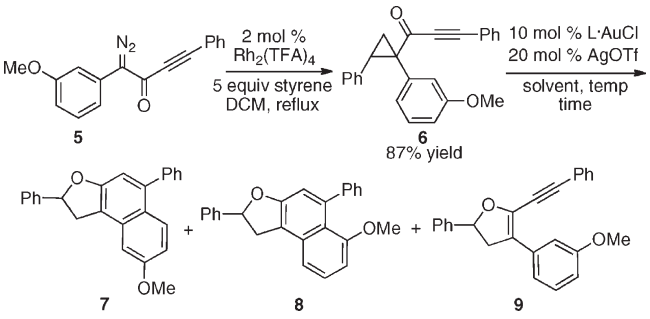



DMB: 2,2-dimethylbutane

The study began with the reaction of the *p*-chlorophenyldiazoketone **1** (Scheme 1). Rhodium-catalyzed cyclopropanation between **1** and styrene generated the cyclopropyl ketone **2** in 90% yield. Treatment of **2** with silver triflate (AgOTf) and tetrabutylammonium fluoride resulted in desilylation and ring expansion to form **3**. The third metal-catalyzed step was projected to be a gold-catalyzed cyclization of the alkyne to generate the fused polycyclic compound **4**. However, under a variety of reaction conditions, no more than trace amounts of the polycyclic product were observed starting from either compound **2** or **3**.

A possible explanation for the failure of the gold-catalyzed cyclization could be that the gold-activated complex

**Table 1.** Optimization of the Cycloaddition Reaction

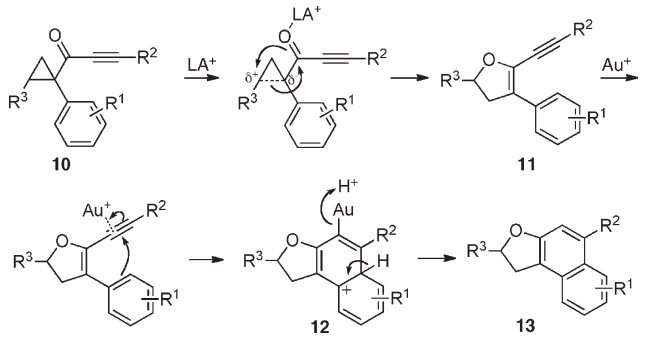



| entry | L·AuCl | solvent (v/v) | temp (°C) | time (h) | ratio[a] (**7:8:9**) | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | AuCl | DCM | reflux | 24 | 2.4:1:1 | 59[c] |
| 2 | $Ph_3PAuCl$ | DCM | reflux | 0.5 | 2.8:1:0 | 78 |
| 3 | $Ph_3PAuCl$ | DCE | reflux | 0.5 | 2.0:1:0 | 83 |
| 4 | $Ph_3PAuCl$ | PhMe | 85 | 0.5 | 2.5:1:0 | 99 |
| 5 | $Ph_3PAuCl$ | DCM/PhMe (1/1) | reflux | 0.5 | 1.6:1:0 | 91 |
| 6 | $Ph_3PAuCl$ | DCM/PhMe (1/2) | reflux | 0.5 | 1.8:1:0 | 99 |

[a] Determinded by crude NMR. [b] Combined yield of compounds **7** and **8**. [c] Combined yield of compounds **7**, **8**, and **9**.

is electrophilic and would require an electron-rich aromatic ring for effective ring closure.[11] Therefore the reaction sequence was repeated with the *m*-methoxy derivative **5** (Table 1). Under these conditions the dihydrobenzofuran derivatives **7** and **8** were observed, together with an uncyclized dihydrofuran compound **9** (entry 1). Complete cyclization was achieved when chlorotriphenylphosphine gold(I) ($PPh_3AuCl$) was used as a catalyst (entry 2). Further optimization studies showed that toluene was the ideal solvent for this gold-catalyzed cycloaddition reaction and the polycyclic products were isolated in nearly quantitative yield (entry 4). A similar yield was also obtained after switching to a cosolvent system consisting of a 1:2 volume ratio of DCM and toluene (entry 6). As will be discussed later, the mixed-solvent system became the foundation of a one-pot cascade sequence for this transformation.

**Scheme 2.** Possible Mechanism of the Cycloaddition Reaction




(8) For recent reviews: (a) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (f) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750.

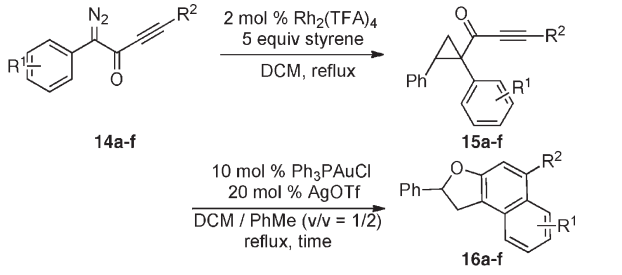
(9) (a) Barluenga, J.; Tudela, E.; Vicente, R.; Ballesteros, A.; Tomás, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2107. (b) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178. (c) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (d) Zhang, X.; Tu, Y.; Jiang, Y.; Zhang, Y.; Fan, C.; Zhang, F. *Chem. Commun.* **2009**, 4726. (e) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814. (f) Zhang, J.; Schmalz, H. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704.

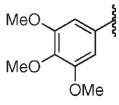
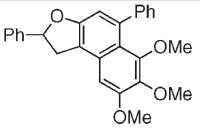
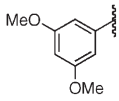
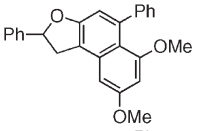
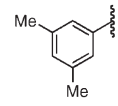
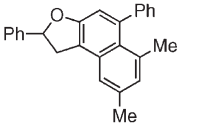
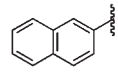
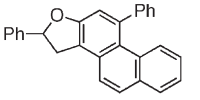
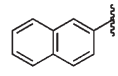
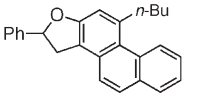
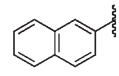
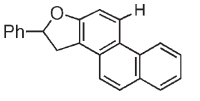
(10) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787.

(11) (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

A reasonable mechanism for the sequential reactions is shown in Scheme 2. AgOTf is expected to act as a Lewis acid and induce rearrangement of the cyclopropyl ketone **10** to form the dihydrofuran **11**. The following gold-catalyzed benzannulation would be expected to form **12**, which upon deprotonation and proto-demetalation would afford the tricyclic product **13**.

**Table 2.** Sequential Reactions of Diazo Ketones with Styrene

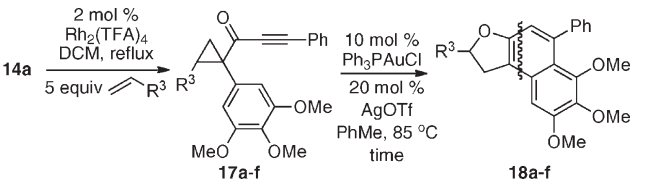


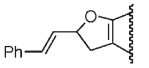
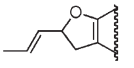
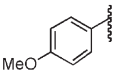
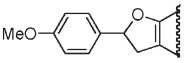
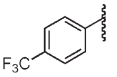
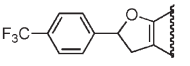
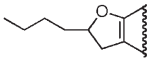

| compd | $R^1$ | $R^2$ | yield[b] **15a-f** (%) | time[a] (h) | product | yield[b] **16a-f** (%) |
|---|---|---|---|---|---|---|
| **a** |  | Ph | 80 | 2 |  | 99 |
| **b** |  | Ph | 89 | 2 |  | 79 |
| **c** |  | Ph | 94 | 2 |  | 99 |
| **d** |  | Ph | 72 | 2 |  | 96 |
| **e** |  | *n*-Bu | 78 | 6 |  | 90 |
| **f** |  | H | 39 | 0.5 |  | 92 |

[a] The reactions were monitored by TLC, and heating was stopped when all the starting materials were consumed. [b] Isolated yields.

To explore the scope of this method, several diazo compounds were subjected to this sequence (Table 2). Although compounds **15a** and **15b** are more sterically hindered than compound **6**, with a methoxy group on each side of the phenyl ring, polycyclic products **16a** and **16b** were obtained in high yields after a period of 2 h. With the 3,5-dimethylphenyl derivative **15c**, both the cyclopropanation and the cycloaddition reactions proceeded in excellent yields. The cycloaddition reaction of the 2-naphthyl derivative **15d** generated the tetracyclic product **16d** as a single regioisomer in high yield. The structure of **16d** was confirmed by X-ray crystallographic analysis.[12] The same selectivity was also observed for the other 2-naphthyl derivatives **16e** and **16f**.

**Table 3.** Sequential Reactions of **14a** with Alkenes




| compd | $R^3$ | yield[b] **17a-f** (%) | time[a] (h) | products **18a-f** | yield[b] **18a-f** (%) |
|---|---|---|---|---|---|
| **a** |  | 80 | 6 |  | 80 |
| **b** |  | 70 | 6 |  | 62 |
| **c** |  | 82 | 6 |  | 21 |
| **d** |  | 66 | 6 |  | 93 |
| **e** |  | 34 | 2 |  | 89 |
| **f** |  | 46 | 6 |  | 48 |

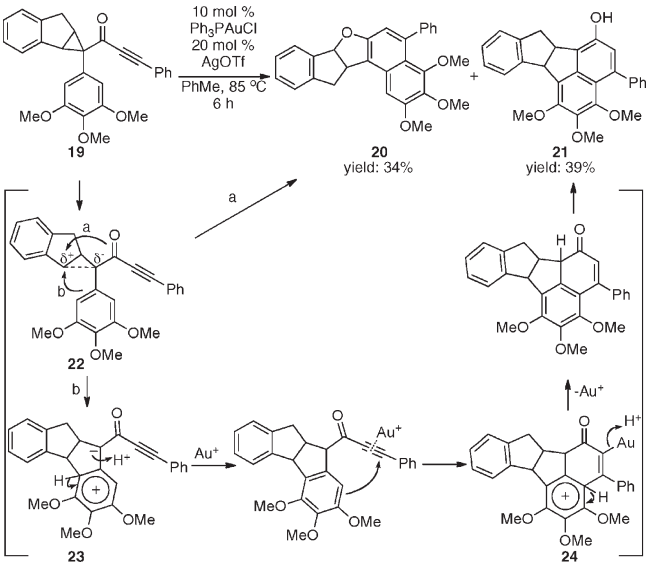
[a] The reactions were monitored by TLC, and heating was stopped when all the starting materials were consumed. [b] Isolated yields.

The reactions with the trimethoxy derivative **14a** were applied to a range of alkenes (Table 3). Different reactivities were observed for the gold-catalyzed reactions of cyclopropane derivatives originating from electron-rich styrenes compared to electron-poor styrenes. The reaction with 4-methoxystyrene provided the polycyclic product **18c** in low yield. In contrast, the reaction with 4-(trifluoromethyl)styrene produced **18d** in excellent yield.

The attempted annulation of **19**, which was derived from **14a** and indene, gave an unexpected result because it produced not only the expected product **20** but also phenol **21** (Scheme 3). The structure of **21** was confirmed by X-ray crystallography.[12] All efforts of converting **20** to **21**, with silver or gold catalysts, or trifluoromethanesulfonic acid, were unsuccessful. This suggested that **20** and **21** are formed by different reaction pathways as indicated in compound **22**: the normal route (route a) constructed **20**, and the other one (route b) would lead to intermediate **23**. This intermediate could then undergo aromatization, protonation, and gold-catalyzed benzannulation to provide **24**. The following proto-demetalation and tautomerization would supply the pentacyclic product **21**.

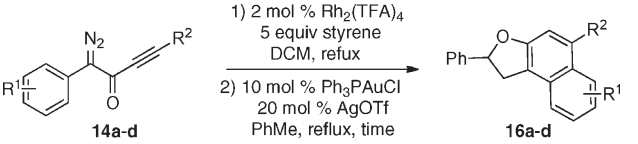
(12) The crystal structures of **16d** and **21** have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 827585 and 827586 respectively.

**Scheme 3.** Conversion of **19** to **20** and **21**




A one-pot procedure was also developed for this sequential reaction (Table 4). This was based on the successful cycloaddition reaction employing the cosolvent system of DCM/toluene. The first step is the rhodium-catalyzed cyclopropanation reaction with DCM as solvent. After finishing this step, the reaction was cooled down to room temperature. To this solution at room temperature was added the silver and gold catalysts and toluene. The resulting mixture was heated to reflux again, and the reaction was monitored by TLC. Heating was stopped after all of the cyclopropane had been consumed. This one-pot procedure resulted in the formation of **16a**–**d** in similar yields to the two-step sequence (Table 2).

**Table 4.** Examples of the One-Pot Procedure




| entry | product | reaction time of step 2 (h) | isolated yield **16a**–**d** (%) |
|---|---|---|---|
| 1 | **16a** | 2 | 74 |
| 2 | **16b** | 2 | 74 |
| 3 | **16c** | 3 | 82 |
| 4 | **16d** | 2 | 72 |

In summary, a class of polycyclic dihydrofuran derivatives was synthesized in high yields by means of three sequential transition-metal-catalyzed reactions. A one-pot procedure for this transformation was also established. This sequence illustrates the potential of carbenoid chemistry to initiate a cascade sequence of reactions. The application of this method to the synthesis of natural products is currently ongoing in our laboratory.

**Acknowledgment.** Financial support of this work by the National Science Foundation (CHE 0750273) is gratefully acknowledged. We thank Dr. Ken Hardcastle, Emory University, for the X-ray crystallographic analysis.

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