Communication

A Au(I)-Catalyzed *N*-Acyl Iminium Ion Cyclization Cascade

Ting Yang, Leonie Campbell, and Darren J. Dixon

More About This Article

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

- Supporting Information
- Links to the 15 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

A Au(I)-Catalyzed *N*-Acyl Iminium Ion Cyclization Cascade

Ting Yang,[†] Leonie Campbell,[§] and Darren J. Dixon*,[†]

School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, U.K. and AstraZeneca,
Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, U.K.

Received June 21, 2007; E-mail: darren.dixon@manchester.ac.uk

The pursuit of synthetic efficiency continues to stimulate the design and development of new concepts and innovative synthetic strategies. One of the most effective ways of achieving synthetic efficiency is to implement reaction cascades, enabling multiple bond-forming and -cleaving events to occur in one synthetic operation, thus circumventing the waste associated with one reaction, one vessel approaches.[1] To this end, gold(I)-catalyzed reaction sequences have taken center stage owing to the metal ion's ability to activate alkyne, alkene, and allene functionality under mild conditions and at low catalyst loadings.[2] The vast majority of the reported cascade sequences employ a single starting material containing multiple functional groups strategically positioned along a chain, terminating with an alkyne functionality. On treatment with gold(I), complexation to the alkyne initiates a reaction sequence leading to carbocyclic or heterocyclic products.[3]

In our search for new and powerful one-pot cascade sequences, we postulated that the gold(I)-catalyzed cyclization of alkynoic acids[4,5] **1** could be exploited as the first step in a sequence leading to an *N*-acyl iminium ion cyclization resulting in the formation of complex multi-ring heterocyclic products of the general structure **2**. Provided irreversible primary amine deactivation of the gold(I) did not occur, we believed the product of cyclization, an activated cyclic enol ester **3**, would be primed for attack by an amine nucleophile **4** present in the vessel. The resulting keto amide **5**, would be poised to undergo Lewis or Brønsted acid-catalyzed *N*-acyl iminium ion formation/cyclization, and we envisaged that the catalyst used in the first stage could also catalyze the second (Scheme 1). With many points of diversity present in the reaction products, this sequence would be a powerful method for both library generation *and* target synthesis. Herein we present our findings.

Proof of concept studies were required to determine the feasibility of the cascade. Alkynoic acid **6** and pyrrolyl ethyl amine **7** were chosen as test substrates.

In the first study, treatment of a toluene solution of 1 mol % AuPPh₃Cl/AgOTf with **6** (1.0 equiv) followed by **7** lead to keto amide **8** in 71% yield. Although the desired heterocyclic product was not formed, these studies confirmed that the cyclization and concomitant attack of amine were feasible. We reasoned, that for the subsequent conversion of **8** to **9** by Au(I), higher temperatures were required to surmount the activation barrier to the *N*-acyl iminium ion. Accordingly, the reaction sequence was repeated using toluene at reflux. After 2 days the desired tricyclic product **9a** was obtained in pleasing 68% yield. The reaction was subsequently optimized to give **9a** in 81% yield by using a temperature ramp (Scheme 2).

With proof of concept established and the desired product isolated in high yield, the scope of reaction cascade was surveyed by probing changes to both the alkynoic acid and the substituted ethyl amine (Chart 1). High yields were obtained when both hexynoic and

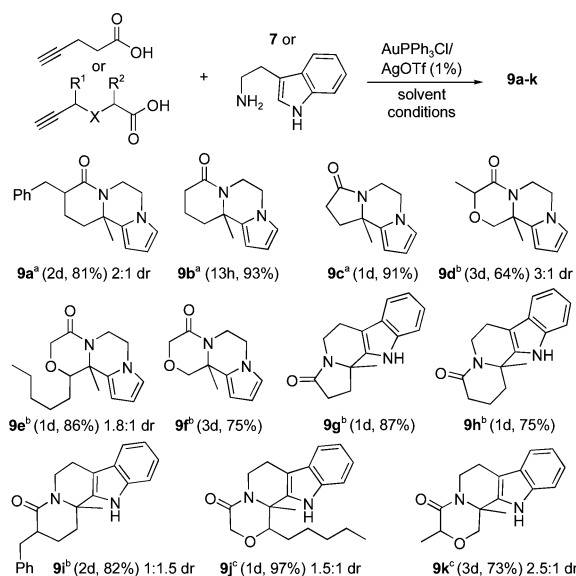**Scheme 1.** Concept of the Au(I)-Catalyzed *N*-Acyl Iminium Ion Cyclization Cascade
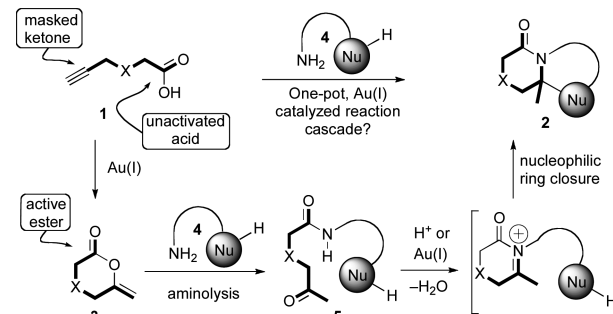
Scheme 2. Proof of Principle Studies[a]
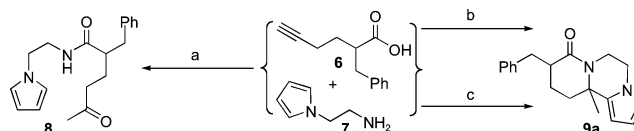
[a] Reaction conditions: (a) AuPPh₃Cl/AgOTf (1 mol %), toluene, room temperature, 71%; (b) AuPPh₃Cl/AgOTf (1 mol %), toluene, reflux, 68%; (c) AuPPh₃Cl/AgOTf (1 mol %), toluene, room temperature, 3 h then reflux, 2 days, 81%.

Chart 1. Scope of the Au(I)-Catalyzed Cascade

9a[a] (2d, 81%) 2:1 dr   **9b**[a] (13h, 93%)   **9c**[a] (1d, 91%)   **9d**[b] (3d, 64%) 3:1 dr

9e[b] (1d, 86%) 1.8:1 dr   **9f**[b] (3d, 75%)   **9g**[b] (1d, 87%)   **9h**[b] (1d, 75%)

9i[b] (2d, 82%) 1:1.5 dr   **9j**[c] (1d, 97%) 1.5:1 dr   **9k**[c] (3d, 73%) 2.5:1 dr

[a] Reaction conditions: toluene, room-temperature 3 h, then reflux. [b] Reaction conditions: toluene, 75 °C, 3 h, then reflux. [c] Reaction conditions: xylene, 75 °C, 3 h, then 125 °C.

pentynoic acids were employed (**9a–c**). Substitution of an oxygen atom into the alkynoic acid chain was tolerated but the reactions required higher temperatures for full conversion (**9d–f** and

[†] The University of Manchester.
[§] AstraZeneca.
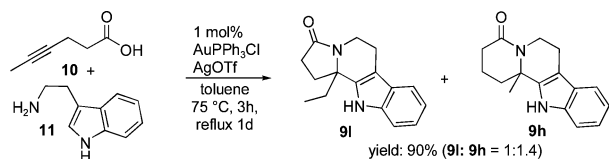
Scheme 3. A Nonterminal Alkynoic Acid Example

yield: 90% (9l: 9h = 1:1.4)

Table 1. Probing the Nature of the Catalyst in the Second Stage *N*-Acyl Iminium Ion Formation/Trap Sequence

entry	additives (time)	conversion/%
1	none (4 days)	0
2	0.0001 mol % HOTf (2.5 days)	50
3	1 mol % AuPPh₃Cl/AgOTf (16 h)	100
4	1 mol % AuPPh₃Cl/AgOTf (1 h)	24
5	0.2 mol % BEMP 1 mol % AuPPh₃Cl/AgOTf (1 h)	11
6	10 mol % BEMP 1 mol % AuPPh₃Cl/AgOTf (2 days)	0

9j−**k**). Spectator alkyl groups adjacent to either the acid or the alkyne functionalities were tolerated (**9a**, **9d,e**, **9i**−**k**). The use of tryptamine as the pendant nucleophilic trap gave good to high yields with the full range of alkynoic acids (**9g**−**k**). Furthermore, when a nonterminal alkynoic acid **10** was tested using tryptamine **11** the cyclization cascade was also successful and a mixture of the possible two regioisomers **9l** and **9h** were obtained in good combined yield (Scheme 3).

To probe the identity of the catalytic species[6] responsible for the *N*-acyl iminium cyclization cascade downstream from the aminolysis reaction, ketoamide **12** was synthesized and subjected to a range of reaction conditions (Table 1). Boiling in toluene for 4 days resulted in no conversion to the desired product. Boiling in toluene with 0.0001 mol % trifluoromethane sulfonic acid for 2.5 days resulted in 50% conversion to product **9c**. Boiling in toluene containing 0.2% of the strong phosphorine base 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) and 1 mol % AuPPh₃Cl/AgOTf resulted in product formation albeit at a retarded rate relative to a control experiment (entry 5 vs 4). Boiling in toluene containing 10 mol % BEMP and 1 mol % AuPPh₃Cl/AgOTf resulted in no conversion to the product **9c**. As the catalytic activity of gold(I) in the cyclization step is *diminished, but not eliminated*[7] by the presence of 10 mol % BEMP, these results suggest the gold species is providing Brønsted acidity *not* Lewis acidity to facilitate *N*-acyl iminium ion formation. Entry 5 suggests that residual TfOH is not responsible as this would be effectively quenched by BEMP (at 0.2 mol %), and thus we postulate that Lewis acid-assisted Brønsted acid catalysis,[8] resulting from the 1% gold in the presence of either water (formed in the reaction) or another proton donor such as **12** or its isomer iso-**12**, provides the activation for the second stage of the cyclization cascade.

In summary, we have developed a one-pot Au(I)-catalyzed *N*-acyl iminium ion cyclization cascade leading to the efficient synthesis of complex multi-ring heterocyclic compounds. Further one-pot reaction cascade sequences catalyzed by single and multiple catalytic entities are under investigation and the results will be reported in due course.

Supporting Information Available: Experimental procedures, and spectral data for compounds **8**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (b) Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(2) For reviews of homogeneous gold-catalyzed reactions, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Hashmi, A. S. K. *Catal. Today* **2007**, *122* (3−4), 211. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (d) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (e) Arcadi, A.; Di Giuseppe, S. D. *Curr. Org. Chem.* **2004**, *8*, 795. (f) Hoffman-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (g) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6690. (h) Dyker, G. *Angew. Chem.* **2000**, *112*, 4407; *Angew. Chem., Int. Ed.* **2000**, *39*, 4237. (i) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. For general surveys of organogold chemistry, see: (j) Puddephatt, R. J. in *Comprehensive Organometallic Chemistry*, 1st ed. Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 2, p 765. (k) Puddephatt, R. J. *The Chemistry of Gold*; Elsevier: Amsterdam, 1978.

(3) For selected examples see: (a) Witham, C. A.; Mauléon, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (c) Lin, C.-C.; Teng, T.-M.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2007**, *129*, 3798. (d) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912. (e) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207. (f) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (g) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480. (h) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274. (i) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (j) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (k) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452. (l) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (m) Fürstner, A.; Hannen P. *Chem. Eur. J.* **2006**, *12*, 3006. (n) Hildebrandt, D.; Dyker, G. *J. Org. Chem.* **2006**, *71*, 6728. (o) Asao, N. *Synlett* **2006**, *11*, 1645. (p) Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2006**, *348*, 1283. (q) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejović, E.; Frost, T. M.; Miehlich, B.; Frey, W.; Bats, J. W. *Chem. Eur. J.* **2006**, *12*, 5806. (r) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. (s) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (t) Marion, N.; Díez-González, S.; Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647. (u) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.

(4) (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Harkat, H.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273. (c) Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *ARKIVOC* **2007**, (*v*), 67.

(5) See also the Au(I)-catalyzed cyclization of carbonates or carbamates: (a) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717. (b) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

(6) Both Lewis acid and Brønsted acids are able to catalyze the final stage, see: (a) Rose, M. D.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *J. Org. Chem.* **2007**, *72*, 538. (b) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373. (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (d) Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465. (e) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (f) Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron* **2004**, *60*, 12075. (g) Nakamura, S.; Tanaka, M.; Taniguchi, T.; Uchiyama, M.; Ohwada, T. *Org. Lett.* **2003**, *5*, 2087. (h) Ardeo, A.; García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2003**, *44*, 8445. (i) Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888. (j) Dittami, J. P.; Xu, F.; Qi, H.; Martin, M. W.; Bordner, J.; Decosta, D. L.; Kiplinger, J.; Reiche, P.; Ware, R. *Tetrahedron Lett.* **1995**, *36*, 4197. (k) Shiroyan, F. R.; Terzyan, A. G.; Khazhakyan, L. V.; Tatevosyan, G. T. *Arm. Khim. Zh.* **1968**, *21* (1), 44. For an excellent review see: (l) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(7) Treatment of 1 mol% AuPPh₃Cl/AgOTf in toluene with 10 mol% BEMP followed by hexynoic acid and refluxing for 2 hours resulted in 60% conversion to the enol lactone cyclization product of type **3**.

(8) For selected examples of where Lewis acid-assisted Brønsted acids were considered as effective proton donors in enantioselective protonations and enantioselective polyene cyclizations, see: (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, *2*, 177. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (c) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (d) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (e) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (f) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (g) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551.

JA074550+