J|A|C|S
COMMUNICATIONS

Published on Web 05/17/2006

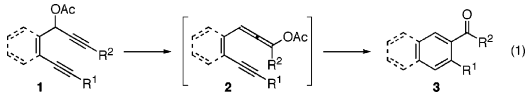
Synthesis of Aromatic Ketones by a Transition Metal-Catalyzed Tandem Sequence

Jing Zhao, Colin O. Hughes, and F. Dean Toste*

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

Received March 21, 2006; E-mail: fdtoste@berkeley.edu

The importance of aromatic compounds continues to inspire the development of general methods for the regioselective construction of benzenes. Traditionally, this has been accomplished by regioselective introduction of substituents onto a preexisting aromatic ring.[1] Transition metal-mediated reactions, such as [2 + 2 + 2] cyclotrimerization of alkynes and [4 + 2] benzannulations of enynes, for the de novo synthesis of aromatic compounds offer powerful alternatives.[2] Additionally, metal-promoted versions of the Bergman cyclization of endiynes have also been investigated.[3] On the other hand, transition metal catalysis of the related Myers−Saito cyclization of enyne allenes has received considerably less attention.[4] We hypothesized that this rearrangement might be catalyzed by transition metal-promoted alkyne activation; however, the utility of this reaction is contingent on an efficient synthesis of the enyne allene precursor. Therefore, we envisioned the development of a catalytic Myers−Saito cyclization for the synthesis of aryl ketones (**3**) in which the required enyne allenes (**2**) are prepared in situ through a metal-catalyzed sigmatropic rearrangement (eq 1).



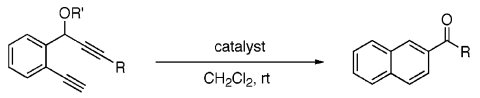
(1)

In light of our recent success employing Ph_3PAuCl with $AgSbF_6$ in methylene chloride for carbon−carbon bond formation,[5] we chose this catalyst system in preliminary studies of the proposed tandem reaction (Table 1). Treatment of propargyl acetate **4** with 5% cationic triphenylphosphinegold(I) afforded the desired naphthyl ketone **5a** in 25% yield (entry 1).[6] A control experiment employing only 5% $AgSbF_6$ as the sole catalyst in methylene chloride only produced a small amount of the desired naphthyl ketone **5a** after 11 h at room temperature (entry 2).[7] Given the presence of triphenylphosphine in the gold-catalyzed reaction, an additional control experiment using 4% PPh_3 and 10% $AgSbF_6$ was conducted. We were surprised to find that under these conditions the desired ketone was isolated in 70% yield (entry 3).[8] We hypothesized that the silver catalyst was being consumed by the acetic acid generated during the course of the reaction. Therefore, addition of MgO, as an acid scavenger, further improved the yield of the Ag(I)-catalyzed reaction to 84% (entry 4).[9] In sharp contrast, the silver catalyst proved ineffective for the rearrangement of pivaloate **4b** (entry 6). Thus, a second catalyst system, employing cationic tri-*tert*-butylphosphinegold(I) in methylene chloride/acetonitrile, was developed and afforded the desired diaryl ketone **5b** in 71% yield (entry 9).

In view of the low cost and simplicity of silver salts, we first set out to define the scope of the silver(I)-catalyzed aromatic ketone synthesis (Table 2). Using only 5 mol % of $AgSbF_6$ with 2 mol % of PPh_3 in CH_2Cl_2, propargyl pivaloates **6a**−**j** cleanly afforded products **7a**−**j** after 11 h at room temperature. The yields remain good to high with electron-withdrawing (entry 3) and electron-donating (entry 5) substituents on the starting aromatic ring. Both terminal (entries 1, 8, and 9) and internal alkynes participated in the Ag(I)-catalyzed tandem cyclization, allowing the preparation of 2-substituted naphthyl ketones and aldehydes. Notably, the Ag(I)-catalyzed tandem reaction proceeded smoothly with substrates containing a cyclopropyl ring (entry 7) and an additional alkynyl group (entry 10). Notably, the regioselectivity of this reaction is complementary to the reported Lewis acid-catalyzed naphthyl ketone synthesis.[6d−f]

The silver-catalyzed reaction also allows for the synthesis of more complex aromatic systems. For example pivolate **8** underwent Ag(I)-catalysis to furnish binaphthyl ketone **9** in 66% yield (eq 2).[10] Additionally substituted anthracene **11** was prepared in 40% yield through a silver-catalyzed double cyclization of diester **10** (eq 3).

Table 1. Catalyst Efficiency for Naphthyl Ketone Synthesis



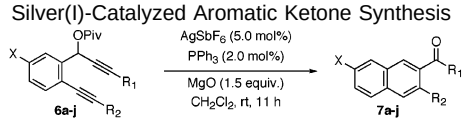
4a R = Me, R' = Ac
b R = Ph, R' = Piv

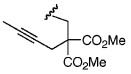
5a R = Me
b R = Ph

entry	substrate	catalyst	additive (equiv)	yield[a] (%)
1	**4a**	5% Ph_3PAuCl, 5% $AgSbF_6$	−	25
2	**4a**	5% $AgSbF_6$	−	<5
3	**4a**	10% $AgSbF_6$, 4% PPh_3	−	70
4	**4a**	10% $AgSbF_6$, 4% PPh_3	MgO (1.5)	84
5	**4a**	10% $AgSbF_6$, 10% PPh_3	MgO (1.5)	0
6	**4b**	10% $AgSbF_6$, 4% PPh_3	MgO (1.5)	0
7	**4b**	5% Ph_3PAuCl, 5% $AgSbF_6$	−	22
8	**4b**	5% *t*-Bu_3PAuCl, 5% $AgSbF_6$	−	30
9	**4b**	5% *t*-Bu_3PAuCl, 5% $AgSbF_6$	CH_3CN[b]	71

[a] Determined by ^1H NMR. [b] Reaction conducted in 1:1 CH_2Cl_2:CH_3CN.

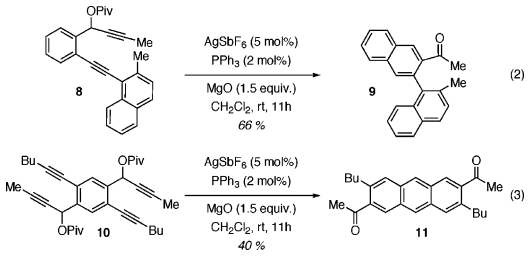
Table 2. Silver(I)-Catalyzed Aromatic Ketone Synthesis



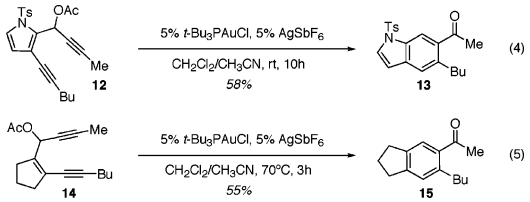
entry	*cmpd*	R_1	R_2	*X*	*% yield*[a]
1	**a**	Me	H	H	82[b]
2	**b**	Me	Bu	H	64
3	**c**	Me	Bu	CF_3	94
4	**d**	Me	Bu	Cl	53
5	**e**	Me	Bu	OMe	64
6	**f**	Me	Ph	H	62[c]
7	**g**	Me		H	60
8	**h**	H	H	H	63[d]
9	**i**	Bu	H	H	83
10	**j**	Me		H	51

[a] Isolated yield after column chromatography. [b] Corresponding propargyl acetate gave 80% yield of **7a**. [c] Analogous 5% $Ph_3PAuCl/AgSbF_6$-catalyzed reaction gave 48% yield. [d] Based on consumed starting material; conversion: 70%.

10.1021/ja061942s CCC: $33.50



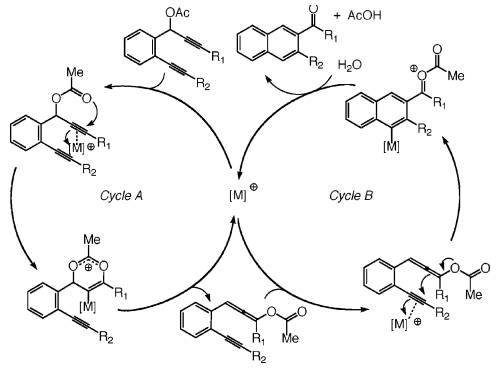
In many cases the silver-catalyzed naphthyl ketone synthesis proceeded as well or better than the analogous gold(I)-catalyzed reaction. For example, the conversion from **6f** to **7f** (entry 6) was catalyzed by 5% cationic triphenylphosphinegold(I) to afford **7f** in 48% yield; however, all attempts at silver-catalyzed rearrangement of pyrrole **12** and enediyne **14** failed to produce the desired aromatic ketones. In these cases, the analogous tri-*tert*-butylphosphinegold(I)-catalyzed reactions delivered indole[11] **13** and acetophenone **15** in 58 and 55% yield, respectively (eqs 4, 5).



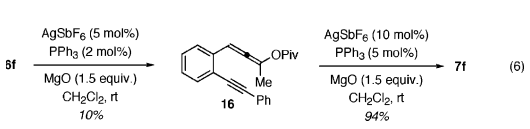
Notably, there is no preexisting aromatic ring required for the latter transformation.

A mechanism involving sequential rearrangements promoted by transition-metal activation of the alkynes is envisioned (Scheme 1).[12] First, coordination of the metal to the propargyl ester produces

Scheme 1. Proposed Mechanism



enyne allene through a [3,3]-sigmatropic rearrangement (*Cycle A)*. Activation of the remaining alkyne induces 6-*endo*-dig addition of the allenyl acetate (*Cycle* B).[13] In accord with this hypothesis, enyne allene **16** could be isolated from the silver-catalyzed reaction of **6f** (eq 6). Resubjecting **16** to the reaction conditions afforded expected naphthyl ketone **7f** in 94% yield (eq 6).



In conclusion, we have developed a transition metal-catalyzed tandem [3,3]-sigmatropic rearrangement/formal Myers−Saito cyclization of propargyl esters to form aromatic ketones. A mechanism in which the metal catalyzes both of these processes through alkyne activation is proposed. Both simple Ag(I) and Au(I) are effective catalysts for this air- and moisture-tolerant transformation that is characterized by mild conditions and excellent functional group tolerance.

Acknowledgment. We gratefully acknowledge the University of California, Berkeley, NIHGMS (R01 GM073932-01), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, Eli Lilly & Co., Pfizer, AstraZeneca, and Abbott 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) Astruc, D., Ed. *Modern Arene Chemistry*; Weinheim: Wiley-VCH: 2002. (b) Rossi, R. A.; Pierini, A. B.; Santiago, A. N. *Org. React.* **1999**, *54*, 1−271. (c) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic: San Diego, 1994. (d) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: Chichester, U.K., 1990. (e) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. For applications of C−H activation to the synthesis of polysubstituted arenes see: (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

(2) For reviews see: (a) Saito, S.; Yamamoto, Y., *Chem. Rev.* **2000**, *100*, 2901. (b) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (c) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, *22*, 4741.

(3) (a) Ohe, K.; Kojima, M.-a.; Yohehara, K.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1823. (b) Manabe, T.; Yanagi, S.-I.; Ohe, K.; Uemura, S. *Organometallics* **1998**, *17*, 2942. (c) Odedra, A.; Wu, C.-J.; Pratap, T. P.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406. (d) O'Connor, J. M.; Friese, S. J.; Rodgers, B. L. *J. Am. Chem*. Soc. **2005**, *127*, 16342. (e) Lo, C.-Y.; Kumar, M. P.; Chang, H.-K.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2005**, *70*, 10482. (f) Taduri, B. P.; Ran, Y.-F.; Huang, C.-W.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 883.

(4) (a) Myers, A. G.; Harrington, P. M.; Kwon, B. M. *J. Am. Chem. Soc.* **1992**, *114*, 1086. (b) Sugiyama, H.; Fujiwara, T.; Kawabata, H.; Yoda, N.; Hirayama, N.; Saito, I. *J. Am. Chem.* Soc. **1992**, *114*, 5573. Mo-mediated carbonylation of allenyl arene-ynes gave byproducts derived from the Myers−Saito rearrangement, see: (c) Datta, S.; Liu, R.-S. *Tetrahedron Lett.* **2005**, *46*, 7985.

(5) (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, 126, 10858. (d) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (e) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (f) Shi, X. D.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (g) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350.

(6) For Au(III)-catalyzed benzannulations see: (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769. (c) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809. (d) Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfe, M.; Frey, W.; Bats, J. W. *Angew Chem., Int. Ed.* **2005**, *44*, 2798. (e) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, 126, 7458. (f) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (g) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc*. **2002**, *124*, 12650.

(7) Reaction of **4a** with 5% $Sc(OTf)_3$ 5% $PdCl_2(MeCN)_2$, 10% CuBr or 10% Cu(OTf) ·$PhCH_3$ did not afford **5a**; 5% $PtCl_4$ gave 13% of **5a**.

(8) The nature of the catalytically active Ag(I) species is not known at this time. Monitoring the reaction by ^{31}P NMR shows the formation of (Ph_3P)-$AgBF_4$; however, independently prepared $(Ph_3P)AgBF_4$ does not catalyze the conversion of **4a** to **5a** at room temperature.

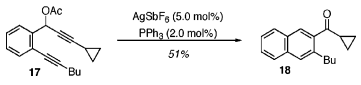
(9) In accord with this hypothesis, 10% AgOAc does not catalyze the reaction. For use of MgO as an acid scavenger, see: Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

(10) Ag(I)-catalyzed reaction of enantioenriched **8** (93% ee) gave racemic **9**.

(11) For synthesis of indoles by [4 + 2]-benzannulation see: Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc*. **2005**, *127*, 5776 and references therein.

(12) For recent examples of Ag(I)- or Au(I)-catalyzed tandem reactions initiated by [3,3]-rearrangements of propargyl acetates see: (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (b) Sromek, A. W.; Kelin, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280.

(13) A mechanism involving a Myers−Saito diradical intermediate is also possible; however, no cyclopropyl ring-opening (see: Dopico, P. G.; Finn, M. G. *Tetrahedron* **1999**, *55*, 29) was observed in the Ag-catalyzed rearrangement of **17** to cyclopropyl ketone **18**.



JA061942S