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Gold- and Silver-Catalyzed Highly Regioselective Addition of Active Methylenes to Dienes, Triene, and Cyclic Enol Ethers

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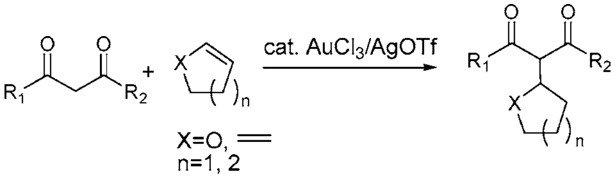
ABSTRACT

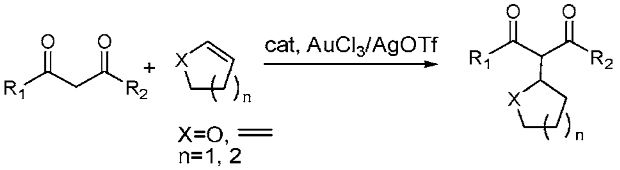


The combination of gold and silver salts catalyzed the addition of active methylenes to dienes, triene, and cyclic enol ethers with high regioselectivity. The catalysis provides a synthetically useful method for functionalized carbocycles and heterocycles through a highly atom-economical carbon–carbon bond formation.

Carbon−carbon bond formation is the essence of organic synthesis. A fundamental method for forming a carbon−carbon bond is via nucleophilic substitution.[1] On the other hand, recent emphasis in green chemistry[2] has called for the development of innovative chemical reactions based on "atom-economy",[3] such as an overall addition reaction. In an effort to develop such reactions, we recently discovered a highly efficient addition of active methylenes to styrene derivatives catalyzed by the combination of AuCl$_3$−AgOTf.[4] This reaction provided an efficient and catalytic alternative to the commonly used stoichiometric alkylation of 1,3-dicarbonyl compounds.[5] The efficiency of the catalysis led us to explore the scope of such additions of alkenes other than styrenes, which could have wide synthetic applications. A large class of synthetically important compounds is carbocycles and heterocycles.[6] There has been sustained effort in developing efficient methods in synthesizing and functionalizing cyclic compounds. Herein, we wish to report that cyclic alkenes and dienes[7] undergo highly regioselective addition with active methylenes efficiently (Scheme 1). The method generates highly useful synthetic intermediates for various applications.

Initial studies were conducted using dibenzoylmethane and 1,3-cyclooctadiene as a prototype reaction (Table 1). The combination of AuCl$_3$[8] and AgOTf[9] in CH$_2$Cl$_2$ provided product **1** as a single isomer in good yield (Table 1, entry

Scheme 1



[†] To whom crystallography inquiries should be addressed.

(1) Trost, B. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; pp 2−267.

(2) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

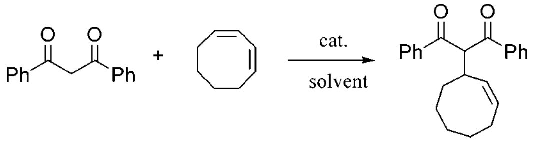
(3) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(4) Yao, X. Q.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 6884.

(5) For similar alternatives, see: (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (c) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

10.1021/ol047543o CCC: $30.25

Table 1. Addition of Dibenzoylmethane to Cyclooctadiene Catalyzed by Gold and Silver



entry[a]	catalyst[b]	solvent	yield[c] (%)
1	$AuCl_3$/AgOTf	CH_2Cl_2	61
2	$(PPh_3)AuCl$/AgOTf	CH_2Cl_2	trace
3	$AuCl_3$/AgOTf	DCE[d]	38
4	$AuCl_3$/AgOTf	MeCN[d]	25
5	$AuCl_3$/AgOTf	$MeNO_2$[d]	55
6	$AuCl_3$/AgOTf	dioxane[d]	26

[a] Reactions were performed in dry dichloromethane. [b] Alkenes were added by syringe pump. [c] Isolated yield. [d] The position of the double bonds was confirmed by COSY-NMR. [e] Reactions were run at 0 °C. [f] The ratio of the two diastereoisomers was determined by ^{1}H NMR.

1). The position of the double bond was confirmed by X-ray crystallography analysis (see Figure 1). The use of (PPh_3)-AuCl (entry 2) instead of $AuCl_3$ as the catalyst led to a very low conversion. There is no increase in yield when the reaction was conducted under refluxing temperature with various solvents (entries 3−6). The use of a more coordinating solvent decreased the yield dramatically (entry 4). Thus, the use of $AuCl_3$ and AgOTf in CH_2Cl_2 at room temperature was found to be the most efficient and was used as the standard conditions.

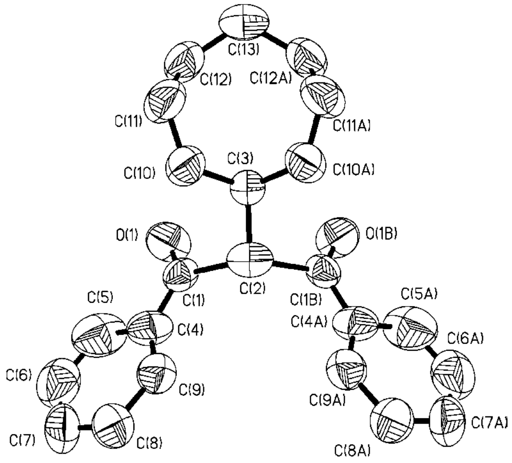
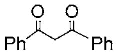
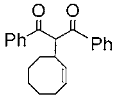
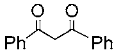
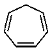
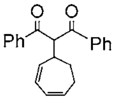
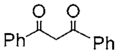
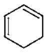
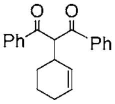
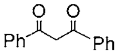
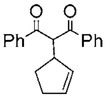
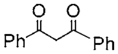
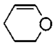
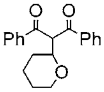
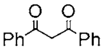
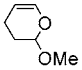
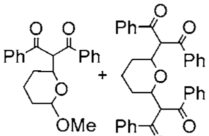
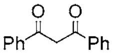
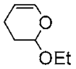
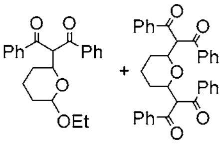
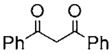
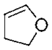
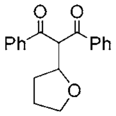
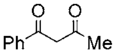
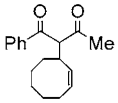
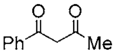
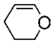
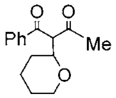


Figure 1. ORTEP diagram of **1** showing atoms related by crystallographically imposed reflection symmetry for the plane defined by C(2), C(3), and C(13). Important bond distances include C(3)−C(10) 1.493(5); C(10)−C(11) 1.387(8); C(11)−C(12) 1.476 (8); C(12)−C(13) 1.5337) Å. Hydrogen atoms have been ommitted for clarity, and 45% probability ellipsoids are shown.

Table 2. Gold-Catalyzed Reaction of Cyclic Alkenes with β-Diketone[a]

entry	β-diketone	cyclic alkene[b]	product	yield (%)[c]
1				65
2^d				42
3^e				51
4^e				50
5				68
6			 47% (1.7:1)[f] 15%	62
7			 44% (1.8:1)[f] 15%	59
8				58
9				38 (1.4:1)[f]
10				35 (1.2:1)[f]

[a] Reactions were performed in dry dichloromethane. [b] Alkenes were added by syringe pump. [c] Isolated yield. [d] The position of the double bonds was confirmed by COSY-NMR. [e] Reactions were run at 0 °C. [f] The ratio of the two diastereoisomers was determined by ^{1}H NMR.

Subsequently, various cyclic dienes and cyclic enol ethers were reacted with dibenzoylmethane (entry 1−8) and 1-benzoylacetone (entry 9−10) under the standard conditions (Table 2). It is noteworthy to mention that the addition to a triene (entry 2) is also selective to generate a diene product. The reaction must be carried out under low temperature in some cases in order to prevent polymerization or dimerization of the diene (Table 2, entries 3 and 4). The use of cyclic

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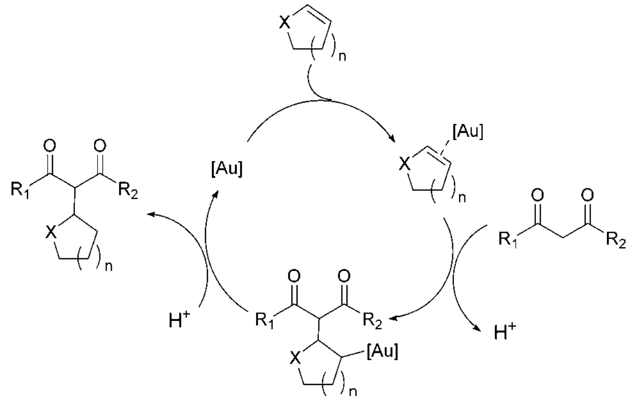
(6) For a recent review, see: Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(7) During the preparation of this manuscript, Hartwig and co-workers reported a similar reaction of dienes with palladium. See: Leitner, A.; Larsen, J.; Steffens. C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552.

alkenes bearing a heteroatom[10] (Table 2, entries 5−8) is also selective. However, addition of dibenzoylmethane to an ether-substituted DHP (Table 2, entries 6 and 7) led to a significant amount of bis-alkylation products. The use of simple cyclic and acyclic alkenes led to very low conversions while acyclic conjugated dienes led to a complicated mixture that is still under investigation. The use of sterically hindered dienes or less activated methylene (such as 2,4-pentadione and cyclic diketones) also led to low conversions under the present conditions.

A tentative mechanism for the addition is proposed in Scheme 2. The coordination of electron-rich alkenes with Au(III) activated the alkenes, which was followed by the addition of the 1,3-diketone−Au(III) complex to generate a gold intermediate. Protonolysis of the C−Au bond generated the final product.[11]

Scheme 2. Tentative Mechanism for the Addition Reaction.



In conclusion, we have developed a selective addition of 1,3-dicarbonyls to cyclic alkenes and dienes. Work is now in progress in our laboratories to improve the scope and yields of the reactions and to probe the mechanism.

Acknowledgment. We are grateful to Canada Research Chair foundation (to D.S.B. and C.J.L.), NSERC, CFI, Merck Frosst Canada, Inc., and McGill University for support of our research.

Supporting Information Available: Representative experimental procedure and the characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For other examples of gold-catalyzed reactions, see: Ito, Y.; Sawamura, T.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, *9*, 4339. Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563. Deetlefs, M.; Raubenheimer, H. G.; Esterhuygen, M. W. *Catal. Today* **2002**, *72*, 29. Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964. Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *34*, 1247. Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarre, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546. Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239. Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556.

(9) For other examples of silver-catalyzed reactions, see: Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475. Patmore, N. J.; Hague, C.; Cotgreave, J. H.; Mahon, M. F.; Frost, C. G.; Weller, A. S. *Chem. Eur. J.* **2002**, *8*, 2088. Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron. Lett.* **1991**, *32*, 2799. Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. Koseki, Y.; Omino, K.; Anzai, S.; Nagasaka, T. *Tetrahedron Lett.* **2000**, *41*, 2377. Xu, C.; Negishi, E. I. *Tetrahedron Lett.* **1999**, *40*, 431. Wipf, P.; Methot, J. L. *Org. Lett.* **1999**, *1*, 1253. Dalla, V.; Pale, P. *New J. Chem.* **1999**, *23*, 803. Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. Burgess, K. *Chem. Ind.* **1999**, *18*, 716. Bianchini, C.; Glendenning, L. *Chemtracts* **1997**, *10*, 339.

(10) Previously, the addition of activated methylene to dihydrofuran and pyrans catalyzed by trifluoroacetic acid has been reported; see: Bihovsky, R.; Kumar, M. U.; Ding, S.; Goyal, A. *J. Org. Chem.* **1989**, *54*, 4291.

(11) We thank the reviewers for their suggestions regarding this mechanism.