

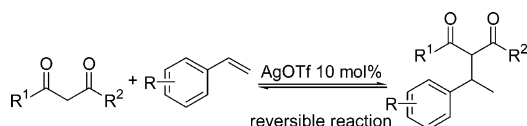
## Highly Efficient, Reversible Addition of Activated Methylene Compounds to Styrene Derivatives Catalyzed by Silver Catalysts

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A highly efficient inter- and intramolecular addition of 1,3-diketone/ $\beta$ -ketoester to alkenes was developed by using silver catalysts. Silver triflate shows the highest catalytic activity. The reaction is reversible through the cleavage of a carbon-carbon bond by silver at an elevated temperature.

Carbon-carbon bond-forming reactions are among the most important types of bond constructions in organic chemistry. As one of the most common methodologies for forming a carbon-carbon bond, the alkylation of 1,3-dicarbonyl compounds usually requires the use of a stoichiometric amount of base and an organic halide, which has an overall low atom economy.<sup>1</sup> An alternative reaction, via a catalytic addition of 1,3-dicarbonyl compounds to alkenes, would provide a more atom-economical approach and has attracted much interest in recent years.

Recently, Widenhofer and Yang reported an elegant intramolecular hydroalkylation of alkenes by carbonyl compounds catalyzed by palladium.<sup>2</sup> Compared with the intramolecular addition, intermolecular hydroalkylation of alkenes involving such activated methylene C-H bonds have been rarely reported. Very recently, Widenhofer reported a platinum- or palladium-catalyzed intermolecular addition of ethylene with  $\beta$ -diketones.<sup>3</sup> On the other hand, Hartwig reported a palladium-catalyzed addition of mono- and dicarbonyl compounds to conjugated dienes.<sup>4</sup>

Previously, we reported a highly effective intermolecular addition of activated methylene compounds to alkenes

TABLE 1. Addition of Pentane-2,4-dione to Styrene Catalyzed by Silver

entry	catalyst <sup>a</sup>	conditions	yield <sup>b</sup> (%)
1	AgI	water, 100 °C	0
2	AgI	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	0
3	AgOTf	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	76 <sup>c</sup>
4	AgOTf	water, 100 °C	0
5	AgOTf	CH <sub>2</sub> Cl <sub>2</sub> , 40 °C	<5
6	AgOTf	DCE, 80 °C	71 <sup>c</sup>
7	AgOTf	dioxane, 100 °C	0
8	AgOTf	[bmim]OTf, 100 °C	0
9	AgNO <sub>3</sub>	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	trace
10	AgBF <sub>4</sub>	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	0
11	AgSbF <sub>6</sub>	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	trace
12	AgCO <sub>2</sub> CF <sub>3</sub>	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	0
13	AgCN	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	0
14	Ag <sub>2</sub> SO <sub>4</sub>	CH <sub>3</sub> NO <sub>2</sub> , 100 °C	0

<sup>a</sup> Conditions: 10 mol % of silver salt was used. <sup>b</sup> Detected by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield.

by using AuCl<sub>3</sub>/AgOTf as combined catalyst.<sup>5,6</sup> In this reaction, silver triflate was used to exchange the anion with gold chloride to activate the gold species. We proposed that gold(I) is the catalytic species generated in situ from the reduction of Au(III) by the activated methylene.

The success of the addition of diketone to styrenes catalyzed by gold(I) species encouraged us to attempt the reaction using silver(I) compounds as catalyst. Traditionally, silver(I) and silver(II) complexes are used as stoichiometric oxidants for the oxidation of various organic or inorganic substrates. In recent years, more and more reports used silver(I) complexes as catalysts in oxidation or group-transfer reactions.<sup>7</sup> Although silver(I) was often used as a Lewis acid,<sup>7a-c</sup> recent studies have shown that silver species exhibited interesting catalytic activities functioning as a transition metal catalyst.<sup>7d-j</sup> We once reported an A<sup>3</sup>-coupling (aldehyde-alkyne-amine) reaction in water or ionic liquids using silver(I) compounds as catalysts, in which the silver(I) catalyst shows catalytic character and reactivity similar to gold(I) catalyst.<sup>8,9</sup> Herein, we wish to describe a silver-catalyzed inter- and intramolecular addition of 1,3-diketone/ $\beta$ -ketoester to alkenes. The silver-catalyzed reaction was found to be

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

(6) Nguyen, R.-V.; Yao, X. Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673.

(7) For some recent examples, as Lewis acid: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734-3735. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (c) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 12766. Others: (d) Cirakovic, J.; Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 9370. (e) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalnage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270. (f) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. (g) Clark, T. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522. (h) Dias, H. V. R.; Browning, R. G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2004**, *23*, 1200. (i) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (j) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993.

(8) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473.

(9) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443.



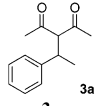

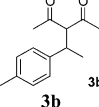
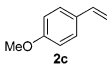
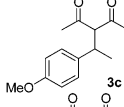

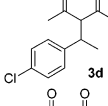

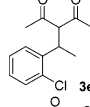

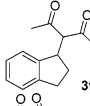

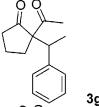
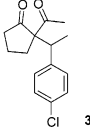

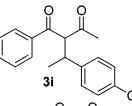
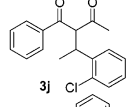
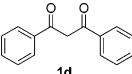
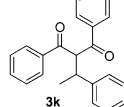
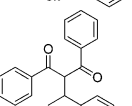
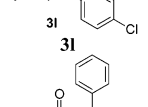

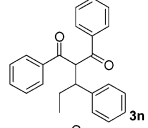

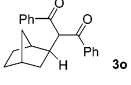
(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(2) (a) Pei, T.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290. (b) Pei, T.; Widenhofer, R. A. *Chem. Commun.* **2002**, 650. (c) Qian, H.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056. (d) Pei, T.; Wang, X.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (e) Wang, X.; Pei, T.; Han, X.; Widenhofer, R. A. *Org. Lett.* **2003**, *5*, 2699. (f) Yang, D.; Li, J. H.; Gao, Q.; Yan, Y. L. *Org. Lett.* **2003**, *5*, 2869.

(3) Wang, X.; Widenhofer, R. A. *Chem. Commun.* **2004**, 660.

(4) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552.

TABLE 2. Addition of  $\beta$ -Diketone to Alkenes Catalyzed by AgOTf

entry	$\beta$ -diketone	alkenes <sup>a</sup>	solvent	product	yield (%) <sup>b</sup>
1	 <b>1a</b>	 <b>2a</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3a</b>	76
2	<b>1a</b>	<b>2a</b>	DCE	<b>3a</b>	71
3	<b>1a</b>	 <b>2b</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3b</b>	72
4	<b>1a</b>	<b>2b</b>	DCE	<b>3b</b>	79
5	<b>1a</b>	 <b>2c</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3c</b>	trace
6	<b>1a</b>	 <b>2d</b>	DCE	 <b>3d</b>	61
7 <sup>c</sup>	<b>1a</b>	 <b>2e</b>	DCE	 <b>3e</b>	27
8	<b>1a</b>	 <b>2f</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3f</b>	trace
9	 <b>1b</b>	<b>2a</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3g</b>	61 (1:1) <sup>c</sup>
10	<b>1b</b>	<b>2d</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3h</b>	49 (1:1) <sup>c</sup>
11	 <b>1c</b>	<b>2d</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3i</b>	92 (1:1) <sup>c</sup>
12	<b>1c</b>	<b>2e</b>	CH <sub>3</sub> NO <sub>2</sub>	 <b>3j</b>	61 (1:1) <sup>c</sup>
13	 <b>1d</b>	<b>2a</b>	DCE	 <b>3k</b>	62
14	<b>1d</b>	<b>2d</b>	DCE	 <b>3l</b>	75
15	<b>1d</b>	<b>2d</b>	CH <sub>3</sub> NO <sub>2</sub>	<b>3l</b>	trace
16	<b>1d</b>	<b>2e</b>	DCE	 <b>3m</b>	84
17	<b>1d</b>	 <b>2g</b>	DCE	 <b>3n</b>	23 <sup>d</sup>
18	<b>1d</b>	 <b>2h</b>	DCE	 <b>3o</b>	74

<sup>a</sup> Conditions: 1.5 equiv or 2 equiv of styrene was added. <sup>b</sup> Isolated yield. <sup>c</sup> The ratio was determined by <sup>1</sup>H NMR. <sup>d</sup> The conversion of **1d** is 31%.

**TABLE 3. Intramolecular Addition of 1,3-Dicarbonyl Compounds to Alkenes Catalyzed by AgOTf<sup>a</sup>**

entry	substrate	product	yield (%) <sup>b</sup>
1			81 <sup>c</sup>
2			86 <sup>c</sup>
3			74 (75:25) <sup>d</sup>
4			79 <sup>c</sup>
5			24 <sup>e</sup>
6			15 <sup>e, f</sup>

<sup>a</sup> Conditions: 10 mol % of AgOTf was used. <sup>b</sup> Isolated yield. <sup>c</sup> In these cases, only one diastereomer was observed. <sup>d</sup> The ratio was measured by GC. <sup>e</sup> The configuration of C=C was determined by NOESY. <sup>f</sup> The five-membered ring structure was determined by H-H COSY.

different from the gold-catalyzed reaction. The addition reaction is reversible under the silver-catalyzed conditions.

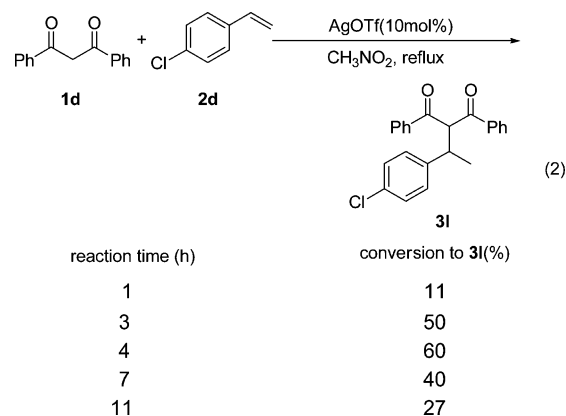
As the first attempt, the addition of 2,4-pentadione with styrene was selected as the prototype. Various conditions involving different solvents and several silver-(I) species were examined.

As shown in Table 1, silver catalysts exhibited good catalytic activity toward the reaction at a temperature higher than that for the combined AuCl<sub>3</sub>/AgOTf catalytic system. The best result was achieved using AgOTf as the catalyst in nitromethane (entry 3). A similar result was observed in DCE solution with the same catalyst (entry 6). It is worth noting that there is no reaction at all when water or ionic liquid was used as solvent (entries 4 and 8). Furthermore, the anion of the silver salt proved to be very important for the reaction; only triflate shows good catalytic activity.

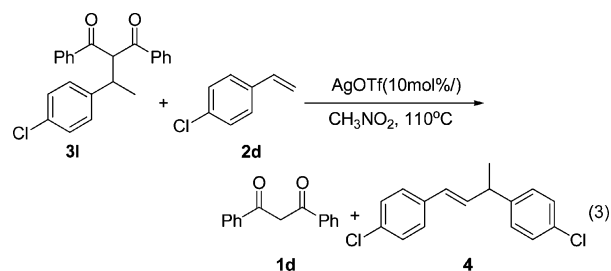
Subsequently, the reaction was examined on a range of substrates. Various diketones were effectively added on to styrene and styrene derivatives under the current reaction conditions (Table 2). It is interesting to note that only a trace amount of the addition product was observed when more reactive styrene derivatives were utilized, which is completely opposite to what we have expected (entries 4 and 6, Table 2).<sup>5</sup> Compared with the gold catalyzed reaction, the silver catalysis is also more sensitive to steric effects.

Generally speaking, the results obtained with nitromethane or DCE as solvent are similar for most substrates (entry 1 vs entry 2, entry 3 vs entry 4). However, there is an interesting solvent effect observed during the reaction of dibenzoylmethane (**1d**), which was the most reactive substrate in the gold-catalyzed reaction. For example, when **1d** was heated with 4-chlorostyrene (**2d**) in the solution of nitromethane at 100 °C overnight, only

a trace amount of addition product **3l** was observed based on the crude NMR analysis. Most diketone was left unchanged while styrene **2d** has been converted into dimer **4** (entry 14 vs entry 15). However, in the gold-catalyzed reaction, 98% of **3l** was achieved in CH<sub>2</sub>Cl<sub>2</sub> at room temperature.<sup>5</sup> The abnormal solvent effect attracted our attention. By following the reaction (eq 2) with <sup>1</sup>H NMR, rather surprising results were observed: after 4 h of stirring, **3l** was generated in 60% yield; however, after an additional 3 h, the conversion dropped down to 40%; after 11h of reaction, only 27% of **3l** remained. After the reaction, most of **1d** was recovered (>95%). These results suggested that this reaction might be reversible under certain conditions.



To verify the reversibility of the reaction, purified **3l** was treated with 10 mol % AgOTf in nitromethane at the refluxing temperature. After 4 h, **1d** and **2d** were observed in low conversions. Considering that an excessive amount of styrene was usually used in the original addition reaction, 2 equiv of **2d** were introduced into the reaction, and the mixture was heated for an additional 6 h. After separation, 84% of **3l** was converted into diketone **1d**, while most **2d** was converted into dimer **4** (eq 3). *Clearly, the addition reaction catalyzed by silver is a reversible reaction and silver-catalyzed carbon-carbon bond cleavage is involved in the process.*<sup>10</sup> In eq 3, an excessive amount of styrene might promote the equilibrium shifting to the right.



The silver-catalyzed decomposition reaction also seems sensitive to both electronic and steric effects. In the presence of the corresponding styrenes, **3k** and **3m** were

(10) Very recently, a nickel-catalyzed carbon-carbon bond-cleavage reaction was reported. The substrate is very similar to **3**, and the 1,3-dicarbonyl structure was needed. See: Necas, D.; Tursky, M.; Kotora, M. *J. Am. Chem. Soc.* **2004**, *126*, 10222.

also detected. In both cases, the desired product was obtained with about 20% conversion upon overnight refluxing.

Intramolecular additions of 1,3-dicarbonyl compounds to alkenes were also investigated by using silver catalyst. The results are summarized in Table 3.

As shown in Table 3, both 1,3-diketones and  $\beta$ -ketoesters were able to undergo additions to conjugated alkenes to afford the corresponding six-membered-ring products effectively. Note that the addition to form the spiro-center is also highly effective (Table 3, entry 3). It is also worth mentioning that the favored diastereomer in entry 3 has been reversed relative to the gold-catalyzed addition (75:25 vs 39:61, respectively).<sup>11</sup> We hypothesized that the thermodynamic isomer might be favored due to reversible nature of the silver-catalyzed reaction, whereas the kinetic product is favored in the gold-catalyzed reaction. Nonconjugated alkenes were also tested in the intramolecular reaction (Table 3, entries 5 and 6). However, no *C*-alkylation product was observed. The only *O*-alkylation products were obtained in low yields.

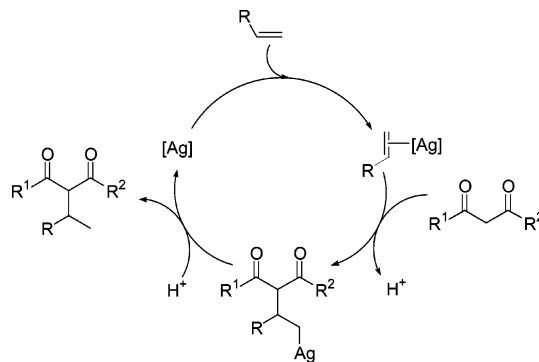
A tentative mechanism is proposed in Scheme 1. The coordination of the alkenes with Ag(I) species activated the alkenes, which was followed by the addition of the 1,3-diketone–Ag(I) complex to generate a silver intermediate. Protonolysis of the C–silver bond generated the final product.<sup>12</sup> However, the exact cause of the reversibility is still unclear.

In conclusion, highly efficient inter- and intramolecular hydroalkylations of 1,3-diketone/ $\beta$ -ketoester and alkenes were developed by using silver catalysts. The reaction is

(11) The same reaction can be catalyzed by 5 mol % of AuCl<sub>3</sub>/15 mol % of AgOTf at refluxing temperature in DCE. The ratio of the two diastereomers is 39:61.

(12) A similar mechanism has been studied elegantly by Reetze and co-worker in gold-catalyzed reaction of arenes with alkynes; see: (a) Reetze, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. See also: (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. We also thank the reviewers for their suggestions regarding this mechanism.

### SCHEME 1. Tentative Mechanism for the Silver-Catalyzed Addition Reaction



reversible through the cleavage of the carbon–carbon bond catalyzed by silver at an elevated temperature. The scope, mechanism, and synthetic applications (including the silver-catalyzed cleavage of carbon–carbon bond) of this reaction are currently under investigation.

### Experimental Section

**Typical Procedure (Entry 1, Table 2).** AgOTf (25.6 mg, 0.1 mmol) was added to 2 mL of nitromethane under N<sub>2</sub>. 2,4-Pentanedione (103  $\mu$ L, 1 mmol) and styrene (172  $\mu$ L, 1.5 mmol) were introduced into the solution. The mixture was stirred and heated to 100 °C overnight, and the solvent was removed under a reduced pressure. The residue was separated by flash chromatography on silica to give the diketone alkylation product **3a** in 76% yield. **3a**: CAS registry no. [5186-08-3]; IR (liquid film)  $\nu_{\max}$  3027, 2964, 1723, 1700, 1602, 1494, 1356, 1185, 1154, 955, 761, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm)  $\delta$  7.29–7.16 (m, 5H), 4.05 (d, *J* = 11.2 Hz, 1H), 3.60 (dq, *J* = 11.2, 7.2 Hz, 1H), 2.26 (s, 3H), 1.83 (s, 3H), 1.21 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm)  $\delta$  203.5, 203.4, 143.2, 129.0, 127.5, 127.2, 76.9, 40.8, 30.3, 30.2, 21.3.

**Supporting Information Available:** General experimental method and characterization data for all new compounds **5c,d,f**, **6c,d**, and **7a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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