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Differences in the Reactivity of $[Ag(PBu_3)I]_4$ and $[Cu(PBu_3)I]_4$ in Promoting Conjugate Addition

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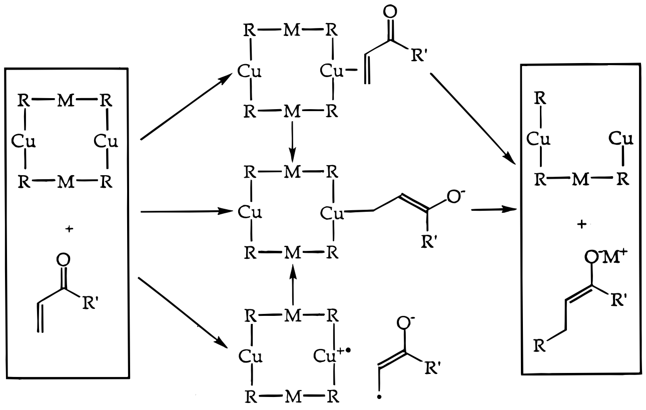
Copper-free $[Ag(PBu_3)I]_4$ ($\mathbf{1}^{\dagger}$) promotes the reaction of *n*-butylmagnesium chloride with 2-cyclohexen-1-one at −45 °C to produce 3-butylcyclohexanone. *n*-Butyllithium affords comparable results at −78 °C. Notably, compound $\mathbf{1}^{\dagger}$ effects a stoichiometric, not a catalytic, reaction. This fact may be easily obscured by the presence of trace copper impurities, which are highly potent catalysts. Contamination with as little as 2.6 ppm of copper affects the results. Highly pure silver complexes, however, give only stoichiometric yields. These complexes may provide insights into the mechanism of conjugate addition.

Introduction

The mechanism of copper-promoted conjugate addition remains open to debate,[1−4] despite the flurry of research activity spurred by the utility of this reaction for the synthesis of pharmaceuticals such as prostaglandins, steroids, and other natural products.[5,6] The transfer of two electrons and an organic moiety may occur in separate, concerted, or partly concerted steps, as illustrated in Scheme 1. Although many stoichiometric reagents for stereoselective conjugate addition have been reported,[7−9] few asymmetric catalysts have been developed.[7,10−12] More efficient catalyst design may depend upon knowledge of the correct pathway.

Mechanistic studies of copper-promoted conjugate addition have been difficult to interpret. Spectroscopic experiments strongly suggest the presence of cuprate dimers $[MCuR_2]_2$ (M = Li, MgCl, MgBr)[13−15] or "higher-order" cuprates[16,17] and organocopper−enone complexes[2,3,18] but have not revealed how such species evolve into products. Kinetic[19] and crystallographic[15] approaches are limited by the high reactivity of copper complexes. Furthermore, both ^{63}Cu and ^{65}Cu are $I = 3/2$ nuclei having large quadrupole moments that prevent direct observation of the metal center and coupling to ligand nuclei by NMR spectroscopy.

Scheme 1. Proposed Mechanistic Pathways for Copper-Catalyzed Conjugate Addition (M = Li, MgCl, MgBr; R = Hydrocarbyl Group)



The present work was undertaken to investigate similar chemistry with silver complexes, ultimately to afford more readily interpretable spectroscopic, structural, and kinetic data. Having two $I = 1/2$ nuclei with a total isotopic abundance of 100%, silver is a candidate for NMR spectroscopy. One-bond $J(^{107}Ag-^{31}P)$ and $J(^{109}Ag-^{31}P)$ couplings in silver−phosphine complexes vary with metal coordination number.[20,21] A congener of copper, silver often forms complexes exhibiting similar structural features.[22] Conjugate addition by organosilver complexes was unknown at the inception of our studies, and we therefore set as our first objective to

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determine whether silver might promote conjugate addition. The synthetic utility of a silver-promoted reaction was not a primary concern, so we focused our attention on a single pair of substrates. As will be demonstrated, trace amounts of copper present in commercially available silver reagents dramatically alter the behavior observed with compounds such as $[Ag(PBu_3)I]_4$ (**1**). We report the successful achievement of stoichiometric conjugate addition promoted by copper-free $[Ag(PBu_3)I]_4$ (**1†**) and compare the reactivity of this reagent with that of $[Cu(PBu_3)I]_4$ (**2**).

Experimental Section

Materials. Except as noted, compounds obtained from commercial suppliers were used as received. Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5 or CaH_2. Hexamethylphosphoramide (HMPA) was stirred over sodium for 3 days, distilled under nitrogen, and stored over 4 Å molecular sieves. 2-Cyclohexen-1-one was stirred over CaH_2 and distilled under nitrogen. Silver compounds were synthesized from silver nitrate having a copper content of approximately 2 ppm by weight (Aldrich). AgI was prepared by metathesis from $AgNO_3$ and NaI. The $[Ag(PBu_3)I]_4$ catalyst was synthesized by a literature procedure.[23] A sample of this material was assayed as having a copper content of 2.6 ppm by Galbraith Laboratories, Knoxville, TN.

Methods. Standard Schlenk techniques were employed in handling all air- and moisture-sensitive reaction mixtures under argon. Glassware used in these manipulations was dried in an oven at 150 °C for at least 10 h. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian XL-300 spectrometer operated at 300.1, 75.1, and 121.4 MHz, respectively. Gas chromatography/mass spectral data were collected on a Hewlett-Packard 5890A gas chromatograph linked with a 5971A mass selective detector (70 eV ion source). GC analyses used Hewlett-Packard HP-1 (dimethylpolysiloxane), Ultra 1 (dimethylpolysiloxane), and HP-FFAP (poly(ethylene glycol)−TPA modified) columns. GC yields were reported as relative percentages of the total amount of product. Thin-layer chromatography was performed by using silica plates that were developed with I_2 and either vanillin or anisaldehyde solutions.

General Procedures for Reactions of Enones with Organometallic Reagents Promoted by 1. Method A. A typical procedure follows for the reaction of 2-cyclohexen-1-one (**3**) and *n*-BuMgCl in the presence of **1** to give 3-butylcyclohexanone (**4b**). A three-necked 100 mL round-bottom flask was fitted with a rubber septum, a 120 mL pressure equalizing addition funnel, and a gas inlet adapter. A solution of enone **3** (0.165 mL, 1.71 mmol), trimethylsilyl chloride (TMSCl, 0.650 mL, 5.1 mmol), and THF (25 mL) was added to a solution of **1** (50 mg, 0.11 mmol) in CH_2Cl_2 (20 mL) at −78 °C. HMPA (0.90 mL, 5.1 mmol) and *n*-BuMgCl (2.5 mmol) in THF (15 mL) were allowed to mix for 5 min and then added dropwise over a 30 min period. The solution was warmed to −45 °C and stirred until the starting material could no longer be observed by TLC. Direct isolation of the ketone followed. The reaction was quenched with saturated NH_4Cl (4 mL) and allowed to warm to room temperature. The reaction mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and then dried with $MgSO_4$. The product was purified by chromatography on silica gel (230−400 mesh) by using gradient elution techniques with Et_2O and pentane. Total isolated yield of **4b**, 200 mg, 76%: ^1H NMR ($CDCl_3$) δ 2.40−2.15 (m, 3 H, H2 and H6), 2.04−1.80 (m, 3 H), 1.77−1.52 (m, 2 H), 1.34-1.20 (m, 7 H), 0.85 (m, 3 H, methyl); ^{13}C NMR (C_6D_6) δ 208.6, 48.1, 41.4, 39.0, 36.5, 31.3, 29.1, 25.3, 23.1, 14.2; GC/MS *m/e* (relative intensity) 154 (8.3, M^+), 111 (23), 97 (100, M^+ − butyl), 69 (10), 55 (37). These ^1H NMR and GC/MS data are similar to those of an authentic sample of **4b** made by known methods.[12,24]

Method B. A typical procedure for the reaction of 2-cyclopenten-1-one (**5**) and *n*-BuMgCl in the presence of **1** and TMSCl to give [(3-butylcyclopenten-1-yl)oxy]trimethylsilane (**6a**) follows. A three-necked 100 mL round-bottom flask was fitted with a rubber septum, a 120 mL pressure-equalizing addition funnel, and a gas inlet adapter. A solution of *n*-BuMgCl (3.0 mmol) and HMPA (1.04 mL, 6.0 mmol) in THF (6 mL) was allowed to mix for 5 min and then added dropwise to a solution of **1** (29.0 mg, 0.066 mmol) in CH_2Cl_2 (7 mL) at −78 °C over a 30 min period. The funnel was rinsed with THF (4 mL). Enone **5** (163 mg, 2.0 mmol) and TMSCl (0.51 mL, 4.0 mmol) in THF (6 mL) were added to the reaction vessel over 30 min. The addition funnel was rinsed once more with THF. The mixture was stirred for several min at −78 °C, warmed to −45 °C, and monitored by TLC until the reaction had ceased, approximately 2.5 h. The reaction mixture was quenched by pouring it into a separatory funnel containing 25 mL of ice-cold 1 N HCl and 150 mL of pentane.[25] The presence of pentane during quenching prevents hydrolysis of the sensitive silyl enol ether. The funnel was shaken briefly and the aqueous layer drained. The organic phase was extracted with cold aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was dissolved in DMSO (25 mL) and extracted with pentane (4 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and dried over Na_2SO_4. Concentration of the resulting organic layer gave an impure, almost colorless oil (390 mg, ~90% **6a**). Product **6a** was obtained in 76% yield after purification by column chromatography on silica (15 × 1.5 cm, pentane/CH_2Cl_2, gradient elution) and identified by its reported NMR spectra[26] and GC/MS analysis: ^1H NMR (C_6D_6) δ 4.75 (d, $J = 1.8$ Hz, 1 H, H2), 2.6 (br, 1 H, H3), 2.34 (m, 2 H, H5), 1.96 (m, 1 H, methylene), 1.43−1.25 (m, 7 H, methylene), 0.90 (t, $J = 7.6$ Hz, 3 H, methyl), 0.18 (s, 9 H, silyl); ^{13}C NMR (C_6D_6) δ 155.3, 107.0, 42.5, 37.7, 33.9, 30.4, 28.7, 23.5, 14.5, 0.1; GC/MS *m/e* (relative intensity) 212 (6, M^+), 155 (100, M^+ − butyl), 75 (15), 73 (49). The nature of **6a** was also confirmed by hydrolysis (1 N HCl) to 3-butylcyclopentanone (**6b**),[26] which was purified by chromatography as before: ^1H NMR (C_6D_6) δ 1.90 (m, 2 H), 1.70 (m, 1 H), 1.52 (m, 2 H), 1.38 (m, 1 H), 1.12 (m, 2 H), 1.10−0.90 (m, 5 H), 0.82 (t, 3 H, $J = 7.4$ Hz); ^{13}C NMR (C_6D_6) δ 216.3, 44.9, 38.2, 37.0, 35.5, 30.2, 29.5, 23.0, 14.2; GC/MS *m/e* (relative intensity) 140 (28, M^+), 112 (12, M^+ − CO), 111 (30, $M^+ - C_2H_5$), 97 (7.3), 96 (16), 84 (8.4), 83 (100, M^+ − butyl), 73 (7.5), 70 (16), 69 (15), 56 (41), 55 (57).

Attempted Synthesis of 4b without 1. To a solution of *n*-BuMgCl (1.5 mmol) and HMPA (0.52 mL, 3.0 mmol) in THF at −78 °C were added cyclohexenone (0.10 mL, 1.0 mmol) and TMSCl (0.65 mL, 5.1 mmol). GC/MS analysis after 2 h at −45 °C showed no **4b** and only traces of **4c**.

Rate Measurement of the Catalyzed Reaction of 3 with *n*-BuMgCl. Reactions were conducted as described above in method B. Typical runs employed TMSCl (0.65 mL, 5.1 mmol), *n*-BuMgCl (2.5 mmol), HMPA (0.9 mL, 5.2 mmol), variable amounts of silver complex **1**, and **3** (see Table 1) in a mixture of 40 mL of THF and 15 mL of CH_2Cl_2 at −78 °C. The reactions were warmed to −45 °C. At 20 min intervals, 0.5 mL aliquots of the mixture were withdrawn by syringe, added to a test tube containing 0.5 mL of saturated NH_4Cl and 2 mL of hexane, and agitated to quench the reaction. The organic layer was separated, dried with $MgSO_4$, filtered through a plugged pipette, and analyzed. Reactions were monitored by GC or GC/MS by using external standards of

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known concentration prepared from pure samples of product and starting material.

Synthesis of 4b without Additives. To complex **1** (44 mg, 0.10 mmol) dissolved in 10 mL of diethyl ether at −78 °C was added *n*-BuMgCl (1.5 mmol) dropwise over 15 min, followed by neat enone **3** (0.10 mL, 1.0 mmol) during the next 15 min. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl and analyzed by GC/MS, which showed 75% **4c** and 15% **4b**.

Reactions Comparing the Activity of 1 and 2. Two reactions were performed according to method B. One reaction employed **1** (26.2 mg) as the catalyst; the other used **2** (0.022 mg). These amounts correspond to 1.07×10^{-9} mol and 5.6×10^{-8} mol of copper, respectively. The latter reagent was measured as 1.0 mL of a dilute solution (5.6×10^{-5} M) in THF. Other quantities and volumes, as well as reaction times, remained the same for the two experiments: *n*-BuMgCl (3.0 mmol), HMPA (1.04 mL, 6.0 mmol), cyclohexenone (0.20 mL, 2.07 mmol), TMSCl (0.51 mL, 4.0 mmol), and THF/CH_2Cl_2 (20 mL: 7 mL). The reactions were performed in parallel. Approximately 30 min after they were warmed to −45 °C, the reactions were quenched with aqueous NH_4Cl and analyzed by GC/MS. Both showed 80% conjugate addition products and 20% starting material.

Reaction Using 2 at Very Low Concentration. This reaction was performed according to method B. Complex **2** (0.40 mg, 8.56×10^{-7} mol catalyst) was measured as 18 mL of the solution described in the previous section. All other volumes and reagent quantities were the same. No product could be measured after 10 min at −78 °C. The reaction vessel was warmed to −45 °C. After 45 min at −45 °C, analysis by GC/MS showed 18% conversion of the starting material to product.

General Procedures Employed in the Synthesis and Reaction of Highly Purified 1†. Methods and Materials. All glassware employed in these reactions was freed of metal contaminants by boiling in nitric acid followed by rinsing with copious amounts of distilled water (resistivity $\geq 10^{16}$ MΩ·cm^{-1}). Removal of residual heavy metal ions was accomplished by rinsing with solutions of 0.003% (w/v) diphenylthiocarbazone (dithizone) in chloroform as outlined in *Reagent Chemicals*.[27] More sensitive tests for metal impurities employed a 0.001% solution. Only glass spatulas were employed to transfer purified solid reagents. Stainless steel needles and cannulas were new and were not reused in manipulations of purified reagents. All solvents and especially solutions of potassium iodide and ammonium chloride were tested with dithizone and extracted as necessary to remove trace metals. Silver nitrate (99.9999%, <0.1 ppm copper) was obtained from Aldrich and used as received.

Synthesis of 1†. The synthesis of this material followed the published procedure,[23] except for special precautions taken to exclude copper contamination. A saturated solution of KI was freed of heavy metals by dithizone extraction. A small amount of this solution (10 g) was diluted to 100 mL and then standardized by titration with an aqueous solution of $AgNO_3$ (99% purity). After standardization, the KI solution was used to precipitate high-purity $AgNO_3$ (1.43 g, 8.41 mmol) dissolved in 25 mL of distilled water. Yellow AgI was collected by using a fritted funnel and was rinsed with alcohol and ethyl ether. The yield was 1.96 g, 99%. Saturated KI solution (∼20 mL) was next added to the funnel to redissolve the silver iodide, and the colorless solution was collected into a 125 mL Erlenmeyer flask by filtration under pressure. Neat PBu_3 (1.52 g, 7.50 mmol, 0.9 equiv) was added, and the mixture was stirred at room temperature for 4 h. Isolation of the product followed the literature procedure. Yield 1.64 g, 50%.

General Procedure for Conjugate Addition of *n*-BuMgCl to Cyclohexenone Promoted by 1†. A typical reaction followed the protocol for method A, with the appropriate precautions to exclude copper contamination. For example, no copper wire was used on any apparatus exposed to solutions of reagents. After addition of the reagents at −78 °C (0.08 mmol **1**†, 3.0 mmol *n*-BuMgCl, 6.0 mmol HMPA, 2.0 mmol cyclohexenone, and 4.0 mmol TMSCl), the reaction was sampled and found not to have formed any products. The solution was then warmed to −45 °C and sampled every 10 min for 1 h and every 20 min thereafter. When the reaction appeared to have stopped, a solution of **1**† (0.69 mmol) in 2 mL of THF was added dropwise. Aliquots were withdrawn repeatedly until the reaction appeared to have ceased. The reaction was then quenched with saturated aqueous NH_4Cl and allowed to stir overnight. Analysis by GC/MS showed that the reaction had proceeded to consume approximately 0.66 mmol of enone (0.85 turnovers).

Synthesis of 4b with *n*-BuLi under Stoichiometric Conditions. A solution of **1** (44 mg, 0.10 mmol) in 10 mL of THF was cooled to −78 °C. Addition of *n*-BuLi (0.10 mmol) by syringe gave a colorless solution. After 10 min, **3** (10 mL, 0.10 mmol) was added. The mixture was stirred for 2 h, by which time GC analysis showed that 50% of the enone had been converted to **4b**. TMSCl (20 mL, 0.16 mmol) was added, and the reaction was allowed to warm to room temperature overnight. After hydrolysis and extraction, analysis showed that the residue contained 95% **4b** and 2% **4c**.

Results and Discussion

Initial studies employing [Ag(PBu$_3$)I]$_4$ (**1**) indicated that it could catalyze conjugate addition. Treatment of 2-cyclohexen-1-one (**3**) with *n*-BuMgCl, hexamethylphosphoramide (HMPA), and trimethylsilyl chloride (TMSCl) in a mixed-solvent system at −45 °C in the presence of 6 mol % of **1** gave the conjugate addition product, which was recovered either as the silyl enol ether of 3-butylcyclohexanone (**4a**, 95%) or as the free ketone (**4b**, 76%). In most cases, couplings involving other enones and Grignard reagents also furnished 1,4-addition products. In the absence of **1**, otherwise identical reaction conditions afforded only a trace of the conjugate addition product (<2%).

Results obtained by using varying concentrations of **1** suggested that each molecule of the silver complex was able to effect ∼50 turnovers per hour at −45 °C (Table 1). Nevertheless, under catalytic conditions, HMPA was needed to suppress 1,2-addition of the Grignard reagent to the enone; in the absence of HMPA, such direct addition to yield **4c** dominated (Scheme 2). Compared to the copper analogue **2**, the activity of the silver complex seemed quite low. Similar reactions with 1.2 mol % of **2** are complete in minutes at lower temperature (−78 °C)[26] and generally do not require additives such as HMPA or TMSCl, although such additives are frequently beneficial. The requirements for HMPA and TMSCl apply to reactions in which the the silver complex is present in substoichiometric amounts. When the silver complex is present at equimolar concentrations, the inhibition provided by HMPA is unnecessary (see below).

Other investigations of silver-promoted conjugate addition were consistent with the results obtained for **1**. One experiment[28] employing **1** but not HMPA or TMSCl gave only direct addition products, evidently confirming the lower reactivity toward enones of organosilver species relative to Grignard reagents and

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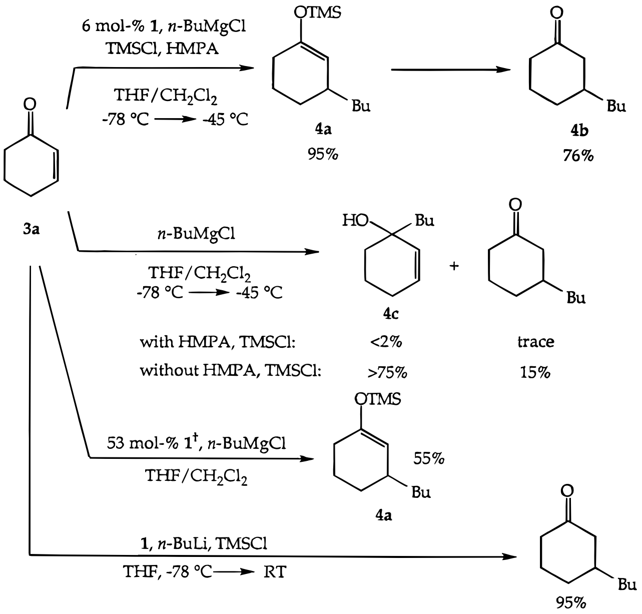
Table 1. Dependence of Turnover Number on Metal Complex:Substrate Ratio[a]

$[Ag(PBu_3)I]_4$			$[Cu(PBu_3)I]_4$		
mole % metal complex	turnovers (mol product per mol catalyst)		mole % metal complex	turnovers (mol product per mol catalyst)	
	per h	total		per h	total
Controls					
0		NR	0		NR
0			8.56×10^{-7}	6×10^5	$>4 \times 10^5$
Copper-Contaminated **1**					
0.097	50	500[b]	3.6×10^{-8} [c]	2.8×10^6	$>2.8 \times 10^7$ [b]
0.54	47	93	1.9×10^{-7} [c]	2.5×10^6	$>5.0 \times 10^6$
3.0	45	34	1.2×10^{-6} [c]	2.4×10^6	$>1.8 \times 10^6$
Copper-Free **1**†					
4.0		0.79			
53		1.04			
54		0.75			
39		0.85			

[a] All reactions were performed at −45 °C as described in the Experimental Section. In each case, the solvent system was THF/CH_2Cl_2 (3:1); HMPA and TMSCl were used to optimize the yields and the rates. The products were either the free ketone or the silyl enol ether. NR means no reaction was observed. [b] The reaction was not taken to completion. [c] These values were calculated on the basis of the assayed level of copper.

Scheme 2



organocopper complexes. Subsequently, silver bromide was reported to effect stoichiometric conjugate addition,[29] albeit with poor efficiency. The role of silver in the latter study is unclear for two reasons: (a) complex product mixtures indicated that several pathways were operating, and (b) copper contaminants may have affected the results (see below). Organosilver compounds derived from AgBr have been reported to decompose rapidly even at low temperatures.[30] Inter- or intramolecular complexation of the organosilver species by phosphines or amines, however, frequently retards such decomposition.[22,30,31]

None of the experiments described above, including our own, examined the effect of copper contaminants. Standard grades of silver salts typically contain ∼2 ppm (by weight) of copper, as determined by a survey of commercial suppliers. Our particular sample analyzed for 2.6 ppm of copper, presumably present in the form of **2**. Hence, the parallels between the chemistry of **1** and **2** warranted further investigation.

In fact, minute quantities of **2** gave results comparable to those obtained with much larger amounts of **1**. Two reactions between **3** and BuMgCl, one using the copper-contaminated **1** and the other using a small amount of **2**, were allowed to proceed for the same length of time and then quenched. By assuming **2** to be the true catalyst in both reactions, the turnover rates could be calculated and compared. Similar turnover rates (mol product per mol catalyst per hour) were obtained for reactions using either **1** or **2** (Table 1). The observed reactivity of **1**, therefore, was concluded to derive from the presence of **2** as a contaminant.

Strikingly different results were obtained when copper-free $[Ag(PBu_3)I]_4$ (**1**†) was used, as reported in Table 1. In each case, the reaction was approximately stoichiometric and never approached the total turnover levels achieved by using **1**, even when monitored for extended periods of time. When monitored by gas chromatography or gas chromatography/mass spectrometry, product formation ceased after a single turnover. These results strongly point to stoichiometric silver-promoted conjugate addition, not a process catalyzed by trace copper impurities.

Results obtained with *n*-BuLi strongly supported this conclusion. Organolithium reagents cannot be used in copper-catalyzed conjugate addition because direct addition of the reagent competes effectively with the process. When 1 equiv each of *n*-BuLi, 2-cyclohexen-1-one, and **1** were allowed to react in THF at −78 °C, the reaction proceeded more than halfway to completion. Subsequent addition of TMSCl increased the rate of reaction, and ketone **4b** was obtained in almost quantitative yield (Scheme 2). Although **1** was employed, copper impurities cannot account for the observed result.

The discovery of stoichiometric silver-promoted conjugate addition is significant in its own right and opens the route to mechanistic studies, one primary objective of this research. In the case of conjugate addition, stoichiometric reagents are better suited than catalysts for such work because they offer greater potential for linking spectroscopic with kinetic studies. The active species in a catalytic process are often difficult to

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identify, owing to their high reactivity. Isolated metal complexes frequently lie on an unproductive, alternative reaction pathway. The nuclear magnetic resonance properties of silver may prove quite useful, providing information about metal−ligand coupling constants and implied geometries.

The silver-promoted conjugate addition reaction reported here is unlikely to find much synthetic utility because its activity is inferior to that of copper. Nevertheless, it is clear that there are similarities in the chemistry of the two metals, and the synthetic value of the copper-promoted reaction may be illuminated by mechanistic studies of the silver-assisted process.

Some questions are raised by our results. First, why is **2** a catalyst, whereas **1** is not? The reactivity of the former is at least *1 million* times greater than that of the latter. Discovering the fate of the silver ions may give an answer. The absence of colloidal silver in reaction mixtures points to the preservation of silver(I) species. Silver enolates seem unlikely, however, because they couple to give 1,4-diketones.[32]

A second question concerns the role of diorganometallic dimers in conjugate addition. Most mechanisms assume initial coordination of the substrate to such a dimer, as indicated in Scheme 1. Does the second metal atom play a functional role in the mechanism, or does it merely participate in equilibria unrelated to the carbon−carbon bond-forming reaction? Several results point to the latter possibility. Polystyrene-supported organocopper−phosphine complexes, prepared so as to minimize aggregation, perform conjugate addition.[33] Furthermore, NMR spectroscopic studies of organosilver−phosphine complexes found no sign of silver aggregates.[34] In our experiments with **1**, selective formation of dicopper species is unlikely, owing to its low concentration. More probable is the formation of mixed copper/silver species. Yet the turnover rates for **1** and pure **2** differ by no more than a factor of 4−5, and further studies may show even this difference to be insignificant. If the second metal atom were required, one might expect copper to have a dramatically enhanced effect over less reactive silver. Further studies should clarify these questions and others.

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