

Ionic and Covalent Copper(II)-Based Catalysts for Michael Additions. The Mechanism[†]

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Received April 15, 2004

Cu(SbF₆)₂-AdamBox and copper(II) bis-(5-*tert*-butylsalicylaldehyde) catalyze the Michael addition in neutral media. Mechanistic studies, based on UV-vis, IR, and electrospray ionization mass spectrometry (ESI-MS), suggest that copper enolates of the β -dicarbonyl formed in situ are the active nucleophilic species.

Introduction

The Michael addition of active methylene compounds to activated π -systems is one of the oldest and most useful carbon-carbon bond-forming methods dating back to more than one hundred years.^{1,2} However, the required basic catalysts generate byproducts due to competing side reactions. Therefore, catalysis by transition metals or lanthanides, which work under neutral conditions, has attracted the attention of the chemical community as witnessed by recent reviews.³

Copper and nickel-based catalysts have been intensively studied. In a pioneering publication, Saegusa et al. described the catalytic action of Cu₂O or Cu(acac)₂ combined with isocyanides in Michael additions to methyl acrylate and acrylonitrile.⁴ Since then, other copper-based catalysts have been proposed by Desimoni⁵ and Jørgensen.⁶ These two groups have studied induction of enantioselectivity at the nucleophile (eq 1, Figure 1) and at the electrophile (eq 2, Figure 1). In particular, Jørgensen's group has reported impressive results based on the combination of Cu(OTf)₂ with (*S,S*)-Ph-Box or (*S,S*)-*t*-Bu-Box. The group of Christoffers has described similar

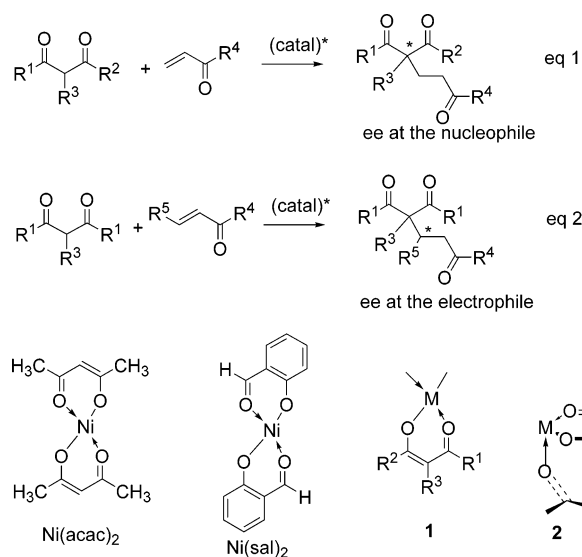


FIGURE 1. Michael additions: covalent catalysts and pre-sumed intermediates.

studies based on enantiopure enamines of β -dicarbonyl compounds, combined with copper catalysts.⁷

Nickel-based catalysts have attracted a great deal of attention since 1980 when Nelson's group reported on the catalytic activity of nickel pentane-2,4-dionate (Ni(acac)₂) (Figure 1).⁸ Further improvements based on the work by Nelson have been proposed. Thus, Nelson's catalyst has been anchored to polystyrene,⁹ as well as to clay,¹⁰ or used in combination with enantiopure amines.¹¹ Other nickel-based catalysts are ionic: Ni(OAc)₂,¹² Ni(ClO₄)₂.¹³ Our

[†] Dedicated to Prof. José Luis Soto on the occasion of his retirement.

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group has contributed improvements on the basic idea presented by Nelson. Thus, we found that the nickel(II) complex of salicylaldehyde ($\text{Ni}(\text{sal})_2$) (Figure 1) is an excellent catalyst for Michael additions giving less side products than $\text{Ni}(\text{acac})_2$.¹⁴ Moreover, a $\text{Ni}(\text{sal})_2$ -based catalyst soluble in perfluoroorganic solvents can be recovered and reused several times.¹⁵

Catalysts based on other metals have met also with success: iron,^{3,16,17} palladium,¹⁸ platinum,¹⁹ rhodium,^{20,21} cadmium, and bismuth.²² Several reports deal with the comparison of the merits of more than one metal.²³ Ruthenium species are also active in Michael additions.^{24–26} However, the supposed catalytic effect of ruthenium(II) hydride tetrakis(triphenylphosphine)²⁷ is due, at least in part, to free phosphine present in the reaction media.²⁸

Finally, scandium triflate²⁹ and different lanthanides such as lanthanum derivatives,³⁰ cerium(III) chloride/ NaI ,³¹ europium(III) derivatives,³² and ytterbium(III) triflate^{33,34} have met with success.

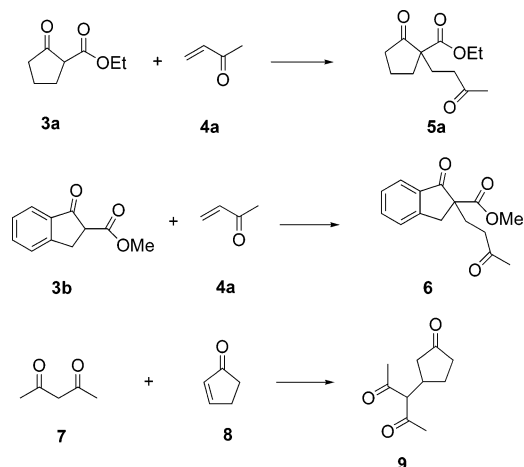
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The richness of information on metal-catalyzed Michael additions is in sharp contrast with the scarcity of mechanistic data. Although rhodium and ruthenium might present peculiar mechanistic features, it is accepted that all other metals share common mechanistic behaviors. It has been suggested that metal enolates of β -dicarbonyl compounds of general structure **1** (Figure 1), formed in situ, are the actual nucleophilic species: copper,^{5b,c,6a,7a,b} nickel,^{8,9,10,12b} iron,^{16a} palladium,¹⁸ scandium,²⁹ lanthanum,^{30a} ytterbium,^{33b,34a} and metals in general.^{3a,23a–c} Very recently, a complex of composition lanthanum/methyl acetoacetate/bidentate ligand has been detected by ESI-MS.^{30c} Whereas it is plausible that metal enolates are formed from ionic metal salts, it is intuitively less compelling to accept such a hypothesis for covalent metal catalysts such as $\text{Ni}(\text{acac})_2$ or $\text{Ni}(\text{sal})_2$.^{14,15} This would require transfer of metal from β -dicarbonyl enolate to β -dicarbonyl. The proposal of metal enolates as active nucleophilic species is based on the activity of independently prepared enolates in front of Michael acceptors.^{35,36} On the other hand, coordination of the electrophilic acceptor to the metal center has been invoked: copper,^{4,7a,b} nickel,^{12b} iron(III),^{10,16a} scandium,^{29b} ytterbium,^{33b,34a} and metals in general.^{3a} If both reagents are simultaneously coordinated in an intermolecular reaction, another requirement ensues as a corollary: the Michael acceptor should adopt a *cisoid* conformation as in **2** (Figure 1).^{3a} In this respect, we found that 4-vinylpyridine was inactive under experimental conditions that were appropriate for $\text{Ni}(\text{sal})_2$ -catalyzed reaction of 2-vinylpyridine.^{14a}

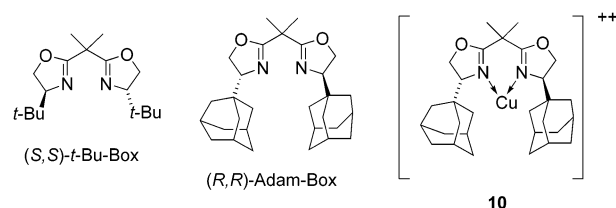
Results and Discussion

Preparative Work. First, we studied the reactions of nucleophiles, **3a,b** and **7**, with unsaturated ketones, **4a** and **8** (Scheme 1). We selected two ionic salts of copper and nickel, $\text{Cu}(\text{SbF}_6)_2$ and $\text{Ni}(\text{ClO}_4)_2$. The metals were coordinated with commercially available (*S,S*)-*t*-Bu-Box or with (*R,R*)-Adam-Box³⁷ to afford $\text{Cu}(\text{SbF}_6)_2$ -(*R,R*)-Adam-Box, **10**, and related complexes. Although in all cases enantiomeric excesses were negligible, the chemical yields were in general excellent. Reaction between **3a** and **4a** did not take place in the absence of catalyst.

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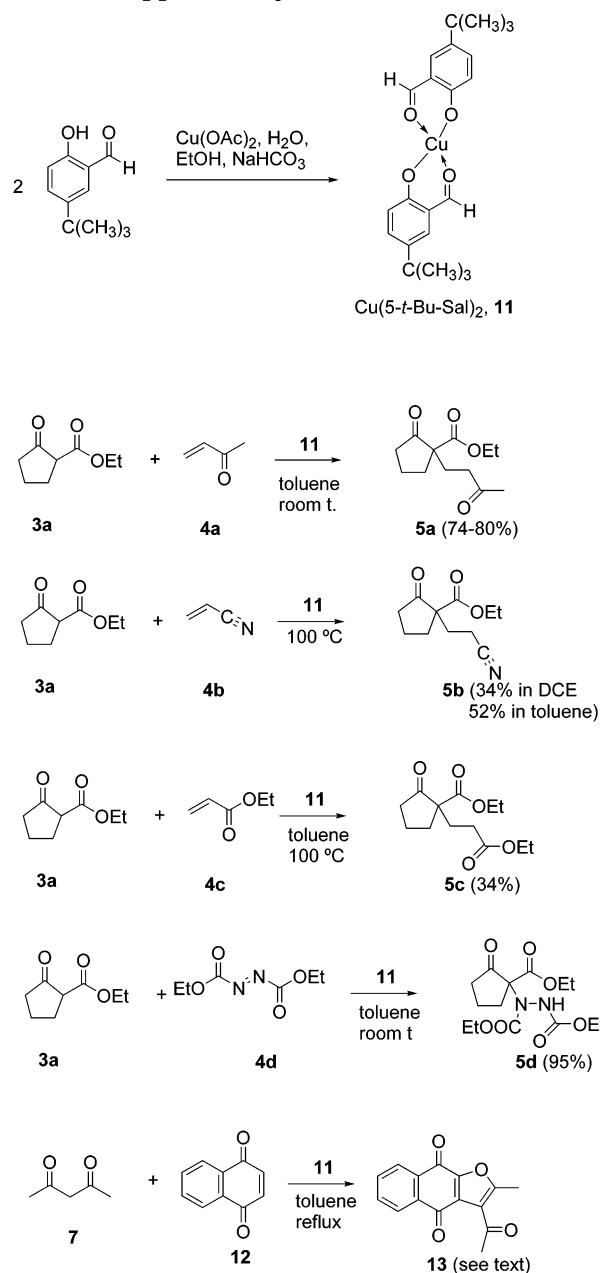
SCHEME 1. Michael Additions Catalyzed by Ionic Catalysts^a


Nucleophile	Electrophile	Catalyst	Product (%)
3a	4a	Cu(SbF ₆) ₂ - (R,R)-Adam-Box	5a (93%)
3a	4a	Ni(ClO ₄) ₂ - (S,S)- <i>t</i> -Bu-Box	5a (90%)
3a	4a	Fel ₃ - (S,S)- <i>t</i> -Bu-Box	5a (96%)
3b	4a	Cu(SbF ₆) ₂ - (S,S)- <i>t</i> -Bu-Box	6 (94%)
3b	4a	Ni(ClO ₄) ₂ - (S,S)- <i>t</i> -Bu-Box	6 (44%)
7	8	Cu(SbF ₆) ₂ - (S,S)- <i>t</i> -Bu-Box	9 (62%)



^a Reactions were performed in dichloromethane at room temperature. Ee values were negligible in all cases.

Then we turned our attention to covalent catalysts. After some experimentation and with our previous experience,¹⁴ we came to the conclusion that a copper(II) complex of salicylaldehyde, Cu(sal)₂, is a good covalent catalyst, slightly better than Ni(sal)₂. Moreover, toluene is slightly better than 1,2-dichloroethane, our previous solvent with Ni(sal)₂.¹⁴ To improve the solubility in toluene without altering the electronic characteristics of the covalent catalysts, we introduced a *tert*-butyl group into the aromatic ring. Thus, complex **11** fulfilled all the conditions (Scheme 2), and the required 5-*tert*-butylsalicylaldehyde is commercially available. One serious limitation of many metal species is that their catalytic activity is limited to very active Michael acceptors, unsaturated ketones, and dialkyl azodicarboxylates, with other acceptors such as acrylates or acrylonitrile being inactive. Only a few reports describe catalysts active for less active acceptors: copper,^{4,5a} nickel.^{8,9,14a} In particular, acrylates and acrylonitrile are clearly inert in metal-catalyzed Michael additions with a few exceptions.^{4,8b,24a,b,29b,34} Complex **11** catalyzed the Michael reactions of 2-ethoxycarbonylcyclopentanone, **3a**, with four model acceptors: butenone, **4a**, acrylonitrile, **4b**, ethyl acrylate, **4c**, and diethyl azodicarboxylate, **4d**. The Michael adducts **5a–d** were obtained in yields from acceptable to good. Furthermore, product **13** was isolated, albeit in low yield, in the reaction of acetylacetone, **7**, with naphthoquinone, **12**, a Michael acceptor that cannot

SCHEME 2. Michael Additions Catalyzed by Covalent Copper Catalyst 11


attain a *cisoid* conformation. Formation of **13** required two consecutive dehydrogenations. Probably, a part of naphthoquinone is consumed in these oxidations. Similar results have been previously described in iron-catalyzed Michael additions to quinones.^{16d}

The Mechanism. First, we checked the reactivity of copper enolate **14**. Indeed, **14** reacts with butenone in dichloromethane to afford **5a** in 84% isolated yield (Scheme 3). However, from a mechanistic viewpoint, it was necessary to prove the formation of **14** in the catalyzed reactions, or at least the formation of copper species of type **1** (Figure 1) with equivalent reactivity.

Mechanism for Covalent Catalyst 11. Copper Goes from β -Dicarbonyl Enolate to β -Dicarbonyl. The overall exchange of ligands between ketoester **3a** and **11** on one side and **14** and 5-*tert*-butylsalicylaldehyde on

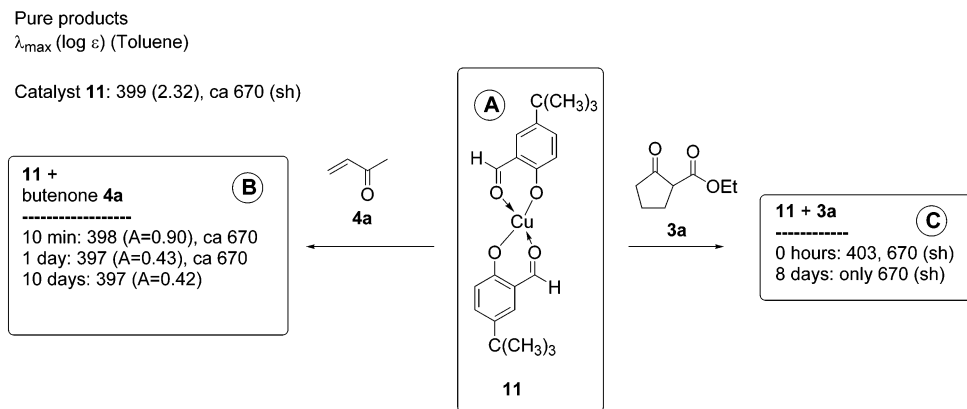
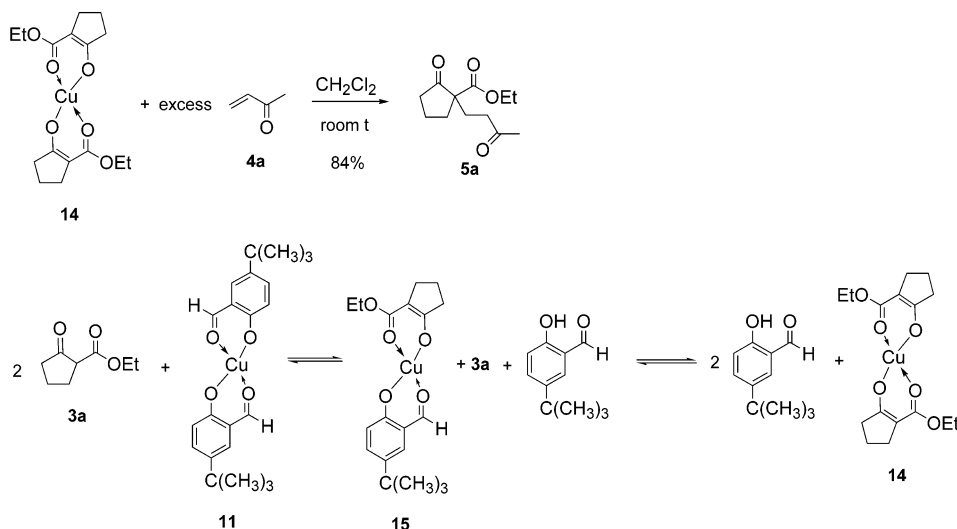


FIGURE 2. Interactions of **11** with reagents in toluene determined by UV–vis spectroscopy.

SCHEME 3. Reactivity of 14 and Possible in Situ Formation of 14 and 15



the other side is represented in Scheme 3. It is reasonable to assume that it requires the formation of intermediate **15** and free 5-*tert*-butylsalicylaldehyde while **3a** is still present. We prepared mixtures of **3a** and **11** (molar ratio = 2:1) in toluene and left them at room temperature. Samples were taken at different times, evaporated, and analyzed by infrared spectroscopy (attenuated total reflectance mode, ATR). 5-*tert*-Butylsalicylaldehyde was formed within 5 min as evidenced by the disappearance of the infrared peak at 1624 cm^{-1} due to complex **11** and the appearance of a new peak at 1655 cm^{-1} assigned to 5-*tert*-butylsalicylaldehyde (1651 cm^{-1} in pure 5-*tert*-butylsalicylaldehyde). Peaks at 1754 and 1719 cm^{-1} of ketoester **3a** were always present. This suggests that at least the first part of the equilibrium was achieved very soon. After a longer time (1 month), the mixture was evaporated and a green solid was isolated after washing with hexanes. Its IR spectrum was very similar although not identical to that of **14**. In particular, intense peaks in the regions 1301 – 1305 , 1265 – 1266 , 1047 – 1060 , and 765 cm^{-1} are present in the isolated solid as well as in **14**, whereas they are absent in **11**. Partitioning between dichloromethane and 1 M HCl hydrolyzed the solid. The ^1H NMR spectrum of the organic fraction coincided with the spectrum of **3a**, with the amount of 5-*tert*-butylsalicylaldehyde present on it being only marginal.

Further evidence was gained by GLC analysis of the reaction mixtures. Complex **11** gave no peak in our GLC conditions (see Experimental Section). However, spurious, weak peaks of 5-*tert*-butylsalicylaldehyde were visible. These could be due to accidental hydrolysis during the analytical procedure. To circumvent this problem, we added an internal standard: *n*-undecane. The GLC analyses showed that the peaks of **3a** (keto + enol) remained, albeit in a lower ratio, and the peak of 5-*tert*-butylsalicylaldehyde grew dramatically with respect to undecane. Therefore, formation of complex **15** is highly probable in our reaction conditions, and its reactivity should be similar to that of complex **14**, with the salicylaldehyde part being inert. The presence of **14** in the reaction mixtures cannot be ruled out. Obviously, structure **15** is a particular case of the general structure **1** (Figure 1).

Mechanism for Covalent Catalyst 11. Interactions of Complex 11 Determined by UV–Vis Spectroscopy. Next, we undertook an examination of interactions of covalent catalyst **11** with the components of the reactions of **3a** with **4a** (Figures 2 and 3). 1,2-Dichloroethane and toluene are transparent above 300 and 330 nm, respectively. Therefore, both solvents were considered in this study. Butenone, **4a**, interacts slowly with **11** in toluene, as shown by a decrease in the absorbance

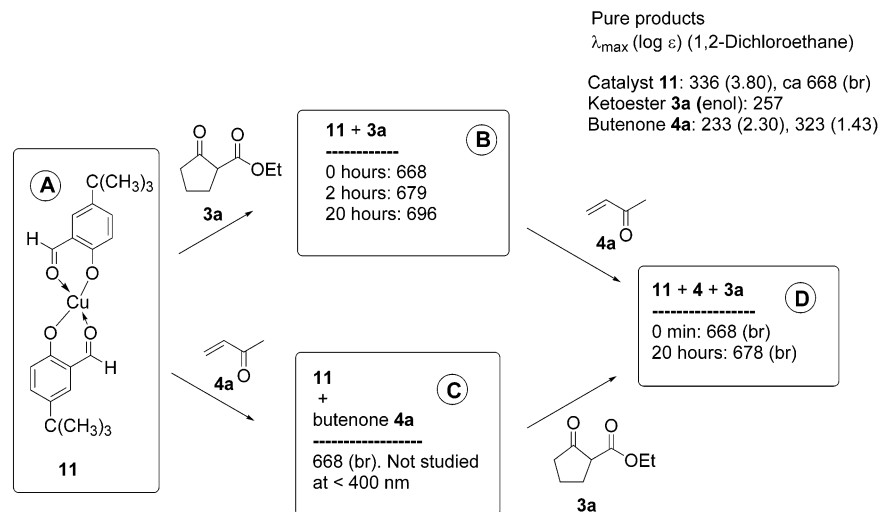


FIGURE 3. Interactions of **11** with reagents in dichloroethane determined by UV–vis spectroscopy.

TABLE 1. Maxima of the UV–Vis Spectra of the Reaction between butanone (**4a**) and Ketoester (**3a**) Catalyzed by 5% Cu(sal-5-*t*Bu)₂ (**11**) in Toluene

reaction time	bands of Cu(sal-5- <i>t</i> Bu) ₂ (11) nm (log ϵ)	new bands (nm)
only 11	399 (2.32), ca. 670 (sh)	
10 min	399 disappeared, ca. 670 (sh)	412
1 h	399 disappeared, ca. 670 (sh)	412
2 h	399 disappeared, ca. 670 (sh)	412
3 h	399 disappeared, ca. 670 (sh)	412
4 h	399 disappeared, ca. 670 (sh)	412
5 h (end of reaction)	402, ca. 670 (sh)	

of the band at ca. 398 nm of **11** (Figure 2, box B). Interaction of **11** with ketoester **3a** in toluene is also evident by the disappearance of the band at ca. 399–403 of copper complex **11** upon mixing with **3a** (Figure 2, box C). The interaction of the three components of the reaction is independent of the type of addition. This is better observed in dichloroethane (Figure 3, box D). When the three components are present, **11** interacts with **3a** rather than with butenone (compare boxes B and D and boxes C and D in Figure 3). Similar results were obtained with ethyl acrylate, **4c**. Interaction of **11** with both acceptors **4a,c** seems to be minimal or nonexistent.

Table 1 shows the evolution of the visible spectra of a reaction of butenone with ketoester **3a**. The band of the catalyst **11** at 399 nm disappears during the reaction to reappear at the end, albeit with decreased absorbance. During the course of the reaction, a new band at 412 nm shows up but then disappears at the end. The new band at ca. 412 nm can be assigned to a reaction intermediate of structure closely related to **14** and **15**, since its wavelength is close to the absorption of copper enolate **14** (416 nm in dichloromethane).

In summary, the above studies suggest the in situ generation of some active species of general structure **1** (Figure 1). For the covalent catalysts **11**, this species is more specifically **14** or **15** (Scheme 3).

Mechanism for Ionic Copper(II) Catalyst. Interactions of Cu(SbF₆)₂ + Adam-Box Determined by UV–Vis Spectroscopy. Any coordination or interaction of nucleophiles or electrophiles with the metal should have a strong effect on the UV–vis absorption, mainly

in the visible region. Therefore, we analyzed the spectra of the components of the reaction of **3a** with **4a** as well as spectra of mixtures of two and more components, including samples of the ongoing reactions (Figure 4). Mixtures are equimolar unless otherwise stated, and Adam-Box was a mixture of racemic and meso isomers.

As anticipated, Cu(SbF₆)₂ and Adam-Box form a complex, probably of structure **10**³⁸ (Scheme 1), as evidenced by the hypsochromic displacement of the shoulder band from 750 to 670–710 nm (box A, Figure 4). Unfortunately, this new band is broad and the maximum is difficult to ascertain. The mixture Cu(SbF₆)₂ + **3a** + Adam-Box shows a definite interaction of the three components (box B) independently of the order of addition, since two new bands appear at 291 and 523 nm.

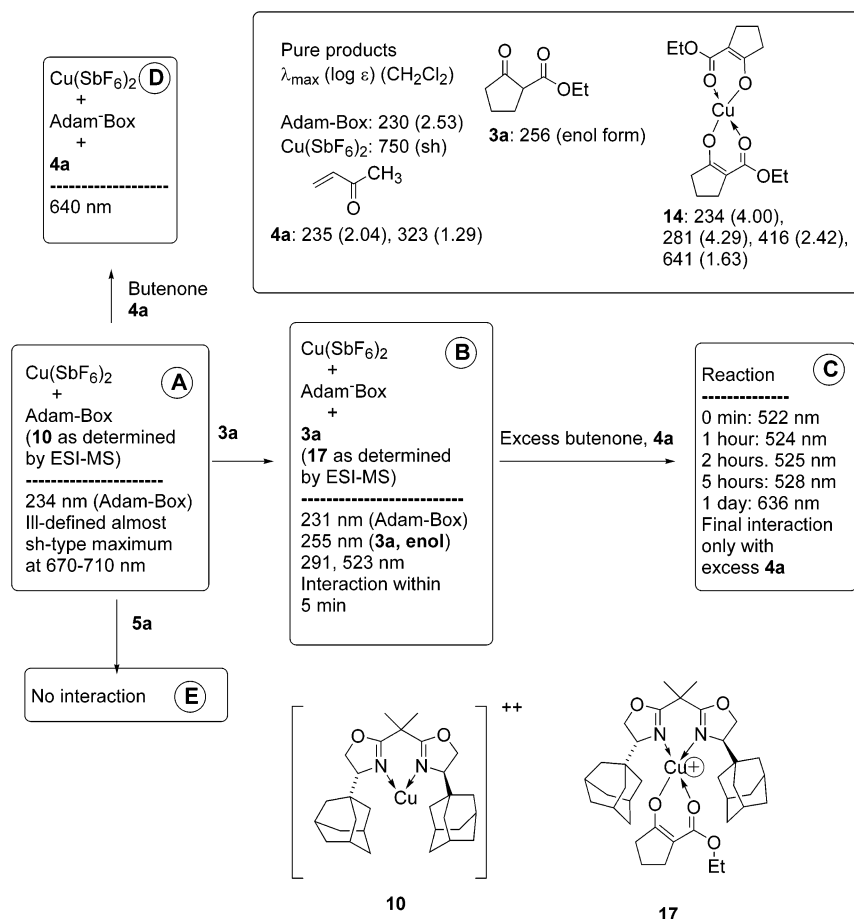
The Michael acceptor, butenone, **4a**, interacts also with the complex Cu²⁺–Adam-Box since the ill-defined absorption is displaced hypsochromically to 640 nm (box D). On the contrary, the final product **5a**, not possessing the enol form, does not appear to interact with the copper species present in the media (box E).

Finally, a reaction with excess butanone was examined, and the results with respect to time are presented in box C. Indeed, the maximum at 522–528 nm detected between 0 and 5 h coincides with the absorption caused by the trio Cu(SbF₆)₂ + **3a** (enol) + Adam-Box (complex **17** as determined by ESI-MS, vide infra). Despite butenone being in large excess, its interaction with copper is not evident until the end of the reaction (636 nm, compare with 640 nm in box D), when no **3a** remains.

The absorptions of copper enolate **14** are shown in the upper part of Figure 4. The absorptions at 416 and 641 nm were never observed. Therefore, no evidence arises for the in situ formation of **14**.

In summary, from the above study no indication of the presence of **14** has been achieved. Nevertheless, from the reactivity viewpoint this is meaningless because species of type **1**, featuring only one enolate, can be active, and **17** is a particular example of general structure **1**.

Mechanism for Ionic Copper(II) Catalyst. Interactions of Cu(SbF₆)₂ + Adam-Box Determined by ESI Mass Spectrometry. To gain insight into the structures of intermediates postulated in Figure 2, we



Conclusions:

Cu(SbF₆)₂ + Adam-Box: they form complex **10**. See ESI-MS experiments.
 Cu(SbF₆)₂ + Adam-Box + **3a**: they form complex **17**. See ESI-MS experiments.

FIGURE 4. Interactions of Cu(SbF₆)₂ + Adam-Box with reagents determined by UV-vis spectroscopy.

performed electrospray ionization mass spectrometry (ESI-MS)³⁹ analysis directly from solution mixtures. It is known that ESI-MS opens a straightforward approach to trap and identify short-lived intermediates in organometallic catalytic cycles.⁴⁰ Therefore, we analyzed the mass spectra of the components of the reaction of **3a** with **4a**, as well as those of mixtures of two or more components. Mixtures were equimolar unless otherwise stated. The identification of the species detected by ESI-MS was aided by comparison between the observed and calculated isotope distribution patterns.

Pure Products. To identify every possible compound in the mass spectra of subsequent mixtures, reagents **3a**

and **4a**, ligand (Adam-Box), copper salt [Cu(SbF₆)₂], and final product **5a** were injected to the mass spectrometer for analysis. Table 2 shows in entries 1–3 data that have been obtained with our standard ESI mass spectrometry conditions (see Experimental Section). In all three cases, the molecular ion [M + H]⁺ could be clearly observed.

Binary Mixtures. The ESI mass spectrum of the solution generated from Adam-Box and Cu(SbF₆)₂ in either CH₃CN or CH₂Cl₂ showed one cluster centered at $m/z = 791$ corresponding to [(Adam-Box)Cu(CH₃CN)-SbF₆]⁺, being consistent with complex **10** (Scheme 1) coordinated with solvent CH₃CN and the counteranion SbF₆⁻ (Table 2, entry 4, and Figure 4, box A). Since Cu(SbF₆)₂ was prepared from a mixture of CuCl₂ and AgSbF₆ in dry dichloromethane (see Experimental Section), residual silver species might be present in the copper solution. Therefore, two clusters were observed centered at $m/z = 600$ and 1009 , respectively, and corresponding to silver species [(Adam-Box)Ag(CH₃CN)]⁺ and [(Adam-Box)₂Ag]⁺, respectively. In addition, two clusters centered at $m/z = 554$ and 963 are consistent, respectively, with Cu(I) species [(Adam-Box)Cu(CH₃CN)]⁺ and [(Adam-Box)₂Cu]⁺ (Table 2, entry 4). The reduction of copper(II) species to copper(I) when electro-sprayed in acetonitrile has been described.⁴¹

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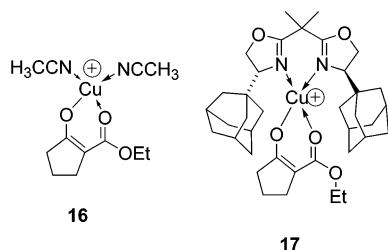
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TABLE 2. Electrospray Mass Spectral Data for Various Mixtures in CH₃CN/H₂O (70:30)

entry	compounds and mixtures	identified species ^a
1 ^b	3a	$m/z = 157 [M + H]^+$
2 ^b	Adam-Box	$m/z = 451 [M + H]^+$
3 ^b	5a	$m/z = 227 [M + H]^+$ $m/z = 244 [M + NH_4]^+$ $m/z = 249 [M + Na]^+$ $m/z = 290 [M + Na + CH_3CN]^+$
4 ^{b,c}	Adam-Box + Cu(SbF ₆) ₂	$m/z = 451 [Adam-Box + H]^+$ $m/z = 554-558 (544) [(Adam-Box)Cu(CH_3CN)]^+$ $m/z = 598-602 (600) [(Adam-Box)Ag(CH_3CN)]^+$ $m/z = 789-794 (791) [(Adam-Box)Cu(CH_3CN)SbF_6]^+$, 10-CH₃CNSbF₆ $m/z = 963-967 (963) [(Adam-Box)_2Cu]^+$ $m/z = 1007-1011 (1009) [(Adam-Box)_2Ag]^+$
5 ^c	3a + Cu(SbF ₆) ₂	$m/z = 300-303 (300) [(enolate-3a)Cu(CH_3CN)_2]^+$, 16 . $m/z = 536-541 (538) [(3a)Cu(CH_3CN)_2SbF_6]^+$ $m/z = 610-614 (612) [(3a)_2CuSbF_6]^+$ $m/z = 628-632 (630) [(3a)_2Cu(H_2O)SbF_6]^+$
6 ^{b,c}	Adam-Box + Cu(SbF ₆) ₂ + 3a	$m/z = 668-672 (668) [(Adam-Box)Cu-enolate-3a]^+$, 17
7 ^c	Adam-Box + Cu(SbF ₆) ₂ + 5a	$m/z = 974-979 (976) [(Adam-Box)Cu(5a)SbF_6]^+$
8 ^c	Adam-Box + Cu(SbF ₆) ₂ + 3a + 4a	0 min, 1 h, 2 h, 5 h: $m/z = 668-672 (668) [(Adam-Box)Cu(enolate-3a)]^+$, 17 1 day: $m/z = 963-967 (963) [(Adam-Box)_2Cu]^+$

^a Reported m/z values are from the lowest to the highest mass in the isotope envelope of the clusters; values in parentheses correspond to the most abundant peak. Unidentified ions in the spectra have not been included. ^b Samples dissolved in CH₃CN and diluted in CH₃CN/H₂O (70:30). ^c Samples dissolved in CH₂Cl₂ and diluted in CH₃CN/H₂O (70:30).

**FIGURE 5.** Enolates detected by ESI-MS.

Next, ESI-MS analysis of a dichloromethane solution of Cu(SbF₆)₂ and ketoester **3a** showed several signals (Table 2, entry 5): three clusters centered at $m/z = 538$, 612, and 630 corresponding, respectively, to **3a**-Cu(II) complexes $[(3a)Cu(CH_3CN)_2SbF_6]^+$, $[(3a)_2CuSbF_6]^+$, and $[(3a)_2Cu(H_2O)SbF_6]^+$ in which **3a**, keto or enol, is not deprotonated. In addition, a cluster centered at $m/z = 300$ was attributable to enolate **1** (Figure 1). It is reasonable to assume that enolate **16** deprived of acetonitrile would have reactivity not very different from or even superior to that of the very reactive bisenolate **14** (Scheme 3).

Ternary Mixtures. When ketoester **3a** was added to a previously formed mixture Adam-Box + Cu(SbF₆)₂ (either in CH₃CN or CH₂Cl₂), a cluster centered at $m/z = 668$ was revealed (Table 2, entry 6). This cluster is in agreement with the in situ formation of copper enolate $[(Adam-Box)Cu(enolate-3a)]^+$, **17** (Figure 4, boxes B and C, and Figure 5). Variation of the order of addition of the three components, namely, Adam-Box over a mixture of **3a** + Cu(SbF₆)₂ in dichloromethane, produced no variation in the ESI mass spectrum.

Addition of butenone **4a** to the mixture Adam-Box + Cu(SbF₆)₂ (in CH₂Cl₂) produced no new clusters corresponding to species containing the three components.

Finally, when an equimolar amount of final product **5a** was added to the mixture Adam-Box + Cu(SbF₆)₂, a new cluster was observed at $m/z = 976$ assigned to copper species $[(Adam-Box)Cu(5a)SbF_6]^+$ (Table 2, entry 7) together with the same peaks detected in entry 4. Since **5a** has no enol form, this is evidence that neutral keto forms can coordinate Cu²⁺ ion.

Ongoing Reaction. Further addition of butenone **4a** to the reaction mixture, Adam-Box + Cu(SbF₆)₂ + **3a**, had no effect on the ESI mass spectrum, with the copper enolate **17** $[(Adam-Box)Cu(enolate-3a)]^+$ being the only intermediate observed until the end of the reaction. Several unidentified peaks and a cluster centered at $m/z = 963$ corresponding to Cu(I) species $[(Adam-Box)_2Cu]^+$ could be observed in the mass spectrum of the completed reaction (Table 2, entry 8).

Conclusion

The ionic catalytic system Cu(SbF₆)₂ + Adam-Box produces in situ complex **17** that probably is a reactive species. Complex **16** is also formed in the MS machine in the absence of Adam-Box. The Michael additions of Scheme 1 occur with excellent chemical yields but with negligible enantiomeric excesses. In this case, enolate **16** (without acetonitrile) rather than **17** could be the reacting species, although lack of efficiency of **17** in generating ees cannot be ruled out.

The covalent catalyst, **11**, transfers copper to the nucleophile β -dicarbonyl. The in situ-formed copper enolates such as **15** and/or **14** are the real nucleophilic species.

Both in the presence of ionic or covalent copper sources, copper enolates formation is a prerequisite for the Michael addition.

Figures 6 and 7 represent the catalytic cycles for covalent and ionic copper species concordant with the described experiments.

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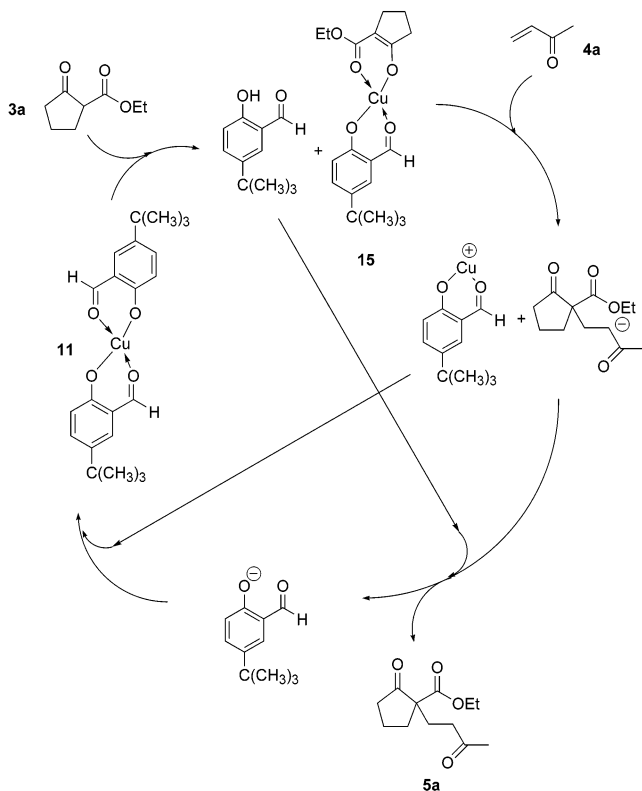


FIGURE 6. Catalytic cycle for covalent catalysts **11**.

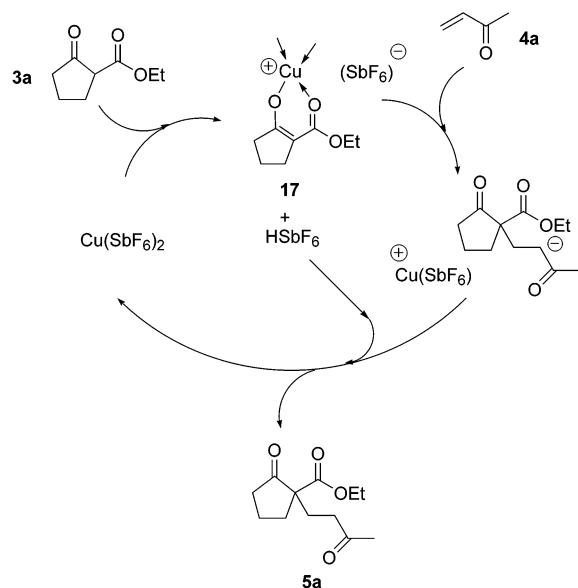


FIGURE 7. Catalytic cycle for ionic copper(II) catalyst. Ligands are omitted.

Experimental Section

General. GLC chromatographies were performed on a TRB-5 capillary column (5% biphenyl and 95% dimethylpolysiloxane) of 15 m × 0.25 mm with a stationary phase diameter of 0.25 μm. IR spectra were determined either by transmission or by attenuated total reflectance mode (ATR).

General Procedure for Reactions of Nucleophiles **3a, **b** and **7** with Unsaturated Ketones **4a** and **8** under Catalysis by Ionic Species (Scheme 1).** A solution of Adam-Box (25.1 mg, 0.056 mmol) and silver hexafluoroantimonate (57.6

mg, 0.167 mmol) in dry dichloromethane (2 mL) was added over anhydrous copper chloride made by dehydrating CuCl₂·2H₂O (6.9 mg, 0.040 mmol) upon heating at 120 °C under vacuum (color changes to brown). The mixture was stirred overnight in the dark and filtered, and the filtrate was used as a catalyst. The nucleophile and the electrophile were added to the catalyst solution in a molar ratio of 1:3 to form mixtures containing 5% catalyst with respect to the nucleophile. The reactions were conducted at room temperature and monitored by thin-layer chromatography (TLC). The final mixtures were chromatographed through silica gel columns with mixtures of hexanes–ether.

2-Ethoxycarbonyl-2-(3-oxobutyl)cyclopentanone, **5a:** bp 155 °C/1 mmHg; IR 2976, 1747, 1718, 1166 cm⁻¹; ¹H NMR (CDCl₃) δ 1.25 (t, *J* = 7.5 Hz, 3H), 1.83–2.14 (m, 5H), 2.15 (s, 3H), 2.24–2.50 (m, 4H), 2.71 (ddd, *J* = 5, 9, and 17 Hz, 1H), 4.17 (q, *J* = 7.5 Hz, 2H); ¹³C NMR δ 14.5, 20.0, 27.4, 30.3, 34.8, 38.4, 39.3, 59.4, 61.8, 171.8, 208.2, 215.3.

2-Methoxycarbonyl-2-(3-oxobutyl)indan-1-one, **6:** IR (KBr) 1734, 1713 cm⁻¹; ¹H NMR (CDCl₃) δ 2.13 (s, 3H), 2.25 (t, *J* = 8.0 Hz, 2H), 2.52–2.58 (m, 2H), 3.05 (d, *J* = 17.3 Hz, 1H), 3.71 (d, *J* = 17.3 Hz, 1H), 3.72 (s, 3H), 7.36–7.50 (m, 2H), 7.65 (dd, *J* = 1.3 and 7.6, 1H), 7.77 (d, *J* = 7.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 28.9, 30.3, 38.2, 39.2, 53.1, 59.5, 125.2, 126.8, 128.4, 135.4, 135.9, 152.9, 171.9, 202.6, 207.7.

3-(3-Oxocyclopentyl)pentane-2,4-dione, **9:** IR (ATR) 2963, 2914, 1739, 1720, 1694, 1357, 1159 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (m, 1H), 1.76 (dd, *J* = 10.9 and 18.2 Hz, 1H), 2.10–2.43 (m, 4H), 2.16 (s, 3H), 2.20 (s, 3H), 2.92 (m, 1H), 3.62 (d, *J* = 10.5 Hz, 1H).

Copper(II) Complex of 5-*t*-Butylsalicylaldehyde, **11.** 5-*t*-Butylsalicylaldehyde (2.54 g, 14.25 mmol) was added over a solution of copper(II) acetate monohydrate (1.87 g, 9.36 mmol) in a mixture of ethanol (3 mL) and water (12 mL). While the mixture was refluxed under stirring for 4 h, sodium hydrogenocarbonate (1.28 g, 15.19 mmol) was added portionwise. The formed precipitate was filtered, washed with water (2 × 15 mL) and then ethanol (3 × 10 mL), and dried to afford copper dienolate **11** (97%): mp 240 °C (dec); IR (ATR) 1625, 1599, 1163, 832 cm⁻¹. Anal. Calcd for C₂₂H₂₆O₄Cu: C, 63.12; H, 6.23. Found: C, 62.50; H, 6.23.

General Procedure for Preparations of **5a–d and **13** under Catalysis by **11** (Scheme 2).** Mixtures of ketoester **3a** (about 1 M in toluene) and a 3–5-fold molar excess of volatile **4a–c** or 2 equiv of **4d** were treated at the temperature indicated in Scheme 2. The reaction crudes were either evaporated and the residues directly distilled in a vacuum (**5a–c**) or chromatographed through a column of silica gel (**5d**) with mixtures of hexanes–ether of increasing polarity to afford **5a–d** in the yields indicated in Scheme 2.

2-(2-Cyanoethyl)-2-ethoxycarbonylcyclopentanone, **5b:** bp 165 °C/3 mmHg; IR (ATR) 2247, 1746, 1717 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26 (t, *J* = 7.2, 3H), 1.83–2.90 (m, 10H), 4.19 (q, *J* = 7.2 Hz, 2H); ¹³C NMR (CDCl₃) δ 12.6, 13.6, 19.2, 28.9, 33.3, 37.4, 58.3, 61.4, 119.0, 170.0, 213.4.

2-(2-(Ethoxycarbonyl)ethyl)-2-ethoxycarbonylcyclopentanone, **5c:** oil, IR (ATR) 1722, 1180, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26 (t, *J* = 7.2 Hz, 6H), 1.72–2.73 (m, 10H), 3.98–4.40 (m, 4H); ¹³C NMR (CDCl₃) δ 13.8, 13.9, 19.3, 28.1, 29.6, 33.3, 37.6, 59.0, 60.2, 61.2, 170.7, 172.7, 214.1.

Ethyl 2-Oxo-1-(1-*N,N*-bis(ethoxycarbonyl)hydrazino)cyclopentanecarboxylate, **5d:** oil; IR (ATR) 3306, 2981, 1714, 1376, 1224, 1095, 1056, 1021, 761 cm⁻¹; ¹H NMR (C₆D₆, 40 °C) δ 0.90–1.20 (m, 9H), 1.45–3.07 (m, 6H), 3.98–4.22 (m, 6H), 7.13 (s, 1H); ESI-MS 353.1 (M + Na), 369.1 (M + K).

3-Acetyl-2-methyl-naphtho[2,3-*b*]furan-4,9-dione, **13:** mp 202–203 °C (lit.⁴⁵ mp 202–203 °C); IR (ATR) 1672 cm⁻¹;

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^1H NMR (CDCl_3) δ 2.69 (s, 3H), 2.81 (s, 3H), 7.80 (m, 2H), 8.22 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.0, 31.7, 120.7, 126.4, 127.1, 131.3, 133.1, 133.7, 133.9, 163.7, 173.2, 180.0, 195.3; MS (70 eV) 254 (M^+ , 89), 239 (100), 183 (20), 43 (53); ESI-MS 277.0 ($\text{M} + \text{Na}$).

Preparation of Copper(II) Complex of 2-Ethoxycarbonylcyclopentanone, 14.⁴⁶ Ketoester **5a** (2.0 mL, 13.49 mmol) in methanol (2 mL) was added over a stirred solution of copper acetate monohydrate (1.35 g, 6.74 mmol) in water (40 mL). The formed precipitate was filtered and dried to afford **14** (68%): IR (KBr) 1607, 1517, 1306, 1059 cm^{-1} .

Preparation of 2-Ethoxycarbonyl-2-(3-oxobutyl)cyclopentanone, 5a, by Reaction of 14 with Butenone. A mixture of copper enolate **14** (375 mg, 1 mmol), butenone (600 μL , 7 mmol), and dichloromethane (5 mL) was stirred at room

temperature for 4 days. The mixture was partitioned between dichloromethane and 1 M HCl. The organic layer was dried and evaporated to afford **5a** (84%).

Acknowledgment. Financial support from DGEIC (Project BQU2002-04002) and CIRIT-Generalitat de Catalunya (Projects 2001SGR00181 and 2001SGR00291) is gratefully acknowledged. R.M.S. was incorporated into the research group through a "Ramón y Cajal" contract (MCYT-FEDER/FSE).

Supporting Information Available: Spectroscopic data for **5a–d**, **6**, **9**, **11**, **13**, and **14**, IR spectrum of the complex resulting from reaction of Scheme 3, and pertinent ESI-MS spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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