3.1 Abstract

Copper(II) Schiff base complex catalyzed Michael additions of methyl 1-oxoindane-carboxylate with methyl vinyl ketone (MVK) were performed in water. Several α-amino acid and α-amino alcohol derived water soluble Schiff base copper(II) complexes were investigated as chiral, water stable Lewis acids. Although an increase of the rate of the 1,4-addition could be accomplished, no enantioselectivity was found when the reaction was performed in water. The reaction suffered from ligand-substrate exchange which prevented the possibility to get high asymmetric induction.

3.2 Introduction

The Michael addition of carbon nucleophiles is one of the most important carbon-carbon bond forming reactions in organic synthesis. However, the base catalyzed reactions often suffer from the formation of side products. These include nucleophilic attack of the base, rearrangements, polymerisation of the Michael acceptor or secondary condensation reactions of the intermediate enolate, transesterifications, cyclocondensations and above all retro Michael reactions.1 To circumvent these problems several catalysts such as phase transfer catalysts,2,3 alumina,4 alkali metal halides or transition metal complexes have been successfully used.5

![Reaction Scheme](image)

Scheme 3.1

3.2.1 Michael additions in water

In the early seventies it was recognized that water could efficiently be used as a solvent for the reaction of relatively acidic carbon compounds with Michael acceptors. Because of the relative high acidity, mild conditions can usually be employed in the conjugate addition of such carbon nucleophiles. When the reaction of cyclic 1,3-diketones and methyl vinyl ketone (MVK) was performed in water, the yield and purity of the products could appreciably be improved by working in an aqueous medium without the use of base, as was found independently by Hajos and Parrish and Wiechert and co-workers.6,7,8 This concept was, for example, successfully used in the synthesis of the starting material for optically pure Wieland-Miescher ketone 3.1,9 an important intermediate in the preparation of a variety of natural products (Scheme 3.1).10

Later Lubineau and Augé discovered that the Michael reaction of nitromethane or nitroethane with MVK, which was considered impossible in 1916,11 proceeded nicely when water, under neutral conditions, was used as a solvent without the use of a catalyst (Scheme 3.2).12 Other polar solvents such as methanol and dimethyl sulfoxide were also investigated but the reaction is more rapid and selective in water then in these solvents. However, other examples of Michael reactions in water are rare.13

![Scheme 3.2](image)

3.3 Preliminary investigations

It was reported in the literature that the Michael addition of nitroalkanes could be catalyzed by chiral and achiral transition metal catalysts in organic solvents.14 In order to see whether beneficial effects of the use of both transition metal catalysis and water as a solvent can even improve the outcome of these reactions, the combination of water as a solvent and transition-metal catalysis was investigated. We found that the reaction of nitromethane with β-substituted enones such as benzalacetone or chalcone 3.2 did not proceed at all in water, either in the absence or in the presence of up to 30 mol% of a transition-metal catalyst such as

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Copper Schiff Base Catalyzed Michael Additions of \( \beta \)-Ketoesters to Methyl Vinyl Ketone in Water

Ni(acac)\(_2\) or a nickel bis (\(l\)-)prolinol complex (Scheme 3.3). The latter complex was successfully employed for similar reactions in organic solvents like benzene by Botteghi.\(^{15,16}\)

\[
\begin{align*}
\text{CH}_2\text{NO}_2 + \text{Ph}\text{C} = \text{C}R & \xrightarrow{30 \text{ mol}\% \text{ Ni(acac)}_2} \text{Ph}\text{C} = \text{C}R \\
\text{3.2} & \xrightarrow{60 \text{ mol}\% \text{N}(\text{acac})_2} \text{Ph}\text{C} = \text{C}R
\end{align*}
\]

\(R=\text{CH}_3, \text{Ph}\)

Scheme 3.3

**3.3.1 Lewis acid Catalyzed Michael additions of \( \beta \)-dicarbonyl compounds**

The 1,4-addition reaction of \( \beta \)-dicarbonyl compounds with Michael acceptors can readily be catalyzed by transition metal complexes based on nickel, copper or palladium.\(^{5,17,18}\) These Lewis acids exhibit yields and selectivities for the Michael adducts that are generally superior to those obtained by using strongly basic catalysts. In the course of the studies of Nelson and co-workers on the reactions of \( \beta \)-dicarbonyl compounds with various nucleophiles catalyzed by Ni(acac)\(_2\),\(^5\) it was found that, for example, the conjugate addition of 2,4-pentandione to MVK was efficiently catalyzed to give the Michael adduct in 90 % yield. Ethyl acetoacetate and diethyl malonate also gave satisfactory yields of the desired Michael adduct with representative Michael acceptors. The \( \beta \)-dicarbonyl compounds are proposed to be activated via a \( \beta \)-diketonate complex 3.3, which is formed by the replacement of the acidic hydrogen of the substrate and a six membered chelate ring is produced (Scheme 3.4). The electrons of the resultant chelate ring are delocalized to give a certain amount of aromatic character. The chelate ring can be viewed as a metal-stabilized nucleophile, in which the charge of the coordinated reagent is partially removed by action of the metal centre. Thus the electron rich methine carbon of the coordinated \( \beta \)-dicarbonyl enolate attacks the electron poor \( \beta \)-carbon atom of the Michael acceptor, giving zwitterionic complex 3.4. Protonation and exchange of 3.4 with another equivalent of \( \beta \)-dicarbonyl compound regenerates the catalyst-substrate complex 3.3 and releases the Michael adduct 3.5 (Scheme 3.4). Lewis acids catalyze these Michael additions under essentially non-equilibrium conditions, whereas base catalyzed reactions often impart equilibrium conditions which frequently result in lower yields.\(^{19,23}\)

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16 The complex was prepared *in situ* from Ni(acac)\(_2\) and two equivalents of (\(l\)-)prolinol which gave a stable green complex in water (Scheme 3.3).
3.3.2 Enantioselective Michael additions

Several catalytic Michael additions of β-ketoesters employing chiral Lewis acid complexes resulted in the formation of enantiomerically enriched products. The mechanism involves a complex of the bidentate Michael donor of which the π-faces become diastereotopic since the complex now offers a chiral environment (Figure 3.1).

Figure 3.1 Schematic representation of the proposed activated β-ketoester.

Brunner reported the addition of methyl-1-oxoindanonecarboxylate 3.9 with MVK in the presence of 3 mol% of chiral cobalt(II) complex derived *in situ* from Co(acac)$_2$ and (-)-1,2-diphenyl-1,2-ethanediame (Figure 3.1), providing the 1,4-adduct with an enantioselectivity of 66%. Desimoni and co-workers showed that copper(II) Schiff base complexes are catalytically active in the Michael addition of β-ketoesters to MVK in organic
Copper Schiff Base Catalyzed Michael Additions of β-Ketoesters to Methyl Vinyl Ketone in Water

All copper complexes 3.6 are based on Schiff base ligands derived from salicylaldehyde and chiral amines or chiral amino alcohols and yielded 3.10 with e.e.'s up to 65 % (Scheme 3.5).

\[ \text{Scheme 3.5 Copper Schiff base complex catalyzed Michael addition of 3.9 in CCl}_4. \]

3.4 Results and discussion

Since the Michael reaction of β-dicarbonyl compounds in water was only reported incidentally, we first investigated the scope of these reactions. In Scheme 3.6 some examples are depicted. Several dialkylmalonates and β-ketoesters were used, but in most cases mainly starting materials were recovered. When dialkylmalonates were tested in the conjugate addition to MVK or cyclic enones, only starting materials were isolated when water was used as a solvent, even after prolonged reaction times or after the addition of catalytic amounts of Brönsted acids or elevated reaction temperature. β-Diketones gave the desired Michael adducts in nearly quantitative yield as the only product in accordance with some related examples in the literature.6,7 When unsubstituted β-diketone 3.7 was used the bis Michael adduct 3.8 was formed in quantitative yield. When β-ketoesters such as ethyl acetoacetate or ethyl 2-methyl-acetoacetate were employed, traces of the Michael adduct were found.26 Only when methyl 2-oxo-indanecarboxylate 3.9 was used, after 6 d complete reaction was observed in the reaction with MVK to give 3.10. This reaction is still sluggish and therefore the combination of water as a solvent and Lewis acid catalysis seemed an obvious step to improve the reactivity of Michael addition of these β-ketoesters and the possibility to perform catalytic asymmetric reactions in water.

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26 Even after 14 d reaction at room temperature only approximately 40 % of the β-ketoester was converted.
3.5 Copper (II) Schiff base complexes

In this section the results of the study of water as a solvent and of Lewis acid catalyst in combination with chiral ligands in the Michael addition of \( \beta \)-ketoesters using copper(II) Schiff base complexes 3.11 are described.\textsuperscript{20,21} Copper(II) Schiff base complexes were used because at the beginning of these studies the best results reported in the literature on Lewis acid catalysis were obtained with copper(II) Schiff base complexes.\textsuperscript{24} Furthermore, the structure of these ligands can easily be altered, by using different \( \alpha \)-amino alcohols 3.12 or amino acids 3.13 in order to improve the solubility of the complex or the enantioselectivity of the reaction (Figure 3.2).
Copper Schiff Base Catalyzed Michael Additions of $\alpha$-Ketoesters to Methyl Vinyl Ketone in Water

The architecture of the ligands can be altered at several sites; among these the following function can be modified (Figure 3.2):

- a) Different coordinating moieties (to increase steric bulk)
- b) $\alpha$-Amino acids or substituents on the amino alcohol
- c) Substituents at the aromatic rings
- d) Additional axial coordinating groups
- e) Type and oxidation state of the metal

3.5.1 **Schiff base copper (II) complexes in water: solubility and stability**

The condensation of primary amines with aldehydes and ketones gives imines. Imines that contain an aryl group bound to the nitrogen or to the carbon atom are called Schiff bases, since their synthesis was first reported by Schiff.\(^ {27}\) The most common method of obtaining a Schiff base is straightforward, as indicated by the condensation reaction between an aldehyde or ketone and a primary amine with the formation of an intermediate hemiaminal (Scheme 3.7).

\[
\begin{align*}
\text{R}_1\text{R}_2\text{C}=\text{O} + \text{R}_3\text{NH}_2 & \rightleftharpoons \text{R}_1\text{R}_2\text{NHR}_3 \rightleftharpoons \text{R}_1\text{R}_2\text{N}^+\text{OH} - \text{H}_2\text{O} \rightleftharpoons \text{R}_1\text{R}_2\text{R}_3\text{N}^+ \\
\text{Scheme 3.7 Condensation of primary amines with aldehydes and ketones.}
\end{align*}
\]

Because imine formation is an equilibrium reaction, it can be imagined that this equilibrium lies on the aldehyde side in water. Therefore first the solubility and stability of various chiral and achiral $\alpha$-amino alcohol and $\alpha$-amino acid based salicylidene Schiff base copper(II) complexes were investigated in aqueous solutions.

Scheme 3.8 In situ formation of copper(II) Schiff base complexes.

Table 1 Solubility of salicylidene Schiff bases 3.14 and the corresponding copper(II) complexes 3.11 in water.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>al/ac</th>
<th>Solubility imine</th>
<th>Solubility complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amino ethanol</td>
<td>H</td>
<td>H</td>
<td>al</td>
<td>Good&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2-Methylamino-propanol</td>
<td>Me</td>
<td>Me</td>
<td>al</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>2-Aminobutanol</td>
<td>Et</td>
<td>H</td>
<td>al</td>
<td>Good</td>
</tr>
<tr>
<td>4</td>
<td>Valinol</td>
<td>i-Pr</td>
<td>H</td>
<td>al</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>Phenylglycinol</td>
<td>Ph</td>
<td>H</td>
<td>al</td>
<td>Poor&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Glycine</td>
<td>H</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Alanine</td>
<td>Me</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Valine</td>
<td>i-Pr</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Phenylglycine</td>
<td>Ph</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Phenylalanine</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Serine</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
<td>H</td>
<td>ac</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Amino phenol</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>OH</td>
<td>al</td>
<td>Very poor&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> al = amino alcohol or ac = amino acid; <sup>b</sup> No crystallisation is observed with a 0.01 M solution; <sup>c</sup> The product crystallizes from the hot 0.01 M solution after cooling to room temperature; <sup>d</sup> Product is insoluble at reflux temperature.
The result of a qualitative study of the solubility of the Schiff bases and copper(II) complexes are summarized in Table 1. The amino alcohol derived Schiff bases 3.14 were prepared according to literature procedures\cite{24} by refluxing the corresponding amino alcohol with an equimolar amount of salicylaldehyde in toluene in the presence of p-TsOH, to give the desired Schiff bases in high yields. The resulting imine was dissolved in water by heating, to give a 0.01 molar solution of the Schiff base as a yellow homogeneous mixture when amino alcohols with aliphatic substituents were employed. The imines derived from amino alcohols with aromatic side chains precipitated from the aqueous solution upon cooling of the mixture. The Schiff base prepared from aminophenol and salicylaldehyde was poorly soluble in water and no homogeneous solution could be obtained.

Although the formation of Schiff bases is generally an equilibrium reaction, the Schiff bases of salicylaldehyde are relatively stable towards hydrolysis and dissociation,\cite{28} probably because of hydrogen bonding between the arylimine nitrogen and the phenolic hydrogen, making these compounds more stable towards hydrolysis then "normal" imines.\cite{28} It was found, however, that the presence of copper(II) stabilizes these Schiff bases, even at acidic pH. Once coordinated to copper, the Schiff bases are not sensitive towards hydrolysis.\cite{29,30}

For the copper(II) complexes the same trend in solubility was observed as for the free ligands. Schiff base copper(II) complexes bearing aliphatic side chains are readily soluble in water, without the use of an additional co-solvent, whereas the complexes of the Schiff bases containing aromatic rings precipitate from the aqueous solution.

The synthesis of salicylidene Schiff bases 3.15 of the \(\alpha\)-amino acids often results in low yields of the desired compounds.\cite{29} However, it was found that the corresponding Schiff base copper(II) complexes could easily be prepared \textit{in situ} by heating equimolar amounts of amino acid 3.13, salicylaldehyde (3.6) and copper(II) chloride in water. The same trend was found as for the solubility of the \(\alpha\)-amino alcohol derived complexes in water. \(\alpha\)-Amino acids with aliphatic substituents are very soluble in water and give at \(10^{-2}\) M a bright green homogeneous solution of the corresponding Schiff base complexes. In contrast, the phenylglycine Schiff base complex was poorly soluble in water, giving a green precipitate upon cooling of the solution to room temperature.

To our surprise the copper complex of the Schiff base derived from serine was also poorly soluble in water and precipitated from the solution. Probably the additional hydroxyl group which was intended to act as an additional coordinating moiety (\textit{vide supra}), functions as an intermolecular hydrogen bond donor. This might result in the formation of an insoluble polymeric hydrogen bonded complex. All complexes that were readily soluble in water, gave bright green solutions.

\begin{itemize}
\item \textsuperscript{30} Gelber, L.R., Karger, B.L., Neumeyer, J.L., Feibush, B. \textit{J. Am. Chem. Soc.} \textbf{1984}, 106, 7729.
\end{itemize}
3.5.2 Copper (II) Schiff base catalyzed Michael additions

Having established that copper(II) Schiff base complexes are readily soluble in water when aliphatic amino alcohols or amino acids are employed, they can be tested as Lewis acid catalysts in the Michael addition of β-ketoesters in aqueous solutions. As a model reaction the conversion of methyl 2-oxo-indanecarboxylate 3.9 with MVK was investigated, using the achiral Schiff base copper(II) complex 3.17 of 2-salicylidene-aminoethanol 3.18. The Michael addition was successfully accelerated in water when 10 mol% of 3.17 was used as the Lewis acid catalyst. Instead of 144 h the reaction was completed in 40 h, and Michael adduct 3.10 was isolated in 95 % yield after column chromatography.

\[ \text{C} = \begin{array}{c} \text{Cu}^2+ \rightarrow \text{Cu}^2+ \text{S} \\ \text{K} \downarrow \text{S} \end{array} \]

\[ \text{Cu}^2+ + \text{S} \rightarrow \text{Cu}^2+ \text{S} \]

\[ \text{K} \downarrow \text{MVK} \]

\[ \text{Cu}^2+ \text{S} \rightarrow \text{Cu}^2+ + \text{S} \]

\[ \text{Scheme 3.9 Copper(II) Schiff base catalyzed Michael addition.} \]

3.5.3 Kinetic experiments

The second order rate constant of this reaction was determined by UV/VIS spectroscopy. A 5.0 \(10^{-5}\) M solution of 3.9 in water was allowed to react with MVK under pseudo-first-order reaction conditions. Under these conditions an apparent second-order rate constant of 2.7 \(10^{-3}\) M\(^{-1}\) s\(^{-1}\) was found. The reaction in the absence of catalyst at the same pH was very slow; unfortunately the rate constant could not be determined under these conditions. From these experiments it was concluded that Schiff base copper complexes indeed function as a Lewis acid catalyst for the Michael addition of 3.9 with MVK in water, and that it was not a Brönsted acid catalyzed reaction.

This acceleration of the reaction was, however, lower under the conditions used on a preparative scale. For the kinetic experiments the solution was homogeneous, but in the preparative scale additions the Michael donor was not completely dissolved. As a consequence the rate with which the β-ketoester dissolves also influences the overall reaction rate of the reaction.


\[ \text{Conversions determined by GC, see experimental section.} \]

\[ \text{The apparent second order rate constant is dependent on the following steps:} \]

\[ \text{No reaction could be observed using UV/VIS spectroscopy.} \]

\[ \text{The following concentrations were used: 0.01 M catalyst, 0.1 M β-ketoester 3.9.} \]
Michael addition. Furthermore it was noticed that the bright green colour of the catalyst solution vanished under the reaction conditions whereas the colour returned after 2 d, when the Michael addition was completed.

Initially it was considered that the copper-β-ketoester complex, as originally proposed by Desimoni,24 was poorly soluble in water and that the precipitation of this complex 3.19 (Figure 3.3) was responsible for the disappearance of the colour of the solution. However, when the other water soluble Schiff base complexes were tested as Lewis acid catalysts for the model Michael reaction, the colour disappeared in all cases as long as 3.9 was present in the reaction mixture and the colour returned when the reaction was complete. Nearly quantitative yields of the Michael adduct were obtained in all cases. However, when optically pure Schiff base complexes were employed, racemic product was isolated.36 For example when (S)-2-salicylidene-2-aminobutanol was used as the chiral ligand 3.10 was isolated with an enantiomeric excess of only 2% when the reaction was performed in water. According to the literature24 the same reaction in carbon tetrachloride gave 50 ± 3% e.e at -20 °C.37 This enantiomeric excess could be reproduced, as judged from the measured optical rotation by working under the same conditions. However, it should be noted that these values are not in agreement with the enantiomeric excess determined by chiral HPLC analysis. On the basis of our analysis the enantiomeric excess was only 28% when the reaction was performed in carbon tetrachloride.

Separation of the enantiomers of 3.10 was achieved by HPLC analysis using a chiral stationary phase (REGIS (R,R) WHELK-O) hexanes:EtOH 4:1.

Desimoni and co-workers24 determined the enantiomeric excess of the product by optical rotation, assuming that the known maximum rotation of the product is correct [α]°578 = 77 (c=2, benzene, 25 °C) according to Wynberg, H. and Helder, R. (Tetrahedron Lett. 1975, 4057). In this article the value for the maximum rotation was calculated, using the enantiomeric excess of non-racemic 3.10 determined by NMR with a chiral shift reagent.
At that point we decided to study the nature of the precipitate in more detail. An equimolar mixture of 3.9 and the copper complex 3.17, prepared *in situ* from anhydrous copper(II) chloride and 2-salicylidene-aminoethanol was stirred at room temperature and the resulting precipitate was filtered and dried. To our surprise the isolated material was not the expected copper Schiff base complex containing the activated $\beta$-ketoester, but the bis (aqua) bis (methyl 1-oxo-indanecarboxylate) copper complex 3.20 as concluded from the elemental analysis and mass spectral data of the complex (Figure 3.4). This was confirmed by independent synthesis of the complex by reaction of two equivalents of methyl 1-oxo-indane carboxylate with copper(II) chloride in water.

The formation of this complex can be explained by the displacement of the Schiff base by a second equivalent of 3.9. Although the formation of 3.20 will be an equilibrium reaction, the precipitation of the complex drives the reaction to completion. The precipitation could partly be prevented by the slow addition of 3.9. Since, the $\beta$-ketoester is also present as an activated nucleophile in complex 3.20 and the complex has no chiral ligand, no enantioselectivity can be expected in the copper catalyzed Michael addition of 3.9 in water (Scheme 3.9).
Several groups have so far tried to enhance the enantioselectivity of the reaction of 3.9 with MVK in organic solvents by optimization of the design of the Schiff base ligand with respect to steric hindrance. In another approach to improve the rigidity of the ligand, for instance, the introduction an additional axial group was examined, however without affecting the stereochemical outcome of the reaction drastically. The possibility that the enantioselectivity can also be influenced by a substrate-ligand exchange reaction was never taken into account. On the basis of our results this exchange cannot be completely ignored to explain the results that were obtained in polar solvent like dioxane or diethyl ether.

### 3.6 Conclusion and prospects

It was demonstrated that the Michael addition of methyl 1-oxoindanecarboxylate 3.9 with MVK could efficiently be catalyzed by copper(II) complexes in water. This finding represents the first example of Lewis acid catalyzed Michael addition of a stabilized carbanion in water. Several salicylidene amino alcohol and amino acid Schiff bases gave stable water soluble copper(II) complexes. However, when these copper(II) salicylidene Schiff base complexes were employed as Lewis acids in the previously mentioned Michael additions, the reaction suffered from ligand-substrate exchange at the copper centre. This exchange prevented the Michael addition of 3.9 with MVK to proceed in an enantioselective manner in water.

Modification of the ligand might be a possible solution to prevent ligand exchange. However, since the number of β-ketoesters that can be used is limited in the copper catalyzed...
Chapter 3

Michael addition,\textsuperscript{39} it was decided to continue our investigations by looking for other metals as stable water soluble Lewis acid catalysts. The results of the Lewis acid catalyzed Michael additions in water, using lanthanides are reported in the next chapter.

3.7 Experimental Section

Instruments and experimental methods

Optical rotations were measured on a Perkin-Elmer 241 MC (at RT). Elemental analyses were performed in the microanalytical department of this laboratory by Mr. H. Draaijer, Mr. J. Ebels and Mr. J. Hommes. Optical rotations were measured at ambient temperature on a Perkin-Elmer 241 polarimeter. $^1$H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a Varian-300 (300 MHz) spectrometer. Chemical shifts are denoted in δ-units (ppm) relative to residual solvent peaks (CHCl$_3$, δ = 7.26 ppm). $^{13}$C NMR spectra (APT) were recorded on a Varian Gemini-200 (50.32 MHz), a Varian-300 (75.48 MHz) or a Varian-500 (125.80 MHz) spectrometer. Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ(CHCl$_3$) = 77.0 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet) and br (broad). $^{27}$Al NMR spectra were recorded on a Varian-300 (78.12 MHz) spectrometer. Mass spectra were obtained on a JEOL JMS-600H mass spectrometer (CI) or a AEI MS-902 mass spectrometer by Mr. A. Kiewiet.

Materials

2-Aminoethanol, 2-methyl-2-aminopropanol, (S)-2-aminobutanol, (S)-2-amino-4-methyl-1-pentanol (valinol), 2-phenyl-2-aminoethanol (glycinol), 1-phenyl-aminopropanol (norephedrine), 2-aminophenol were commercial products (Aldrich or Fluka) or were prepared by LiAlH$_4$ reduction of the corresponding amino acid methyl esters. All $\alpha$–amino acids were commercial products (Aldrich or Fluka) and used without further purification. Methyl 2,3-dihydro-1-oxo-1H-Indane-2-carboxylate \textit{3.9} was prepared according to the literature procedure.\textsuperscript{40} Methyl vinyl ketone (Aldrich or Fluka) was distilled immediately prior to use.

Uncatalyzed Michael additions of $\beta$-dicarbonyl compounds in water, general procedure:

A mixture of the $\beta$-dicarbonyl compound (1.0 mmol) and freshly distilled MVK (0.03 mmol) in water (10.0 mL) was stirred at room temperature for 48 h (144 h for \textit{3.9}). The mixture was extracted with methylene chloride (15.0 mL), the combined organic layers were washed with

\textsuperscript{39} Several other $\beta$-ketoesters were also tested in the copper catalyzed Michael addition towards MVK in water, however, in all cases the reaction was still very slow and less efficient catalysis was found.
brine (10.0 mL), dried (MgSO\(_4\) or Na\(_2\)SO\(_4\)) and the solvent was evaporated under reduced pressure. The results are summarized in scheme 3.6. The products were investigated by \(^1\)H NMR. All spectroscopic data were in accordance with the expected structures and with the data reported in literature.\(^7,21,41\)

**Amino alcohol Schiff bases 3.14, general procedure:**

Salicylaldehyde 3.6 (2.44 g, 20 mmol) and the corresponding amino alcohol (20.0 mmol) were refluxed in toluene (100-150 mL) using a Dean-Stark apparatus until all water was completely separated. The solvent was evaporated and the residue was crystallized from ethanol or toluene. Schiff bases were isolated in 80-95\% yield. The spectroscopic data of each product was in accordance with those reported in the literature\(^{24,25,42}\) and in full agreement with the expected structure.

**Amino alcohol and amino acid Schiff base copper(II) complex solutions, general procedure:**

*Method A:* The amino alcohol Schiff base 3.14 (1.0 mmol) was dissolved in double distilled water (100 mL) and heated until a homogeneous solution was obtained. Anhydrous CuCl\(_2\) was slowly added (1.0 mmol) to the stirred reaction mixture to give the corresponding bright green copper (II) Schiff base complex solution (0.01 M). The \textit{in situ} prepared Schiff base copper (II) complex solutions were used for the reactions without further treatment. The colour of the solutions of the \textit{in situ} prepared complexes remained unchanged for at least three months.

*Method B:* Salicylaldehyde (1.0 mmol) and the amino acid (1.0 mmol) or amino alcohol (1.0 mmol) were dissolved in doubly distilled water (100 mL) by heating. To this solution was slowly added anhydrous copper (II) chloride (1.0 mmol) and the resulting bright green solution was allowed to cool to room temperature. The \textit{in situ} prepared Schiff base copper (II) complex solutions were used for the reactions without further treatment.

**Kinetic experiments**

Second-order rate constants were determined by UV/VIS spectroscopy (Perkin Elmer Lambda 2 or 5 spectrometer) in a thermostated quartz UV cell (1.0 cm) at 25.0 ± 0.1 °C. The Michael addition of 3.9 to MVK was followed by monitoring the decrease of absorption at 280 nm. The reported rate constant is the average of at least three runs. Excess of MVK was used. The rate constants were determined using conventional pseudo-first-order kinetics and were reproducible to within 2 %.


Copper (II) catalyzed Michael reaction of 3.9 with MVK, general procedure for the synthesis of methyl 3-oxo-2-(3-oxobutyl)-indan-2-carboxylic acid 3.10:

To a suspension of 3.9 (0.190 g, 1.0 mmol) and 10.0 mL of aqueous 0.01 M copper Schiff base complex solution, prepared according to the general procedure, was added freshly distilled MVK (3.0 mmol). The resulting suspension was stirred at room temperature and the progress of the reaction was followed with GC (HP-1, cross linked methylsilicon gum, 15m x 0.35 mm, oven temperature: 220 °C, injection temperature 275 ° C, 3.9: t_r = 1.08; 3.10: t_r = 4.87) until all starting material was converted (ca. 2 d). The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic fractions were washed with brine (25 mL), dried (NaSO₄) and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO₂, hexanes:ethyl acetate 65:35) to give 3.10, 0.223-237 g (90-95% yield) as a white solid, mp 104-106 °C (lit. 104-105 °C).

**1H-NMR (CDCl₃, 200 MHz)**
\[ \delta = 2.13 \text{ (s, 3H), 2.2-2.3 (m, 2H), 2.4-2.8 (m, 2H), 3.04 (d, J = 17.5 Hz, 1H), 3.67 (d, 17.5 Hz, 1H), 3.70 (s, 3H), 7.38-7.80 (m, 4H, Ar)}; \]

**13C-NMR (CDCl₃, 75 MHz)**
\[ \delta = 28.57 \text{ (t), 29.92 (q), 37.86 (t), 38.78 (t) 52.74 (q), 59.08 (t), 124.86 (d), 126.39 (d), 127.96 (d), 135.02 (s), 135.53 (d) 152.49 (s), 171.56 (s), 202.21 (s), 207.42 (s)}. \]

**Synthesis of complex 3.20**

**Method A:** To a stirred 0.01 M solution (100.0 mL) of 3.17 was added 3.9 (0.190 g, 1.0 mmol) and the green colour slowly disappeared. The mixture was stirred overnight and the precipitate was filtered and dried under vacuum to give a greenish yellow (0.160 g, 0.33 mmol) solid mp 104-106 °C (lit. 104-105 °C). IR (KBr): 3450, 1630, 1605, 1580, 1543, 1476, 1460, 1404, 760, 729; MS (CI): calcd. for C₂₂H₁₈O₆Cu: 441.0 found: 441.0; Anal. calcd. for C₂₂H₁₈O₆Cu.2H₂O: Cu 13.30 C 55.29, H 4.64, N 0.0; found Cu 13.25 C 54.94, H 4.44, N 0.0.

**Method B:** To a stirred 0.01 M CuCl₂ solution (100 mL) was added 3.9 (0.380 g, 2.0 mmol) and the mixture was stirred overnight. The precipitate was filtered off and dried under vacuum to give a greenish yellow solid that had an identical molecular mass and identical infrared absorptions as the solid prepared according to Method A.

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