Chapter 5

Dramatic micellar rate enhancement of the Cu\textsuperscript{II}-catalyzed vinologous Friedel-Crafts alkylation in water

A dramatic rate enhancement of the Cu\textsuperscript{II}-catalyzed Friedel-Crafts alkylation in water was achieved in the presence of sodium dodecyl sulfate (SDS) micelles. We found that the reaction conducted in the presence of copper and surfactant undergoes an unprecedented acceleration up to $9.3 \times 10^3$ fold compared to the reaction performed in the presence of copper but in the absence of surfactant. The extremely short reaction times, the easy work up and the good product yields represent the main advantages of this approach.

This chapter has been published:
5.1 Introduction

5.1.1 Water as a unique medium for organic reactions

For decades, in organic synthesis and especially in catalysis, water has been a solvent to be avoided. The solvents of choice for organic reactions have been organic solvents due to the disadvantages associated with the use of water such as, for instance, the deactivation and insolubility of catalysts and often low solubility of substrates.

Recently, water has been promoted as an ideal solvent in ‘green chemistry’.\[1a\] its use as solvent is desirable over organic solvents not only because water is arguably the cheapest, non-toxic, readily available and environmentally friendly solvent, but also because it brings several advantages to organic reactions.\[1b\] Among these, simplified procedures: easy isolation of organic products, the possibility to recycle water-soluble catalysts and reagents and the fact that the need of protecting-groups strategies in the presence of acidic hydrogens or hydrophobic derivatization of several substrates involved in the reactions under study is reduced.\[1c\] Finally, in some cases, water has been demonstrated to have a beneficial effect on the catalytic event increasing both rate and selectivity: key examples are, in addition to the Diels-Alder reaction - for which Breslow and Grieco observed early in the 1980s a positively increase of rates and selectivities\[2-7\] - aldol reactions,\[8-10\] Claisen rearrangments,\[11\] allylation reactions\[12\] and hydrogenations\[13\] that are among the most useful transformations for synthetic chemists.

Since the first discovery, the positive effects of water in the Diels-Alder reaction in terms of rate and also selectivity enhancement, were extensively studied.\[14\] For this reaction, the enhancement of the reaction rate has been commonly ascribed to two major contributions:\[14a,c\] 1) hydrophobic effect: this refers to both the tendency of apolar solutes to stick together in the water medium (hydrophobic interactions), and to the unfavourable solvation of the apolar substrates by water molecules which forces the reaction partners into close contact in the activated complex, leading to a relatively less destabilized transition state and to rate acceleration (hydrophobic hydration); 2) secondly, hydrogen bonding between the water and the activated complex.\[15\]

It was reported that also the endo/exo selectivity of the Diels-Alder reaction was influenced by water: the more compact endo product was favoured due to
the hydrophobic effects and it was thus preferentially formed.\[16\]

5.1.2 Solubility of organic compounds in water: surfactants as a way to expand the scope of water-based organic synthesis

These surprising results triggered a broad interest in the field of aqueous phase synthesis and nowadays the potential and versatility of using water as reaction medium also for transition metal catalyzed reactions is increasingly recognized.\[13b,17\] However, sometimes, the poor solubility of reactants represents an obstacle. Several approaches have been proposed to overcome this problem including the functionalization of the catalyst with solubilizing ionic groups\[18,19\] or the use of organic cosolvents: these reduce the hydrogen-bond density of the aqueous system which is then less effective in pushing the non polar solutes out of the solution. However, also in this case there is a drawback since this process will occur at the cost of high polarity, cohesive density and the hydrophobic effect that are all attractive features of water as medium.\[19\] Another alternative is represented by the use of surfactants, that is, micellar media.\[20\]

Surfactants are amphiphilic molecules which comprise a polar or ionic head group, which interacts strongly with water, and a non-polar tail (usually made of one or more alkyl chains) within the same molecule (Figure 1).

**Figure 1.** Schematic representation of a surfactant molecule and simplified representation of a micellar aggregate.

In an aqueous medium, these molecules orient themselves, thus minimizing the contact between the non-polar region and water molecules. Upon increasing the concentration, at a certain point, when the concentration of surfactant molecule exceeds the solubility limit (the so-called critical micellar concentration (cmc)), micellization occurs. After reaching this value, within the aggregates, which are quite dynamic, the non-polar tails will stick together, shielded
from the water and the polar head groups will protrude towards the water phase.\[^{[21a]}\] The organic solutes interact with these aggregates according to their own polarity and their uptake is driven by hydrophobic and electrostatic interactions: polar substrate molecules tend to reside at the outer region of the micelle; moderately polar ones are located closer the polar surface; non polar solutes reside in the inner region of the aggregate. Such compartmentalization can lead to enhancement of the rate of a reaction or to inhibition.\[^{[21b]}\]

The exceptional results obtained in certain cases by using surfactants, have been generally explained with the solubilization power and the ability of the micellar aggregate to concentrate reactants in a small reaction volume; however the detailed mechanism of action depends on the nature of the substrates/surfactants and on the type of reaction investigated.

### 5.2 LASCs

In the context of metal catalyzed reactions, most of the commonly used Lewis acids (LA’s) are water-intolerant: they operate trough coordination to one or more Lewis-basic sites on an organic substrate; also water has one available basic site, so the hydration of the Lewis acid will hamper the coordination of the latter to the substrate especially when water is present at high concentration, that is, when it is used as a solvent. Kobayashi and coworkers showed that a series of lanthanide triflates and other metal salts can be used as water-tolerant LA’s.\[^{[1b,22,23]}\] Cosolvents are generally needed to increase the efficiency of the catalyzed reaction; alternatively, it was found that surfactants were beneficial in LA-catalyzed aldol\[^{[24]}\] (Scheme 1) and allylation reactions\[^{[25]}\] in water.

**Scheme 1.** LA-catalyzed aldol reaction in the presence of surfactant (SDS).
After these early observations, the same group developed the concept of Lewis acid-surfactant-combined catalysts (LASCs),\cite{26} a new type of LA-system in which the active metal ion carries long anionic hydrocarbon sulfate or sulfonate ligands. LASCs have emerged as a powerful approach to achieve efficient Lewis acid catalysis in water\cite{26,27} (Scheme 2).

**Scheme 2.** Reactions catalyzed by LASCs in water.\cite{27}

a) Aldol reaction

\[
\text{PhCHO} + \text{OSiMe}_3 \rightarrow \text{PhCO}_2\text{H} + \text{PhCHO} + \text{vSiMe}_3 \rightarrow \text{PhCO}_2\text{H}
\]

b) Michael-type reaction

\[
\text{CO}_2\text{t-Bu} + \text{Sc(DS)}_3 \rightarrow \text{CO}_2\text{t-Bu}
\]

c) Three-component Mannich-type reaction

\[
\text{PhCHO} + \text{OCH}_2\text{NH}_2 + \text{vSiMe}_3 \rightarrow \text{PhCO}_2\text{H}
\]

d) Three-component α-amino phosphonate synthesis

\[
\text{PhCHOH} + \text{RNH}_2 + \text{P(OEt)}_3 \rightarrow \text{PhCO}_2\text{H}
\]

e) Friedel-Crafts type reaction of aromatic compounds

\[
\text{X} + \text{R}^* \rightarrow \text{R}^* \rightarrow \text{X}
\]
They are based on the synergy between two components: Lewis acidic metal cations and anionic surfactants that form micellar aggregates. Whereas the Lewis acid generally is the key to the observed catalysis, the presence of micellar aggregates provides an additional rate acceleration. The favourable micellar effect has been attributed to an increased local concentration of reagents and/or a favourable microenvironment for the catalyzed reaction.

In an early demonstration of the power of LASCs, Engberts et al. reported a million fold rate enhancement compared to the uncatalyzed reaction for the Cu$^{2+}$ dodecyl sulfate (CuDS)$_2$ catalyzed Diels-Alder reaction (Scheme 3).

**Scheme 3.** Cu(DS)$_2$-catalyzed Diels-Alder reaction.

For the reaction conducted in the presence of the surfactant only - SDS or CTAB - a slight inhibition of the reaction was observed. In contrast, the combination of SDS with a catalytically active counterion (Cu$^{2+}$, Zn$^{2+}$, Co$^{2+}$) resulted in an extremely potent catalyst for the reaction between aza-chalcone with cyclopentadiene.

It is noteworthy that these results are strictly dependent on the nature of the substrates, the features of the surfactant molecule used and the shape of the aggregates formed, which could affect the distribution of the substrates/reactants. Furthermore, comparison with the reaction catalyzed by Cu(NO$_3$)$_2$ alone, in the absence of surfactant, showed that the micellar contribution to the rate acceleration was limited to one order of magnitude.

The LASC concept has been expanded significantly by Kobayashi et al., who have
reported a variety of reactions catalyzed by Sc(DS)$_3$\textsuperscript{[27]} including the Friedel-Crafts alkylation of indoles (Scheme 2, e).\textsuperscript{[27g,30]}

In the present chapter, a dramatic rate acceleration of up to $9 \times 10^3$ fold in the Cu\textsuperscript{II}-catalyzed vinologous Friedel-Crafts alkylation of indoles in the presence of sodium dodecyl sulfate (SDS) micelles is reported (Figure 2).

**Figure 2.** Cu\textsuperscript{II}-catalyzed Friedel-Craft reaction in micellar medium.

### 5.3 Friedel-Crafts reaction catalyzed by Cu\textsuperscript{2+}-SDS

The Friedel-Crafts alkylation of indoles gives rise to heteroaromatic products that are useful synthons for pharmacologically interesting compounds.\textsuperscript{[31]}

Recently, our group has reported the first catalytic enantioselective vinologous Friedel-Crafts alkylation in water, using a DNA-based Cu\textsuperscript{II}-catalyst.\textsuperscript{[32]} The reaction involves the conjugate addition of a neutral heteroaromatic π-nucleophile to an α,β-unsaturated 2-acyl-(1-methyl)imidazole substrate, which can bind efficiently to Cu\textsuperscript{2+} under aqueous conditions.\textsuperscript{[32]}

The Cu(NO$_3$)$_2$ catalyzed reaction of 5-methoxyindole with the enone carrying a $p$-methoxyphenyl moiety at the β-position (1a), was selected as the benchmark reaction for the present study (Scheme 4). The reactions were performed at 25 °C and monitored by UV/Vis absorption spectroscopy, following the decrease of the enone substrate in time. The apparent second-order rate constants were determined using the methods developed previously;\textsuperscript{[29,32]} an excess of Cu(NO$_3$)$_2$ compared to the enone substrate was used in the kinetic experiments, which means that the contribution of the dissociation of the product from the Cu\textsuperscript{2+} ion to the observed rate is negligible.
5.3.1 Results and discussion

Initially, a range of different SDS concentrations was screened, using a constant Cu(NO₃)₂ concentration of 0.15 mM (Table 1). Compared to the reaction in the absence of SDS, a significant increase of the $k_{\text{app}}$ was already found using low concentrations of SDS. The rate acceleration increased dramatically around the critical micelle concentration (cmc), which was determined to be 5.1 mM under these conditions (Figure 3), and reached a maximum at 8 mM SDS: at this concentration a rate acceleration of $1.2 \times 10^3$ fold compared to the reaction with Cu²⁺ alone was found (entry 6). Further increasing of the SDS concentration to 15 mM led to a decrease in the $k_{\text{app}}$.

The influence of the Cu(II) concentration on the reaction rate was investigated using a fixed SDS concentration of 8 mM (Table 1). Unsurprisingly, lowering the Cu(NO₃)₂ concentration led to a decrease in $k_{\text{app}}$. However, even at Cu(NO₃)₂ concentrations as low as 0.03 mM the reaction has proven to be highly efficient.[33]

A notable observation is that the reaction conducted in the presence of 8 mM SDS and in the absence of Cu(NO₃)₂ is significantly faster than the Cu¹⁺-catalyzed reaction in the absence of SDS. This is in marked contrast with the previously reported Diels-Alder reaction where micelles without Cu(II) slowed down the reaction.[29]
Figure 3. Cmc determination of SDS in the presence of 0.15 mM Cu(NO₃)₂.

This observation underlines the synergistic effect of the Cu²⁺ ion and the SDS micelles in the present reaction. The observed rate enhancement is proposed to originate from a high local concentration of the reagents in the micelles, analogous to what has been proposed in case of the Diels-Alder reaction. This is supported by UV/Vis absorption spectrum of a solution of 4e and Cu(NO₃)₂, with and without 8 mM SDS (Figure 4).

Table 1. Effect of the [SDS] and [Cu²⁺] on the rate of the reaction of 4e with 5-methoxyindole (7).[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>[SDS] (mM)</th>
<th>[Cu²⁺] (mM)</th>
<th>$k_{app}$ (M⁻¹·s⁻¹)</th>
<th>acceleration factor[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--[c]</td>
<td>0.15</td>
<td>0.008 ± 0.0015</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.15</td>
<td>0.19 ± 0.028</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.15</td>
<td>0.34 ± 0.22</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>0.15</td>
<td>4.9 ± 1.83</td>
<td>$6.2 \times 10^2$</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>0.15</td>
<td>2.9 ± 0.93</td>
<td>$3.6 \times 10^2$</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>0.15</td>
<td>9.5 ± 1.01</td>
<td>$1.2 \times 10^3$</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>0.15</td>
<td>8.9 ± 2.00</td>
<td>$1.1 \times 10^3$</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>0.15</td>
<td>0.97 ± 0.13</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>0.075</td>
<td>5.9 ± 0.48</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>0.03</td>
<td>3.68 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>0.0075</td>
<td>0.73 ± 0.063</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>0.003</td>
<td>0.31 ± 0.049</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>0.00015</td>
<td>0.46 ± 0.32</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>8[d]</td>
<td>-</td>
<td>0.30 ± 0.0006</td>
<td></td>
</tr>
</tbody>
</table>

[a] Conditions: MOPS buffer, 20 mM, pH = 6; [4e] = 0.015 mM; [5-methoxyindole] = 0.68 - 2 mM, unless noted otherwise. [b] Defined as $k_{app}$ with SDS / $k_{app}$ without SDS.  [c] [5-methoxyindole] = 6.4 - 48.0 mM. [d] [5-methoxyindole] = 1.6 - 4.8 mM.
In the absence of SDS, only the absorption of unbound 4e is visible, which suggests that there is only a low concentration of the active substrate bound Cu\textsuperscript{II} complex present. However, in the presence of 8 mM SDS, a second absorption at higher wavelengths (450 nm) appeared. This absorption is proposed to originate from Cu\textsuperscript{II} bound-4e, which is activated to undergo conjugate addition by 5-methoxyindole (7).

Thus it can be concluded that the high local concentration of the active complex in the presence of SDS gives rise to a dramatically increased reaction rate. The lower $k_{\text{app}}$ found when further increasing the SDS concentration to 15 mM is in agreement with this hypothesis; the presence of more micelles leads to a lowering of the local concentrations of substrates and Cu\textsuperscript{2+} ions, resulting in a decreased reaction rate.

**Figure 4.** UV/Vis absorption spectra of the substrate 4e/Cu(NO\textsubscript{3})\textsubscript{2} in absence (—) and in the presence of 8 mM (—) SDS.

![UV/Vis absorption spectra](image)

$[\text{Cu}^{2+}] = 0.15 \text{ mM}; [\text{1a}] = 0.015 \text{ mM}$

### 5.4 Substrate Scope

The substrate scope of the catalyzed reaction was investigated using a variety of α,β-unsaturated 2-acyl-(1-methyl)imidazole substrates carrying different substituents at the β-position (Scheme 5, Table 2). For every substrate the reaction kinetics were determined either in the presence and in the absence of 8 mM...
SDS. Some of these reactions proved to be so fast that the concentrations of the Cu(NO_3)_2 and the enone substrate had to be lowered to 0.015 mM and 0.008 mM, respectively, in order to allow accurate determination of the kinetics of the reactions.

The most dramatic rate accelerations were observed with enone substrates carrying an aromatic moiety at the β-position (entries 1-4); an up to 9.3 × 10^3 fold rate acceleration was found in case of substrate 4f in the presence of micelles compared to the reaction without SDS (entries 3-4). The rate accelerations observed for the substrates 4b and 4d is slightly lower, but still a three order of magnitude rate enhancement was observed (entries 5-8). Only in the case of substrate 4a the rate enhancement was less pronounced (entries 9-10), which is tentatively ascribed to the steric hindrance provided by the t-butyl moiety at the β-position.

### Table 2. Substrate scope.^[a]^  

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>[SDS] (mM)</th>
<th>k_{app} (M^{-1}·s^{-1})</th>
<th>acceleration factor^[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4e</td>
<td>8</td>
<td>6.1 ± 0.3</td>
<td>4 × 10^3</td>
</tr>
<tr>
<td>2</td>
<td>4e</td>
<td>-</td>
<td>0.0015 ± 0.0005</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4f</td>
<td>8</td>
<td>10.2 ± 0.8</td>
<td>9.3 × 10^3</td>
</tr>
<tr>
<td>4</td>
<td>4f</td>
<td>-</td>
<td>0.001 ± 0.00028</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4b</td>
<td>8</td>
<td>9.7 ± 0.4</td>
<td>2.1 × 10^3</td>
</tr>
<tr>
<td>6</td>
<td>4b</td>
<td>-</td>
<td>0.0045 ± 0.0023</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4d</td>
<td>8</td>
<td>6.1 ± 0.59</td>
<td>2.2 × 10^3</td>
</tr>
<tr>
<td>8</td>
<td>4d</td>
<td>-</td>
<td>0.0028 ± 0.0025</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4a</td>
<td>8</td>
<td>0.33 ± 0.024</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>4a</td>
<td>-</td>
<td>0.0044 ± 0.0028</td>
<td></td>
</tr>
</tbody>
</table>

^[a]^ Conditions: MOPS buffer, 20 mM, pH = 6; [Cu(NO_3)_2] = 0.015 mM. [4] = 0.008 mM; [5-methoxyindole] = 0.68-2 mM. [b] Defined as k_{app} with SDS / k_{app} without SDS.

In the case of substrate 4c, which carries an n-pentyl substituent on the alkenyl moiety, a competing side reaction was observed. Based on ESI-MS measurement, in which an additional product with m/z = 430.3 was observed, the side product 9 is proposed to result from the hydration of 4c followed by a tandem addition of the corresponding enolate product to another molecule of 4c (Scheme 5). The reason for the formation of this product, which was not observed in case of other substrates 4a, b, d, e, f, is unclear at present.

The Friedel-Crafts alkylation reactions of 5-methoxyindole with 4e, 4d and 4f were performed on a 0.3 mmol (≈70 mg) scale; in every case, full conversion...
was obtained within 30 min and the corresponding Friedel-Crafts alkylation products were obtained in isolated yields of 66-76% after column chromatography.

**Scheme 5.** Proposed side reaction observed in case of enone 4c.

![Scheme 5](image)

### 5.5 Conclusions

In conclusion, a dramatic rate enhancement is reported for the CuII-catalyzed vinologous Friedel-Crafts alkylation reaction in water by the presence of SDS micelles; up to $9.3 \times 10^3$ fold rate acceleration was found in the presence of 8 mM SDS compared to the reaction catalyzed by Cu(II) alone, in the absence of SDS. The possibility to perform this reaction in water with very short reaction times and in good yields makes this an attractive procedure for this transformation.

### 5.6 Experimental Section

**General remarks:**

All the substrates were synthesized following published procedures.$^{[32, 34-36]}$ 5-methoxyindole, SDS and Cu(NO$_3$)$_2$ were purchased from Sigma-Aldrich and used without further purification. The UV-Vis absorption spectra were measured on a JASCO V-660 at 25 °C.

**Cmc measurement:**

The measurements were performed under reaction conditions (MOPS buffer, 20 mM, pH = 6 and [Cu(NO$_3$)$_2$] = 0.15 mM) using LAUDA Drop-volume tensiometer device (TVT1).
Representative procedure for catalytic Friedel-Crafts reactions:

An aliquot of a stock solution of Cu(NO$_3$)$_2$ (0.15 mM final concentration) was added to a buffered solution (MOPS 20 mM, pH = 6) of SDS (8 mM final concentration) in a final volume of 250 mL. To this solution 2-acyl imidazole 4d-f (0.30 mmol) and 5-methoxyindole (7, 1.5 mmol), both dissolved in a minimal amount of DMSO, were added consecutively. The reaction was performed at room temperature and it was stopped after 30 min by addition of diethyl ether. The organic layer was separated and dried over Na$_2$SO$_4$ and concentrated in vacuo. The product was purified by column chromatography (SiO$_2$ ethyl acetate: pentane 1/1).

Kinetic measurements:

All kinetic measurements were performed using UV/Vis absorption spectroscopy (JASCO V-560 or JASCO V-570 spectrophotometers) monitoring the decrease of the absorption of the dienophile at 25 °C. The decrease of the absorption at 326 nm (4a, 4b, 4d) and at 440 nm (4c, 4e) was followed in time until the reaction was complete. Pseudo first-order rate constants were obtained using Grafit 3.0 (Erithacus software Ltd., 1992), giving the observed rate constants ($k_{obs}$) directly. The ($k_{obs}$) was plotted against the concentration of 5-methoxyindole, and the $k_{app}$ was subsequently determined from the slope of this graph.

Synthesis of substrates 4b, 4c, general procedure:

To a vacuum flame-dried 100 mL three-necked round bottom flask filled with 20 mL of anhydrous THF, 2 eq. of 1-(1-methyl-1H-imidazol-2-yl)-1-ethanone were added under N$_2$ atmosphere. The mixture was cooled to -78 °C with liquid nitrogen/acetone bath for 15 min after which time 2 eq. of a 1.6 M n-BuLi solution were added drop wise. The mixture was stirred for 15 min at -78 °C and then it was warmed to 0 °C. The solution was cooled again to -78 °C and the carboxylic acid dissolved in THF was added slowly. After stirring for 15 min at this temperature the reaction mixture was allowed to reach room temperature and slowly quenched with aq. NaHCO$_3$ saturated solution. The aqueous layer was extracted with 3 x 30 mL of ethyl acetate and the combined organic layers dried over Na$_2$SO$_4$. After removal of the solvent, the crude product was purified by column chromatography (ethyl acetate/n-heptane).
(E)-1-(1-methyl-1H-imidazol-2-yl)but-2-en-1-one (4b).\[34a\]

Starting from 0.95 mL of N-methyl imidazole (1 g, 11.93 mmol) and 0.5 mL of crotonic acid (0.5 g, 5.9 mmol), the crude product was obtained. Purification by column chromatography (SiO2, ethyl acetate/n-heptane 2:3) yielded 4b as orange-brown solid (0.18 g, 1.23 mmol; 21%).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta = 7.41\) (s, 1 H), 7.37 (s, 1 H), 7.15 (s, 1 H), 7.02 (s, 1 H), 4.03 (s, 3 H), 1.96 (d, \(J = 8.2\) Hz, 3 H); \(^13\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta = 180.60, 173.60, 143.91, 129.38, 127.81, 126.99, 36.10, 18.33\). HRMS calcd for [M-H]+' C\(_8\)H\(_{10}\)N\(_2\)O = 150.0793, found = 150.0781 (ESI\(^{+}\)).

(E)-1-(1-methyl-1H-imidazol-2-yl)oct-2-en-1-one (4c).\[32\]

Synthesized directly from 1.12 mL of 2-octenoid acid (1.07 g, 7.5 mmol) and 1.19 mL of N-methyl imidazole (1.23 g, 15 mmol), using the methodology described by Evans et al.\[34\] After purification by column chromatography (SiO2, ethyl acetate/hexanes 3:2), the product 4c was obtained as pale yellow oil (1.05 g, 4.8 mmol; 64%).

\(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta = 7.39\) (dt, \(J = 15.6\) Hz, \(J = 1.5\) Hz, 1 H), 7.16 (s, 1 H), 7.12 (dt, \(J = 15.6\) Hz, \(J = 7.0\) Hz, 1 H), 7.03 (s, 1 H), 4.04 (s, 3 H), 2.27 (m, 2 H), 1.48 (m, 2 H), 1.25 (m, 4 H), 0.84 (m, 3 H); \(^13\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta = 13.9, 22.4, 27.8, 31.4, 32.6, 36.2, 126.1, 127.0, 129.0, 143.6, 149.0, 180.7\). HRMS calcd for [M-H]+' C\(_{12}\)H\(_{18}\)N\(_2\)O = 206.1419, found = 206.1417 (ESI\(^{+}\)).

Synthesis Substrate 4a:

(E)-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pent-2-en-1-one (4a).\[35\]

To a 100 mL roundbottom flask filled with 20 mL of THF, 2.88 g (23.86 mmol) of 1-(1-methyl-1H-imidazol-2-yl)-1-ethanone,\[34b\] 4 pellets of KOH (dissolved in a minimum amount of EtOH) and 2.59 mL of pivaldehyde (2.05 g, 23.86 mmol) were added. The mixture was stirred for 2 days after which time the solvent was evaporated. The crude product was dissolved in ethyl acetate, washed with brine and dried over Na\(_2\)SO\(_4\). Removal of the solvent and purification by column chromatography (SiO2, ethyl acetate/pentane 1:4) yielded 1.2 g of 4a (6.2 mmol, 26%) as a colorless oil.
1H-NMR (CDCl₃, 400 MHz) δ = 7.33 (d, J = 15.8 Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 15.8 Hz, 1H), 7.04 (s, 1H), 4.05 (s, 3H), 1.15 (s, 9H); 13C-NMR (CDCl₃, 100 MHz) δ = 29.0, 34.3, 36.5, 121.5, 127.3, 129.4, 144.1, 158.6, 181.5. HRMS calcd for [M-H]+ C₁₁H₁₇N₂O = 192.1335, found = 192.1332 (ESI²⁺).

Characterization Friedel-Crafts products:

3-(5-methoxy-1H-indol-3-yl)-3-(4-methoxyphenyl)-1-(1-methyl-1H-imidazol-2-yl)propan-1-one (8e).[32]

1H-NMR (CDCl₃, 400 MHz) δ = 8.20 (brs, 1H), 7.15 (m, 1H), 7.05 (d, J = 2.2 Hz, 2H), 6.98 (d, J = 2.4 Hz, 1H), 6.92 (s, 1H), 6.74 (m, 3H), 4.93 (t, J = 7.6 Hz, 1H), 3.92 (dd, J = 16.3 Hz, J = 7.1 Hz, 1H), 3.89 (s, 3H), 3.78 (dd, J = 16.3 Hz, J = 8.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H); 13C-NMR (CDCl₃, 100 MHz) δ = 191.2, 157.8, 153.7, 143.2, 136.4, 131.7, 128.9, 128.8, 127.2, 126.9, 122.1, 119.4, 113.7, 112.0, 111.6, 101.5, 55.8, 55.2, 45.5, 37.4, 36.1; HRMS calcd for [M-H]+ C₂₃H₂₃N₃O₃ = 389.1739; found = 389.1813 (ESI²⁺).

3-(5-methoxy-1H-indol-3-yl)-1-(1-methyl-1H-imidazol-2-yl)-3-phenylpropan-1-one (8f).[36]

1H-NMR (CDCl₃, 400 MHz) δ = 8.20 (brs, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.18 (m, 2H), 7.11 (m, 2H), 7.07 (d, J = 2.3 Hz, 1H), 6.98 (m, 1H), 6.91(d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 4.98 (t, J = 7.6 Hz, 1H), 3.96 (dd, J = 16.4 Hz, J = 7.3 Hz, 1H), 3.89 (s, 3H), 3.80 (dd, J = 16.4 Hz, J = 7.9 Hz, 1H), 3.75 (s, 3H); 13C-NMR (CDCl₃, 100 MHz) δ = 192.6, 142.5, 129.2, 128.2, 127.8, 127.7, 127.1, 126.2, 123.8, 121.5, 111.3, 110.6, 103.6, 101.3, 59.5, 54.8, 37.9, 28.6.; HRMS calcd for [M-H]+ C₂₂H₂₁N₃O₂ = 359.1634; found = 359.1639 (ESI²⁺).

3-(5-methoxy-1H-indol-3-yl)-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (8d).[36]

1H-NMR (CDCl₃, 400 MHz) δ = 7.87 (brs, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.12 (m, 1H), 7.01 (dd, J = 6.1 Hz, J = 2.4 Hz, 2H), 6.93 (s, 1H), 6.78 (dd, J = 8.8 Hz, J = 2.3 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.56 (m, 2H), 3.40 (m, 1H), 2.04 (m, 1H), 0.95 (d, J = 4.2 Hz, 3H), 0.93 (d, J = 4.2 Hz, 3H); 13C-NMR (CDCl₃, 100 MHz) δ = 192.8, 153.9, 131.4, 129.0, 128.9, 126.9, 122.8, 118.1, 112.0, 111.7, 101.6, 56.2, 56.1, 42.1, 38.6, 33.1, 20.7, 20.5. HRMS calcd for [M-H]+ C₁₉H₂₃N₃O₂ = 325.1790; found = 325.1782 (ESI²⁺).
5.7 References


Dramatic micellar rate enhancement of the Cu\textsuperscript{II} - catalyzed vinous Friedel-Crafts alkylation in water


[33] Even though the change in Cu(NO\textsubscript{3})\textsubscript{2} concentration affects the cmc, micelles are still formed under these conditions since the SDS concentration used corresponds to the cmc in the absence of Cu(NO\textsubscript{3})\textsubscript{2}.  

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