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Enantioselective synthesis of 4H-pyranonaphthoquinones via sequential squaramide and silver catalysis\textsuperscript{†}

Uğur Kaya,\textsuperscript{a} Pankaj Chauhan,\textsuperscript{a} Daniel Hack,\textsuperscript{a} Kristina Deckers,\textsuperscript{a} Rakesh Putterreddy,\textsuperscript{b} Kari Rissanen,\textsuperscript{b} Dieter Enders*\textsuperscript{a}

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An enantioselective one-pot Michael addition/hydroalkoxylation reaction between 2-hydroxy-1,4-naphthoquinones and alkyne-tethered nitroalkenes catalyzed by a cinchona-derived squaramide and a silver(I) salt has been developed. The sequential protocol provides a direct access to 4H-pyranonaphthoquinones in moderate to very good yields and good to excellent enantioselectivities at a very low catalyst loading (0.5 mol%) of the squaramide.

Natural products bearing a 1,4-naphthoquinone skeleton are distributed widely throughout the plant kingdom. Among these, the pyranonaphthoquinones show a plethora of biological activities including anticancer,\textsuperscript{7} antitumor,\textsuperscript{8} and antibiotic\textsuperscript{9} properties. The naturally occurring pyranonaphthoquinones I and II (α-lapachones) exhibit antitumor property,\textsuperscript{4,5} whereas the pyranokunthone A (III) and B (IV) show strong antimalarial activity.\textsuperscript{6} Due to their interesting bioactivities much effort has been devoted to the development of efficient synthetic methods for the asymmetric synthesis of naphthoquinone derivatives.\textsuperscript{7}

The combination of transition metal catalysis and organocatalysis became an interesting and important area of research.\textsuperscript{10} The merger of two catalytic systems has led to powerful strategies for the development of desirable transformations, which are not possible by using an organocatalyst or metal catalyst independently. This merger led to the development of new and previously inaccessible reactions in a one-pot procedure with the advantages of step-, redox-, and pot-economy and reduced costs and time. The main challenge of this approach is to ensure that the catalysts, substrates, intermediates or solvents are compatible during the whole reaction sequence.\textsuperscript{10d} Predominantly expensive gold or palladium complexes were used in combination with organocatalysts, whereas the sequential merger of silver- and organocatalysis has been less explored.\textsuperscript{11,12} Recently our group has observed that silver is a suitable candidate for π-activation providing better catalyst compatibility and lower catalyst costs compared to the Au(I) catalysts.\textsuperscript{13}

Recently, Namboothiri and da Silva Júnior have reported an asymmetric synthesis of pyranonaphthoquinones using Morita-Baylis-Hillman acetates of nitroolefins.\textsuperscript{8} Furthermore, Singh \textit{et al.} published an asymmetric synthesis of pyranonaphthoquinones catalyzed by a bifunctional bis-squaramide catalyst (Scheme 1).\textsuperscript{9} To the best of our knowledge, there is no report on the asymmetric synthesis of pyranonaphthoquinones by merging organo- and metal-catalysis.

\textbf{Scheme 1} Recent approaches for the asymmetric synthesis of pyranonaphthoquinones

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1}
\caption{Bioactive compounds containing pyranonaphthoquinone scaffolds}
\end{figure}

\textsuperscript{a} Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 5, 52074 Aachen, Germany. E-mail: enders@rwt-aachen.de
\textsuperscript{b} Department of Chemistry, University of Jyväskylä, 40014 Jyväskylä, Finland.
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COMMUNICATION

Owing to the interesting biological activities associated with the naphthoquinone derivatives and knowing the catalytic power of the squaramide and silver catalysts, we herein report on the enantioselective synthesis of 4H-pyranonaphthoquinones using alkyl-tethered nitroolefins 2 and 2-hydroxy-1,4-naphthoquinones 1 in the presence of a cinchona-derived squaramide and AgOTf as catalysts.

Our initial exploration focused on the Michael addition of 2-hydroxy-1,4-naphthoquinone (1a) to the alkyl-tethered nitroolefin 2a. The reaction of 1a with 2a in CH₂Cl₂ at room temperature in the presence of 10 mol% of the bifunctional squaramide A gave the desired product 3a in 91% yield and 84% ee (Scheme 2). Fortunately, all cinchona-derived squaramides as well as the thiourea catalysts afforded the Michael adduct in very good yields and enantioselectivities with the exception of the thiourea catalyst P (Scheme 2). This suggests that the presence of a tertiary amine is pivotal for the catalytic efficiency. The best result was obtained with the squaramide K which gave 94% yield and 96% ee of 3a. Hence, we decided to use K for further optimization studies.

Further investigations were carried out by screening different solvents. In all solvents the reactions resulted in very good yields of 3a and performing the reaction in CH₂Cl₂ provided a good enantiomeric excess of 3a within 30 minutes. Decreasing the catalyst loading slightly improved the yield and the enantioselectivity. Studies on the effect of the catalyst loading and of the temperature showed that the reduction of the catalyst loading to 0.5 mol% afforded the Michael adduct in 95% yield and 96% ee at room temperature (see supporting information).

Next, we focused on the hydroalkoxylation through the activation of the alkyne 3a by late transition metal complexes. The Michael adduct was transformed selectively to the 6-endo-dig-product in the presence of 10 mol% of the Au(I) catalyst in 95% yield (Table 1, entry 1). The Au(I) catalysts II and III also afforded the 4H-pyranonaphthoquinones in satisfactory yields (entry 2-3), while the yield in the case of PPh₃AuCl was only moderate (entry 4). Ag(I) salts also provided the desired product 4a in moderate yields (entry 9-11).

Table 1 Optimization studies for the hydroalkoxylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I/AgNTf₂</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>II/AgNTf₂</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>III/AgNTf₂</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃AuCl/AgNTf₂</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>PtCl₂</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>AgCO₃</td>
<td>24</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>AgNO₃</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>AgOTf</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>AgNTf₂</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>AgBF₄</td>
<td>24</td>
<td>71</td>
</tr>
</tbody>
</table>

*Reaction conditions: Michael adduct 3a (0.2 mmol), M-cat (10 mol%) and toluene (2 mL, 0.1 M).*

Pt(II) and Cu(I) were not able to promote the desired hydroalkoxylation although those metals have found wide application as carbophilic π-acids.

For the desired one-pot protocol we investigated the combination of both catalytic reactions. First, we studied the reaction using squaramide K and Au(I) catalyst I under relay catalytic conditions. Unfortunately, only traces of 4a could be isolated (Table 2, entry 1). The same reaction was conducted under sequential catalytic conditions. We could observe that the Michael reaction was not working well and the annulated product was obtained in only 7% yield and 96% ee (Table 2, entry 2). Afterwards, the reaction of 1a with 2a by combining the squaramide K and AgOTf was investigated. Again the reaction afforded only traces of the product under relay catalytic conditions, maybe due to the disturbance of the catalyst-substrate interaction in the Michael addition step.

Scheme 2 Catalyst screening for the asymmetric Michael addition of 1a and 2a.
Fortunately, changing to sequential catalytic conditions provided the product with 83% yield and 98% ee (Table 2, entry 3). Increasing the catalyst loading of Ag(I) gave 4a in 93% yield and 98% ee (Table 2, entry 4).

With the optimized conditions in hand, the substrate scope of the reaction was investigated by changing the substituents on the nitroalkenes 2 and 2-hydroxy-1,4-naphthoquinones 1 (Table 3). The electron neutral 1-naphthyl and 2-naphthyl nitroalkenes reacted efficiently with 1a and afforded the desired products 4b and 4c in high yields and excellent enantioselectivities. The nitroalkenes bearing electron-withdrawing groups also worked well under this sequential reaction protocol and provided promising results in terms of product yield and enantioselectivity, except for the 4-CF$_3$C$_6$H$_4$ group which gave a high ee, but a low yield of 25% (4f). The electron-rich nitroalkenes also led to the formation of the desired products 4g-j in good to high yields and high enantioselectivities. However, heteroaryl substituted nitroalkenes are not suitable substrates for the transformation and alkyl substituted nitroalkenes led to poor product yield, albeit with excellent enantioselectivities (4k-n). The variation of the substituents on the naphthoquinone substrate 1 is also possible with electron-releasing and electron-withdrawing substituents leading to good yields and high ee’s, except for 4s which gave 89% ee.

The proposed structure including the absolute configuration was determined by X-ray crystal structure analysis of compound (R)-4e. For all other pyranonaphthoquinones the absolute configuration was assigned by analogy to (R)-4e (Figure 2).

A plausible reaction mechanism, which is based on the experimental results described above, is given in Scheme 3. The proposed mechanism contains two different catalytic cycles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>M-Catalyst</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>I (10 mol%)/AgN$	ext{O}_2$</td>
<td>DCM/ toluene</td>
<td>24</td>
<td>traces</td>
<td>n.d.</td>
</tr>
<tr>
<td>2$^a$</td>
<td>I (10 mol%)/AgN$	ext{O}_2$</td>
<td>DCM/ toluene</td>
<td>24</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>AgN$	ext{O}_2$ (10 mol%)</td>
<td>DCM</td>
<td>4.5</td>
<td>83</td>
<td>98</td>
</tr>
<tr>
<td>4$^a$</td>
<td>AgN$	ext{O}_2$ (15 mol%)</td>
<td>DCM</td>
<td>3.5</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>5$^a$</td>
<td>AgN$	ext{O}_2$ (20 mol%)</td>
<td>DCM</td>
<td>5</td>
<td>83</td>
<td>98</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1,4-naphthoquinone 1a (0.25 mmol), nitroalkene 2a (1.1 eq.), cat. K (1 mol%), solvent (2.5 mL, 0.1 M). $^b$Relay catalytic condition. $^c$Sequential catalytic condition: after full conversion of 1,4-naphthoquinone 1a, M-cat was added to the reaction. $^d$The reaction was carried out with cat. K (0.5 mol%), $^e$Yield of 4a after flash chromatography. $^f$The enantiomeric excess was determined by HPLC on a chiral stationary phase.

In the first cycle the squaramide K acts as a bifunctional catalyst. The plausible transition state (TS) involves the synergistic activation of the nitroolefin 2a by the squaramide moiety and the deprotonation of the 2-hydroxy-1,4-naphthoquinone (1a) by the tertiary amine to facilitate the Michael addition. Concurrently, the deprotonated 1a attacks the fixed nitroolefin 2a from the Re-face to provide the Michael adduct 3a. In the second catalytic cycle the silver catalyzes the electrophilic activation of the alkyne to facilitate the hydroalkoxylation in a 6-endo-dig fashion selectively resulting in the vinylsilver intermediate, which undergoes protodeauration to provide the desired pyranonaphthoquinone 4a.

In conclusion, we have developed an enantioselective one-pot sequential Michael addition/hydroalkoxylation reaction by combining hydrogen-bonding catalysis and $\pi$-activation. The merger provided substituted 4H-pyranonaphthoquinones in moderate to very good yields and excellent enantioselectivities by using a low cat-

![Fig. 2 X-ray crystal structure of (R)-4e](#)
alyst loading of the squaramide. Further studies on the combination of squaramide with transition metal catalysis are ongoing in our laboratories.

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Notes and references


Scheme 3 Proposed catalytic cycles of the Michael addition/hydroalkoxylation reaction.