Copper-catalysed asymmetric allylic alkylation of alkylzirconocenes to racemic 3,6-dihydro-2H-pyrans

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Full Research Paper

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Abstract

Asymmetric allylic alkylation is a powerful reaction that allows the enantioselective formation of C–C bonds. Here we describe the asymmetric alkylation of alkylzirconium species to racemic 3,6-dihydro-2H-pyran. Two systems were examined: 3-chloro-3,6-dihydro-2H-pyran using linear optimization (45–93% ee, up to 33% yield, 5 examples) and 3,6-dihydro-2H-pyran-3-yl diethyl phosphate with the assistance of a design of experiments statistical approach (83% ee, 12% yield). 1H NMR spectroscopy was used to gain insight into the reaction mechanisms.

Introduction

Asymmetry is found in many natural products and biologically active molecules. Using racemic starting materials to synthesise enantiomerically enriched products is a powerful and underdeveloped strategy [1-4]. In some cases transition metal-catalysed asymmetric allylic alkylation (AAA) reactions [5-7] can be used in dynamic kinetic asymmetric transformations (DYKAT) [8-15] to provide single enantiomer products from racemic starting materials. Mechanistically some of these have been shown to occur by direct enantio-convergent transformations [16-18]. We have developed Cu-catalysed asymmetric conjugate additions of alkylzirconium reagents generated in situ by hydrometallation of terminal alkenes [19-25], and recently demonstrated that zirconium nucleophiles may undergo highly enantioselective copper-catalysed AAAs to racemic cyclic allyl halides, such as 1 (Scheme 1a) [26,27].

Tetrahydropyrans are a common motif in natural products and pharmaceuticals and are useful synthetic intermediates. However, the direct asymmetric derivatization of pyrans is rare [28] and enantioenriched tetrahydropyranis are often obtained by ring-closing methods [29,30]. To extend our previously reported DYKATs beyond all-carbon electrophiles we decided to examine 3-chloro-3,6-dihydro-2H-pyran (2a, Scheme 1b). This was envisaged to be a challenging substrate.
The presence of oxygen in the ring would modify the electronics, and likely the reactivity, of the starting material. The oxygen lone pairs on 2a could potentially interact with the copper-catalyst or alkyl metal nucleophiles.

Results and Discussion

We first examined the in situ hydrometallation/AAA of 4-phenyl-1-butene (4) to racemic 3-chloro-3,6-dihydro-2H-pyran (2a, Table 1). Interestingly, no product was formed using our previously reported conditions for AAA to racemic carbocyclic substrates (Cu, ligand A, CHCl₃, Table 1, entry 1) [26] and only unreacted starting material was recovered. Different Cu salts were examined (Table 1, entries 2–7) and more strongly electron withdrawing counterions were found to provide the desired product, with CuClO₄ giving the best ee (70% ee, Table 1, entry 3). A solvent screen lead us to the conclusion that chlorinated solvents are best (CH₂Cl₂, CHCl₃, 70% ee and CHCl₃ (67% ee), Table 1, entries 7 and 10, respectively). Extensive examination of phosphoramidite ligands (for example, Table 1, entries 2 and 11–13) did not improve the ee. We then tested many different additives (TMSCl, AgOTf, borates, ZrCl₄, Si(OEt)₄, etc, for example Table 1, entries 14–18). Using B(OiPr)₃, which presumably acts as a Lewis acid, improved the ee to 80% (Table 1, entry 18) and so we re-examined different ligands using CuClO₄ in CH₂Cl₂ with B(OiPr)₃ (Table 1, entries 19–21). Derivatives of ligand B were tested and ligand F gave 83% ee (Table 1, entry 21), while electronically similar E was much less selective (47% ee, Table 1, entry 20). The effects of concentration, temperature and catalyst loading were also investigated (not shown) with no improvement on the enantioselectivity. After extensive optimization, the highest enantiomeric excess obtained was only 83% ee and so we decided to examine other leaving groups (Table 2). Like allyl chloride 2a, allyl bromide 2b gave no desired product when using our previously reported conditions [26] (Table 2, entry 2). The use of 2b also only gave low ee when using the conditions optimized above (38% ee, Table 2, entry 1). Allyl acetate 2c did not give the desired product under any conditions examined, however, allyl phosphate 2d was found to provide 5 with good selectivity (77% ee, Table 2, entry 5). 3,6-Dihydro-2H-pyran-3-yl diethyl phosphate (2d) was also the only substrate to react using our previously reported AAA conditions (Cu, ligand A, CHCl₃) [26], albeit with poor enantioselectivity (29% ee, Table 2, entry 6).

Design of experiments (DoE) [31-37] is a powerful tool for efficient screening and is commonly used in industry, since traditional one-factor-at-a-time optimization poorly covers the available parameter space and may not locate the most optimal conditions. As DoE rapidly explores the response space efficiently and can reveal interdependence of factors at no extra experimental cost, we decided to briefly examine DoE in this complex asymmetric transformation. We note that there are important limits to this investigation. Understanding what interactions give rise to asymmetric induction (particularly in transformations where mechanisms are not understood) is extremely challenging, and it is not obvious how to parameterize the multiple variables present in key factors such as ligand structure [38].

Nevertheless, a Principal Component Analysis using JMP® 12.1.0 (SAS) in 3 waves was carried out using 2d as the starting material. In each experiment, the most promising variables were chosen based on results from previously published methods, the procedure optimised for 2a (above), and the results of previous waves. The first wave was as a third factorial design with 3 categories: Ligand (A, B, C, F and G), counter-ion (ClO₄⁻, I⁻ and OTf⁻) and solvent (CH₂Cl₂, Et₂O and TBME, Table 1, entries 1–17; Figure 1, for more details see Supporting Information File 1). This first DoE study suggested that neither CuI nor TBME were good fits for the reaction (both consistently giving low ee). The combination of CuOTf in CH₂Cl₂ gave the best enantioselectivity (up to 83% ee, Table S1 entry 3, Supporting Information File 1) with ligand G. Unlike with 2a, CuClO₄ did not give high ee with 2d; the highest value obtained was 43% ee (Table S1, entry 14). Interestingly Et₂O gave mixed results with some low (e.g., 1% ee, Table S1, entry 1) and moderate (e.g., 56% ee, Table S1, entry 6) ee values obtained.

Based on those results, a second wave of DoE was designed as a 6⁴ factorial design with 4 factors: Ligand (G, H, I, J), counter-ion (OTf⁻ and NTF₂), solvent (CH₂Cl₂, Et₂O and CHCl₃) and TMSCl equivalent (0, 1 and 5) (Table S1, entries...
Table 1: Asymmetric alkylation to 3-chloro-3,6-dihydro-2H-pyran (2a)\textsuperscript{a}.

\begin{tabular}{cccccc}
Entry & Copper & L* & Solvent & Additive & ee\textsuperscript{b} \\
--- & --- & --- & --- & --- & --- \\
1 & CuI & A & CHCl\textsubscript{3} & & NP \\
2 & CuClO\textsubscript{4} & A & CH\textsubscript{2}Cl\textsubscript{2} & & 68\% \\
3 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & & 70\% \\
4 & CuOTf & B & CH\textsubscript{2}Cl\textsubscript{2} & & 64\% \\
5 & CuNTf\textsubscript{2} & B & CH\textsubscript{2}Cl\textsubscript{2} & & 52\% \\
6 & CuTC & B & CH\textsubscript{2}Cl\textsubscript{2} & & 12\% \\
7 & CuSbF\textsubscript{6} & B & CH\textsubscript{2}Cl\textsubscript{2} & & NP \\
8 & CuClO\textsubscript{4} & B & Et\textsubscript{2}O & & 55\% \\
9 & CuClO\textsubscript{4} & B & Me-THF & & 38\% \\
10 & CuClO\textsubscript{4} & B & CHCl\textsubscript{3} & & 67\% \\
11 & CuClO\textsubscript{4} & C & CH\textsubscript{2}Cl\textsubscript{2} & & 53\% \\
12 & CuClO\textsubscript{4} & D & CH\textsubscript{2}Cl\textsubscript{2} & & 36\% \\
13 & CuClO\textsubscript{4} & E & CH\textsubscript{2}Cl\textsubscript{2} & & 12\% \\
14 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & TMSCl & 73\% \\
15 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & Si(OEt)\textsubscript{4} & 63\% \\
16 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & Ti(OiPr)\textsubscript{4} & 25\% \\
17 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & AlCl\textsubscript{3} & 15\% \\
18 & CuClO\textsubscript{4} & B & CH\textsubscript{2}Cl\textsubscript{2} & B(OiPr)\textsubscript{3} & 80\% \\
19 & CuClO\textsubscript{4} & C & CH\textsubscript{2}Cl\textsubscript{2} & B(OiPr)\textsubscript{3} & 78\% \\
20 & CuClO\textsubscript{4} & E & CH\textsubscript{2}Cl\textsubscript{2} & B(OiPr)\textsubscript{3} & 47\% \\
21 & CuClO\textsubscript{4} & F & CH\textsubscript{2}Cl\textsubscript{2} & B(OiPr)\textsubscript{3} & 83\% \\
\end{tabular}

\textsuperscript{a}Conditions: 4-phenyl-1-butene (2.5 equiv), Cp\textsubscript{2}ZrHCl (2.0 equiv), 2a (1.0 equiv), CuL* as specified (0.1 equiv), additive as specified (1.0 equiv), in specified solvent (2.0 mL), room temperature. \textsuperscript{b}ee determined by HPLC. NP = no product. For more information on procedures see Supporting Information File 1.
Table 2: Effect of leaving groups.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Copper</th>
<th>L*</th>
<th>Solvent</th>
<th>Additive</th>
<th>ee (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>CuClO(_4)</td>
<td>F</td>
<td>CH(_2)Cl(_2)</td>
<td>B(OiPr)(_3)</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>CuI</td>
<td>A</td>
<td>CHCl(_3)</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>OAc</td>
<td>CuClO(_4)</td>
<td>F</td>
<td>CH(_2)Cl(_2)</td>
<td>B(OiPr)(_3)</td>
<td>NP</td>
</tr>
<tr>
<td>4</td>
<td>OAc</td>
<td>CuI</td>
<td>A</td>
<td>CHCl(_3)</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OPO(OEt)(_2)</td>
<td>CuClO(_4)</td>
<td>F</td>
<td>CH(_2)Cl(_2)</td>
<td>B(OiPr)(_3)</td>
<td>77%</td>
</tr>
<tr>
<td>6</td>
<td>OPO(OEt)(_2)</td>
<td>CuI</td>
<td>A</td>
<td>CHCl(_3)</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Conditions: 4-phenyl-1-butene (2.5 equiv), Cp\(_2\)ZrHCl (2.0 equiv), 2 (1.0 equiv), CuL\(^*\) (0.1 equiv), additive (1.0 equiv), in solvent (2.0 mL), room temperature. \(^b\)ee determined by HPLC. NP = no product. For more information on procedures see Supporting Information File 1.
Figure 1: DoE from 3,6-dihydro-2H-pyran-3-yl diethyl phosphate (2d). Conditions: 4-phenyl-1-butene (2.5 equiv), Cp₂ZrCl (2.0 equiv), 2d (1.0 equiv), CuL* as specified (0.1 equiv), additive as specified (1.0 equiv or 5.0 equiv), in specified solvent (2.0 mL), room temperature. ee determined by HPLC. For more information on the procedures see Supporting Information File 1. ● (wave 1, entries 1–17), ♦ (wave 2, entries 18–30), ▼ (wave 3, entries 31–38).
both the conditions and leaving groups differ in the two reactions it is not clear why 2a, but not 2d, dimerizes. 11 can exists as 3 isomers, a meso compound and two enantiomers. Upon comparison to literature data [44], we concluded that we form a mixture of all three, as a 1:1 mixture of the meso and racemic material. Our samples did not rotate plane polarized light, emphasizing the racemic nature of the sample and suggesting that 11 is formed in a completely non-selective pathway.
In the case of allyl phosphate 2d, the system appears to lack reactivity and the reaction quickly dies, so that 10 (Figure 3) is formed with poor conversion, and we speculate that the phosphate leaving group inhibits the catalyst which would explain why only \(~10\%\) of product is formed.

To obtain further mechanistic information we followed the ee of these reactions in time (Figure 4 and Figure 5). In the system using chloride 2a, the ee of product 5 remains constant throughout the reaction (\(~75\%\) ee, Figure 4). Starting chloride 2a was found to be quite robust so that we could also determine its...
enantiomeric excess during the course of the reaction. Initially 2a is racemic but it becomes scalemic to slowly reach 34% ee when the reaction is complete (~12 hours). From these observations and our experimental demonstration that 2a is much more stable than all-carbocyclic 1, it appears that 2a undergoes kinetic resolution. However, this system is clearly complicated by the fact that the majority of 2a is consumed during byproduct 11’s formation.

In the phosphate system based on 2d, the ee of product 5 was found to increase during the course of the reaction (Figure 5) so that 5 was ~26% ee after a few minutes, and increased to ~82% ee after 5 hours. Unfortunately, analytical conditions to separate the enantiomers of 2d, so we could measure the enantiomeric excess of this starting material, could not be found. At this stage it is not possible to provide a full mechanistic rationalization of these reactions. It is also not immediately obvious how to improve yields and enantiomeric excesses. The kinetic studies suggest that the two reactions work through very different mechanisms and it strikes us as remarkable how both systems give roughly the same enantioselectivity and poor yield, yet have significantly different pathways.

Conclusion
The Cu-catalyzed AAA of alkylzirconium reagents to racemic heterocyclic electrophiles was explored. After extensive examination, two different methods for obtaining 3,6-dihydro-2H-pyran derivatives with respectable levels of ee (~83% ee) were developed. Unfortunately, the yields were poor in both cases. Kinetic studies were performed to help to understand the difficulties associated with these reactions. While we were not able to resolve the issues of yield in these studies, this work reveals remarkable mechanistic diversity in Cu-catalysed asymmetric alkylation reactions to racemic starting materials.

Supporting Information
Supporting Information File 1
Additional material.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-264-S1.pdf]

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