Kinetic resolution of alkyne-substituted quaternary oxindoles via copper catalysed azide-alkyne cycloadditions

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The synthesis and kinetic resolution of quaternary oxindoles through copper catalysed azide–alkyne cycloadditions is presented. Selectivity factors ($s$) up to 22.1 ± 0.5 are reported. Enantioenriched alkynes and triazoles were obtained in $\geq 80\%$ enantiomeric excess (e.e.).

Click chemistry was first outlined in 2001 by K. B. Sharpless and co-workers, the copper catalysed azide alkyn cycloaddition (CuAAC) has lived up to Sharpless’ accolade as “the cream of the crop” in this area.1 The CuAAC reaction predictably delivers 1,4 substituted triazoles in good yields, from the reaction of terminal alkynes with organic azides in the presence of a Cu(i) catalyst. Despite the ubiquity of the CuAAC reaction there are relatively few reports of asymmetric variants.3 Yet enantioenriched triazoles and alkynes are potentially important in many areas of chemistry and biology.3

Kinetic resolution (KR) of a racemic mixture takes advantage of a difference in the rate of the reaction of either enantiomer through diastereomeric interactions.5 Fu and co-workers have championed non-enzymatic catalytic methods for the KR of secondary alcohols and other substrates.5 In this area recent advances have built on Fu’s findings and resolution of chiral alcohols is a relatively mature field.5 A particular advantage of KR is that it is possible to obtain high e.e.s of both unreacted starting materials and products dependent upon the selectivity factor ($s$) and the conversion. Kagan showed that for a given KR it is relatively straightforward to relate conversion and starting material e.e. to selectivity factor. KR of chiral alkynes or azides through triazole formation is one strategy open to exploitation to access enantioenriched triazoles and starting materials, thus enabling recovery of non-racemic alkynes which could be further derivatised.

To the best of our knowledge there are no reports of successful KRs of alkynes via the CuAAC reaction. Kinetic resolution of terminal alkynes is therefore of importance to the overall development of stereoselective click chemistry. Research into asymmetric click methodology thus far has been mainly focused on desymmetrisation and only a single successful report on KR (of azides) has been published.

Resolution of racemic azides via the CuAAC reaction has been achieved by Meng et al.7 using a Cu–PyBox catalyst,8 selectivity factors ($s$) up to $s = 8$ were obtained.9 Meng et al. were unable to kinetically resolve racemic terminal alkynes ($s = 1$).7 A range of five different terminal alkynes were tested and no enantiomeric discrimination was observed whatsoever with any compounds tried. They accounted for this observation using a mononuclear transition state model. However, more recently evidence has emerged that Cu–PyBox systems might not always follow a mononuclear arrangement. Panera et al. reported X-ray crystal structures of binuclear phenyl and isopropyl PyBOX copper(i) chloride complexes, and used these solid state structures to rationalise the stereochemical outcome of their asymmetric catalytic synthesis of propargylamines.14 It struck us that this binuclear PyBox model could have synergy with the binuclear model for the CuAAC, proposed by Fokin et al.15 and Kuang et al.16 Work by Jin et al. and Makarem et al. has provided strong evidence to support this catalytic model with stable dinuclear copper acetylide intermediates being successfully crystallised.17

Our team has a long-standing interest in quaternary oxindoles,18 and a relevant report on desymmetrisation,20 prompted us to begin investigation of their potential as substrates for catalytic kinetic resolution. Oxindole derivatives (Fig. 1) can possess potent biological activity as calcium channel blockers,19 antiangiogenics,20 antitumor agents32 and analogues.19,22 For example, the antitumor agent 1, the natural products donaxaridine 2, dioxibrassinine 3 and the popular natural product target gelsamine 4 (Fig. 1). Therefore, efficient access to nonracemic quaternary oxindoles is of considerable interest to the
medicinal chemistry\textsuperscript{13} and veterinary science\textsuperscript{24} communities. Not only is access to non-racemic triazoles of interest but access to high e.e. alkynes is of importance. Access to enantioenriched all carbon quaternary stereogenic centres bearing alkyne functionality is demanding,\textsuperscript{25} and alkynes are a versatile synthetic handle capable of undergoing a diverse array of transformations.\textsuperscript{26} Access to enantioenriched alkynes therefore could lead to a plethora of stereocontrolled derivatives. In order to test whether kinetic resolution of allene appended quaternary oxindoles is possible (generically represented in Scheme 1a) we prepared compound 1. Propargylation of 3-methyl-2-oxindole (see ESI†), followed by N-benzylation gave racemic 1 (Scheme 1b), our substrate for KR.

To our delight, an initial probe reaction of racemic 1 with benzyl azide, in acetone under control of a combination of Cu(I)Cl and PhPyBOX (L1) (12.5 and 15 mol\% respectively) gave benzyl azide, in acetone under control of a combination of Cu(I)Cl and Cu(II) and Cu(0) species, under standard 6 h (Table 1). Of copper sources tested, our first choice, Cu(i)Cl was confirmed as the superior choice selectivity factor (Table 1, entry 1). Cu(i)Br gave a lower conversion and selectivity factor (Table 1, entry 2); Cu(i) offered improved conversion but selectivity factor was again compromised (Table 1, entry 3). Of the other copper sources tried Cu(OTf)\textsubscript{2}, Cu(i)(OAc)\textsubscript{2} and CuSO\textsubscript{4} combined with NaAsc (Table 1, entries 4, 6 and 7 respectively) gave approximately stoichiometric conversion with respect to catalyst loading, Cu(i)OAc, Cu(i)(OTf)\textsubscript{2} and Cu(0) NaAsc (Table 1, entries 5, 8 and 9 respectively) did not deliver any triazole-containing products. Increasing the reaction temperature did not improve the reaction outcomes and Cu(i)Cl was selected as the copper source of choice for further optimisation studies.

Next, the choice of solvent was investigated (Table 2), acetone had already been shown to give a promising selectivity and is restated in Table 2 (entry 1) to aid comparison. Surprisingly 2-butanone was ineffective (Table 2, entry 2) giving no conversion. Since Zhou et al. had already reported dicarbonyl containing solvents were effective for a related desymmetrisation reaction we also included this class of solvent in our screening.\textsuperscript{20,27} 2,5-Hexanediene (Table 2, entry 3) gave a huge jump in selectivity factor \((s = 22.1 \pm 0.5)\) and good conversion (42\%), 2,3-butanediene (Table 2, entry 4) gave poorer conversion and poorer selectivity (34\% and \(s = 2.5\) respectively). A mixture of acetone and 2,5-hexanediene (Table 2, entry 5) gave 61\% conversion (against 0.6 equiv. of azide, i.e. full conversion) but selectivity factor was also poor \((s = 3.5)\). THF gave a promising selectivity factor of \(s = 8.7\) (Table 2, entry 6), and all other solvents tried gave inferior results (Table 2, entries 7–12). We speculated that 2,5-hexanediene may be acting as a ligand for copper but use in stoichiometric amounts (equivalent to catalyst loading) had a negative effect on the selectivity. During the course of this optimisation study the order of addition was found to be crucial to obtaining reproducible results. Importantly, the alkyn must be added to a solution of in situ formed catalyst at room temperature before cooling to 0 °C (see ESI† for full details).

### Table 1 KR of 1 with PhPyBox and various copper sources

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper Source</th>
<th>Conv.\textsuperscript{a} (%)</th>
<th>e.e. SM\textsuperscript{b} (%)</th>
<th>e.e. 2a\textsuperscript{b} (%)</th>
<th>Selectivity factor (s^c)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>37</td>
<td>34</td>
<td>43</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>51</td>
<td>29</td>
<td>29</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)\textsubscript{2} -toluene 0.5</td>
<td>10</td>
<td>3</td>
<td>16</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)\textsubscript{2}</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)\textsubscript{2}</td>
<td>8</td>
<td>4</td>
<td>57</td>
<td>2.8</td>
</tr>
<tr>
<td>7</td>
<td>CuSO\textsubscript{4} NaAsc</td>
<td>13</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Cu metal</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conversion determined by inspection of \(^1\)H NMR spectra (see ESI).

\textsuperscript{b} e.e. of recovered starting material (HPLC). \(s = \ln[(1 - c)/(1 - ee)]/\ln[(1 - c)/(1 + ee)]\).

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**Fig. 1** Exemplar biologically active quaternary C-3 oxindoles: I: antitumor agent;\textsuperscript{10} II: donaxaridine;\textsuperscript{11} III: dioxibrassinine;\textsuperscript{12} IV: gelsemine.\textsuperscript{13}

**Scheme 1** (a) General scheme for the CuAAC KR strategy; (b) application of KR to alkynyl C-3 quaternary oxindoles.
Despite a broad range of alternative chiral ligands being screened, in our hands, it was only PhPyBox that permitted effective KR. Ligand classes screened that were inferior to PhPyBox included other PyBox variants, PhOx ligands, Trost ligands, phosphoramidites, BINAPE and BINOL. For full details of ligand screening see ESI. Further investigation is needed to probe the ligand requirements for this reaction.

The scope of the benzyl azide was investigated next. Initially we ran experiments using in situ prepared azides (from sodium azide and benzyl halide derivatives). Whilst in situ preparation of azides offers the advantage of minimising the number of discrete azide manipulations, conversions were very poor. Further investigation is required to judge any effects due to electronic parameters. In both cases similar selectivity factors (13.1 and 11.1) were obtained with a slightly lower conversion when 3d was used.

Finally, as with any kinetic resolution, by judicious choice of reaction time, and therefore conversion, it is possible to obtain higher e.e. of starting material or product. Indeed, in our case we can obtain ≥80% e.e. of 2a (albeit low conversion), see Scheme 2.

These preliminary findings demonstrate that not only is it possible to perform catalytic kinetic resolution with the CuAAC reaction, but selectivity factors greater than 20 are possible. Optimised conditions for the CuAAC kinetic resolution, demonstrating ≥80% e.e. starting material and product can be obtained with biologically relevant substrates. Order of addition, choice of ligand and choice of solvent were key to achieving reproducible results. It was shown that dependant on reaction conversion high e.e. alkynes are recoverable and these could be used for further derivatisation.

Further expansion of substrate scope and detailed mechanistic studies remain to be carried out and we look forward to the opportunity to report on that in due course.

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Notes and references
