Click Chemistry

Induction of Planar Chirality Using Asymmetric Click Chemistry by a Novel Desymmetrisation of 1,3-Bisalkynyl Ferrocenes‡


Abstract: The new asymmetric click CuAAC reaction is used for the first time to induce asymmetry in planar chiral compounds. There are only three classes of stereogenicity (atom-centred, axial, and planar), and these results are therefore of fundamental importance as well as practical significance, providing access to chiral ferrocenes at near enantiopurity. Here, we report asymmetric induction (AI) and kinetic resolution (KR) studies on a novel library of prochiral 1,2,3-trisubstituted bisalkynylferrocenes, obtained by diiodination, derivatisation (including reduction and etherification), double Sonogashira coupling and finally transesterification, azidation or silylation. Desymmetrisation using chiral ligands to modify the CuAAC reaction proceeds in up to 60 % yield and >99.5 % ee, yielding planar chiral ferrocenes. The absolute configuration of two of the preferred products was proved by chemical correlation and related to the entire series by circular dichroism spectroscopy (CD).

1. Introduction

Thousands of papers have been published on the copper-catalysed azide-alkyne cycloaddition (CuAAC) click reactions,[1] but only eleven[2] (one of them ours[2a]), report examples of asymmetric “click” chemistry in which a chiral ligand is used to influence the stereochemistry of desymmetrisation reactions of prochiral diazides[2b] and dialkynes[2a,2c–2f,2i,2h] or in kinetic resolutions.[2g,2j,2k] We now provide the first example of a novel induction of planar chirality, achieving ees as high as 99.5 %. Previously-reported applications of asymmetric click chemistry have addressed only carbon-centred[2a–2c,2f–2k] and axial[2d–2e] stereogenicity, and until our work on this topic, the third fundamental class of molecular stereogenicity,[3] the stereogenic plane,[4] has been unexplored. The results reported here fill this gap and complete the range of types of enantioPURE structures that can be addressed using the new asymmetric “click” approach. Planar chiral multiply-substituted ferrocenes are an important class of molecules,[5] and in recent years they have come into prominence as scaffolds for chiral ligands that now find widespread use in asymmetric catalysis.[5] While there are already many important examples of preparations of non-racemic substituted ferrocenes in the literature, most rely on classic directing groups such as oxazolines,[7a] acetals[7b] and Ugi’s amine.[7c] Examples of desymmetrisation approaches are far rarer, but include a series of asymmetric C-H activation reactions,[8a–8d] a lithiation using a chiral amine base[8e] and a two-step asymmetric esterification process.[8f] Our work, reported here, adds a novel alternative to the range of methods that can be employed to access enantiopure planar chiral compounds.

2. Results and Discussion

2.1. Choice of Prochiral Substrates

Because of the ready availability of the starting material, our work on the asymmetric click chemistry of prochiral ferrocenes began with a study of 1,2-diethynylferrocene,[9] but this gave almost entirely the achiral bis-triazole product, and only very low yields of the required mono-triazole. This acceleration of the second click reaction relative to first one is suspected be a consequence of coordination of the catalytic copper to the first triazole.[10] To be useful as a method of asymmetric synthesis, the copper catalysed reaction of the second alkyne must be slower than that of the stereochemically preferred initial site of reaction. To address this issue, we turned to a new series of trisubstituted 1,3-bis-alkynes, in which a central functional group was present to separate the two enantiotopic alkynes and shut down any intramolecular assistance to the second click step. In these circumstances, the remaining alkyne after the initial desymmetrisation should be mismatched with respect to the stereogenicity of the controlling ligand, leading to a slower cycloaddition reaction. Furthermore, with this class of substrate, the nature of the central group can be varied to open...

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[b] Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201901192.
[t] Asymmetric click chemistry, Part 2; for Part 1, see ref.[2a]
All data supporting this study is provided as supplementary information accompanying this paper.

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the way for studies (for examples, see Scheme 1) of the scope of the reaction.

Scheme 1. Examples of the synthesis of alcohol and ether derivatives; i) DIBAL-H, THF, 0 °C to r.t., 10 min; ii) NaH, THF, 0 °C to r.t., 20 min, Mel/BnBr, 16 h; iii) TMS acetylene, bis(triphenylphosphane)palladium(II) chloride, CuII, triethylamine, 45 °C, 16 h; iv) KF, methanol, rt., 16 h.

We report here asymmetric induction (AI) and kinetic resolution (KR) experiments on a library of such trisubstituted bis-alkynylferrocenes, using a representative selection of chiral ligands prominent in asymmetric reactions chosen because of their importance in other asymmetric "click" methodologies,[2] affording planar chiral ferrocenes with up to 60 % yield and >99.5 % ee. The synthesis of one enantiomer, by the application of a conventional directing group approach,[7a] has provided a proof of absolute configuration by chemical correlation, allowing the absolute configuration of the entire series of desymmetrisation products to be determined by comparison of circular dichroism (CD) spectra. The stereochemical features that control the enantioselectivity of these new asymmetric click reactions, and the influence of KR, which forms achiral bis-triazoles, on the observed levels of stereoselectivity in the mono-triazole products from the asymmetric induction step itself (a "secondary KR effect"), have both been defined in this work.

2.2. Synthesis of Starting Materials and Induction of Asymmetry in Planar Chiral Products

The first trisubstituted bis-alkyne in this series was synthesised from the known[11] methyl 2,5-diiodoferrocenecarboxylate 1 by means of a double Sonogashira coupling with TMS acetylene, followed by desilylation. Desymmetrisation of the resulting compound, methyl 2,5-diethynylferrocenecarboxylate 2, using conditions based on recently established[2c] asymmetric CuAAC "click" reactions [CuICl with (R,R)-Ph-Pybox[12] as the chiral ligand], gave good selectivity for monocycloaddition. Although an initial test using 0.9 equivalents of benzyl azide gave only 16 % ee, the chiral mono-triazole was obtained in a 67 % yield. To investigate the possibility that a secondary KR effect might increase the ee, the reaction was repeated with 1.5 equivalents of the azide; resulting in an improved 31 % ee but a reduced chemical yield (51 %) due to increased formation of the bis-triazole (Scheme 2). This level of ee was sufficient, however, for us to begin a systematic study of differently substituted ferrocenyl 1,3-diynes in which the central (C-2) substituent was varied, using the same asymmetric click conditions in each case (Table 1). These starting materials were obtained (see Supporting Information) by functional group interconversions of the methyl ester. Reduction of 1 to produce 5 gave access to a series of ethers and 3,3-dimethylbutanoate and benzoyl esters were prepared by double Sonogashira coupling followed by esterification of the alcohol. Ferrocenylmethyl azides were also prepared, but attempted intramolecular CuAAC reactions gave poor results. Successful CuAAC reactions were achieved, however, by using bis-alkynes that were synthesised from 1 by double Sonogashira coupling then hydrolysis and esterification (3), and by double attack with a methyl Grignard reagent (4). These gave contrasting results (a switch in enantioselectivity, Table 1; for assignments of absolute configurations, vide infra). We next examined the less hindered alcohol derivative 6, obtained from 5 by double Sonogashira coupling and desilylation, and the related series of ethers (compounds 7–10). These later examples all showed the same sense of enantioselectivity as that obtained with the first substrate (2).

Table 1. Desymmetrisation of dialkynylferrocenes (Scheme 2) using CuICl and (R,R)-Ph-Pybox, with 1.5 equiv. of benzyl azide.

<table>
<thead>
<tr>
<th>Structure</th>
<th>R Group</th>
<th>Monotriazole yield / %</th>
<th>e.e. / %</th>
<th>Starting material yield / %</th>
<th>Bis-triazole yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>OMe</td>
<td>51</td>
<td>31</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>OBn</td>
<td>34</td>
<td>38</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>19</td>
<td>29%</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>42</td>
<td>97%</td>
<td>--</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>OBn</td>
<td>51</td>
<td>42</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>OTMS</td>
<td>20%</td>
<td></td>
<td>24</td>
<td>35%</td>
</tr>
<tr>
<td>10</td>
<td>OTBOPs</td>
<td>60</td>
<td>79</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

[a] TMS deprotected product. [b] Gave the opposite enantiomer to the one that is drawn in Scheme 2.

The asymmetric CuAAC click reaction using alcohol 6 gave a hugely improved 97 % ee and an acceptable 42 % yield of the
mono-triazole product. Ethers 7 and 8 gave slightly better conversion, but at the cost of a considerable reduction in ee when compared to the desymmetrisation of 6.

Further functionalisation of 6 with TMS to form 9 gave only moderate results. Using tert-butyldiphenylsilyl chloride (TBDPSCl) gave bis-alkyne 10, which after desymmetrisation produced the highest yield of a mono-triazole, 60 %. This reaction also gave a high enough ee to prove that a true desymmetrisation must be taking place, since the combination of 79 % ee and 60 % chemical yield cannot arise from a non-selective first cycloaddition reaction followed by a highly efficient KR of the resulting near-racemic monotriazole.

2.3. Ligand Screen

After this initial investigation of the influence of different central substituents, we tested a number of ligands that have been shown to be effective in previously published asymmetric click reactions,[2] using our most efficient example, 6, as the substrate (Scheme 3, and Table 2). The ligand screen produced a range of yields and ees. All the ligands were effective to some extent in promoting the desymmetrisation of 6, except for L4, which produced copper complexes that were not sufficiently catalytically active to consume all the starting material, nor did it generate a good ee. This survey includes three N-coordinating and three P-coordinating ligands, all commercially available. L3 gave the product (R)-6a in almost enantiopure form, but in the lowest chemical yield. In contrast, L6 gave a high ee of the S config., as well as a good conversion.

2.4. Possibility That Kinetic Resolution Might Be Influencing Apparent Stereoselectivity

Since the formation of the bis-triazole 6b is also catalysed by copper bound to the chiral ligand, the possibility that this might influence the apparent enantioselectivity of the desymmetrisation reaction (a secondary KR effect) was probed using a racemic sample of 6 in standard KR experiments (Scheme 4) comparing ligands L1 and L6. An authentic sample of rac-6a was synthesised from 6 through a CuAAC reaction catalysed by the very bulky rac-BINAP (to prevent conversion into the unwanted bis-product 6b).

Table 3. Results of the KR reactions (Scheme 4) using CuCl and 0.5 equiv. of benzyl azide.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>6a yield / %</th>
<th>ee / %</th>
<th>6b yield / %</th>
<th>6b yield / %</th>
<th>Azide consumed / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>54</td>
<td>32</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L6</td>
<td>53</td>
<td>7</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on these findings, the influence of the secondary KR effect was then directly demonstrated by performing a series of KR reactions using CuCl and 0.5 equiv. of benzyl azide.
of desymmetrisation reactions of compound 6, using ligand L1 and employing differing quantities of azide. The results reveal that the KR effect is synergistic with the initial asymmetric induction, as the ee of 6a increases with increasing amount of azide (and the consequent increase in the yield of 6b). This effect is illustrated in Figure 1, which plots the observed ee of 6a, the residual starting material 6, and the yields of both 6a and 6b, against the amount of benzyl azide used in the reaction.

2.5. Determination of Absolute Configuration of the Preferred Product of Asymmetric Induction

The absolute configuration of the mono-triazole products of the asymmetric click reactions was determined by chemical correlation (Scheme 5) based on the synthesis of an authentic sample of the R<sub>p</sub> enantiomer of 6a starting from a ferrocenyl carboxylic acid (S<sub>p</sub>)-11 of known absolute configuration.[7a] The required starting material (S<sub>p</sub>)-11 was prepared in four steps following a literature procedure[13] that used a chiral oxazoline directing group,[7a] making (S<sub>p</sub>)-11 available in high ee. Our conversion of (S<sub>p</sub>)-11 into (R<sub>p</sub>)-6a was performed by esterification, Sonogashira coupling and iodination of the resulting alkyne. Desilylation and a CuAAC click reaction under standard (achiral) conditions was followed by a further Sonogashira reaction and a second desilylation. Crystallisation of the intermediate (R<sub>p</sub>)-14 allowed access to the final product in enantiopure form, and the absolute configuration was confirmed unequivocally by X-ray crystallography (Figure 2).

The CD curve for (R<sub>p</sub>)-6a (Figure 3, black trace) shows a strong characteristic[14] negative band at 486 nm. The CD curves for the products with alternative central functionality (2–4 and 7–10) were also recorded. With one exception, all showed similar negative band maxima in the range 437–486 nm, establishing that all were in the same configurational series (i.e. that the faster reacting enantiotopic alkyne was consistently pro-R<sub>p</sub> in all these cases). The one exception (4a, which had a strong positive band at 478 nm, magenta trace) was examined in more detail by the preparation of an authentic sample from (R<sub>p</sub>)-15 in two steps (see Supporting Information). This confirmed that this product was indeed (S<sub>p</sub>)-4a, and that with the very bulky central substituent (CMe<sub>2</sub>OH), the enantioselectivity of the

![Image](https://example.com/image.png)

Figure 2. ORTEP diagram for the crystal structure of (R<sub>p</sub>)-14, CCDC deposition number 1934870 (thermal ellipsoids are drawn at the 50 % probability level).

Figure 3. The circular dichroism curves of the mono-triazoles used to correlate the absolute configurations.
asymmetric click reaction is reversed to favour the pro-$S_1$ pathway.

3. Conclusions

We have shown the first examples of the use of the new asymmetric click reaction to induce planar chirality, giving monotria
deficient chiral recognition in the desymmetrisation re-
actions for efficient chiral recognition in the desymmetrisation re-
action itself have been demonstrated.

CCDC 1934870 (for ($R_9$)-14), and 1934883 (for 19, See Sup-
porting Information for structure 19) contain the supplementary
crystallographic data for this paper. These data can be ob-
tained free of charge from The Cambridge Crystallographic
Data Centre.

Experimental Section

Representative procedure for the asymmetric CuAAC click reac-
tion

Copper(I) chloride (10 mol-%) and ($R,R$)-Ph-Pybox ($L1$, 20 mol-%)
were stirred in anhydrous dichloromethane (0.1 M) for 10 min. A
solution of the bis-alkyne (1 equiv.) in anhydrous dichloromethane
(0.1 M) was added. Benzyl azide was added and the reaction mixture
was stirred at 25 °C for 24 h. Distilled water was added, and the
reaction mixture was extracted three times with dichloromethane.
Combined organic phases were dried with sodium sulfate, filtered
and the solvent was removed in vacuo. The products were sepa-
rated by column chromatography (see Supporting Information).

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