Coetaneous catalytic kinetic resolution of alkynes and azides through asymmetric triazole formation

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A non-enzymatic simultaneous (coined coetaneous) kinetic resolution of a racemic alkyne and racemic azide, utilising an asymmetric CuAAC reaction is reported. The use of a CuCl (\(R,R\))-Ph-Pybox catalyst system effects a simultaneous kinetic resolution of two racemic starting materials to give one major triazolic diastereoisomer in the ratio 74:12:4:10 (dr 84:16, 90\% ee \textsubscript{maj}). The corresponding control reaction using an achiral copper catalyst gives the four possible diastereoisomers in a 23:27:23:27 ratio, demonstrating minimal inherent substrate control.

The copper-catalysed azide-alkyne cycloaddition (CuAAC) pioneered by both Meldal and Sharpless has become a ubiquitous molecular fragment-linking reaction\textsuperscript{1-3}. The product 1,4-substituted, 1,2,3-triazoles, along with their alkyne and azide building blocks, in enantioenriched forms are important motifs\textsuperscript{4-9}. Triazoles for example, have become crucial to research arenas including fragment based drug discovery (FBDD) and supramolecular chemistry\textsuperscript{10}. Whilst scalemic alkynes and azides are important building blocks for a myriad of transformations\textsuperscript{4,5}.

Catalytic kinetic resolution (KR) occurs when one enantiomer of a racemic substrate is preferentially activated towards reaction by a chiral catalyst (through competing diastereomeric transition states), leading to more rapid formation of one enantiomer of product. At 50\% conversion of starting racemic material, effective catalytic KR will have occurred if high \textit{ee} of product and high \textit{ee} of unreacted starting material are obtained. The effectiveness of a kinetic resolution may be judged by a criterion named selectivity factor (\(s\)). Selectivity factor is the ratio of the rate constants for reaction of each enantiomer in a given asymmetric transformation\textsuperscript{11}. Enzymes are capable of performing catalytic KR, albeit under a narrow range of conditions with limited substrate scope\textsuperscript{12,13}. Catalytic kinetic resolution has been widely studied\textsuperscript{11}. Fu and co-workers have championed catalytic KR, applying planar chiral DMAP-derivative catalysts to the successful KR of secondary alcohols\textsuperscript{14-16}. Catalytic KR has also been successfully employed in copper-catalysed azide-alkyne cycloadditions leading to enantioenriched chiral triazoles and the recovery of enantioenriched starting materials (Scheme 1i and ii)\textsuperscript{17-21}, and complete consumption of starting materials in the case of dynamic kinetic resolution\textsuperscript{22}. Desymmetrisation by asymmetric triazole formation has also been successfully achieved\textsuperscript{23-25}.

Parallel kinetic resolution is a well-established field, where a single chiral starting materials’ enantiomers undergo simultaneous divergent asymmetric transformations yielding different enantioenriched products from either enantiomer of starting material\textsuperscript{26-29}. For example Fu and co-workers utilised parallel kinetic resolution to resolve 4-alkynals (Scheme 2)\textsuperscript{30}.

Herein, we investigate a simultaneous, rather than parallel, kinetic resolution of two racemic substrates, under control of a single chiral catalyst, and coin the term coetaneous resolution to describe it. Upon coetaneous resolution of two racemic substrates, the ideal scenario would be formation, at 50\% conversion, of a single diastereoisomer of the product formed from one enantiomer of each substrate. This ideal process would leave the opposite

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enantiomers of the substrates unreacted in high enantiopurity. Thus, simultaneously kinetically resolving two chiral starting materials under one reaction and product manifold.

We chose to focus on the CuAAC of racemic substrates, such that, under catalyst control, the starting materials (chiral azides and alkynes) could react selectively to give a major stereoisomer, among the four possible expected diastereomeric triazole products. Conversely, in the case where no substrate control exists, the use of an achiral catalyst will lead to equal consumption of starting material enantiomers and delivery of an equimolar distribution of the four stereoisomers of product (Fig. 1). Asymmetric synthesis using two catalysts to control the formation of two stereogenic centres has been elegantly demonstrated by Carreira and co-workers. See refs26,27,31,32.

Results and Discussion

Based on previous work on catalytic kinetic resolution of alkynes and azides, we chose the PyBox ligand family for creation of a chiral copper catalyst and selected (R,R)-Ph-PyBox as a suitable ligand for our investigations20,25,33,34.

To investigate the potential for coetaneous catalytic kinetic resolution we focused on substrates with demonstrable efficacy in standard catalytic kinetic resolutions. Quaternary oxindole 1 (as employed in Scheme 1i), was selected as the alkyne-containing component. Oxindoles are important, biologically-relevant, scaffolds having found wide application, including as calcium channel blockers35, anti-angiogenics36, antitumour agents37–39 and analgesics35. Azide 3 (as employed in Scheme 1ii) was chosen owing to its previously reported application in the first catalytic kinetic, copper-catalysed triazole forming, resolution by Fokin and co-workers20.

We have previously explored the selectivity of alkyne 1 towards kinetic resolution and found an intriguing solvent dependency upon selectivity35, however resolution of azide 3 had not been employed under those same conditions (shown in Scheme 1i). In order to probe this azide 3 was reacted with 0.5 equivalents of phenyl acetylene, 15 mol% L1 and CuCl (12.5 mol%) in acetone-d6 and the reaction progress was monitored in-situ via proton nuclear magnetic resonance (1H NMR) spectroscopy.

From the resolution of azide 3 in acetone a selectivity factor of $s = 7.4$ was determined (Table 1, entry 1).

![Scheme 1. Previous Work: (i) Kinetic Resolution of Alkynes by Brittain et al.18. (ii) Kinetic Resolution of Azides by Meng et al.20.](Image)
was used as solvent \( s = 7.1 \), (Table 1, entries 1 and 2 versus 3 and 4) suggesting that the dione solvent-effect is manifest primarily in alkyne rather than azide selectivity.

The inherent diastereoselectivity of the CuAAC of a reaction of 1 with 3 was probed (Scheme 3i), to determine any contribution to diastereoselectivity from substrate bias. Compounds 1 and 3 were reacted together with tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) as an achiral ligand giving a product diastereoisomer ratio of 23:27:23:27 via HPLC, thus demonstrating there was little inherent diastereoselectivity between the two substrates in the CuAAC reaction (Scheme 3ii).

The coetaneous kinetic resolution of 1 and 3 was then attempted. To our delight, it was found that a mixture of 1:1 of 3 and 1 in the presence of 15 mol% L1 and 12.5 mol% CuCl catalyst provided a 74:12:4:10 diastereoisomeric ratio of product 6 (Scheme 3iii). This showed that indeed the reaction successfully resolved the two starting materials simultaneously.

To enable comparison of the selectivity for each enantiomer in this diastereo- and enantio- selective process the selectivity factors for each enantiomer of alkyne 1 and azide 3 were determined as follows. Using enantiopure...
substrates as the limiting reagent the selectivity towards that component could be analysed (Table 2). The absolute
configuration of 1 was evidenced by X-ray diffractometry of a single crystal of an iodo alkyne derived from one
enantiomer of enantiopure alkyne 1 (see compound 7 ESI) and the absolute configuration of 3 by comparison to
it and by employing in the synthesis literature data and protocols (see ESI). Thus, also allowing for assignment of
the absolute stereochemistry of the products (6, as noted in Scheme 3, and see ESI).

From the data presented in Table 2 it can be seen that consumption of racemic alkyne is faster and more
selective (in a reaction catalysed by a catalyst derived from L1) in combination with (S) azide. As well as the
observation that consumption of racemic azide is essentially equally rapid in combination with either enantiomer
of alkyne (in a reaction catalysed by a catalyst derived from L1), with only a slight difference in selectivity, it being
subtly better with (R) alkyne. These, and earlier, data reveal two important features, firstly issues of selectivity are
more dependent upon alkyne than azide stereochemistry (in this example) and secondly that across these four
experiments with a single enantiomer component the faster reacting and more selective examples involve
(S) azide and (R) alkyne, which corresponds to the major product (of Scheme 3 iii) being formed from these same
two enantiomers. Thus, adding support for the hypothesis that a coetaneous kinetic resolution is taking place.

Conclusions

These preliminary findings are to the best of our knowledge the first non-enzymatic example of two racemic start-
ing materials being successfully kinetically resolved by the same catalyst to an enantioenriched diastereomeric
product. We recognise that in this first study substrate scope is limited and hope this strategy can be applied to
other types of substrates and increase the efficiency of resolution procedures. It is interesting to consider if this
kind of selectivity may be operating in any systems of nature and we hope to be able to explore the scope and
mechanistic aspects of this reaction.

Methods

Synthesis of (1-Azidoethyl)benzene (3). To a solution of sodium azide (105 mg, 1.61 mmol, 1.10 equiv.)
in DMSO (6 mL) was added (1-bromoethyl)benzene (200 μL, 271 mg, 1.47 mmol, 1 equiv.). The reaction mix-
ture was allowed to stir at rt for 2 h. To this mixture was added water (10 mL) and subsequently extracted with
ether (3 × 10 mL). The organic extracts were combined, washed with water (2 × 10 mL) and brine (10 mL) and
then dried over MgSO4, filtered and concentrated under reduced pressure to give (1-azidoethyl)benzene
3 as a
pale yellow oil, in 40% (84.0 mg) yield. Characterisation was in agreement with reported literature values40. 1H
NMR (300 MHz, CDCl3) δ 7.25–7.40 (m, 5H, Ar-H), 4.60 (q, J = 6.8, 1H, CH3), 1.52 (d, J = 6.8, 3H, CH3); 13C NMR
(101 MHz, CDCl3) δ 140.90, 128.80, 128.15, 126.41, 61.12, 21.59; IR νmax (ATR)/cm−1 3032, 2979, 2090, 1244;
MS AP+ m/z 120.1 [M-N2]+, 105.0 [M-N3]+; GC (CP-Chirasil-Dex CB), FID, tS = 28.1 min, tR = 28.4 min.

General procedure for the synthesis of enantiopure azides. Under an atmosphere of nitrogen, the
corresponding alcohol (2.54 mmol, 1.00 equiv.) was dissolved in anhydrous toluene (4 mL) to this was added
diphenylphosphoryl azide (DPPA) (633 μL, 810 mg, 2.94 mmol, 1.20 equiv.). The mixture was cooled to 0°C for
5 mins and DBU (440 μL, 448 mg, 2.94 mmol, 1.20 equiv.) added. The reaction mixture was allowed to warm to
room temperature and stirred for 18 h. The reaction was subsequently quenched with water (10 mL) andaq. HCl
5% v/v (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic fractions were dried over MgSO4
and concentrated under reduced pressure, the crude residue was purified by flash column chromatography (20:1
hexane/EtOAc).

| Entry | R1 | R2       | Solvent  | Selectivity Factor (s) |
|-------|----|----------|----------|------------------------|
| 1     | Ph (4) | C6H5CHCH3(3) | Acetone  | 7.4                    |
| 2     | Ph (4) | C6H5CHCH3(3) | 2,5-Hexanedione | 7.1                |
| 3     | Oxindole (1) | C6H5CHCH3(3) | Acetone  | 5.3*                  |
| 4     | Oxindole (1) | Bn       | 2,5-Hexanedione | 22.1*               |

Table 1. Kinetic resolution of alkyne 1 and azide 3 under the same reaction conditions. Reaction was carried
out with 0.6 equiv. non-chiral material to 1 equiv. chiral substrate. *Selectivity is that which has been previously
reported by Brittain et al.17.
Scheme 3. (i) Coetaneous Kinetic Resolution of Azides and Alkynes. Conversion was determined by $^1$H NMR spectroscopy. Enantioenrichment of 6 and 1 was determined by HPLC using a chiral stationary phase.

“Stereochnamic nomenclature to describe diastereoisomers as follows: The first letter inside the brackets refers to the stereochnamic descriptor at the oxidine stereogenic centre, the second letter within the brackets refers stereochnamic descriptor at the stereogenic centre adjacent to the triazole ring”. Enantioenrichment of azide 3 was determined by GC using a chiral stationary phase. (ii) HPLC trace of outcomes using conditions: (a) Alkyne 1 (1 equiv.) to azide 3 (1 equiv.), TBTA (15.0 mol%), CuCl (12.5 mol%) in 2,5-hexanedione at 0 °C for 96 h. (iii) HPLC trace using conditions; or (b) Alkyne 1 (1 equiv.) to azide 3 (1 equiv.), CuCl (12.5 mol%), L1 (15.0 mol%) in 2,5-hexanedione at 0 °C for 96 h.

**Table 2.** Kinetic resolution with enantiopure partners. Reactions were run with 0.5 equiv. of single enantiomer substrate to 1 equiv. of racemic substrate. Enantiopure alkyne 1 was obtained by preparative chiral HPLC (see ESI). Enantiopure azide 3 was synthesised according to literature procedure (see ESI). Conversion was determined by integration of $^1$H NMR spectra (see ESI). SM refers to the recovered alkyne/azide following resolution (rac component before resolution).

**(S)-(1-Azidoethyl)benzene (3 (S)).** Prepared from (R)-phenylethanol according to general procedure, colourless oil 3 (S) (131 mg, 35%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.50–6.97 (m, 5H, Ar-$H$), 1.49 (d, $J$ = 6.8, 3H, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 140.90, 128.80, 128.14, 126.41, 61.12, 21.80; MS ESI$^+$ m/z 147.1 [M]$^+$, 105.1 [M-N$_3$]$^+$, 77.0 [M-C$_2$H$_4$N$_3$]$^+$; GC (CP-Chirasil-Dex CB), FID, t = 28.1 min.

**(R)-(1-Azidoethyl)benzene (3 (R)).** Prepared from (S)-phenylethanol according to the general procedure, colourless oil 3 (R) (150 mg, 40% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42–7.18 (m, 5H, Ar-$H$), 1.48 (d, $J$ = 6.8, 3H, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 140.90, 128.80, 128.14, 126.41, 61.12, 21.58; MS ESI$^+$ m/z 147.1 [M]$^+$, 105.1 [M-N$_3$]$^+$, 77.0 [M-C$_2$H$_4$N$_3$]$^+$; GC (CP-Chirasil-Dex CB), FID, t = 28.4 min.
Synthesis of racemic 4-phenyl-1-(1-phenylethyl)-1H-1,2,3-triazole (5). Phenylacetylene (20.0 mg, 0.20 mmol, 1.00 equiv.), (1-azidoethyl)benzene 3 (30.0 mg, 0.20 mmol, 1.00 equiv.) and sodium ascorbate (39.0 mg, 0.20 mmol, 1.00 equiv.) were added to a solution of CuSO4.5H2O (5.00 mg, 0.020 mmol, 10 mol%) in MeOH (4 mL). The reaction mixture was allowed to stir for 24 h at rt. The reaction was quenched with aq. ammonia solution 5% v/v (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with water (10 mL) and concentrated under reduced pressure. The crude residue was purified by automated flash column chromatography. 

Synthesis of 1-benzyl-3-methyl-3-(1-(1-phenylethyl)-1H-1,2,3-triazol-4-yl)methylindolin-2-one (6). To a solution of 1-benzyl-3-methyl-3-(prop-2-yn-1-yl)indolin-2-one 1 (100 mg, 0.36 mmol, 1.00 equiv.) in acetone (5 mL) was added copper (I) chloride (1.80 mg, 0.018 mmol, 5 mol%), TBTA (9.60 mg, 0.022 mmol, 20 mol%) and (1-azidoethyl)benzene 3 (60.0 mg, 0.40 mmol, 1.10 equiv.) in acetone (1 mL). The mixture was heated to reflux and stirred for 96 h. The reaction mixture was then quenched with aq. ammonia solution 5% v/v (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and dried over MgSO4 and concentrated under reduced pressure. The crude residue was purified by automated flash column chromatography.
at 0 °C. The reaction mixture was then quenched with the addition of aq. ammonia solution 5% v/v (5 mL) then extracted with ether (2 × 10 mL). The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. Conversion of the reaction was determined through 1H NMR spectroscopy of the recovered crude material. Enantiomeric excess was determined by chiral GC. The remaining azide and triazolic product were isolated by automated flash column chromatography Combiblifl Rf (0–40% hexane/EtOAc, 15 mins).

**General procedure for the kinetic resolution of 1 with Azide 3.** To an oven dried Radley's multi-reactor tube L1 (6.70 mg, 0.018 mmol, 15.0 mol%) and CuCl (1.50 mg, 0.015 mmol, 12.5 mol%) followed by 2,5-hexanedione (1 mL) were added. After stirring at rt for 1 h, compound 1 (33.4 mg, 0.12 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was added. The reaction mixture was stirred for a further 15 mins before being cooled to 0 °C for 15 min. Azide 3 (R) (8.90 mg, 0.06 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was then added. The reaction mixture was stirred at 0 °C for 96 h. The reaction was then quenched by addition of aqueous ammonia 5% v/v (5 mL). The reaction mixture was then extracted with ethyl acetate (2 × 10 mL), dried over MgSO4 and concentrated under reduced pressure. Conversion was determined by integration of the 1H NMR spectrum of the recovered material. The remaining starting material and the triazolic product were subsequently isolated by automated column chromatography Combiblifl Rf (0–100% hexane/EtOAc gradient 12 mins). Enantiomeric excess and diastereomer ratio of 6 and enantiomeric excess of 1 were determined by chiral HPLC.

**General procedure for the kinetic resolution of 3 with Alkyne 1.** To an oven dried Radley's multi-reactor tube was added L1 (6.70 mg, 0.018 mmol, 15.0 mol%) and CuCl (1.50 mg, 0.015 mmol, 12.5 mol%) followed by 2,5-hexanedione (1 mL), the resulting solution was allowed to stir at rt for 1 h. After this time compound 1 (33.4 mg, 0.12 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was added. The reaction mixture was stirred for a further 15 mins before being cooled to 0 °C in an ice bath and stirred for a subsequent 15 mins. After this time had passed azide 3 (17.8 mg, 0.12 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was added. The reaction mixture was stirred for 96 h at 0 °C before being quenched by the addition of aqueous ammonia 5% v/v (5 mL). The reaction mixture was then extracted with EtOAc (2 × 10 mL), the combined organic fractions were dried over MgSO4 and concentrated under reduced pressure. Chiral GC was carried out on the crude recovered material to measure the ee of the remaining azide 3. The remaining crude material was the purified by automated flash column chromatography Combiblifl Rf (0–100% hexane/EtOAc gradient, 12 mins). The dr and ee of the triazolic product was then determined by chiral HPLC.

**General procedure for simultaneous kinetic resolution of 1 and 3.** To an oven dried Radley’s multi-reactor tube was added L1 (6.70 mg, 0.018 mmol, 15.0 mol%) and CuCl (1.50 mg, 0.015 mmol, 12.5 mol%) followed by 2,5-hexanedione (1 mL), the resulting solution was allowed to stir at rt for 1 h. After this time compound 1 (33.4 mg, 0.12 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was added. The reaction mixture was allowed to stir at rt for a further 15 mins after which it was cooled to 0 °C in an ice bath and stirred for a subsequent 15 mins. After this time had passed azide 3 (17.8 mg, 0.12 mmol, 1 equiv.) dissolved in 2,5-hexanedione (0.5 mL) was added. The reaction mixture was stirred for 96 h at 0 °C before being quenched by the addition of aqueous ammonia 5% v/v (5 mL). The reaction mixture was then extracted with EtOAc (2 × 10 mL), the combined organic fractions were dried over MgSO4 and concentrated under reduced pressure. Chiral GC was carried out on the crude recovered material to measure the ee of the recovered alkyne 1. The remaining crude material was the purified by automated flash column chromatography Combiblifl Rf (0–100% hexane/EtOAc gradient, 12 mins). The dr and ee of the triazolic product 6 and ee of the recovered alkyne 1 was then determined by HPLC with a chiral stationary phase.

Supplementary information is available that includes detailed experimental procedures, NMR spectrums, HPLC traces and X-ray crystallographic information. Citations therein should be referred to in relation to published procedures and a pre-peer reviewed preprint was submitted prior to peer assessment of this manuscript.

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Competing interests
The authors declare no competing interests.

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