

Organic & Biomolecular Chemistry

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ISSN 1477-0520



COMMUNICATION

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175 YEARS



Cite this: *Org. Biomol. Chem.*, 2016, **14**, 10778

Received 29th July 2016,
Accepted 15th August 2016
DOI: 10.1039/c6ob01623e

www.rsc.org/obc

The Bull–James assembly as a chiral auxiliary and shift reagent in kinetic resolution of alkyne amines by the CuAAC reaction†‡

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The Bull–James boronic acid assembly is used simultaneously as a chiral auxiliary for kinetic resolution and as a chiral shift reagent for *in situ* enantiomeric excess (ee) determination by ¹H NMR spectroscopy. Chiral terminal alkyne-containing amines, and their corresponding chiral triazoles formed *via* CuAAC, were probed *in situ*. Selectivity factors of up to *s* = 4 were imparted and measured, accurate to within ±3% when compared to chiral GC.

One of the bottlenecks in the analysis of asymmetric reaction outcomes is the enantiomeric excess (ee) determination by HPLC analysis using a chiral stationary phase.² The development of enantiomer separation conditions, followed by often lengthy elution times means that even a relatively fast reaction can require hours to properly analyse the stereochemical efficiency of the transformation. Therefore, the development of high-throughput screening (HTS) techniques to determine ee is important, especially where hundreds to thousands of reactions need to be analysed swiftly in order to avoid holding up industrial processes.^{2,3}

Nuclear magnetic resonance (NMR) spectroscopy is one method that could be utilised in some cases as a HTS ee determination strategy. Proton NMR spectra can usually be obtained in less than five minutes, whereas HPLC runs often require approximately tens of minutes.⁴ The increased throughput in combination with circumvention of chiral chromatography method development makes ¹H NMR spectroscopy an attractive approach for HTS.⁵ Determination of enantiopurity has been successfully carried out *via* NMR

spectroscopy previously. One popular strategy is the use of chiral shift reagents, with the most common reagents being relatively expensive lanthanide-based complexes *e.g.* Eu(hfc)₃.⁶ A weakly paramagnetic chiral lanthanide complex forms an *in situ* mixture of diastereoisomers whose diastereomeric ratio (dr) is measured to determine the ee of the chiral analyte.^{6c}

Chiral derivatisation of compounds to form distinguishable diastereomers is one strategy for indirect determination of ee *via* NMR spectroscopy.⁷ This technique was most notably employed by Mosher (Mosher's acid) for the analysis of enantiomer ratios of chiral alcohols and amines.⁸ However, this method requires one to sacrifice a small amount of sample in order to carry out the analysis and is therefore less than ideal for HTS applications.⁹

A boronic acid-based supramolecular assembly for the ¹H NMR spectroscopic analysis of the enantiopurity of chiral amines and diols were first reported by Bull, James and co-workers.¹⁰ This system takes advantage of the diastereomeric complexes formed from a boronic acid, chiral diol and a chiral primary amine. Using a stereo-defined amine component, the ee of a chiral alcohol could be analysed, and *vice versa*.^{10a–e,g,k} The commercial availability and relatively inexpensive nature of the Bull–James assembly components gives it an economic edge over lanthanide-based chiral shift reagents.

Following previously published work from some of the co-authors of this report (Brittain, Buckley and Fossey), we wished to tackle the difficult task of kinetic resolution (KR) of terminal alkynes using copper catalysed azide alkyne cycloadditions (CuAACs) (Scheme 1). As there is, to the best of our knowledge, only one reported example of this type of resolution,¹¹ we believed this to be a robust test of the Bull–James sensing assembly in the challenging forum of kinetic resolution, where both the ee of starting material and of product are simultaneously probed. Kinetic resolution takes advantage of the difference in rate of reaction of enantiomers¹¹ and allows for the recovery of enantioenriched starting materials and products. Additionally, it is an asymmetric approach that has been successfully used to obtain many enantioenriched

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† Dedicated to the 60th Birthday of Tony Czarnik.¹

‡ Electronic supplementary information (ESI) available. CCDC 1477891. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob01623e



The authors thank Tony D. James and Steven D. Bull for inventing and developing the ee analysis protocol. Without

Reaction scheme showing the synthesis of copper(I) complexes 4 and 5:

1 + 2 + 3 $\xrightarrow{\text{CDCl}_3}$ 4 AMS

4 + 5 $\xrightarrow[\text{rt, 24 h}]{\text{BnN}_3 \text{ (0.5 equiv.)}, \text{Copper Source (10 mol\%)}}$ 5

Entry	Copper source	Conv. ^a (%)	%ee 1 ^b	%ee 6 ^b	s
1	CuCl	30	23	39	4.1
2	CuBr	34	25	48	3.7
3	CuI ^c	39	21	13	2.4
4	Cu(OTf)·0.5toluene ^c	31	18	31	2.8
5	[Cu(CH ₃ CN) ₄]PF ₆	50	36	16	3.0

The figure displays the chemical structure of compound **7** and its corresponding crystal structure. The chemical structure on the left shows a complex molecule with a central boron atom coordinated by two oxygen atoms, forming a five-membered ring. This ring is part of a larger system that includes a phenyl group, a benzimidazole ring, and a biphenyl moiety. The crystal structure on the right shows the molecule in a 3D arrangement, with atoms represented by spheres and bonds by lines. The structure is labeled with the number **7**.

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their breakthrough technology none of this work would have been possible. WDGB and WZ are grateful to the University of Birmingham for PhD support. The China Scholarship Council (CSC) are also thanked for providing support (WZ). JSF thanks the University of Birmingham for support, the Royal Society for an Industrial Fellowship (6955) and the EPSRC for funding (EP/J003220/1). WDGB, WZ, BMC, JSF and EVA thank the Royal Society International Joint Project and Research Grant Schemes for underpinning this project. WDGB would like to thank the Royal Society of Chemistry, School of Chemistry at the University of Birmingham and The Society of the Chemical Industry for travel grants. EVA also thanks the Welch Regents Chair (F-0046) and the NIH (GM077437) for support. The Catalysis and Sensing for our Environment (CASE) group is thanked for providing essential networking opportunities.²⁰

Notes and references

- Two co-authors to this manuscript are pleased to be inaugural winners of MSMLG 2016 Czarnik Award (EVA) and MSMLG 2016 Czarnik Emerging Investigator Award (JSF).
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- In this report wedged and dashed bonds are used as follows: (i) wedges and dashes with the same width as either end indicates relative stereochemistry; (ii) wedges and dashes with a thin and thick end indicate absolute stereochemistry the thin end if the bond is the furthest away.
- Organic azides in pure forms especially with low molecular weights or C : N ratios <2 can spontaneously explode.
- Author contributions: JSF and EVA are the primary investigators and corresponding authors, who led the research across their laboratories jointly. JSF initiated the use of the Bull–James assembly for monitoring ee of starting material and product whilst at the same time using it as a chiral auxiliary. WDGB, BMC and WZ carried out experimental work at



both the University of Birmingham (UK) and the University of Texas at Austin (USA). VML solved the crystal structure and helped with preparation of ESI.† BRB gave intellectual input and contributed to preparation of the manuscript.

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