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ARTICLE TYPE

Point-to-helical chirality transfer for a scalable and resolution-free synthesis of a heliceneoidal DMAP organocatalyst

Matthew R. Crittall,^a Nathan W. G. Fairhurst^a and David R. Carbery^{*a}

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The synthesis of a second-generation [6]-heliceneoidal DMAP organocatalyst is reported. The synthesis is reliant upon a highly diastereoselective Rh-catalysed [2+2+2] triyne cycloisomerization, using an existing stereocentre to control the sense of forming helicity. Taken together, a scalable (>1 g), resolution-free entry to a helical DMAP with the capacity for subsequent functionalization, has been achieved.

Chirality, according to Kelvin's original definition, centres upon the geometrical non-superimposability of mirror images. Accordingly, molecules are deemed to be either chiral or non-chiral. Synthetic chemists however, have had a tendency to additionally "classify" chiral molecular topographies into more familiar subsets. For example, chiral structures are regularly described as possessing centres, planes and axes of chirality. The drive to synthesise chiral molecules with non-traditional stereoelements, such as those which contain planar or axial chiral elements, has arguably been motivated by the continued development of novel catalyst-ligand designs and the advancement of modern asymmetric synthetic methodologies. Regularly, a class of ligand, for example chelating bisphosphine ligands,¹ evolve a certain level of synthetic utility which cannot be improved upon unless novel chiral stereochemical space away from the ready availability of the chiral pool is examined.

In the arena of organocatalysis, one example which has seen a pronounced level of creative molecular design is the development of chiral analogues of the Lewis basic catalyst 4-dimethylamino pyridine (DMAP, **1**, Fig 1).² The challenge of effectively desymmetrising the pyridine ring has led to some impressive and imaginative applications of non-traditional chirality elements to the synthesis of chiral DMAP analogues. For example, Fu has synthesised the planar chiral, ferrocene-based catalyst **2**³ and Spivey has reported the examination of atropisomerism as a chirality element in the synthesis of **3**⁴ (Fig 1).^{5,6}

Fig.1 DMAP and non-traditional chiral analogues

In addition to their wide-ranging applications in functional materials chemistry⁷, helicenes have recently been examined as the basis of a number of chiral organocatalysts.⁸ Inspired by these studies, we chose DMAP as our context to examine helicity as a viable chiral scaffold in organocatalyst design. Accordingly, we have recently reported the design, synthesis, resolution and benchmarking of helical catalyst **4**.^{9,10} This catalyst is based upon a helicene-like structure and was found to be an effective catalyst for the acylative kinetic resolution of chiral secondary alcohols. Selectivity factors of up to $S=116$, with loadings as low as 0.05 mol% on preparative scale reactions were achieved. Whilst this report on chiral 2° alcohols was encouraging, the primary reason for study was to gauge the efficacy of helicene-like structures as a design element in asymmetric catalysis. A subsequent re-evaluation of this study pinpointed three key deficiencies. Firstly, the synthesis of **4** required HPLC resolution of the racemic material, ultimately restricting synthetic applicability. Secondly, a number of intermediates *en route* to **4** were found to be sensitive, leading to limited scalability. Thirdly, it is reasonable to assume that the incorporation of additional functionality upon the helicene body of **4** may, in a general sense, allow enhanced selectivities and efficacies to be attained in enantioselective transformations. Therefore, the introduction of a method by which late-stage functionalization could be achieved was seen to be advantageous. We were keen to address these short-comings and develop an asymmetric synthesis of a functionalized heliceneoidal DMAP. Inspired by the Starý laboratory¹¹ which has reported excellent levels of point-to-helicity chirality transfer during Co-catalysed [2+2+2]-triyne cycloisomerizations *en route*

to helicene-like molecules, we have opted to design pyridine **5** (Fig. 1).

The synthesis of an appropriate chiral triyne is outlined in Scheme 1. This sequence mirrors our original route to **4** but now relies upon the formation of chiral propargyl ether *S*-**9** via a Mitsunobu reaction using an enantiopure propargylic alcohol and a functionalised 2-naphthol (Scheme 1). Conversion of naphthol **6** to **7** was achieved via regioselective Sonogashira coupling with trimethylsilylacetylene. Mitsunobu reaction of **7** and propargylic alcohol *R*-**8** formed ether *S*-**9** with no loss of enantiopurity. A second Sonogashira coupling between *S*-**9** and **10** proceeded without incident before ultimate conversion to **12** using the sequence of transformations previously utilised in the synthesis of **4** (Scheme 1).

Scheme 1 Chiral pyridyl triyne formation

Our previous experience had pointed towards the sensitivity of the electron-rich naphthalene unit, which ultimately restricted attempted scale-up of **4**. However, a beneficial outcome of incorporating the bromide functionality is that the discussed instability is now controlled and as a result, triyne **12** can be prepared on a multi-gram scale.

Application of the Rh(I)-catalysed triyne cycloisomerization reaction to **12** resulted in the smooth formation of heliceneoid **5** in 88% yield. We were delighted to observe an excellent level of diastereoselectivity (95:5), with the major isomer cleanly recovered as a single diastereomer after chromatography.

Scheme 2 Point-to-helical chirality transfer

This diastereoselective cycloisomerization has been performed in good yield on a reasonable scale (0.5 mmol). We have looked to scale-up this cycloisomerization, but when performed on a 3 g scale **5** was formed in 33% yield. Despite a lower yield, this larger-scale reaction still enables formation of **5** in over 1 g quantities. A recent discussion has pointed out the difficulties and importance of accessing enantiopure helicenes on scale.¹² The level of point-to-helical transfer employed in this route to heliceneoid DMAP **5** is excellent and deserves commenting upon. We believe stereocontrol is founded upon a minimization of A^{1,3}-like strain between the propargylic methyl group and the phenyl group during the construction of the central hexasubstituted aryl ring. This model places the methyl group (c.f. **I** and **II**, Fig. 2) in a *pseudo*-axial position, ultimately controlling the configuration of forming helicity i.e. *S*-**12** → *P,S*-**5**.

Fig.2 Suggested rationale for chirality transfer

Having demonstrated a scalable, resolution-free synthesis of a heliceneoid DMAP, we have in turn examined the third of our perceived drawbacks regarding our initial helical catalyst synthesis. Preliminary studies have demonstrated the feasibility of late-stage functionalization by performing a Pd-catalysed Kumada coupling between **5** and an aryl Grignard reagent to form **13** (eq 1, Scheme 3). Though unoptimized, we feel this represents a significant result due to the structural sensitivity of **5** due to the strongly Lewis basic pyridyl nitrogen and sp³ centres adjacent to *N*- and *O*-centres.[‡] Finally, we have demonstrated that the structural changes made to the periphery of the heliceneoid scaffold have not resulted in a deleterious effect on catalysis, with **14** resolved with identical selectivity as initially reported by ourselves (eq 2, Scheme 3).

Scheme 3 Preliminary late-stage functionalization studies and demonstration of catalysis

Conclusions

In conclusion a second-generation synthesis of a heliceneoid-

DMAP organocatalyst has been achieved. By harnessing point-to-helical chirality transfer a scalable, resolution-free synthesis of a functionalised helical aminopyridine is possible. The potential for late-stage Pd(0)-catalysed functionalization has also been demonstrated. A systematic optimization study is currently underway in our laboratory to improve this late-stage coupling strategy to a useful synthetic process. Practical quantities of active helical Lewis basic organocatalysts are now available from this study.

Notes and references

^a Department of Chemistry, University of Bath, Claverton Down, United Kingdom; Tel: +44 1225 386144; E-mail: d.carbery@bath.ac.uk

† Electronic Supplementary Information (ESI) available: Full experimental details and NMR data for novel compounds. See DOI: 10.1039/b000000x/

‡ Isolation of analytically pure **13** has so far not been possible due to co-elution with **5** during attempted chromatographic purification and postulated catalyst ligation. See ESI for reaction conversion data (NMR and mass spectral).

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