Design, Synthesis, and Evaluation of a Helicenoidal DMAP Lewis Base Catalyst
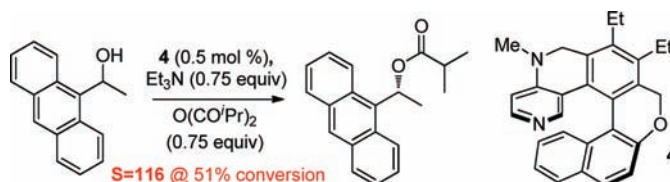
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ABSTRACT

The design, synthesis, and study of a helical dialkylaminopyridine Lewis base catalyst is reported. Helical DMAP analogue 4 is based upon a helicenoid structure and displays good to excellent levels of selectivity ($S \leq 116$) in the kinetic resolution of chiral secondary alcohols. Catalyst 4 displays excellent reactivity with exceptionally low loadings of 0.05 mol % effecting practical levels of selectivity in kinetic resolutions.

Helical structures attract extensive interest within the chemistry community by virtue of their chirality. The importance of helicity in biochemistry with respect to DNA and peptide tertiary structures is patent.[1] Structures which are chiral exclusively due to their helical shape, particularly helicenes,[2] currently demand attention. For example, a number of important optical and electronic materials[3] and telomerase inhibitors[4] are reliant on the chiroptical properties of helicenes. In contrast, one specific area of functional molecules where helicenes have been underdeveloped is that of asymmetric catalysis and, in particular, organocatalysts.[5] Takenaka has made considerable strides in recent years by demonstrating the value of helicity with reports of effective helicenyl pyridine N-oxides[6] and 2-aminopyridinium[7] catalysts.

The Lewis base catalyst dimethylaminopyridine (DMAP, **1**) is the prototypical synthetic nucleophilic catalyst, dramatically enhancing the rate of transfer of C-electrophiles to O-, N-, and C-nucleophiles.[8] The area of synthetic chemistry associated with DMAP has matured to the extent that developing effective chiral DMAP analogues for asymmetric synthesis has become not only an important exercise in synthesis but also as a contextual testing ground for applying new design principles to asymmetric catalysis.[9] The difficulties in successfully desymmetrizing two planes of symmetry present in **1** have led to the application of less

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(2) For a review of recent helicene syntheses, see: Urbano, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3986.

(3) For reviews discussing helicenes and helicenoidal compounds in electronic and optical contexts, see: (a) Rajca, A.; Miyasaka, M. In *Functional Organic Materials: Syntheses, Strategies, and Applications*; Müller, T. J. J., Bunz, U. H. F., Eds.; Wiley-VCH: Weinheim, 2007; p 543. (b) Rajca, A.; Miyasaka, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448. (c) Nuckolls, C.; Shao, R. F.; Jang, W. G.; Clark, N. A.; Walba, D. M.; Katz, T. J. *Chem. Mater.* **2002**, *14*, 773. (d) Osuga, H.; Tanaka, K. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 593. (e) Katz, T. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1921. (f) Grimme, S.; Harren, J.; Sobanski, A.; Vögtle, F. *Eur. J. Org. Chem.* **1998**, 1491.

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(8) (a) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97. (b) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed.* **1969**, *8*, 981.

(9) For a review of chiral DMAP catalysts in asymmetric synthesis, see: Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.
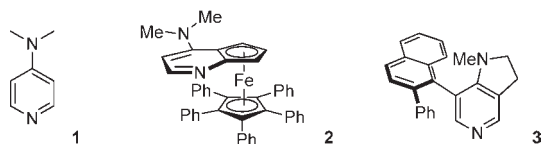
Figure 1. DMAP, planar chiral, and axially chiral DMAP analogues.

common chirality elements with Fu's planar chiral **2**[10] and Spivey's axially chiral **3**[11] designs arguably offering the most imaginative solutions to this scientific problem (Figure 1).[12] The efficacy of **2** and **3** in contexts such as the kinetic resolution of chiral alcohols[13] mean chiral DMAP analogues offer themselves as valuable chiral acylation catalysts, complementing the phosphine,[14] oligopeptide,[15] amidine,[16] amidine–ferrocene hybrids,[17] and *N*-heterocyclic carbene[18] catalyst approaches additionally reported in recent years.
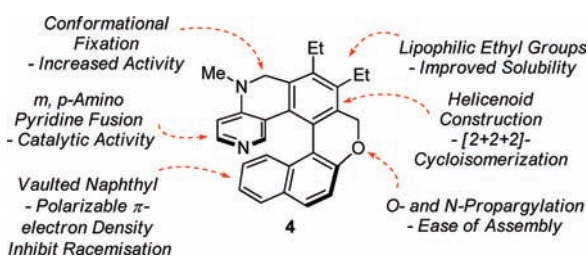
Figure 2. Design concept of helicenoidal DMAP catalyst **4**.

As DMAP acts as a genuine molecular challenge to assess unusual asymmetry elements in catalysis, we have chosen to examine the feasibility of a DMAP structure adapted to a helical environment (Figure 2).[19]

Our design concept is centered upon the placement of the catalytically crucial 4-dialkylaminopyridine moiety within a helicenoidal[20] framework. Importantly, this design consideration promised a highly active catalyst by conformational fixation through ring-fusion of the DMAP core.[21,22] A [2 + 2 + 2]-cycloisomerization[23] of a suitable triyne would allow for a convergent synthesis, with suitable lipophilic functionality assisting solubility.[24] The aminopyridine moiety would be desymmetrised by the placement of π-electron density from a suitable aromatic moiety, ultimately controlled by the chirality of the helix.

Scheme 1. Synthesis of Helicenoidal DMAP **4**[a]
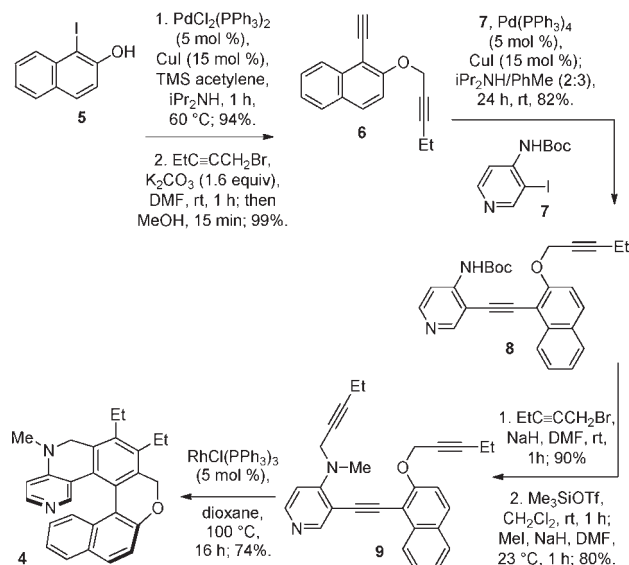
[a] Catalyst **4** was resolved by preparative-scale chiral HPLC, both enantiomers > 99% ee (Chiralpak IC).

The synthesis of catalyst **4** is outlined in Scheme 1. Sonogashira reaction of 1-iodo-2-naphthol **5** and TMS-acetylene with subsequent *O*-propargylation and in situ desilylation accessed **6** in an excellent 94% yield. A second Sonogashira reaction between **6** and iodopyridine **7** formed diyne **8**. Triyne **9** was synthesized after sequential *N*-propargylation of **8** and Boc deprotection with telescoped *N*-methylation. The synthesis of helicenoidal

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(19) For our work concerning the synthesis of helicenyl carboxylic acids, see: Pearson, M. S. M.; Carbery, D. R. *J. Org. Chem.* **2009**, *74*, 5320.

(20) We use the word helicenoidal to differentiate **4** from bona fide helicenyl pyridine nucleophilic catalysts with the "oid" suffix used to clarify the helicene-like nature of **4** as conferred by the break in aromaticity.

(21) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826.

(22) The use of a [6]azahelicene as a nucleophilic catalyst has been reported. This system was reported to offer moderate selectivity (*S* = 8 for **10a**) and reactivity (5−25 mol % loading); see: Šámal, M.; Míšek, J.; Stará, I. G.; Starý, I. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1151.

(23) For transition-metal-catalyzed [2 + 2 + 2]-cycloisomerization approaches to helicenoidal (helicene-like) molecules, see: (a) Stará, I. G.; Alexandrová, Z.; Teplý, F.; Sehnal, P.; Starý, I.; Šaman, D.; Buděšínský, M.; Cvaka, J. *Org. Lett.* **2005**, *7*, 2547. (b) Tanaka, K.; Kamisawa, A.; Suda, T.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 12078. (c) Sehnal, P.; Krausová, Z.; Teplý, F.; Stará, I. G.; Starý, I.; Rulíšek, L.; Šaman, D.; Cářšařová, I. *J. Org. Chem.* **2008**, *73*, 2074.

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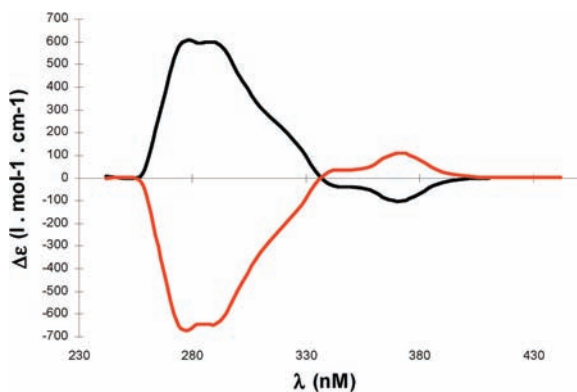
Figure 3. Circular dichroism spectra of resolved **4**: (red line) (*M*)-**4**; (black line) (*P*)-**4** (2.5×10^{-3} M in CH_3CN, 25 °C).

DMAP **4** was completed by a Rh(I)-catalyzed triyne cycloisomerization, offering a synthesis of **4** in six steps with 41% overall yield and subsequent resolution through preparative-scale chiral HPLC. Circular dichroism spectra of the resolved enantiomers (*M*)-**4** and (*P*)-**4** are displayed (Figure 3). The sense of helicity has been assigned as (*P*)-**4** (black plot $[\alpha]_D = +540$) and (*M*)-**4** (red plot $[\alpha]_D = -560$) on the basis of sign of optical rotation and supported by computational studies (see the interactive table) which have been calibrated against the helicene-like structures studied by Starý.[23a,25]

As catalyst **4** was based upon novel design principles with an assessment of helicity our key consideration, benchmarking of **4** was conducted through the kinetic resolution of chiral secondary alcohols, with **10a** initially examined (Scheme 2). A short process of optimization (see the Supporting Information) led to the conclusion that resolutions conducted in *tert*-amyl alcohol using isobutyric anhydride at 0 °C offered optimal selectivity and practicality, a scenario consistent to that observed by Fu.[26]

Having optimized conditions on **10a**, a range of alkyl aryl chiral alcohols was selected to probe the generality of catalyst **4** in this kinetic resolution process (Scheme 2). Aminopyridine **4** offers selective resolutions on all substrates examined at a low catalyst loading of 0.5 mol %. We believe **4** is noteworthy due to the relative rate of acylation of secondary alcohols, at a lower loading, than other chiral DMAP systems or other successful Lewis base catalysts.[16] Scheme 2 reveals some interesting structure−selectivity trends. While improvements to selectivity are observed with increased size of substrate alkyl group (**10a,c,d**), we find this structural effect to be minimal with this catalyst system. Enhanced selectivities are observed in this particular catalyst system when the substrate aryl group bears *ortho*-substitution (**10e−l**) although not to the extent of the Fu[10,26] and Vedejs[14] catalysts. Finally, anthracenyl substrate **10l** offered optimal selectivity (*S* = 116) in this screen. This substrate

(25) Efforts have been made unsuccessfully to obtain an assignment of configuration through crystallographic means. These efforts are ongoing.

(26) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

Scheme 2. Substrate Scope[a,b]
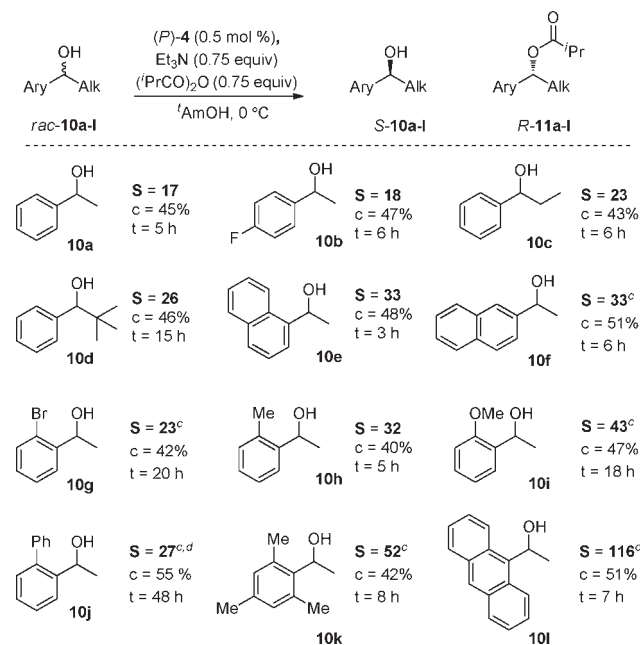
[a] Each substrate run in duplicate; data is averaged. [b] Data presented as: selectivity $S = \ln[(1 - c)(1 - ee_A)]/\ln[(1 - c)(1 + ee_A)]$ (A = substrate alcohol); conversion $c = 100 \times ee_A/(ee_A + ee_E)$ (E = product ester); time *t*. [c] Catalyst (*M*)-**4** used; *S*-**11f,g** and *S*-**11i−l** formed. [d] 1 mol % of catalyst used.

has not been examined in an asymmetric organocatalytic context before but has been resolved via Pd-catalyzed oxidation with substantially lower selectivity (*S* = 12).[27] These chiral anthracenyl alcohols have found considerable application in synthesis as effective chiral auxiliaries.[28]

We have endeavored to rationalize the sense of selectivity observed in this kinetic resolution. Catalyst (*P*)-**4** results in a faster acylation of the (*R*)-**10a** enantiomer. Simple modeling is suggestive of π-stacking arrangements between substrate aryl group and catalyst aminopyridine unit in combination with the minimization of steric clash between the methyl group of **10a** and electrophile *i*Pr group (Figure 4).
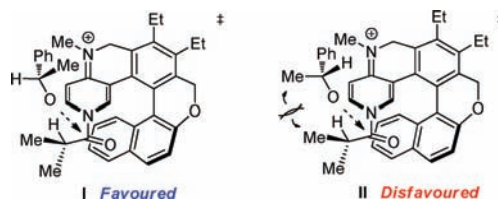

Figure 4. Proposed model of stereoselectivity.

This model largely mirrors that recently discussed by Birman and Houk.[29] Indeed, a trend of improving selectivity is observed in three *ortho*-substituted alcohols (**10g−i**, *S* = 23 to *S* = 43) where increased aryl electron density would improve electrostatic aromatic π-stacking.

In an attempt to demonstrate the synthetic potential and excellent reactivity of catalyst **4**, we have performed a resolution of **10e** at a minimized loading of 0.05 mol % on a 5 mmol scale (Scheme 3).

Scheme 3. Preparative-Scale, Low-Loading Kinetic Resolution
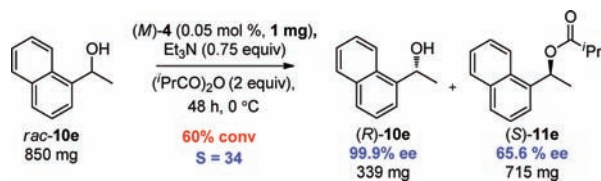
A conversion of 60% was attained after 48 h, offering a selectivity of $S = 34$. This example is noteworthy for the exceptionally low loading attainable with catalyst **4**, which we believe is the lowest loading reported for a preparative scale organocatalytic kinetic resolution of chiral carbinols.[30]

In conclusion, the first helicenoidal asymmetric organo-catalyst has been designed, synthesized and assessed in the kinetic resolution of chiral secondary aryl alkyl alcohols. Catalyst **4** offers good to excellent levels of selectivity and particularly excellent levels of reactivity when compared with other chiral nucleophilic catalyst systems. Attempts are underway in our laboratory to enhance catalyst stereo-selectivity through further design iterations and further probe substrate−stereoselectivity trends commented upon in this Letter.

Supporting Information Available. Experimental procedures, HPLC chromatograms, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6367.

(28) For recent examples, see: (a) Liu, X.; Snyder, J. K. *J. Org. Chem.* **2008**, *73*, 2935. (b) Adams, H.; Elsunaki, T. M.; Ojea-Jiménez, I.; Jones, S.; Meijer, A. J. H. M. *J. Org. Chem.* **2010**, *75*, 6252.

(29) Li, X.; Peng, L.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836.

(30) There has been one preceding report of a 0.05 mol % loading using a chiral DMAP catalyst on an analytical-scale kinetic resolution of **10f** with isobutyric anhydride; see ref 12d.