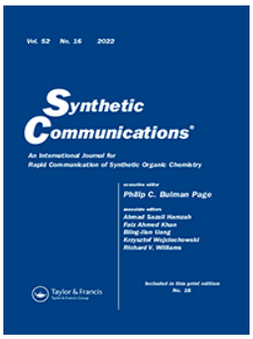

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Design and synthesis of novel pyrrolidine-bipyridine structures

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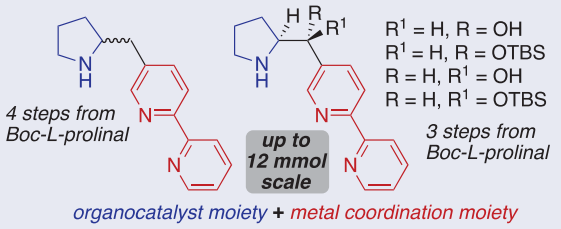
ABSTRACT

Disclosed herein are structures designed to incorporate pyrrolidine, which is a privileged organocatalyst structure, and bipyridine, which is among the most widely used metal ligands. Robust and scalable synthetic routes to five such compounds have been established. These novel structures may be useful in metal-organic cooperative catalyzed transformations, or as organocatalysts or metal ligands.

GRAPHICAL ABSTRACT



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KEYWORDS
2,2′-bipyridine; amino alcohols; synthesis design; organocatalysis

Introduction

During the course of our recent development of an organo- and metal co-catalyzed transformation,[1] we became interested in amine structures that could participate in (di)enamine- or iminium ion formation, and which also incorporated a moiety for coordination to a metal center. While there have been numerous such examples using achiral 2-aminopyridines and 7-azaindolines,[2] *chiral* structures for this purpose are limited. The vast majority of transformations reported utilize primary amines that coordinate to metal centers via tethered carboxylic acids (i.e., α-amino acids).[3] There are, however, additional examples entailing primary amines that coordinate to metal centers via tethered amides (i.e., α-amino amides)[4] or π-donors,[5] or even via the imine N (i.e., formed in situ from the primary amine and a carbonyl substrate) itself.[6] Examples of chiral secondary amines are rare, and include pyrrolidines appended to phosphines,[7] a π-donor,[8] and a tridentate Cu-coordinating ligand.[9] Similarly, while bipyridine (bipy) is a commonly employed ligand for metal- and photocatalyzed transformations of organic substrates,[10] it has rarely been tethered to an organocatalytic

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moiety to enable dual coordination, to both organic substrate and metal catalyst. In these rare instances, however, bipyridine has been combined with a non-covalent hydrogen bonding,[11] or ionic organocatalyst motif.[12] Discussed herein is the design and synthesis of five novel pyrrolidine-bipyridine structures (Figure 1), which we believe may find use as bifunctional organocatalysts or ligands.

Results and discussion

The generic target structures shown in Figure 2 were initially envisioned. While the functionality "X" could conceivably influence the relative orientations of the bipyridine and pyrrolidine moieties, and/or could incorporate a vicinal stereocenter, ease of synthesis was a primary consideration. Thus, originally, a ketone ($X = O$) at this position was pursued.

To start, bipyridyl bromide **6** was accessed using a known procedure (Scheme 1).[13] While lithium-halogen exchange between *n*-BuLi and 3-bromopyridine enabled successful addition to Boc-*L*-Pro-OMe to produce the corresponding ketone, no such reaction was observed when **6** was used instead. There was precedent for addition of the lithium species derived from bipyridyl iodide **7** to a carbonyl group (i.e., of a lactone),[14] albeit in low yield (32% over two steps).[14] Thus, **6** was converted into **7** via a Cu-catalyzed Finkelstein reaction.[14] Here again, however, addition to Boc-*L*-Pro-OMe did not occur.

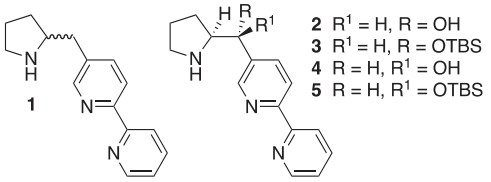


Figure 1. Novel pyrrolidine-bipyridine structures synthesized.

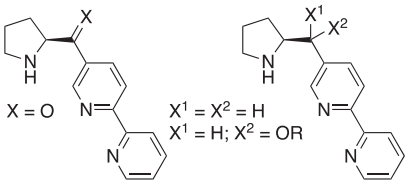
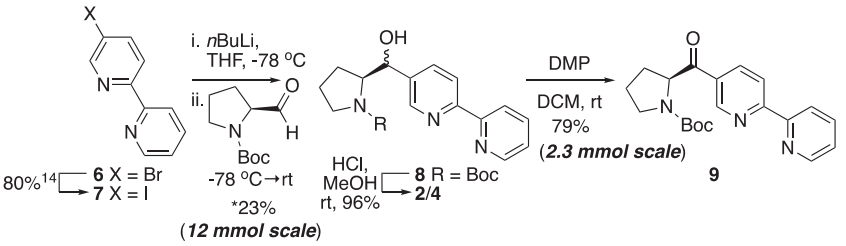
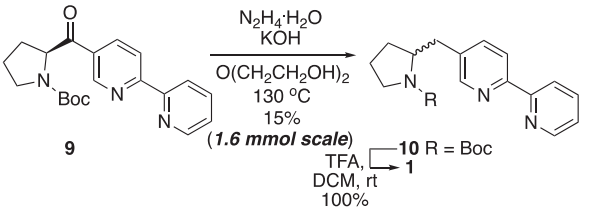


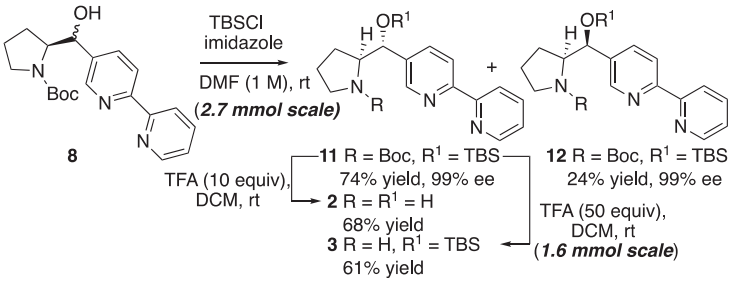
Figure 2. Initial structure design.



Scheme 1. Synthetic efforts toward a pyrrolidine-bipyridine ketone. *Indicates result was done in duplicate



Scheme 2. Synthesis of pyrrolidine-bipyridine **1**.

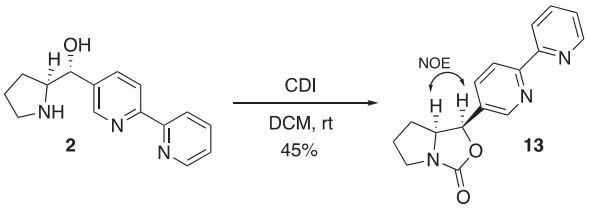


Scheme 3. Synthesis and isolation of pyrrolidine-bipyridine compounds **2**-**5**.

Isolation of bypyridine from this reaction mixture was evidence that lithium-halogen exchange had occurred, suggesting instead that the ester was not a reactive enough electrophile. Switching to Boc-*L*-prolinal (Scheme 1) provided the desired corresponding alcohol product, **8**, though also in low 23% yield. Importantly, this transformation, and others highlighted throughout, can be run on multi-millimolar scale. Efforts at magnesium-halogen exchange between either **6** or **7** and *i*PrMgCl did not furnish the desired product from Boc-*L*-prolinal.

Oxidation of alcohol **8** to ketone **9** proceeded uneventfully. *N*-Boc deprotection of ketone **9** to afford the ammonium salt, followed by basification to afford the free amine, however, did not provide the target ketone structure. Instead, the target ketone structure presumably underwent spontaneous air oxidation to the corresponding pyrroline during basic work-up, which has previously been observed by others.[15] Thus, as an alternative, *N*-Boc deprotection of **8** provided amino alcohols **2** and **4** as an inseparable mixture and in nearly quantitative combined yield. Oxidation of **2**/**4** under neutral conditions (MnO_2) again failed to provide the target ketone structure. Use of CBz-*L*-prolinal instead of Boc-*L*-prolinal in the first step of the sequence shown in Scheme 1 directly provided a cyclic carbamate (i.e., **13**, Scheme 4), which would present the same synthetic challenges as **8**.

At this stage, since the primary consideration for targeting the ketone structure was ease of synthesis, but the presence of the ketone functionality was instead complicating synthesis, the corresponding methylene structure (Figure 2, $X^1 = X^2 = H$) was next targeted. Initially, adaptation of a procedure for the nucleophilic ring opening of a cyclic sulfamate of *L*-prolinol,[16] for use with lithiated **7**, failed to provide the target compound. Next, reduction of the ketone in **9** to the corresponding methylene was attempted (Scheme 2). Whereas the Caglioti reaction and hydrogenation failed to generate product,[17] Wolff-Kishner conditions ultimately proved successful, however, yields



Scheme 4. Assignment of configuration of alcohol stereocenter.

were low (≤15%) and racemization of the stereocenter occurred (Full experimental detail, ^{1}H and ^{13}C NMR spectra, HPCL traces. This material can be found via the "Supplementary Content" section of this article's webpage). Deprotection of **10** proceeded smoothly and in quantitative yield, providing target compound **1** as a racemic mixture.

Next, since the presence of an exocyclic ketone was unattainable (Scheme 1), and the absence of an exocyclic ketone via reduction of the ketone was accompanied by racemization (Scheme 2), our attention turned back to alcohols **2** and **4**. Alcohols **2** and **4** preserved the chiral center on the ring, and contained an additional chiral center that could potentially reinforce the influence of the former. Additionally, a free alcohol at the exocyclic position could potentially hydrogen bond to a substrate or be another point of coordination to a metal center, or it could be protected to avoid this. As mentioned, however, alcohols **2** and **4** were generated as an inseparable, ~3:1 mixture of diastereomers. Silyl protection of the mixture with TBSCl enabled separation of the diastereomers, both of which were nearly enantiopure (Scheme 3). Finally, silyl-protected compound **11** could undergo either global deprotection or selective Boc-deprotection by adjusting reaction conditions. Use of TFA (10 equiv) or CCl_3CO_2H afforded globally deprotected **2** as the major reaction product, whereas a large excess of TFA (50 or 75 equiv) provided silyl ether **3** as the major reaction product (Full experimental detail, ^{1}H and ^{13}C NMR spectra, HPCL traces. This material can be found via the "Supplementary Content" section of this article's webpage). These same conditions enabled access to compounds **4** and **5** from **12**.

The relative configuration of the alcohol stereocenter in **2** was established through analysis of the NOESY NMR spectrum of the corresponding cyclic carbamate, **13** (Scheme 4), generated using carbonyldiimidazole (CDI) (Full experimental detail, ^{1}H and ^{13}C NMR spectra, HPCL traces. This material can be found via the "Supplementary Content" section of this article's webpage). Structures **1**, **2**, and **3** were evaluated in a Pd-catalyzed allylation of enals, however none provided improvement over other catalyst structures tested (see Supporting Information for ref[1]). Nonetheless, since chiral pyrrolidines are a privileged catalyst structure, these structures may be useful to others developing new organocatalyzed reactions or chiral ligands, which is why we disclose these structures and their syntheses herein.

Conclusion

In conclusion we have designed novel chiral pyrrolidine structures that incorporate a bipyridine moiety. We have established robust and scalable synthetic routes to five such compounds, one of which is racemic and the others are enantiopure. As chiral

pyrrolidines are a privileged organocatalyst structure and since bipyridines are a prevalent metal ligand, these structures may find use as novel organocatalysts or chiral ligands.

Experimental section

Preparation of tert-butyl (S)-2-((R)-[2,2′-bipyridin]-5-yl((tert-butyldimethylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (11)

Bromide **6** was prepared according to a known procedure,[13] and iodide **7** was prepared from bromide **6** according to a known procedure.[14] The reaction flask was oven-dried and cooled to rt under vacuum, then backfilled with Ar. Iodide **7** (3.38 g, 12 mmol) and dry THF (72 mL) were then added under Ar. The reaction flask was cooled to −78 °C, and a solution of *n*-BuLi (7.5 mL, 12 mmol, 1.6 M in hexane) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h. Then, Boc-*L*-prolinal (2.39 g, 12 mmol) was added dropwise at −78 °C. The reaction was stirred at −78 °C for 3 h, then warmed to rt and stirred at rt overnight. The reaction was diluted with brine (90 mL) and extracted with DCM (2 × 40 mL). After organic layers were combined, dried, filtered, and concentrated, purification via column chromatography using petroleum ether:EtOAc (9:1→7:3→1:1→0:100) afforded **8** as a pale yellow oil (988 mg, 2.78 mmol, 23% yield), which was a mixture of diastereomers and rotamers.

To a round-bottom flask was added **8** (963 mg, 2.71 mmol), DMF (3 mL), TBSCl (817 mg, 5.42 mmol), and imidazole (369 mg, 5.42 mmol). The reaction was stirred overnight at rt. The reaction was diluted with EtOAc (30 mL), and washed with aq. NH_4OH (5%, 3 × 30 mL). The EtOAc layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotavapor. The crude product was purified by column chromatography using petroleum ether/EtOAc = 90:10 to provide **11** and **12**, each as a rotameric mixture. Compound **11** (TLC: petroleum ether/EtOAc/TEA = 65:30:5, R_f=0.66) was isolated as a colorless oil (942 mg, 74% yield), 99% ee: $[\alpha]_D^{22} = -6.8$ ($c = 1.0$ in DCM); HPLC with an AD-H column (*n*-hexane/*i*-PrOH= 98:2 at 1.0 mL/min, UV detector $\lambda = 254$ nm); major enantiomer t_R = 11.18 min, minor enantiomer t_R = 8.69 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 − 8.60 (m, 2H), 8.42 − 8.30 (m, 2H), 7.88 − 7.76 (m, 2H), 7.33 − 7.27 (m, 1H), 5.55 − 5.30 (m, 1H), 3.95 − 3.79 (m, 1H), 3.50 − 3.30 (m, 2H), 2.13 − 1.95 (m, 3H), 1.75 − 1.65 (m, 1H), 1.47 (d, J = 24.5 Hz, 9H), 0.92 (s, 9H), 0.05 (d, J = 4.7 Hz, 3H), −0.10 (d, J = 6.5 Hz, 3H).;^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.9*, 154.8*, 154.8, 154.3, 149.2*, 149.1, 147.2*, 147.2, 138.5*, 138.5, 137.0*, 137.0, 135.0*, 134.7, 123.7*, 123.6, 121.1*, 121.0, 120.7*, 120.5, 79.7*, 79.3, 73.1*, 71.9, 64.1*, 63.9, 47.7*, 47.3, 28.7*, 28.6, 25.9*, 25.9, 25.9*, 25.8, 24.6*, 24.5, 23.9*, 23.7, 18.1*, 18.1, −5.0*, −5.1, −5.6*, −5.6 (* denotes rotamer); HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{26}H_{40}N_3O_3Si$ 470.2839; Found 470.2839.

Preparation of 5-((R)-((tert-butyldimethylsilyl)oxy)((S)-pyrrolidin-2-yl)methyl)-2,2′-bipyridine (3)

Compound **11** (740 mg, 1.58 mmol), DCM (15 mL), and TFA (6.0 mL, 78.77 mmol) were added to a round bottom flask. The reaction was stirred at rt for 1 h, and was then diluted with aq. NH_4OH (5%) until pH > 11. The organic phase was separated from

the aq. layer, which was further extracted with DCM (2×60 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed by rotavapor, and the crude product was purified by column chromatography using pure EtOAc, then *i*Pr-NH_2:$CHCl_3$=1:99, then *i*Pr-NH_2:$CHCl_3$=3:7. Compound **3** was isolated as yellow solid (356 mg, 61% yield). Compound **2** can be isolated from these conditions in 26% yield. Data for compound **3**: mp 46–48 °C; $[\alpha]_D^{22} = -60.0$ ($c = 1.0$ in DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 − 8.64 (m, 2H), 8.40 − 8.32 (m, 2H), 7.84 − 7.78 (m, 2H), 7.33 − 7.27 (m, 1H), 4.70 (d, $J = 5.9$ Hz, 1H), 3.19 (q, $J = 6.6$ Hz, 1H), 3.06 − 2.99 (m, 1H), 2.87 − 2.78 (m, 1H), 1.85 (broad-s, 1H), 1.80 − 1.65 (m, 4H), 0.90 (s, 9H), 0.08 (s, 3H), −0.16 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.1, 155.4, 149.2, 147.8, 139.3, 136.9, 135.3, 123.6, 121.0, 120.6, 75.3, 66.0, 46.8, 27.3, 25.8, 25.2, 18.1, −4.4, −5.0; HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{21}H_{32}N_3OSi$ 370.2309; Found 370.2310.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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