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Fine Tuning Reactivity: Synthesis and Isolation of 1,2,3,12b-Tetrahydroimidazo[1,2-*f*]phenanthridines

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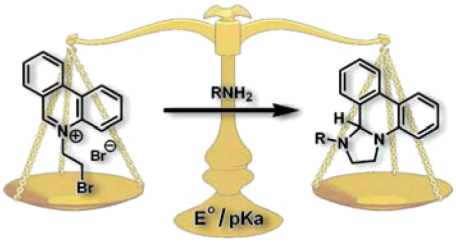

A facile route for the synthesis and isolation of 1,2,3,12b-tetrahydroimidazo[1,2-*f*]phenanthridines (TIPs) has been developed. The heterocycle is a reactive intermediate in the three-step cascade synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*f*]phenanthridinium cations (DIPs), a biologically active DNA intercalating framework; however, the intermediate has previously only been characterized in situ. Derivatization of the structure at the imidazo-*N* position controls the reactivity of the intermediate with respect to electronic potential and pK_a allowing isolation of a selection of TIP structures. Correlations between these parameters and reaction outcome have been made, and other influences such as steric and solvent effects have also been investigated.

Introduction

Nitrogen-containing heterocycles are prevalent in medicinal chemistry due to the fact that many natural and synthetic biologically active compounds share this common architectural feature.[1−5] The number and structural diversity of heterocyclic motifs are great. However the discovery and synthesis of new classes of heterocycles, especially if the synthetic methodology is modular and reliable, is always a welcome addition as it offers routes to new substrates which may possess advantageous therapeutic activities or chemical reactivity.[6−11]

A family of nonplanar aromatic heterocycles with attractive chemical and biological activities has been synthesized: 1,2,3,12b-tetrahydroimidazo[1,2-*f*]phenanthridines (TIPs) are sensitive to both changes in pH and electrochemical potential, two very important biological stimuli.[12−16] There are a large number of other structurally similar heterocycles reported, but to the best of our knowledge there are currently no examples for the isolation of heterocycles containing the

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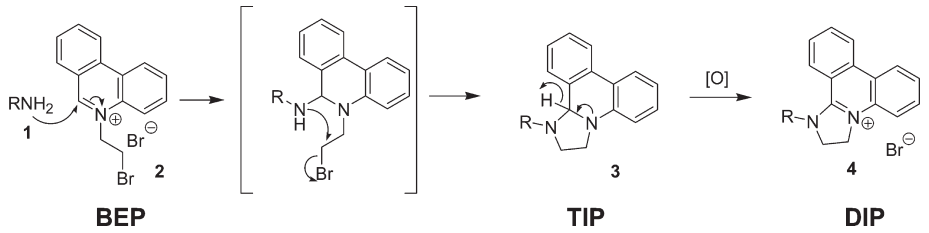
SCHEME 1. Mechanism for DIP Synthesis from BEP via TIP Intermediate



N-substituted TIP motif.[17−23] The majority of these similarly nonplanar heterocycles exhibit high levels of biological activity and have applications as antibacterials, fungicides, anticancer therapeutics, and other bioactive agents.[24−29] Compounds with similar aryl-fused 5-membered dinitrogen ring systems, such as 2,3-dihydrobenzo[*d*]imidazoles, have also been shown to be very effective organic hydride donors.[30,31] There are many examples for the application of these hydride donors as reducing reagents for use in organic synthesis.[32−35] These systems are capable of reducing many functional groups such as aldehydes, ketones, olefins, imides, and organic halides; however, since they are all achiral they require the presence of a chiral catalyst to perform desired asymmetric reductions. The intrinsic chirality, high reducing power, and potential bioactivity of the TIP heterocycles synthesized could therefore make them the focus of multiple areas of ongoing research within the chemical and biological communities. Recently, we utilized a TIP-based moiety as a key component in the development of a "lockable molecular switch" which exploited the pH-based cyclization and ring-opening process which could then be "locked" by a redox process.[36] However, we were not able to isolate the TIP-based moiety previously.[36] Herein we show how we were able to develop the TIP chemistry to isolate a range of TIP-based compounds, and we report an attractively simple procedure for their synthesis along with a discussion of the mechanism and scope of the reaction.

The TIP framework (Scheme 1, structure **3**) is in fact an intermediate in a multistep reaction between a primary amine and 5-(2-bromoethyl)phenanthridinium bromide (BEP, **2**) to produce a cationic 2,3-dihydro-1*H*-imidazo[1,2-*f*]phenanthridinium heterocycle (DIP, **4**).[37,38] Compounds incorporating the DIP framework are an important class of heterocycles in their own right and have been the focus of recent biological studies due to their potent and unusual activity in ovarian cancer cell lines.[39−41] The mechanism for the synthesis of DIPs involves three key steps; α addition of the amine to the iminium moiety, a 5-*exo*-*tet* cyclization, and an oxidation via "hydride loss" (Scheme 1).

The TIP intermediate is formed between steps two and three of the mechanism so in order to isolate the TIP intermediate the reaction conditions had to be optimized to allow α addition and cyclization yet prevent further oxidation. The initial monophasic procedure reported for the synthesis of DIPs[38] required 2 equiv of BEP starting material per mole of primary amine, as 1 equiv combined with the amine to generate the TIP intermediate and the second 1 equiv was consumed as the stoichiometric oxidant via a hydride transfer in the final oxidation step. A more efficient biphasic procedure was subsequently developed to maximize the reaction yield with respect to both reactants.[38] This procedure utilizes phase transfer to separate the TIP intermediate from the incompatible BEP starting material and generates the TIP intermediate quantitatively. This method is, however, limited to hydrophilic primary amines only as the α addition step must occur in the aqueous phase and the TIP structures generated from these aliphatic amines have as yet only been characterized in situ by MS and NMR spectroscopy.[36,38] Isolation has proven to be difficult, and attempts to isolate these compounds via solvent evaporation, precipitation, and crystallization have all been unsuccessful. The lack of success with respect to isolating TIP structures of this nature has been attributed to their high reactivity toward acidic and oxidative conditions and the constraints this places on product isolation and purification; these issues and other problematic side reactions are discussed in the subsequent sections. In order to isolate the TIP intermediate,

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it was therefore necessary to develop a methodology that could either (i) provide a suitable technique for the isolation of TIPs generated from hydrophilic primary amine substrates via the biphasic methodology or (ii) accommodate hydrophobic amine substrates that would lead to the generation of TIP structures that were compatible with the oxidative phenanthridinium framework of the BEP starting material. The effects of solvent, steric bulk, and electronic character of the primary amine side-chain were investigated, and all were found to contribute significantly to the outcome of the reaction.

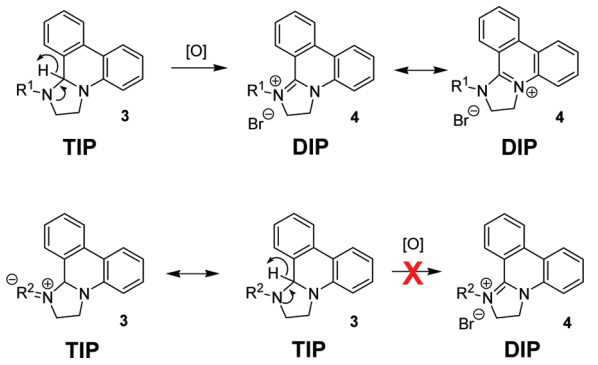
Results and Discussion

The key parameters investigated were alteration of the amine substrate and alteration of the solvent system. The first issue to be tackled was that of solvent choice. The solvent was required to be nonprotic to prevent pseudobase formation of the BEP under the basic conditions yet remain polar enough to solvate the cationic species. DMF and DMSO were the natural solvents of choice, and initial assays carried out in deuterated solvents and analyzed in situ by ^{1}H NMR spectroscopy showed promising results. However, it was thought that due to their high boiling points and miscibility with water isolation of the sensitive product would be problematic. Chloroform was subsequently established as the solvent of choice as it overcame the previous issues of product isolation and was still able to solvate the reactants, although somewhat sparingly with respect to BEP. This, however, proved to be an advantageous trait as it created a visual aid for monitoring the reaction process: The BEP starting material is largely insoluble in chloroform, but the products are completely soluble so as the reactants are consumed the reaction mixture gradually evolves from an off-white suspension to a bright orange solution, thus indicating when the reaction has reached completion. The mother liquor can then be washed with water to remove the salt byproduct followed by low temperature evaporation of solvent and excess organic base under vacuum to isolate the TIP product. A range of amines were investigated and a number of products containing the desired TIP framework were isolated using this general methodology (Table 1, for detailed methods and spectra see the Experimental Section and ESD).

From the list of amine substrates investigated it can be seen that there is a correlation between the availability of the amino *N* lone pair and reaction success. It was hypothesized that the susceptibility of the TIP structure to acidic and oxidative conditions could be controlled by the degree of conjugation of the *N* lone pair, which can be easily tuned by judicious selection of the side chain. Higher degrees of conjugation with the side chain will decrease the ability of the lone pair to stabilize the positive charge in the DIP product, thus reducing the driving force for the oxidation. Scheme 2 shows the resonance representations of TIP and DIP structures **3** and **4** with nonconjugating side chain R^1 and conjugating side chain R^2.

Conjugation will also decrease the pK_a of the nitrogen center, making it less susceptible to protonation and subsequent generation of 5-(2-aminoethyl)phenanthridinium (AEP) adducts **5** via ring-opening (Scheme 3, step 1). Preventing this process is equally as important since once the

SCHEME 2. Inhibition of TIP Oxidation via Conjugation



AEP core has formed it can also act as a "hydride acceptor", in a similar fashion to BEP, leading to further oxidation and complete consumption of the TIP intermediate (Scheme 3, step 2).

This concept was addressed in previous work where we used a biphasic solvent system to overcome this undesired side reaction for operation of a solution-based switchable organic system.[36] As the incompatible TIP and AEP forms **3** and **5** exist in equilibrium it is easy to see why the relative stability of the aliphatic-TIP analogues is so low, especially in monophasic solutions: The position of the equilibrium will tend to favor one form over the other depending on the availability of protons in solution, and the probability of a successful collision and subsequent hydride transfer between the two forms will be dependent upon concentration. However, over time, the two forms will irreversibly react and ultimately lead to the consumption of TIP. This complicated series of reactions was confirmed by monitoring the acidification of a solution of TIP **3b** in DMSO-d_6 with DCl by ^{1}H NMR spectroscopy. From the spectra in Figure 1 it can

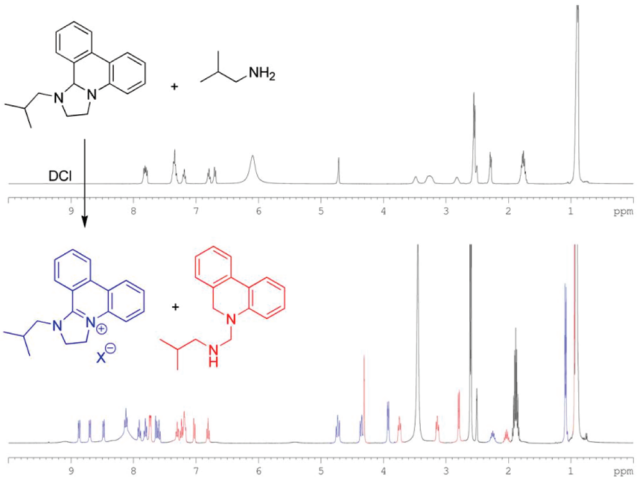
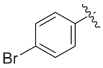
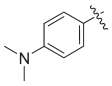
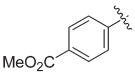
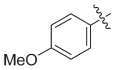
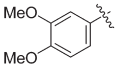
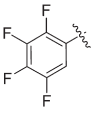
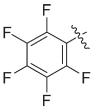


FIGURE 1. TIP **3b** consumption via protonation and subsequent hydride transfer: Structure and assigned peaks for DIP **4b** in blue; structure and assigned peaks for AEDP **6b** in red. This figure shows the general process that results in the conversion of the reactive TIP, (top) TIP **3b**, and excess isobutylamine before DCl addition and (bottom) equimolar amounts of DIP 2 (blue) and AEDP **4b** (red) and excess isobutylamine hydrochloride after DCl addition, as we have previously reported; see ref 36. In this work we were able to tune the reaction methodology so that the TIP compounds could be isolated; see Table 1.

TABLE 1. TIP Products Obtained via Reaction of Primary Amines with BEP[a]

Entry	TIP **3(a-x)** R =	pK_a[b] Amine **1(a-x)**	Yield (%)[c]	Entry	TIP **3(a-x)** R =	pK_a[b] Amine **1(a-x)**	Yield (%)[c]
a		10.57 ± 0.10	0[d]	m		3.20 ± 0.10	68
b		10.72 ± 0.10	0[d]	n		4.66 ± 0.10	85
c		10.80 ± 0.10	0[d]	o		1.10 ± 0.10	0[e]
d		10.80 ± 0.10	0[d]	p		3.37 ± 0.10	76
e		10.68 ± 0.10	0[d]	q		2.54 ± 0.10	0[e]
f		10.75 ± 0.20	70	r		3.90 ± 0.10	78
g		6.65 ± 0.12	88[d]	s		2.47 ± 0.10	68
h		5.21 ± 0.10	89	t		3.64 ± 0.10	98
i		4.77 ± 0.10	89	u		2.62 ± 0.10	60
j		4.61 ± 0.10	73	v		1.23 ± 0.10	0[f]
k		4.84 ± 0.10	95	w		-0.16 ± 0.10	0[f]
l		4.31 ± 0.10	0[e]	x		-1.54 ± 0.25	0[f]

[a]BEP (1.0 equiv), RNH_2 (1.0 equiv), TEA (3.0 equiv), $CHCl_3$, rt. [b]pK_a values calculated using Advanced Chemistry Development (ACD/Laboratories) Software V8.14 for Solaris (1994−2009 ACD/Laboratories). [c]Isolated product yield after normal workup. [d]5.0 equiv of TEA. Biphasic reaction conditions can overcome the hydride transfer to provide short-lived solutions able to be characterized by MS and NMR spectroscopy (ESD). [e]No TIP formed due to steric hindrance. [f]No TIP formed due to reduced amine nucleophilicity. [g]5.0 equiv of TEA.

be seen that the solution of TIP **3b** and isobutylamine (acting as excess base) is converted to an equimolar mixture of DIP **4b** and AEDP **6b** by addition of submolar equivalents of DCl.

The thermodynamic driving forces for this reaction are likely to arise from the reduction of steric strain and increased delocalization of the positive charge in the DIP/AEDP products **4** and **6** compared to the TIP/AEP reactants **3** and **5**. This is corroborated by consideration of the standard electronic potential of the cell. Equations 1 and 2 show the electron half-equations and reduction potentials for the reacting species (CV data in ESD).

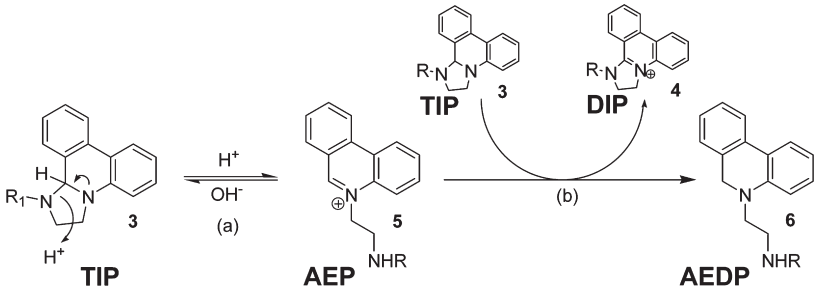
$$\mathrm{DIP} + \mathrm{H^+} + 2\mathrm{e^-} \rightarrow \mathrm{TIPE} = \sim -1.3\mathrm{V} \qquad (1)$$

$$\mathrm{AEP} + \mathrm{H^+} + 2\mathrm{e^-} \rightarrow \mathrm{AEDPE} = \sim -0.6\mathrm{V} \qquad (2)$$

The resulting electronic potential for the cell is therefore calculated as approximately +0.7 V, which would result in a highly negative value for $\Delta G°$ and a spontaneous redox reaction under standard conditions.

The results for the selection of amines investigated in Table 1 clearly demonstrate a dependency upon the electron-withdrawing capacity of the R group for inhibition of the oxidation step. Entries a−e in Table 1 showed no observation of the corresponding TIP products after work-up, which demonstrates that a lack of conjugation from the aliphatic side chain increases the reactivity of the TIP with respect to oxidation and protonation. This was verified by

SCHEME 3. Intermolecular TIP−AEP Hydride Transfer[a]



[a]Key: (a) protonation and ring-opening of TIP to form AEP hydride acceptor and contrasting reverse reaction; (b) hydride transfer between TIP and AEP to form the oxidation product, DIP, and the reduction product, 5-(2-aminoethyl)-5,6-dihydrophenanthridine (AEDP).

the presence of the oxidation product, DIP, in the product mixture. In contrast, arylamines of varying electron deficiency can be reacted with the BEP starting material to generate the corresponding TIP structures in moderate to excellent yields (Table 1, entries g−u). Partial conjugation of the *N* lone pair to the π-system of the aromatic ring reduces the potential for "hydride transfer" from the TIP intermediate to the BEP starting material, allowing complete conversion of the BEP to the TIP product. Direct conjugation of the *N* lone pair to the side chain in the form of an amide or conjugation to a highly electron-deficient aromatic system did not lead to production of any of the corresponding TIP structures (Table 1, entries v−x). This can be explained by the loss of sufficient nucleophilicity. In these cases, the majority of the BEP starting material is recovered by filtration; however, the presence of phenanthridine in the filtrate indicated conversion of some of the material via an elimination reaction.

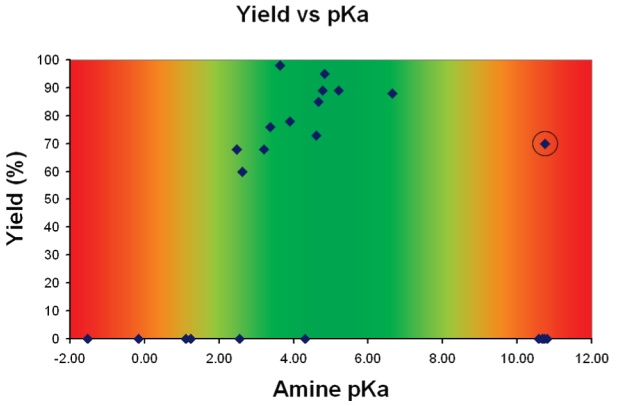


FIGURE 2. TIP product yield vs amine pK_a. Circled data point for adamantyl-TIP **3f**.

In terms of electronic effects, isolation of TIP structures can be seen as a balancing act between having enough nucleophilicity for the primary amine to undergo the first two steps while retaining enough electron-withdrawing capacity to prevent further oxidation. It is proposed that the pK_a value of the primary amine substrate would be a quick and simple measurement that could be useful in predicting the reaction outcome. From the plot in Figure 2 it can be seen that a window for successful TIP isolation can be estimated for amines with pK_a values of between approximately 2 and 7. It is notable that a direct correlation between pK_a and reaction outcome cannot be formed here as the steric effects of the amine side chains must also be considered.

The reduction potentials of a selection of DIP analogues **4a**,**b**,**i**,**j**,**t** containing a mixture of aryl and aliphatic side chains were measured to corroborate the influence of the side chain on the electronic potential of the DIP framework (Figure 3).

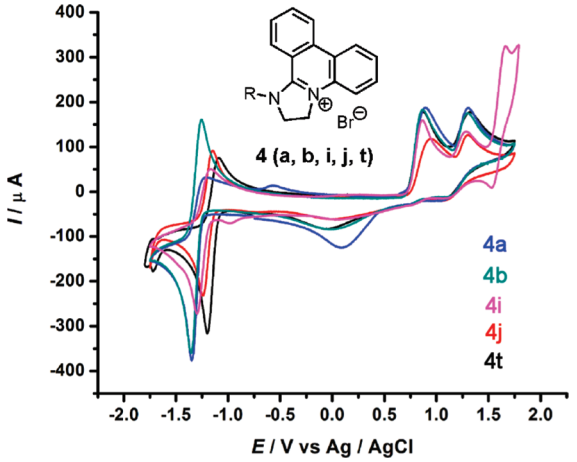


FIGURE 3. CV diagrams of compounds: **4a**, R = cyclohexyl; **4b**, R = isobutyl; **4i**, R = 3,4-dimethoxyphenyl; **4j**, R = phenyl; **4t**, R = 3,4-difluorophenyl; at 100 mV/s. A decrease in reduction potential with decreasing electron-withdrawing effect is observed.

From the plot, it can be seen that the values for the reduction potentials decrease with the decreasing electron-withdrawing character of the R groups. This supports the hypothesis that the amine *N* lone pair is involved in stabilizing the positively charged DIP core and that alteration of the R group has a direct influence on this. This data, however, does not allow for the electronic effects to be considered as the sole contributing factor for stabilization of the TIP structure under the standard reaction conditions as the reduction potentials for the aryl-DIPs are still highly negative, > -1.0 V. This would theoretically still result in a spontaneous hydride transfer between the aryl TIPs and phenanthridinium based reactants **2** or **5**. This reaction is possible, and there is precedence for the synthesis of aryl DIPs from TIPs using BEP as the oxidant.[38] The effect of using an arylamine on the reaction outcome must therefore be kinetic rather than thermodynamic: The rate of the hydride transfer reaction simply becomes relatively slower than amine addition and

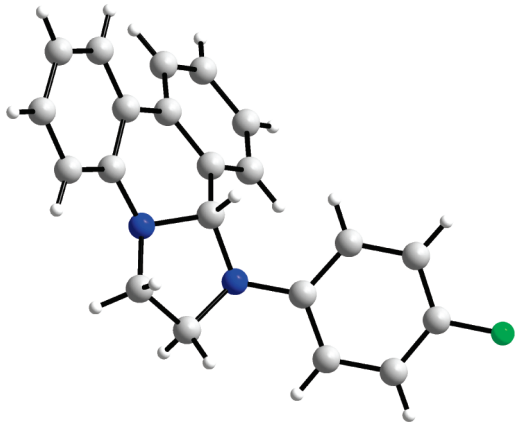


FIGURE 4. X-ray crystal structure of **3n**.

cyclization, thus favoring TIP production. Electronic effects from the amine substituents could contribute to lowering the rate of hydride transfer relative to α addition and cyclization but are unlikely to be solely responsible. Other effects such as sterics must also be considered.

It was found that steric effects are indeed highly influential on the reaction outcome and have an effect at each stage of the multistep mechanism. From the series of successfully isolated TIP structures **3f**−**u**, a set of structural isomers were selected to compare these effects. From the comparison of electronically similar isomeric pairs (Table 1, entries k−r) it can be seen that aryl substrates functionalized with bulky substituents at the ortho positions are unable to form the TIP products unlike those that are either meta or para substituted. The only ortho-functionalized substrate able to undergo conversion to the TIP product **3m** was 2-fluoroaniline **1m**, where the fluorine atoms relatively small steric bulk is not sufficient to hinder the addition and cyclization steps. Observing the reactions in DMSO-d_6 for 2- and 4-bromoaniline **1q** and **1r** showed that the BEP starting material was consumed but no signals correlating to the TIP intermediate **3q** were observed after 2 h for the reaction of 2-bromoaniline **1q**, compared to the reaction of 4-bromoaniline **1r** which had reached complete conversion to TIP **3r** after <15 min. The ^{1}H NMR spectra of the 2-bromoaniline reaction showed signals correlating to the amine starting material and also phenanthridine free base indicating that in these cases the highly reactive BEP starting material undergoes an elimination reaction rather than the desired addition and cyclization (^{1}H NMR spectra in ESD).

The isolation of the TIP analogue of adamantamine **3f** was a very important discovery as this highlighted the stabilization of the TIP structure primarily through steric effects rather than electronic inhibition. The amine substrate is a nonconjugated aliphatic amine with a relatively high pK_a value of 10.75. With no conjugation of the amino *N* lone pair with the adamantyl group it can be assumed that this compound will have a similar electronic potential to other aliphatic TIP analogues. The inhibition of the hydride transfer and subsequent TIP stabilization must therefore be influenced by the steric bulk of the amino side chain alone. The crystal structure of 1-(4-fluorophenyl)-TIP **3n** shows the phenyl side chain deflecting out of the plane of the TIP ring system on the same face as the α hydrogen (Figure 4.)

Bulkier amino substituents must protect this face of the TIP structure by blocking the approach of the oxidative phenanthridinium cations and inhibit the undesired hydride transfer process. This was confirmed by studying the reactions of isobutyl and adamantyl TIPs **3b** and **3f** with BEP in DMSO-d_6: In the former case the reaction resulted in almost instant conversion of TIP **3b** to DIP **4b**, whereas in the latter case both TIP **3f** and BEP reactants were visible in the reaction mixture even after 9 h (^{1}H NMR spectra in ESD).

Conclusions

In summary, we have developed a general methodology for the synthesis and isolation of a number of heterocyclic compounds containing a 1,2,3,12b-tetrahydroimidazo[1,2-*f*]-phenanthridine framework. Compounds of this structure type will have interesting interactions with biological systems. Our preliminary studies show the TIPs to have comparable cytotoxicity levels to DIPs, and they are also likely to show activity against certain bacteria, fungi, and other biological targets.[24−29] The high reducing power of the chiral TIP framework coupled with their facile tunability also make them interesting targets for the development of organic reducing agents. The initial synthetic methodology developed is unquestionably limited to aryl primary amines however our investigations and demonstration of understanding of the reaction processes will enable us to modify our procedures to accommodate other primary amines and enhance the scope of the methodology. Our future work will look toward functionalizing the phenanthridine ring and the subsequent effects on the stability of the TIP frameworks generated and also toward application of the methodology for functionalizing aromatic systems other than phenanthridines, such as quinolines, quinazolines, and pteridines to generate other new heterocycles. We then aim to investigate the chemical and biological applications of these compounds as well as the TIPs in the areas discussed.

Experimental Section

5-(2-Bromoethyl)phenanthridinium Bromide (2). Synthesized following procedure reported by Parenty et al.:[38] mp 235−236 °C dec; ^{1}H NMR (DMSO, 400 MHz) δ 10.43 (s, 1H), 9.26 (d, 1H, $J = 8.0$ Hz), 9.21 (d, 1H, $J = 8.0$ Hz), 8.71 (d, 1H, $J = 8.0$ Hz), 8.68 (d, 1H, $J = 8.0$ Hz), 8.48 (t, 1H, $J = 8.0$ Hz), 8.18 (m, 3H), 5.57 (t, 2H, $J = 6.0$ Hz), 4.24 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR (DMSO, 100 MHz) δ 156.5 (CH), 138.7 (CH), 134.7 (C), 133.1 (CH), 132.7 (C), 132.3 (CH), 130.7 (CH), 130.5 (CH), 125.8 (C), 125.2 (CH), 123.4 (CH), 123.1 (C), 119.9 (CH), 58.1 (CH_2), 30.6 (CH_2).

General Method for Synthesis of TIPs (3). To a stirred suspension of BEP **2** (700 mg, 1.91 mmol, 1.0 equiv) in $CHCl_3$ (50 mL) were added primary amine **1a**−**x** (1.91 mmol, 1.0 equiv) and TEA (798 μL, 5.73 mmol, 3.0 equiv). The resultant suspension was stirred under a nitrogen atmosphere until a solution formed (0.5−18 h depending on the amine). The reaction mixture was transferred to a separating funnel and washed with water (2 × 20 mL) and brine (1 × 20 mL). The organic phase was then dried over $MgSO_4$ and the solvent was removed under vacuum to give the crude TIP product, usually a pale colored powder. In some cases, an optional methanol trituration was used to improve the purity or to vitrify crude products that formed oils rather than powders. Full experimental details and characterization data for all compounds and intermediates

are available in ESD. An example for compound **3g** is shown below.

1-(4-Dimethylaminophenyl)-1,2,3,12b-tetrahydroimidazo[1,2-*f*]phenanthridine (3g). General TIP synthesis method. Product isolated as a pale grey powder (574 mg, 1.68 mmol, 88.1%): mp 197−199 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, 1H, J = 7.8 Hz), 7.79 (d, 1H, J = 7.8 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.26 (m, 2H), 7.04 (t, 1H, J = 7.8 Hz), 6.83 (m, 3H), 6.77 (m, 2H), 5.30 (s, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.68 (m, 1H), 3.37 (m, 1H), 2.91 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.4 (C), 143.7 (C), 141.4 (C), 134.6 (C), 131.9 (C), 129.1 (CH), 127.7 (CH), 127.2 (CH), 124.6 (CH), 124.2 (C), 123.7 (CH), 123.3 (CH), 119.7 (CH), 115.6 (2 × CH_2), 115.0 (2 × CH_2), 112.8 (CH), 75.6 (CH), 52.1 (CH_2), 44.8 (CH_2), 41.9 (2 × CH_3); IR (KBr, cm^{-1}) 3433 (w), 3045 (w), 2927 (w), 2870 (w), 2841 (w), 2787 (w), 1597 (m), 1514 (s), 1493 (m), 1442 (m), 1372 (m), 1337 (m), 1297 (s), 1210 (m), 809 (m), 749 (s), 734 (m); MS (FAB) m/z 342.4 $(M + H)^+$ (100), 206.6 (10), 193.7 (37), 180.8 (23), 136.3 (25); HRMS (FAB) calcd for $(C_{23}H_{24}N_3)^+$ 342.1970, found 342.1965.

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Supporting Information Available: Details of instruments and materials, extended Experimental Section, CV data, NMR spectra of products and intermediates, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.