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Exploring the limits of inductive electron withdrawal in fused bicyclic azaheterocycles

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The ability to easily modify the electronic properties of aromatic azaheterocycles has led to their ubiquitous application across all disciplines of chemistry. The electronic properties of the aromatic π -system are most often modified by π -electron donating and withdrawing groups, naturally. Nearly fifty years ago, an important exception to this trend was reported, when the single-step synthesis of 5,7-bis(trifluoromethyl)-1,8-naphthyridine was described—a highly electron deficient system based exclusively on inductive electron withdrawing groups (CF_3) and the inherent effect of nitrogen for carbon substitution. Herein, we report on efforts to extend these substitutions to create maximally electron withdrawn fused bicyclic azaheterocycles using only inductive effects. DFT calculations support the assignment of these structures as being strongly electron withdrawing, with ground-state LUMO energies as low as -2.91 eV obtained. Host-free OLEDs featuring these acceptor structures as part of polymer emissive layers show colors consistent with their electron-deficient character.

In the 1970s, researchers at Merck reported the one-step synthesis of electron-deficient 1,8-naphthyridine **1** (Fig. 1),¹ and described the use of this heterocycle for anti-hypertensive and bronchodilator development.^{2–4} Given its facile synthesis this heterocycle has found application in several fields, for example as a pH- and metal-sensitive fluorescent probe (**2**),⁵ as a large Stokes-shift fluorophore (**3**),⁶ and as an amine-reactive cell imaging agent (**4**).⁷ Specifically, we were most drawn to the fact that the aromatic system is rendered very electron poor without the use of π -electron withdrawing groups. One cannot discount the successful use of canonical π -electron withdrawing groups

(e.g. $-\text{CN}$) in countless applications—but having alternatives that lack the functional group chemistry inherent to such groups would be useful for the synthetic chemist. Modifying the parent scaffold (**1**) to provide new electron deficient building blocks for a range of applications became our goal. Beginning with naphthalene itself, there are seven C–H positions available for modification (with one position reserved for connection to the rest of the molecule). While there are many permutations of N/ CF_3 substitution possible, we targeted the hypothetical molecule **5** (Fig. 1) with an alternating substitution pattern. Flanking $-\text{CF}_3$ groups would reduce the availability of the nitrogen lone pairs, while the nitrogen atoms would alleviate potential steric clashes between $-\text{CF}_3$ groups at adjacent positions on the same ring, or 1,3-related across the ring junction. Herein, we describe the incorporation of additional N/ CF_3 to the 1,8-naphthyridine scaffold and the production of model small molecules and polymers that are representative of potential applications for such systems.

Synthetic approaches to building blocks: amino-naphthyridine **1** can be converted into the corresponding chloride through a two-step sequence (**1** \rightarrow **6** \rightarrow **7**) as previously reported (Fig. 2).⁸ While 7

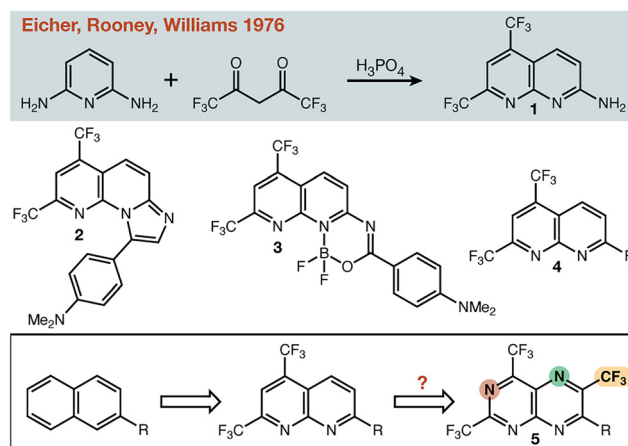


Fig. 1 Representative applications of the 5,7-di-trifluoromethyl-1,8-naphthyridine scaffold and a hypothetical maximally withdrawn target.

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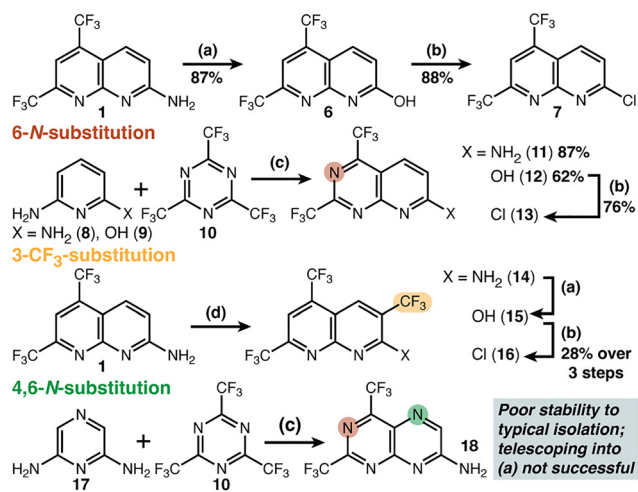


Fig. 2 Synthetic strategy for C/N substitution and CF_3 addition at remaining unsubstituted positions. (a) H_2SO_4 , NaNO_2 , H_2O 0 to 80°C (b) POCl_3 , DMF 0 to 100°C (c) AcOH , 0 to 80°C (d) NaSO_2CF_3 , $t\text{BuOOH}$ (5.5 M in decane), $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, rt.

has been known for more than a decade, its C–Cl bond has been used almost exclusively to make new heteroatom bonds, with only a single example of C–C bond formation (*i.e.* the addition of benzylium anion) reported;⁹ developing C–C bond forming reactions for these heterocycles became our focus (*vide infra*). Other potential cross-coupling partners at this position (*i.e.* $-\text{Br}$, $-\text{I}$, $-\text{OSO}_2\text{R}$) have never been reported. To achieve a nitrogen-for-carbon swap at the 6-position, we used commercially available triazene **10**. This reagent has been reported to undergo cyclization reactions to yield bis(trifluoromethyl) pyrimidine derivatives.^{10–25} Our specific target (**11**) had not been described in the academic literature, though one patent report suggested the potential for success.²⁶ We found **10** is reactive towards both diamino-(**8**) and amino-hydroxy pyridine (**9**), affording **11** and **12**, respectively. Next, we installed an additional trifluoromethyl group in the 3-position using the radical strategy reported by Baran.²⁷ We found these conditions delivered a mixture containing a small amount of unreacted starting material (**1**) that was difficult to separate from the desired product **14**. The simplest solution proved to be carrying this mixture through diazotization (to **15** and **6**), and finally chlorination (to **16** and **7**), at which stage separation is easy. Addition at positions adjacent to—or across the ring junction from—existing $-\text{CF}_3$ groups was less favourable as expected.

OH/NH_2 -containing compounds (*i.e.* **1**, **6**, **11**, **12**, **14**, and **15**) displayed consistent colours (*i.e.* yellow to red fluorescence) and TLC behaviour. The exposure of 2,6-diaminopyridine (**17**) to our standard cyclization conditions initially looked promising by similar TLC analysis. Isolation of the desired pteridine proved far more difficult. Compounds that were initially yellow fluorescent (on TLC) were isolated as black solids with complex spectra after either aqueous work-up or silica gel chromatography. Quick filtrations through alumina and telescoping into diazotization—including anhydrous conditions with *iso*-amyl nitrite—were also unsuccessful. We suspect that the fully-substituted target **5** would share similar sensitivity to (presumed) **18**, which features

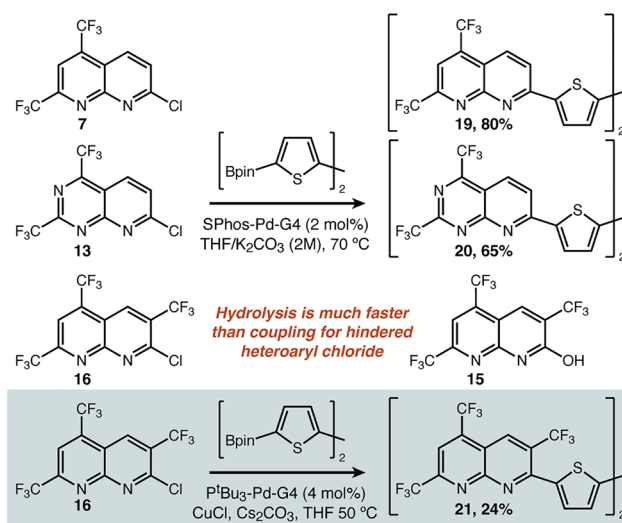


Fig. 3 Conditions for C–C bond formation via cross coupling for both sterically accessible and sterically hindered substrates.

only one unsubstituted position—and so did not further pursue that target here.

C–C bond formation and model molecules: we next sought to apply **7**, **13**, and **16** as building blocks in contexts where their electron deficient nature would be relevant. We began with cross-coupling onto 2,2'-bithiophene as a proxy for the canonical acceptor-donor-acceptor oligothiophene structure.^{28,29} Our successful conditions are described in Fig. 3. Use of a modern catalyst well-known to be effective for Suzuki coupling (*i.e.* SPhos-Pd-G4³⁰) was compatible both with the parent substrate **7** and 6-*N*-substituted **13**, delivering the double-coupling products **19** and **20**. When the heteroaryl chloride was hindered (**16**), such conditions only return hydrolysed starting material (**15**). Using anhydrous conditions was therefore one necessary modification. The second was the use of copper(i) additives, which has been shown to greatly improve the coupling of CF_3 -substituted pyridines,³¹ and proved to be critical here. In the referenced report, the pyridine is the nucleophile of the reaction unlike in our case—so we do not suggest that the impact of Cu(i) on the mechanism of the reaction is necessarily identical. Regardless of the underlying reason, these conditions were uniquely able to afford **21**.

Estimation of electron withdrawing ability: with confirmation that these building blocks could be elaborated by cross-coupling, we sought to demonstrate their electron withdrawing ability. Since the breakthrough report of Adachi in 2012,³² it has been realized that organic small molecules with linked electron-rich donors and electron-poor acceptors—often constructed so there is a significant twist between their donor/acceptor π -systems—commonly display thermally-activated delayed fluorescence (TADF) behaviour and have LUMO energy levels determined mostly by the structure of the acceptor.^{33–37} Density functional theory calculations were carried out on a suite of model compounds (Fig. 4) using PBE0 functional³⁸ and 6-31G(d,p) basis set.³⁹ We also synthesized three of these compounds (**22–24**) to ensure the fluorinated heterocycle could be used as shown (see SI). DFT results show that the LUMO is



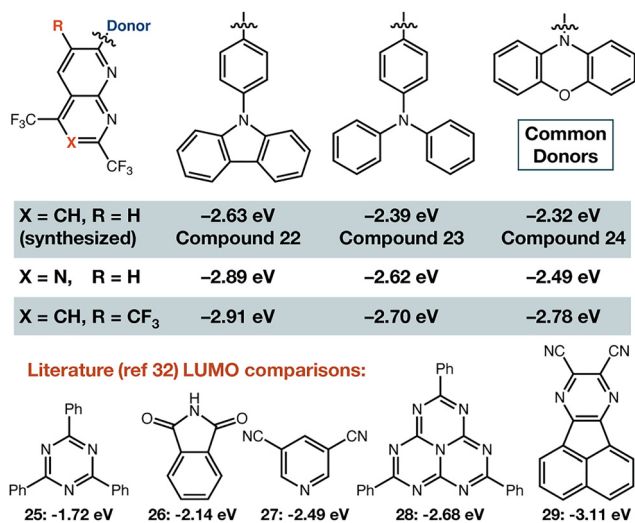


Fig. 4 LUMO energies for representative molecules. DFT was performed with PBE0 functional and 6-31G(d,p) basis set in both this work and ref. 37.

centred on the fluorinated acceptor, and thus the energy of this molecular orbital reveals their highly electron-deficient nature. Many of these compounds have LUMO levels that are lower in energy than triazine (25), phthalimide (26), dicyanopyridine (27), or heptazine (28). Our compounds in general are predicted to be around heptazine, or between heptazine and a very electron deficient pyrazine acceptor (29) that has emission in the near infrared when combined with a diphenyl amine donor.⁴⁰

One of our laboratories recently reported the fabrication of host-free OLED devices under air.⁴¹ That report used an organic polymer (*i.e.* “Super Yellow”⁴²) as the emissive layer, so we sought to incorporate 7 into an appropriate polymer. Creating building blocks for polymerization (Fig. 5, 31 and 32) also allowed us to further demonstrate the chemistry of these systems (see SI). We selected the backbone polymer described by Bryce⁴³—which uses fluorene 33 and sulfone 34 as the major components—to incorporate our building blocks by Suzuki polymerization (Fig. 5). Incorporation of 31 and 32 in both low (2 mol%) and high (10 mol%) amounts led to excellent yields of polymer, with emitter loading having a significant effect on emissive properties. Molecular weight analysis of the polymers (at both heterocycle loadings) displayed reasonable M_N (32–62 kDa), M_W (50–89 kDa), and PDI (1.39–1.56). Our recently described OLED fabrication procedure (with no additional optimization) delivered devices for initial analysis.⁴¹ Polymers derived from 31 and 32 show green-yellow and orange-red electroluminescence, respectively (see SI). When compared to previous reports using heptazine acceptors in combination with carbazole⁴⁴ and phenoxazine⁴⁵ donors, the observed emission maxima further support the electron deficient nature of these systems.

We set out to increase the electron deficient nature of the naphthalene ring system without using π -electron withdrawing groups. Azaheterocycles that feature five of the seven possible C–H positions modified to N or CF₃ were produced. Catalytic and stoichiometric chemistry shows that these building blocks can

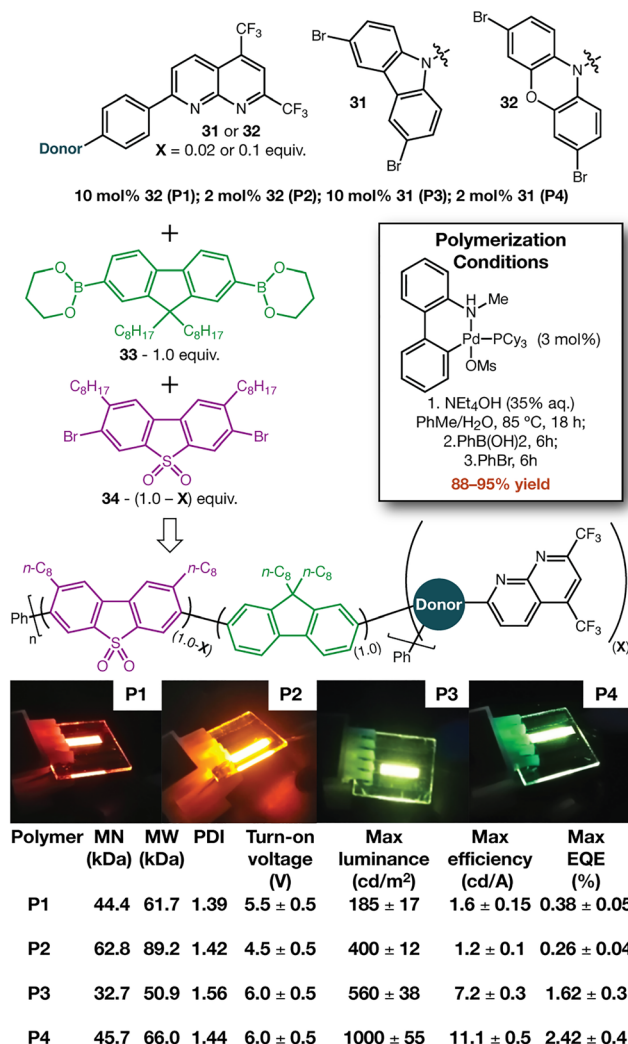


Fig. 5 Synthesis of light-emitting polymers with electron deficient heterocycles incorporated. OLED devices were fabricated and tested as in ref. 41.

be incorporated into more elaborate organic molecules. DFT calculations and the observed colours of the OLEDs produced speak to the highly electron withdrawn nature of these systems.

SSB synthesized small molecules and polymers. DRT synthesized small molecules and performed preliminary calculations. SP conducted the theoretical study and produced illustrations. AC fabricated and tested polymer OLEDs. EZ-C analysed results. GCW co-conceptualized project and analysed results. JVH co-conceptualized project, analysed results, and drafted manuscript. All authors edited the draft manuscript.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures, spectral information, OLED characteristics, and detailed DFT outputs. See DOI: <https://doi.org/10.1039/d5cc04446d>.

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