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Synthesis of fused-ring aza-dipyrromethenes from aromatic nitriles†

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Aza-dipyrromethenes are ligands for a number of useful fluorescent dyes and electronic materials. They have high absorption in the red and NIR range. Fused-ring aza-dipyrromethenes cannot be synthesized through the same methods used to make aza-dipyrromethenes, which are common commercial dyes. The current synthesis is limited to treating a phthalonitrile-based electrophile with a Grignard reagent followed by reduction with formamide at high temperature. In this work, we introduce a new fused-ring aza-dipyrromethene synthesis from *ortho*-lithiated aromatic nitriles. This method allows for a much wider range of functional groups, less complicated starting materials, and yields that are consistent with the highest reported for aza-dipyrromethenes of any kind.

Dipyrromethene is a versatile monoanionic bidentate ligand that coordinates main group elements as well as transition metals. Its most common use is as a boron coordinated complex referred to as boron dipyrromethene[1] (BODIPY), many examples of which are commercially available. Aza-dipyrromethenes (**A** in Fig. 1) are a class of ligands that are identical to dipyrromethene, where the methene bridge is replaced by a nitrogen atom. Aza-dipyrromethenes are useful for reaching peak absorbance and emission at wavelengths greater than 700 nm when coordinated with boron (aza-BODIPYs). Fused-ring aza-dipyrromethenes (**B** in Fig. 1) have been used in complexes with even lower bandgaps than aza-dipyrromethenes.[2] Recent examples have been able to reach peak emission wavelengths past 900 nm with high quantum yields.[3] They have been less explored due to their reduced solubility and the difficulty by which they are prepared.

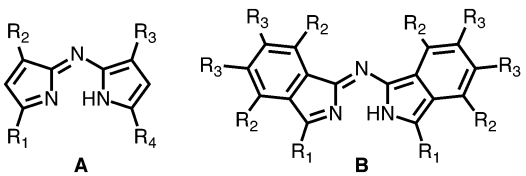

Fig. 1 Structures of aza-dipyrromethenes (**A**) and fused-ring aza-dipyrromethenes (**B**), as synthesized.

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Because of their limited derivatization, aza-BODIPYs have been mostly used as p-type materials.[4,5] p-type materials are relatively well-developed, with aza-BODIPYs having more potential application if more n-type derivatives could be synthesized. Aza-dipyrromethenes have also seen promising applications outside of their boron-coordinated complexes, especially as complexes of Zn(II), which have successfully been incorporated as active components in organic photovoltaics (OPVs).[6–8]

Aza-dipyrromethenes are most commonly synthesized from 4-nitro-1,3-diarylbutan-1-ones in one step by heating with an ammonia source.[9,10] The reaction pathway is very complex, but yields of 35% can be routinely achieved with simple purification.[11] However, the reaction is limited to derivatives which are functionalized only on the 2 and 4 positions of each pyrrole unit. Access to expanded fused-ring systems through this method requires further modification of the aza-dipyrromethene core by adding aromatic groups to the 3-positions and oxidizing.[12] Because the carbon atoms flanking the nitrogen bridge are quite electrophilic, aza-dipyrromethenes are sensitive to harsh conditions which limits the scope of how they can be derivatized.

Fused-ring aza-dipyrromethenes were exclusively synthesized from Grignard reagents and phthalonitrile derivatives,[13–15] until recently when Zheng *et al.* reported a synthesis of asymmetric aza-diisoindolmethines from phthalonitrile derivatives and a potassium *tert*-butoxide.[16] Although Zheng's synthesis is a significant improvement, it is limited to asymmetric derivatives bearing a pendant aryl group on one side only. While fused-ring aza-dipyrromethenes ligands have the potential to be a useful class of optoelectronic materials, the existing synthetic options leave very little room for derivatization.

In the present work, we report the discovery that fused-ring aza-dipyrromethenes can be synthesized from *ortho*-lithiated aromatic nitriles. The fused-ring is not limited to phenyl rings, as demonstrated by compound **1c** in Fig. 3. Fig. 2 compares the mechanism of the electrophilic nitrile cascade of phthalonitrile

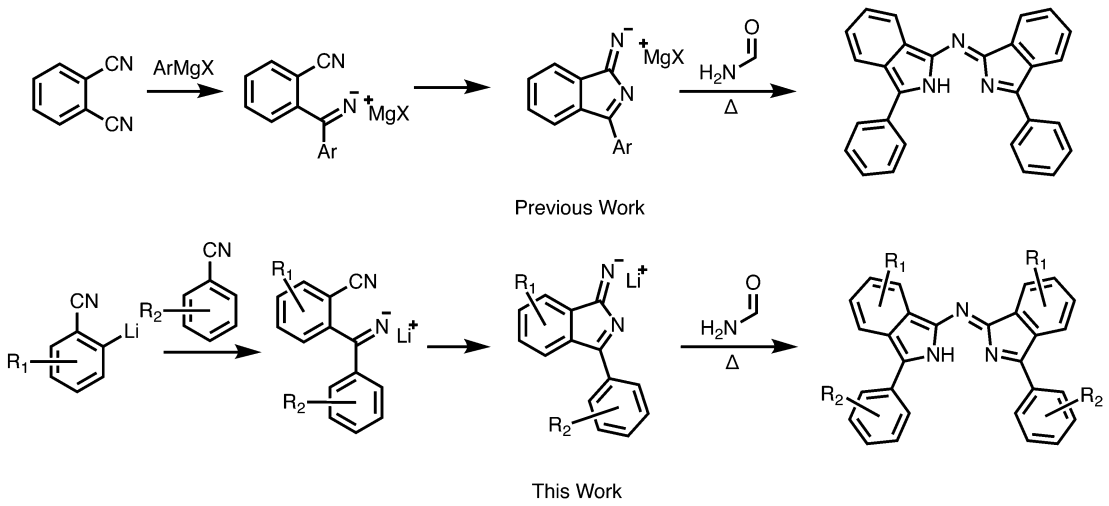


Fig. 2 New synthesis of aza-diisoindolmethines from aromatic nitriles.

in previous work to the same nitrile cascade between nitriles originating from two different molecules in this work. They key difference is that two different benzonitriles can be incorporated into the reaction cascade allowing R_1 and R_2 to be varied independently. We were also able to use a much broader library of benzonitriles. The five-membered ring is formed by an intramolecular reaction between an anionic imine and a nitrile *ortho* to it on an aromatic framework. The dimeric intermediate at the end of the cascade is identical to that formed in the phthalonitrile reaction, but the original reactant can include any aromatic compound that can be quantitatively lithiated *ortho* to the nitrile.

Many aromatic nitriles can be quantitatively lithiated by lithium diisopropylamide (LDA) in a position *ortho* to the cyano group. Most notable are 1,3-dicyanobenzene and 1,4-dicyanobenzene (at −98 °C in THF), and they can react with electrophiles in high yields.[17] They will also form the intermediate shown in Fig. 2, which can condense on itself after reductive amination with formamide. Benzonitrile and 3-thiophenecarbonitrile can also be lithiated in the same fashion, though benzonitrile requires lithium 2,2,6,6-tetramethylpiperidine (LiTMP) as a base, as LDA is not selective at the 2-position.[18]

ortho-Lithiated nitriles can similarly be prepared from the reaction of *n*-BuLi with *ortho*-brominated nitriles at low temperature, but we have found this method to be inferior because it is very difficult to separate partially brominated derivatives from the desired product. Furthermore, *ortho*-brominated functional benzonitrile compounds are not as easily accessible as those which can be lithiated by deprotonation.

The synthetic scheme in Fig. 2 depicts both the homocoupling reaction ($R_1 = R_2$) and the heterocoupling reaction ($R_1 \neq R_2$). In the first case, the dimeric intermediate is generated simply by lithiating half of the nitrile in solution at low temperature. In the latter, the initial nitrile is lithiated with a full equivalent of base before transferring the cold mixture by cannula into a room temperature solution of the nitrile bearing R_2. In this case, it is not necessary that the second nitrile can be quantitatively lithiated in any position, as it does not act as a carbon nucleophile at any point. Between the two reactions, it is possible to generate a very large variety of aza-diisoindolmethines, including aza-dipyrromethenes fused to heterocycles such as thiophene (**1c**).

This reaction is not limited to benzonitrile derivatives. Heterocycles, such as 3-thiophenecarbonitrile, can also undergo the same process after being metallated in the 2-position. Because 3-thiophenecarbonitrile is more acidic than benzonitriles, it can be deprotonated using a Grignard reagent. As the mechanism of this reaction is identical, any base works for this reaction so long as it is able to quantitatively deprotonate the aromatic nitrile while avoiding nucleophilic attack on the cyano groups present. For this reason, *n*-butyllithium is unsuitable to use in these reactions.

With the exception of the previously reported aza-diisoindolmethine **1d**, none of the other compound synthesized could be made from phthalonitrile derivatives. The currently existing method requires that the phthalonitrile is symmetric

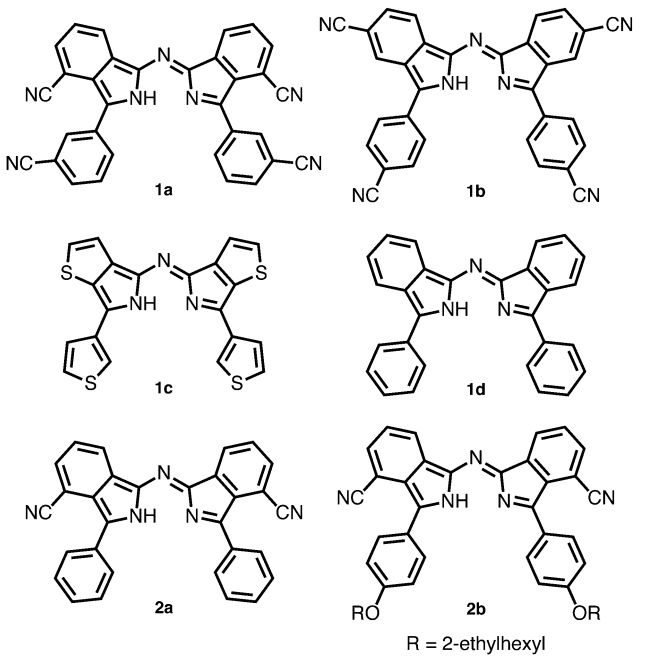
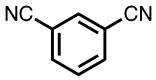
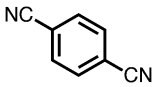
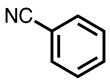
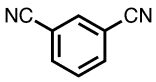
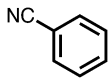
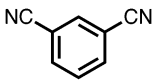
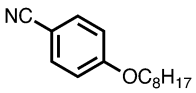


Fig. 3 Products of homocoupling (**1a–d**) and heterocoupling (**2a–b**) reactions.

Table 1 Synthetic results of aza-diisoindolmethines

Product	Nitrile 1	Nitrile 2	Base	Temperature	Scale (g)	Yield (%)
1a		—	LDA	−98 °C	10	50
1b		—	LDA	RT	10	50
1c		—	LDA or CH_3MgCl	−98 °C	1	2
1d		—	LiTMP	−98 °C	1	10
2a			LDA	−98 °C	5	47
2b			LDA	−98 °C	5	4

across the plane between the two nitriles, as there is no control over which nitrile group is added to first. The structure of **1c** determined by X-ray crystallography shows that the thiophene units fused to the aza-dipyrromethene structure are oriented in one direction (Fig. 4).

The second step (Fig. 2) requires that only one nitrile is *ortho* to the imine anion. For example, if the same reaction is done with 1,2-dicyanobenzene, the intermediate is asymmetric and also has two cyano groups it can attack. For this reason, derivatives of phthalonitrile are incompatible with these reaction conditions.

Each of the compounds synthesized are shown in Fig. 3. Table 1 lists the conditions and yield for each reaction. Because the solubility of 1,4-dicyanobenzene in cold THF is so low, the more soluble lithiated compounds react with each other to generate a complex and inseparable mixture. However, all four protons of 1,4-dicyanobenzene are identical, which allows room temperature lithiation to generate a single product. An essential requirement for this reaction is that the lithiated compounds preferentially attack nitriles that are not lithiated, but it is impossible to avoid these reactions if the nitrile is not soluble at low temperature.

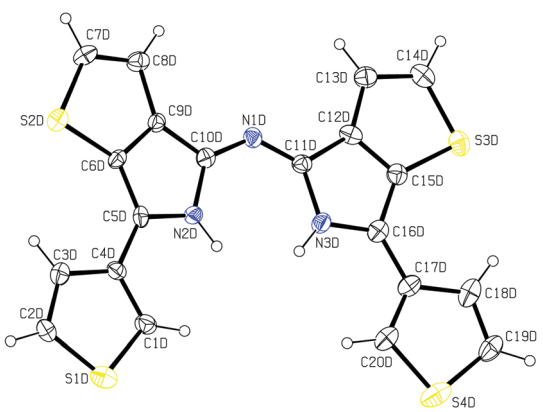


Fig. 4 The molecular structure of **1c** protonated with TFA. Displacement ellipsoids are shown at the 30% probability level.

The workup and purification of the aza-diisoindolmethines varies depending on the solubility of the product. **1d** and **2b** are soluble in common organic solvents, which allows them to be purified on a silica column. The solubility of **1a–c** and **2a** are very low in most organic solvents (with the exception of DMF and DMSO), which makes them unable to be purified on a silica column. However, these reactions only produce small amounts of higher molecular weight compounds, which allows them to be purified by trituration with methanol, acetone and dichloromethane sequentially.

When compared with examples like **1a** and **2a**, the yield of **1c** and **2b** are very low. This likely has to do with the reduction step. For **1c**, the reaction produces an intense sulfur smell, indicating the decomposition of individual thiophene rings in the harsh conditions. Greasy compounds like **2b** tend to phase separate from formamide at high temperature, which greatly reduces the efficiency of the reaction. Further optimization of the reductive amination (*e.g.* using mild conditions) is required to improve the synthesis of the low-yield compounds. In contrast, the yield of **1d** suffers from low selectivity during lithiation, as the 2-lithium species is not quantitatively made.

The alkylated aza-diisoindolmethine is the sole compound with solubility greater than $\sim$20 mg mL^{-1} in common organic solvents. Because the borylated compounds are even less soluble, purification is a major issue in the synthesis of aza-BODIPYs from these compounds. The corresponding aza-BODIPY from compound **2b** was successfully purified and characterized, but the others were unable to be separated from impurities generated during the reaction. In contrast, the Zn(II) complexes of most of the aza-diisoindolmethines are much more soluble than the ligands themselves and can be purified in small quantities by column chromatography. The insoluble Zn(II) complex **1a-Zn** was successfully

Table 2 Optical and electrochemical properties in DCM

	Aza-dipyrromethene			Zn(II)
	λ_{max} (nm)	$E_{1/2}^{ox\ a}$ (V)	$E_{1/2}^{red\ a}$ (V)	λ_{max} (nm)
1a	621	0.6	−0.9	659
1b	648	—	—	647
1c	640	—	—	—
1d	653	0.1	−1.3	631
2a	624	0.5	−1.0	658
2b	632	—	—	641

[a] Half-wave potentials were measured in CH_2Cl_2/TBAPF$_6$ (0.1 M) *vs.* Ag/Ag$^+$, scan rate 100 mV s^{-1}, using Fc/Fc$^+$ as an internal standard.

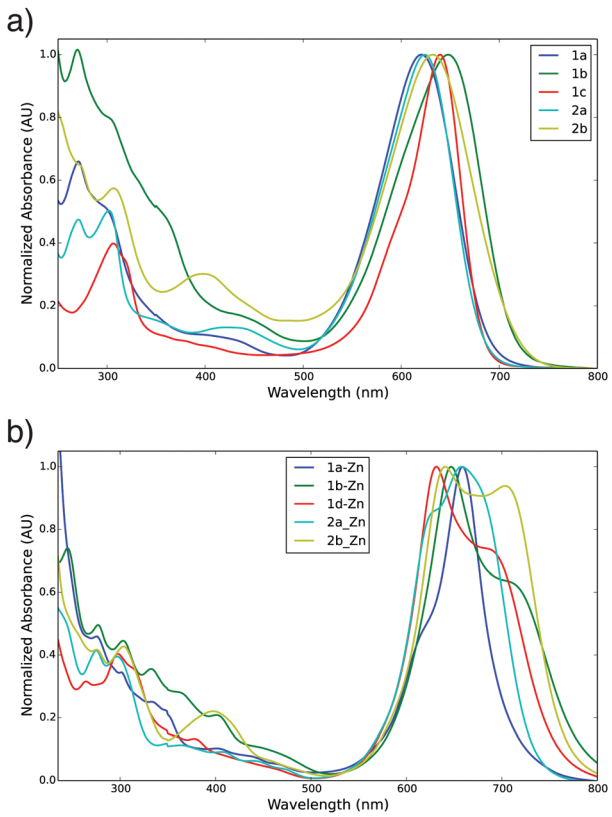


Fig. 5 Normalized absorption spectra of (a) fused-ring aza-dipyrromethenes in DCM and (b) their Zn(II) complexes.

purified by trituration, as the zinc insertion reaction generates very little side product compared to the equivalent reaction with $BF_3{\cdot}OEt_2$.

As with other Zn(II) aza-dipyrromethene complexes reported, the Zn(II) species show strong absorption peaks in the red/NIR region and do not fluoresce. Cyclic voltammetry of compounds **1a**, **1d**, and **2a** shows a trend of decreasing HOMO/LUMO energies with an increasing number of cyano groups. This shows that the newly accessible aza-dipyrromethene compounds should possess previously unattainable electronic properties. These properties are summarized in Table 2.

While the aza-isoindolmethines appear to strongly absorb through one major transition (Fig. 5), their Zn(II) complexes show two strong absorbance peaks between 600 and 800 nm (Fig. S40, ESI†). The relative strengths of these transitions vary depending on the specific ligand. Finally, we made a test OPV device using P3HT as a donor and 2b-Zn as an acceptor. While aggregation of 2b-Zn limited the current, the device shows that these new aza-dipyrromethene compounds can accept electrons from p-type materials (Fig. S42, ESI†).

In conclusion, we have developed a novel synthetic procedure for the production of aza-diisoindolmethines. The technique has three main benefits over existing syntheses. Firstly, the aromatic nitrile does not have to be symmetric, which allows for the selective synthesis of regioregular products. The second benefit is that the reaction produces aza-diisoindolmethines with nitrile groups, something that would not have been possible with the existing syntheses. Finally, aromatic nitriles are much more readily available than *ortho*-dicyano compounds, which provides access to a much larger product scope from less expensive materials. Further research is required to learn more about the device properties of the newly-accessible aza-diisoindolmethines and their complexes.

Conflicts of interest

There are no conflicts to declare.

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