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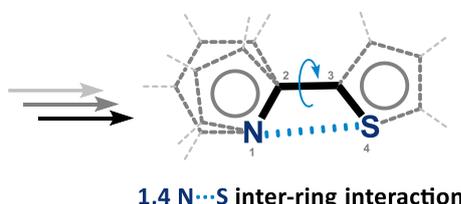
# Synthesis of Heterobiaryls Featuring 1,4 N...S Inter-ring Interaction

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**Abstract** Because of its low-lying  $\sigma^*$  orbitals, the C-S bond can interact with electron donors. In this Short Review, our goal is to focus on intramolecular interactions between bivalent sulfur and basic nitrogen atoms. In particular, we will consider the synthesis of selected heterobiaryls for which 1,4 N...S inter-ring interaction can be identified from X-ray diffraction data. Finally, we will briefly get onto the use of such conformational preferences for different applications.

- 1 Introduction
- 2 Cross-coupling with C-C bond formation
- 3 Cross-coupling with C-N bond formation
- 4 Nucleophilic addition to azine followed by oxidation
- 5 Multicomponent reactions
- 6 Heterobiaryl formation by azine building
- 7 Heterobiaryl formation by sulfur-containing heterocycle building
- 8 Cycloaddition reactions
- 9 Other syntheses
- 10 Conclusion

**Key words** N...S Inter-ring Interaction, heterobiaryls, nitrogen, sulfur, azine, sulfur-containing heteroaromatic, cross-coupling, X-ray diffraction data

## 1 Introduction

When bivalent, sulfur can interact with electron donors such as groups containing oxygen or nitrogen atoms, and  $\pi$ -systems. This behavior is in relation with the low-lying  $\sigma^*$  orbital of the C-S bond and the resulting two areas of positive electrostatic potential.<sup>1</sup>

In particular, the intramolecular interaction between nitrogen lone pair of electrons and C-S  $\sigma^*$  orbital has been calculated as an element capable of stabilizing a specific conformation for the same reasons as intramolecular hydrogen bonds, unfavorable steric hindrance, attractive or repulsive nonbonding contacts, intramolecular dipole-dipole interactions, gauche effect of fluorine, and even halogen bonding.<sup>2</sup>

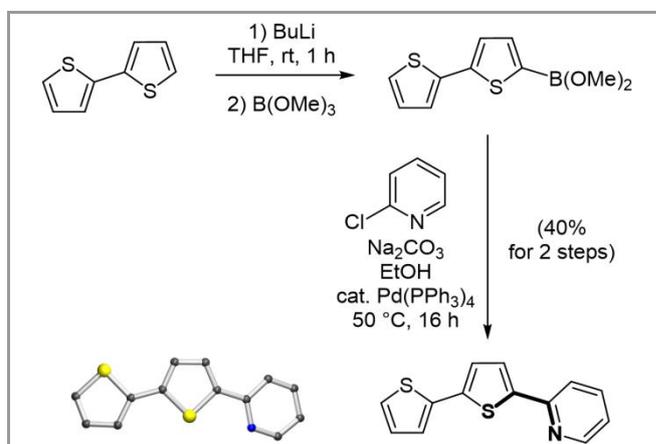
Because of the huge impact control of molecular conformations has in fields at the interface with biology and physics,<sup>1-2,3</sup> we have embarked in an exhaustive search of single-crystal X-ray structures of heterobiaryls featuring a 1,4 N...S inter-ring fragment (i.e. distance between sulfur and nitrogen shorter than the sum of the van der Waals radii of sulfur (1,80 Å) and nitrogen (1,55 Å),<sup>4</sup> and, as a consequence of this atomic contact interaction between sulfur and nitrogen, possible coplanarity between the rings containing them,<sup>5</sup> and sulfur and nitrogen

atoms pointing to the same direction). In this Short Review, our goal is to focus on examples selected from this study in order to display the various methods by which these compounds can be synthesized and to give some idea of the applications they can find. It is important to mention that 1,5- and 1,6-interactions also exist,<sup>1b</sup> but have been excluded from the contents of this Short Review.

## 2 Cross-coupling with C-C bond formation

Suzuki-Miyaura reaction belongs to the most common cross-couplings found in biaryl synthesis. Skene and co-workers published in 2010 the synthesis of pyridine-thiophene acceptor-donor polyheterocycles as well as their photophysical and electrochemical properties.<sup>6</sup> To this purpose, 2-(2-thienyl)thiophene was converted to the corresponding boronic ester by deprotonation-borylation, and the cross-coupling was next performed with 2-chloropyridine under palladium catalysis to afford 2-(5-(2-thienyl)-2-thienyl)pyridine (ICOJER, Scheme 1). In addition to a nearly coplanar structure (dihedral angle  $\sim 5.5^\circ$ ), both pyridine nitrogen and sulfur atom of the central ring are located on the same side.

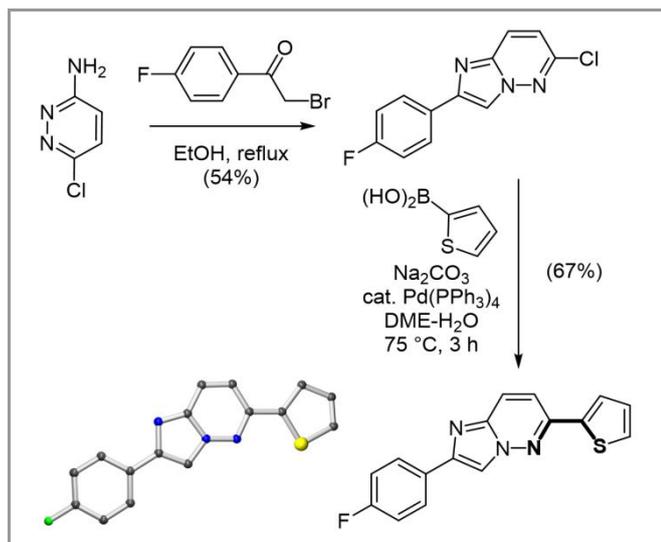
Pyridine-thiophene derivatives exhibiting similar structural features were also reached by Suzuki-Miyaura cross-coupling using 2-bromopyridine.<sup>7</sup>



**Scheme 1** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 2-(5-(2-thienyl)-2-thienyl)pyridine (ICOJER,  $d_{S...N} = 2.938$  Å,  $\phi_{SCCN}$

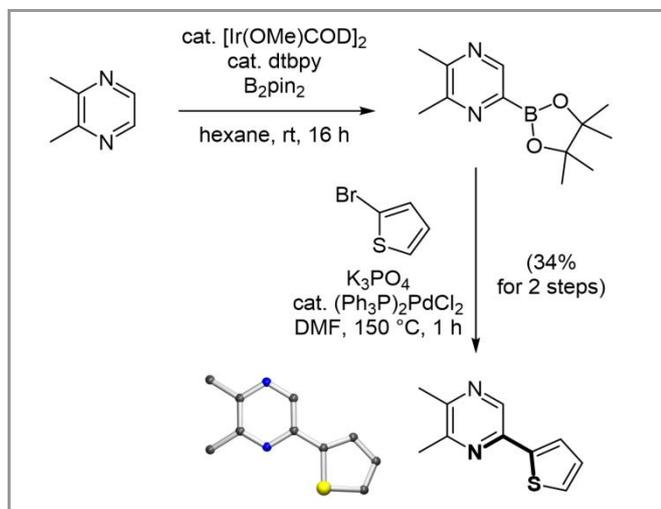
= 5.53°) using a Suzuki coupling.

Gueffier and co-workers described in 2001 the conversion of a 6-chloroimidazo[1,2-*b*]pyridazine, obtained by reaction of 3-amino-6-chloropyridazine with  $\alpha$ -bromo-4-fluoroacetophenone, to the corresponding 6-(2-thienyl) derivative XIDBIV by Suzuki-Miyaura coupling.<sup>8</sup> Reaction using catalytic tetrakis(triphenylphosphine)palladium(0) and Na<sub>2</sub>CO<sub>3</sub> (2 equiv) in a mixture of 1,2-dimethoxyethane (DME) and water similarly led to a compound possessing a N...S intramolecular nonbonding interaction (Scheme 2).



**Scheme 2** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 6-(2-thienyl)imidazo[1,2-*b*]pyridazine (XIDBIV,  $d_{N-S} = 2.886 \text{ \AA}$ ,  $\phi_{NCS} = 0.89^\circ$ ) using a Suzuki-Miyaura coupling.

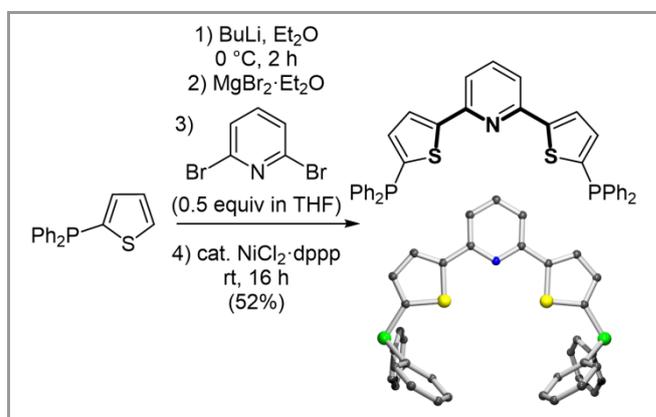
Iridium-catalyzed direct C-H bond borylation using bis(pinacolato-*O,O'*)diboron (B<sub>2</sub>pin<sub>2</sub>) combined with palladium-catalyzed Suzuki-Miyaura cross-coupling using 2-bromothiophene was also reported for the conversion of 2,3-dimethylpyrazine to the corresponding bisheterocycle (SEDXAB, Scheme 3).<sup>9</sup> Albeit less marked with a dihedral angle of  $\sim 10^\circ$  and  $\sim 3.0 \text{ \AA}$  between the N and S atoms, the interaction still exists for this compound.



**Scheme 3** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 2-thienylpyrazine (SEDXAB,  $d_{N-S} = 2.994 \text{ \AA}$ ,  $\phi_{NCS} = 10.32^\circ$ )

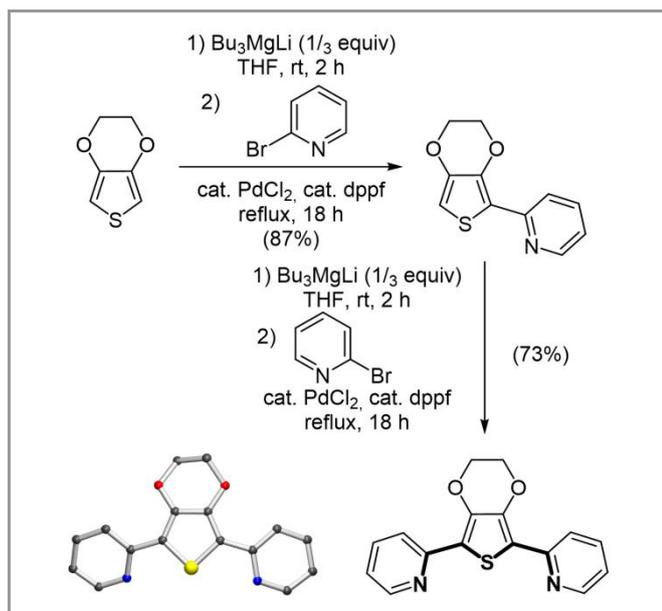
using a sequence including direct C-H bond borylation and Suzuki-Miyaura coupling (COD = cyclooctadiene; dtbpy = 4,4'-*t*-Bu<sub>2</sub>-2,2'-bipyridine).

Due to the ease with which 2-thienylmetal compounds can be generated, couplings using them are common in thienylazine synthesis. Field and co-workers documented in 2001 the synthesis of a 2,6-di(2-thienyl)pyridine using a Kumada-Tamao-Corriu reaction as key step (ACUHAH, Scheme 4).<sup>10</sup> From 2-(diphenylphosphino)thiophene, deprotolithiation employing butyllithium in diethyl ether occurs next to sulfur. After transmetalation to the Grignard reagent, the coupling is performed in THF (THF = tetrahydrofuran) with 2,6-dibromopyridine (0.5 equiv) in the presence of NiCl<sub>2</sub>-dppp (dppp = 1,3-bis(diphenylphosphino)propane). The crystal structure shows an essentially planar trisheterocycle, with a *cis* arrangement adopted by the heteroatoms from the adjacent rings with respect to rotation around the interannular bonds.



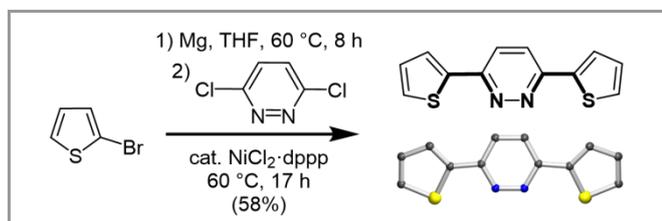
**Scheme 4** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 2,6-di(2-thienyl)pyridine (ACUHAH,  $d_{S-N} = 2.933$  and  $2.949 \text{ \AA}$ ,  $\phi_{SCN} = 2.63$  and  $0.11^\circ$ ) using a Kumada-Tamao-Corriu coupling.

Pyridine-thiophene oligomers such as the 2,5-di(2-pyridyl)thiophene depicted in Scheme 5 (GISYUD01) show similar specific geometrical features (coiled structure).<sup>11</sup> Such a compound can be synthesized in THF by repeating deprotomagnesation of 3,4-ethylenedioxythiophene using Bu<sub>3</sub>MgLi (1/3 equiv) and subsequent cross-coupling with 2-bromopyridine in the presence of PdCl<sub>2</sub> and dppf (dppf = 1,1'-bis(diphenylphosphino)ferrocene).



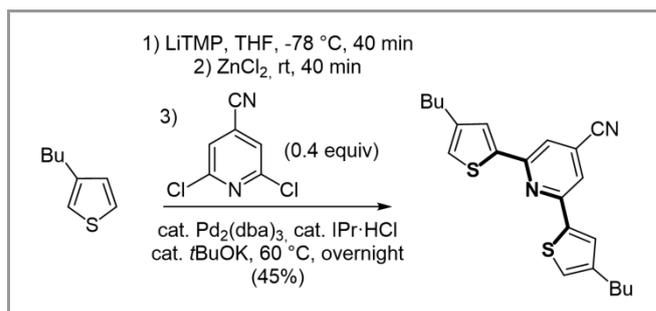
**Scheme 5** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 2,5-di(2-pyridyl)thiophene (GISYUD01,  $d_{N-S} = 2.920$  and  $2.957$  Å,  $\phi_{NCS} = 1.06$  and  $19.14^\circ$ ) using a Kumada-Tamao-Corriu coupling.

The synthesis of donor-acceptor  $\pi$ -conjugated systems containing both thiophene and pyridazine was reported by Yamamoto and co-workers in 2005 (Scheme 6).<sup>12</sup> For example, 3,6-di(2-thienyl)pyridazine (IHEMOX) can be prepared from 2-bromothiophene by Grignard reaction followed by nickel-catalyzed coupling with 3,6-dichloropyridazine. The compound adopts a similar conformation, close to planar (dihedral angles between  $10$  and  $13^\circ$ ) and with the four heteroatoms located on the same side.<sup>13</sup>



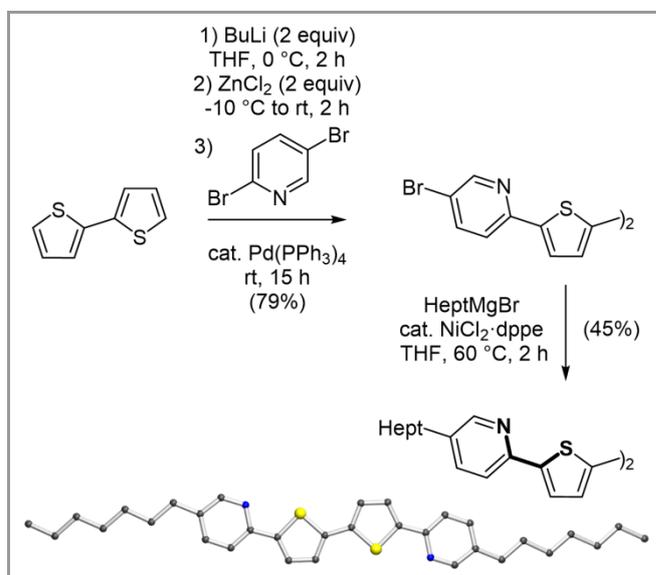
**Scheme 6** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 3,6-di(2-thienyl)pyridazine (IHEMOX,  $d_{S-N} = 2.942$  and  $2.929$  Å,  $\phi_{SCCN} = 12.68$  and  $10.29^\circ$ ) using a Kumada-Tamao-Corriu coupling.

Compared with Kumada-Tamao-Corriu coupling, Negishi reaction is in general more compatible with the presence of reactive functional groups. Thus, in the course of the synthesis of alternating 2,6-linked pyridine-thiophene oligomers for studying their optical and electrochemical properties, Rocha and Finney involved 2,6-dichloro-4-cyanopyridine in the reaction with 4-butyl-2-thienylzinc chloride (Scheme 7). The structure of the coupling product is quite similar to that depicted in Scheme 4.<sup>14</sup>



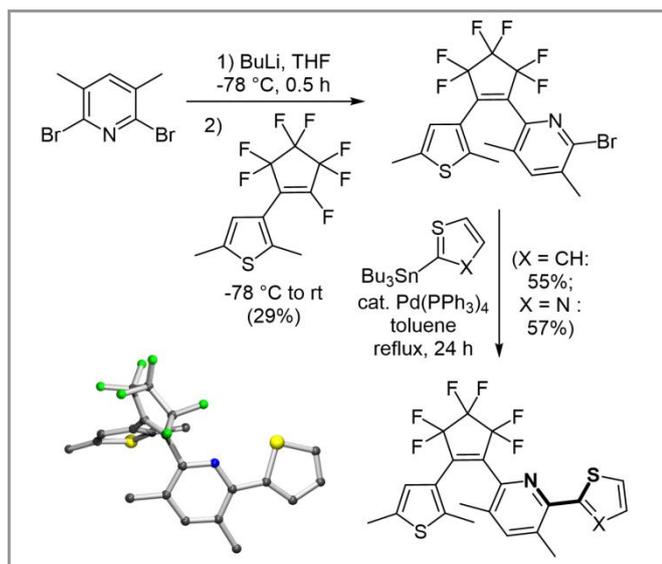
**Scheme 7** Synthesis of a 2,6-di(2-thienyl)pyridine using a Negishi coupling (LiTMP = lithium 2,2,6,6-tetramethylpiperidine; dba = dibenzylideneacetone; IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride).

In the course of the synthesis of liquid crystalline materials, both Negishi and Kumada-Tamao-Corriu couplings were employed by Twieg and co-workers.<sup>15</sup> 5,5'-Di(alkylpyridyl)-2,2'-bithiophenes (such as CITKUN) were obtained by two-fold deprotonation/transmetalation to zinc/nickel-catalyzed Negishi coupling followed by Kumada-Tamao-Corriu introduction of the alkyl chains (Scheme 8).



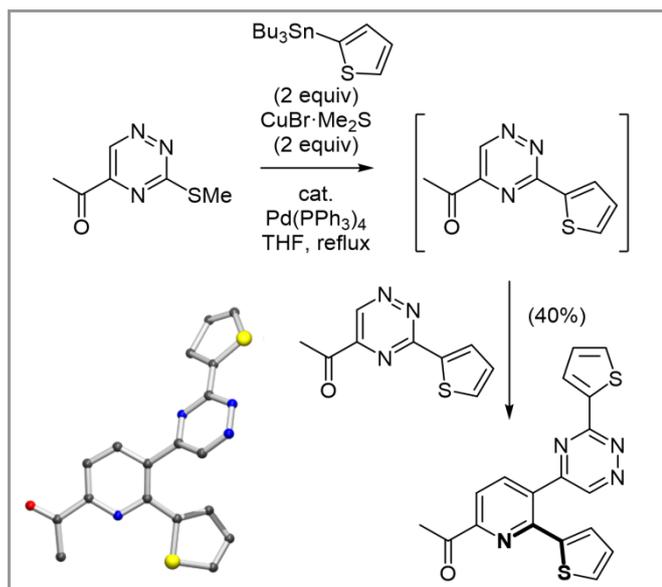
**Scheme 8** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 5,5'-di(5-heptyl-2-pyridyl)-2,2'-bithiophene (CITKUN,  $d_{N-S} = 2.914$  Å,  $\phi_{NCS} = 3.74^\circ$ ) (dppe = 1,3-bis(diphenylphosphino)ethane).

With the aim of enhancing the cyclization quantum yields of perfluorodiarylethenes, Pu, Sun and co-workers introduced in their structure a 2-(2-thienyl)pyridyl (UFIRUY) or 2-(2-thiazyl)pyridyl fragment by Stille coupling (Scheme 9).<sup>16</sup> As a consequence of the  $N\cdots S$  contact, the coplanarity between the thienyl/thiazyl and pyridyl rings is supposed to enhance the  $\pi$ -conjugation (lowered ground state energies) and thus the photochromic performances of the diarylethenes.<sup>17</sup>



**Scheme 9** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a perfluorodiarylethene (UFIRUY, X = CH,  $d_{N-S} = 2.784 \text{ \AA}$ ,  $\phi_{NCCS} = 4.95^\circ$ ) containing a 2-(2-thienyl)pyridyl or 2-(2-thiazyl)pyridyl fragment by Stille coupling.

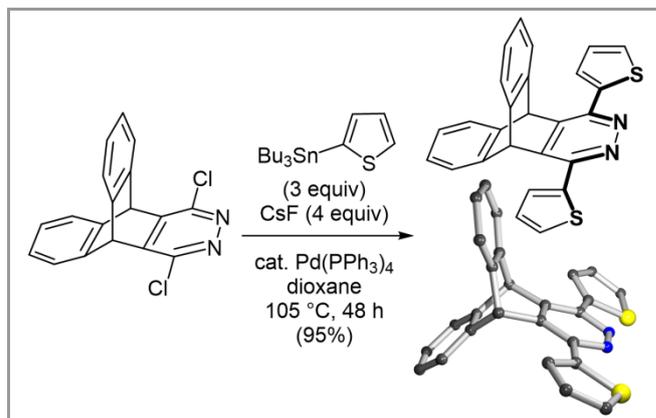
In the course of the synthesis of 5-acyl-3-(2-thienyl)-1,2,4-triazines by Stille coupling using a triazinic sulfide, Branowska and co-workers did not only observe the expected reaction but a subsequent aza Diels-Alder reaction giving pyridyltriazines (e.g. BALSIS, Scheme 10);<sup>18</sup> to explain the formation of the latter, enolization of the present acyl group in the presence of metal ions is suggested. X-ray diffraction data show nearly coplanar pyridine and thiophene rings, with their nitrogen and sulfur atoms located on the same side. Probably because of higher lone pair availability in the case of pyridine compared with triazine (in addition to potential for dipole-dipole interactions), the thiophene sulfur atom rather aligns with the azine nitrogen atom in the adopted topology.



**Scheme 10** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a pyridyltriazine bearing 2-thienyl fragments (BALSIS,  $d_{N-S} = 2.841 \text{ \AA}$ ,  $\phi_{NCCS} = 14.44^\circ$ ).

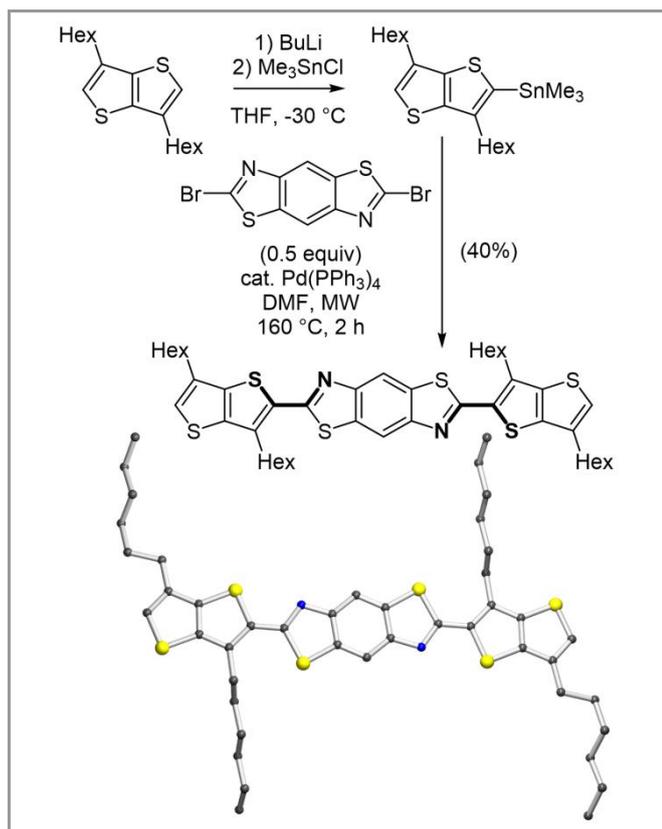
Iptycene-derived bipyridazines and bipthalazines are promising building blocks as conjugated electronics materials or

ligands for transition metals. In the course of the synthesis of such compounds, Swager and co-workers employed Stille coupling to connect 2-thienyl groups to a pyridazine scaffold (MIWTOC, Scheme 11).<sup>19</sup> As already observed in Scheme 6, 3,6-di(2-thienyl)pyridazine adopts a conformation close to planar in which the four heteroatoms are on the same side. It is of interest to note that, in spite of steric interference created between the bridgehead hydrogen atoms and those at the 3 position of the thienyl rings, such a topology is observed.



**Scheme 11** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 3,6-di(2-thienyl)pyridazine (MIWTOC,  $d_{S-N} = 2.791$  and  $2.793 \text{ \AA}$ ,  $\phi_{SCCN} = 5.05$  and  $8.42^\circ$ ) using a Stille coupling.

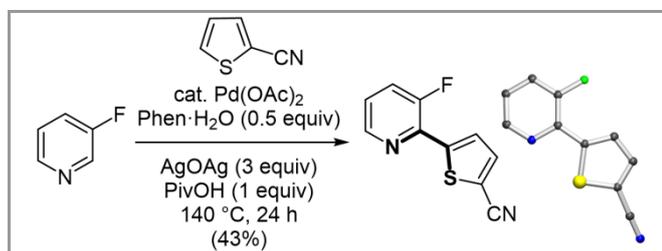
In the search of new materials for organic semiconductor devices, Skabara and co-workers reported in 2011 the synthesis of a disubstituted benzo[1,2-*d*;4,5-*d'*]bithiazole by Stille coupling between a benzobithiazolyl dibromide and two thienothiophenyl stannanes (ELAQOY, Scheme 12).<sup>20</sup> Noncovalent N...S interaction between the benzobithiazole core and the connected dithienothiophenes plays an important role in the good coplanarity observed; the enhanced conjugation is at the origin of improved charge transport.<sup>21</sup>



**Scheme 12** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a disubstituted benzo[1,2-*d*;4,5-*d'*]bithiazole (ELAQOY,  $d_{S-N} = 2.968 \text{ \AA}$ ,  $\phi_{SCNN} = 3.03^\circ$ ) by Stille coupling.

Conjugated polyaryl compounds made of a 1,3,4-thiadiazole core and of thiophene or selenophene substituents were also synthesized using the Stille reaction, and most of them proved to have similar structural features.<sup>22</sup>

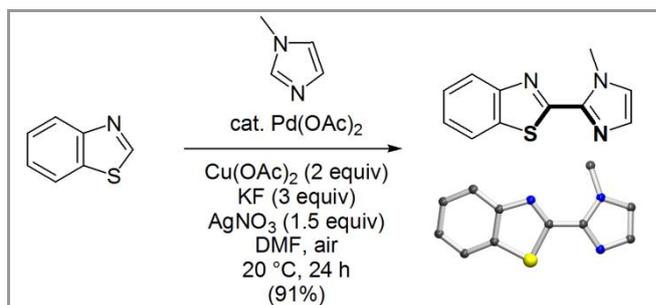
You and co-workers developed a selective method for the arylation of pyridines at their 2 position through a two-fold C-H activation. For example, palladium-catalyzed oxidative reaction of 3-fluoropyridine and 2-cyanothiophene afforded 2-(5-cyano-2-thienyl)-3-fluoropyridine using  $\text{Ag}_2\text{O}$  as oxidant, 1,10-phenanthroline monohydrate (Phen- $\text{H}_2\text{O}$ ) as ligand and pivalic acid as additive (PETZUL, Scheme 13).<sup>23</sup>



**Scheme 13** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 2-(2-thienyl)pyridine (PETZUL,  $d_{N-S} = 2.863 \text{ \AA}$ ,  $\phi_{NCS} = 0.88^\circ$ ) by oxidative C-H/C-H cross-coupling.

Ofial and co-workers published in 2011 the generation of benzothiazole-imidazole systems by palladium-catalyzed dehydrogenative cross-coupling in the presence of  $\text{Cu}(\text{OAc})_2$  (supposed to catalyze the oxidation of Pd(0) by  $\text{O}_2$ ), KF and  $\text{AgNO}_3$  (considered as terminal oxidant) (e.g. OMIKIF, Scheme 14).<sup>24</sup> As in the previous example, the linked aryl moieties are

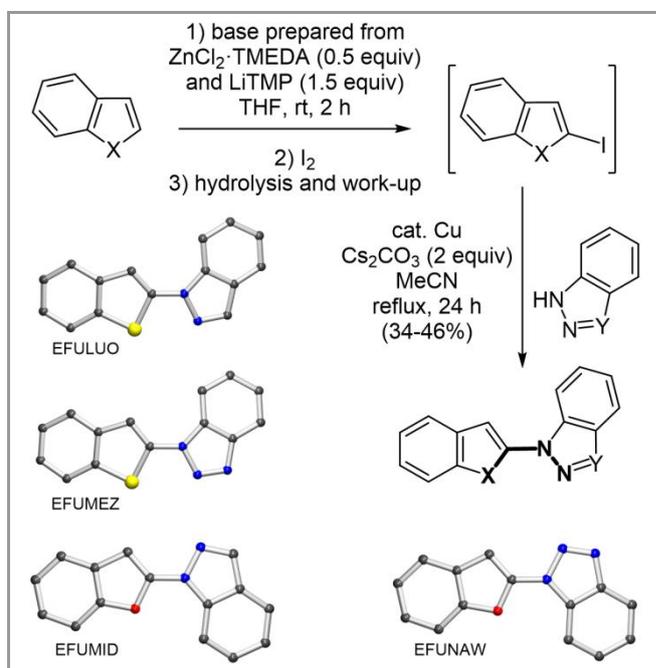
almost coplanar, with thiazole sulfur and basic imidazole nitrogen lying *syn* to each other.



**Scheme 14** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 2-(2-imidazolyl)benzothiazole (OMIKIF,  $d_{S-N} = 3.020 \text{ \AA}$ ,  $\phi_{SCNN} = 7.14^\circ$ ) by oxidative C-H/C-H cross-coupling.

### 3 Cross-coupling with C-N bond formation

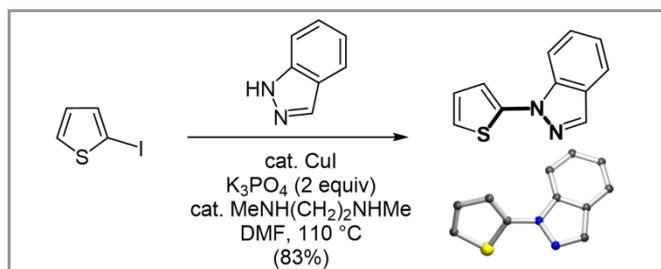
Mongin and co-workers reported in 2014 the synthesis of 1-(2-benzothienyl)-indazole (EFULUO) and -benzotriazole (EFUMEZ) using a lithium-zinc base-mediated deprotonation-iodolysis followed by copper-catalyzed *N*-arylation (Scheme 15).<sup>25</sup> In contrast with 1-(2-benzofuryl)-indazole (EFUMID) and -benzotriazole (EFUNAW), for which the O-C-N-N fragment adopts an *s-trans* arrangement, the sulfur-containing bisheterocycles show a planar structure with a *s-cis* arrangement. The  $\text{N}\cdots\text{S}$  interaction displayed in the case of indazole (2.791  $\text{\AA}$ , 1.68° dihedral angle) is slightly more marked than in the case of benzotriazole (2.853  $\text{\AA}$ , 5.42° dihedral angle).



**Scheme 15** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 1-(2-benzothienyl)indazole (EFULUO, X = S, Y = CH,  $d_{S-N} = 2.791 \text{ \AA}$ ,  $\phi_{SCNN} = 1.68^\circ$ ), 1-(2-benzothienyl)benzotriazole (EFUMEZ, X = S, Y = N,  $d_{S-N} = 2.853 \text{ \AA}$ ,  $\phi_{SCNN} = 5.42^\circ$ ), 1-(2-benzofuryl)indazole (EFUMID, X = O, Y = CH) and 1-(2-benzofuryl)benzotriazole (EFUNAW, X = O, Y = N) by a sequence including deprotonation-iodolysis and *N*-arylation.

By comparing 1-(2-benzothienyl)indazole (EFUMID) and 1-(2-thienyl)indazole (XOJBAB, the latter being also prepared by copper-catalyzed *N*-arylation of indazole as shown in Scheme

16),<sup>26</sup> we can identify a much more weaker N...S interaction for the latter, with 3.215 Å and 51.58° dihedral angle.

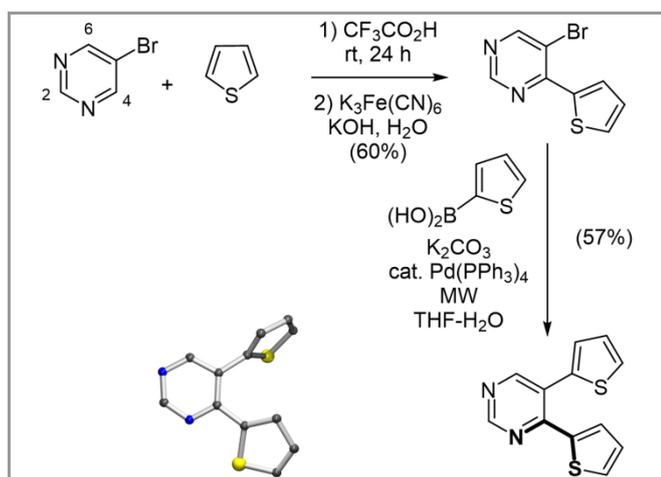


**Scheme 16** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 1-(2-thienyl)indazole (XOBIAB,  $d_{\text{S-N}} = 3.215 \text{ \AA}$ ,  $\phi_{\text{SCNN}} = 51.58^\circ$ ) by copper-catalyzed *N*-arylation.

In the course of the synthesis of acceptor-donor-acceptor metal ligands, Ullmann-type cross-couplings have also been employed by Huang and co-workers to generate 2,5-bis[1-(1,2,4-triazolyl)]thiophene.<sup>27</sup>

#### 4 Nucleophilic addition to azine followed by oxidation

Diazines being prone to nucleophilic attacks, they can react with thiophenes in such reactions to afford azine-thiophenes after subsequent oxidation. Verbitskiy and co-workers reported access to pyrimidine-thiophene scaffolds by this way.<sup>28</sup> By using 5-bromopyrimidine in the presence of  $\text{CF}_3\text{CO}_2\text{H}$ , and  $\text{K}_3\text{Fe}(\text{CN})_6$  as oxidant together with KOH, thiophenes were converted to 4-(2-thienyl)pyrimidines. In the case of 4,5-di(2-thienyl)pyrimidine (GECZUL, Scheme 17), the dihedral angle between the 2-thienyl group connected to C4, and for which sulfur can interact with pyrimidine nitrogen, and the diazine ring is  $\sim 16^\circ$  whereas it is much more important between the 2-thienyl ring at C5 and the diazine ring ( $\sim 73^\circ$ ).

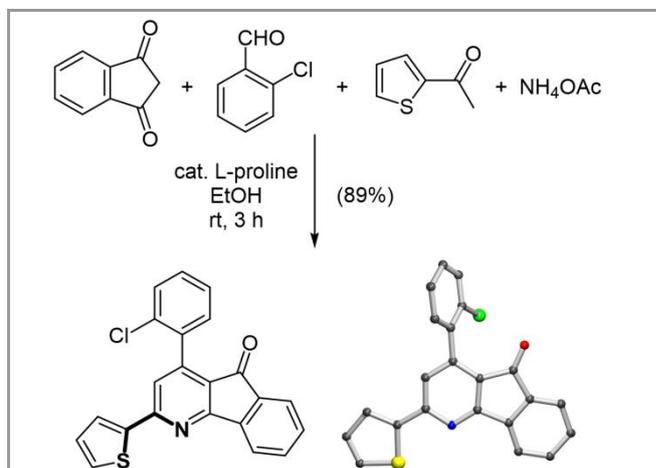


**Scheme 17** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 4-(2-thienyl)pyrimidine (GECZUL,  $d_{\text{N-S}} = 2.872 \text{ \AA}$ ,  $\phi_{\text{NCCS}} = 16.42^\circ$ ) by nucleophilic addition of thiophene to 5-bromopyrimidine followed by oxidation.

#### 5 Multicomponent reactions

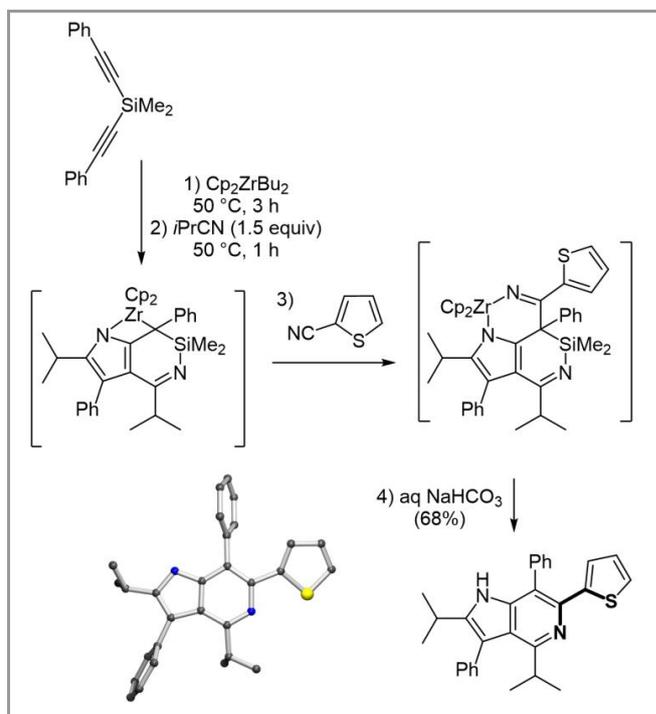
Using catalytic L-proline, Mukhopadhyay and co-workers developed a multicomponent reaction involving indan-1,3-dione, an aromatic aldehyde, 2-acetylthiophene and ammonium acetate to provide 1-substituted 3-(2-thienyl)-4-

azafluorenes.<sup>29</sup> As shown by X-ray diffraction data, the compound featured in Scheme 18 (HUXYAB) shows almost coplanar pyridine and thiophene rings, with both heteroatoms pointing toward the same direction. Indeed, even if there is an electron-withdrawing carbonyl group on the pyridine, it is located at its 3 position and has thus very little effect on the ring and nitrogen atom electron deficiency.



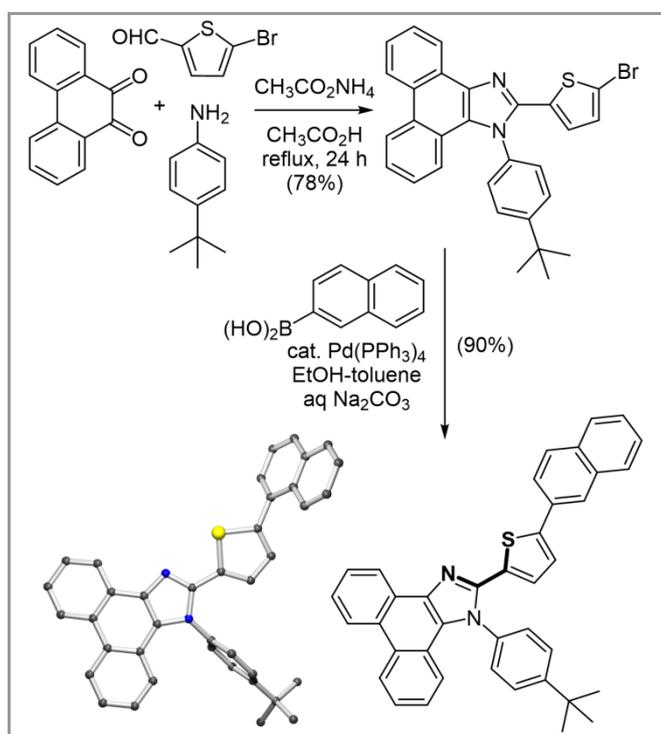
**Scheme 18** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 3-(2-thienyl)-4-azafluorenone (HUXYAB,  $d_{\text{S-N}} = 2.936 \text{ \AA}$ ,  $\phi_{\text{SCNN}} = 2.69^\circ$ ) by a multicomponent reaction.

During the zirconocene-mediated multicomponent synthesis of azaindoles, Xi and co-workers synthesized derivatives containing the 2-(2-thienyl)pyridine skeleton.<sup>30</sup> The synthesis involving a silicon-tethered diyne, the Negishi reagent ( $\text{Cp}_2\text{ZrBu}_2$ ), *i*PrCN (2 molecules) and 2-cyanothiophene proceeds as shown in Scheme 19 (HUJTEM).



**Scheme 19** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 6-(2-thienyl)-5-azaindole (HUJTEM,  $d_{\text{N-S}} = 2.818 \text{ \AA}$ ,  $\phi_{\text{NCCS}} = 14.45^\circ$ ) by a multicomponent reaction (Cp = cyclopentadienyl).

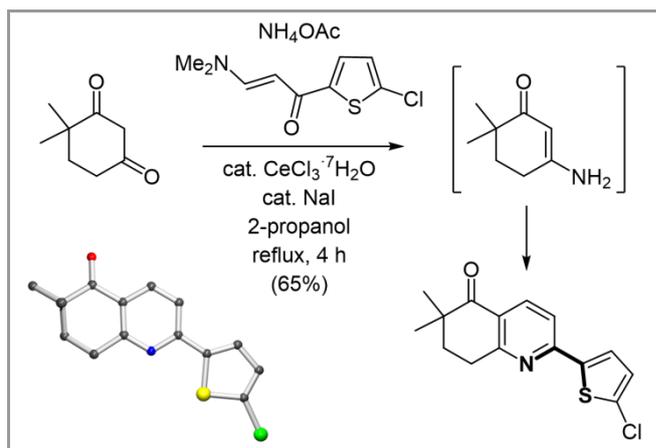
In the course of developing light-emitting materials, Tong, Lee and co-workers synthesized thiophene-substituted phenanthroimidazoles.<sup>31</sup> The key step to access the target shown in Scheme 20 (AQQQON) is a multicomponent reaction involving 9,10-phenanthrenequinone, 5-bromothiophene-2-carbaldehyde, 4-(*tert*-butyl)benzamine and ammonium acetate; the naphthyl group is next introduced by Suzuki-type cross-coupling. In the single crystal structure, the (electron-donating) thiophene and (electron-accepting) imidazole rings adopt an almost coplanar configuration, at the origin of a more extended conjugation system. In addition, the imidazole basic nitrogen and thiophene sulfur lie *syn* to each other, reducing intramolecular motion. As a consequence, higher fluorescent quantum yield are favored. Such a phenomenon is also present in 2,5-di(2-imidazolyl)thiophene<sup>32</sup> and 2,5-di(2-benzimidazolyl)thiophene.<sup>33</sup>



**Scheme 20** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a thiophene-substituted phenanthroimidazole (AQQQON,  $d_{N-S} = 2.933 \text{ \AA}$ ,  $\phi_{NCS} = 5.53^\circ$ ) by a multicomponent reaction.

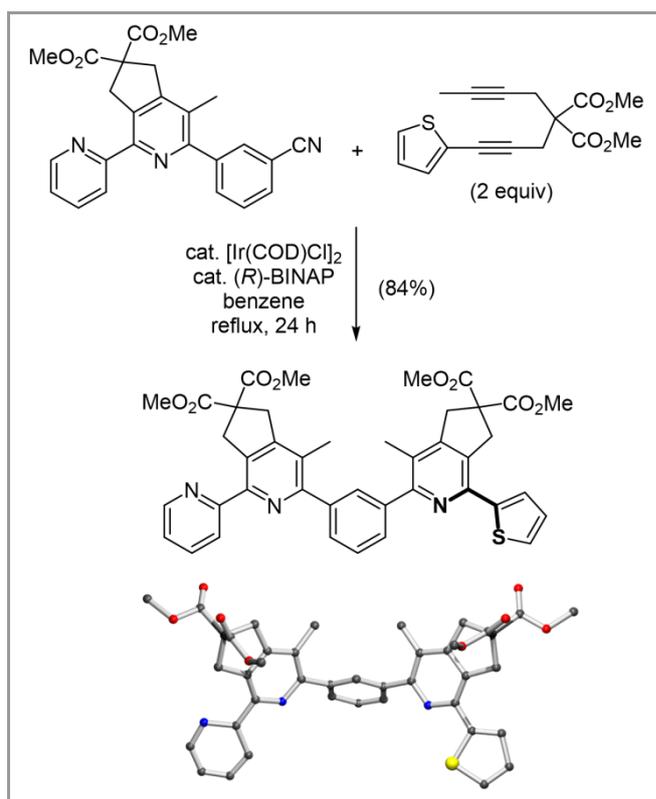
## 6 Heterobiaryl formation by azine building

Variants of the Bohlmann-Rahtz reaction were reported in 2011 by Kantevari and co-workers.<sup>34</sup> In the presence of catalytic  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  and NaI, 2-aryl dihydroquinolinones such as the 2-(2-thienyl)-6,6-dimethyl-7,8-dihydro-5(6*H*)-quinolinone shown in Scheme 21 (PICYIL) were synthesized by building the pyridine ring.



**Scheme 21** Crystal structure (hydrogen atoms are omitted for clarity) and pyridine building (PICYIL,  $d_{N-S} = 2.886 \text{ \AA}$ ,  $\phi_{NCS} = 4.04^\circ$ ) using a Bohlmann-Rahtz variant.

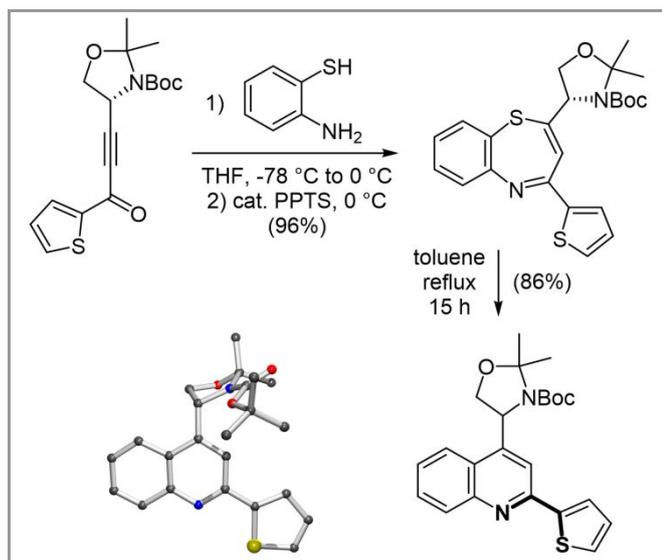
Takeuchi and co-workers also described in 2012 pyridine building, but by iridium-catalyzed cycloaddition of  $\alpha,\omega$ -diynes with nitriles.<sup>35</sup> Notably, the 2-(2-thienyl)pyridine skeleton was formed by this way in the compound shown in Scheme 22 (MEHYAB); the crystal structure features a short N...S distance ( $\sim 2.9 \text{ \AA}$ ) together with pyridine and thiophene rings close to being coplanar ( $\sim 26^\circ$ ).



**Scheme 22** Crystal structure (hydrogen atoms are omitted for clarity) and pyridine building (MEHYAB,  $d_{N-S} = 2.942 \text{ \AA}$ ,  $\phi_{NCS} = 26.15^\circ$ ) by iridium-catalyzed cycloaddition.

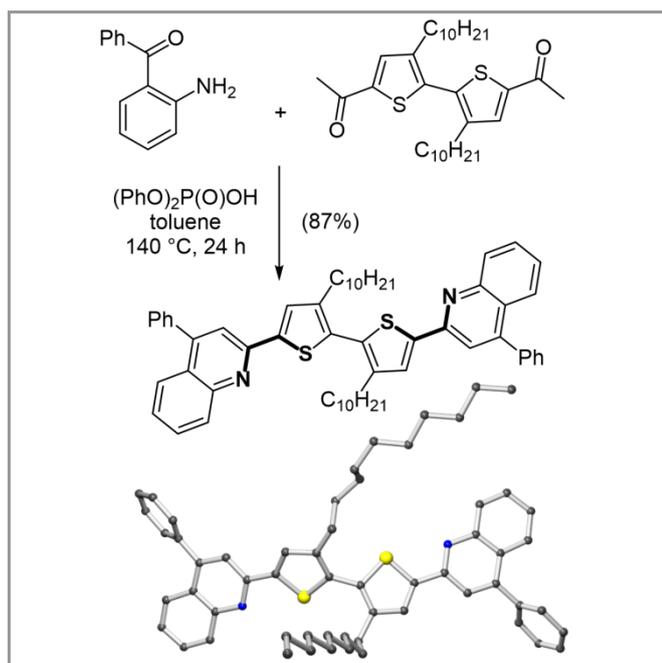
Villalgorido and co-workers documented in 2001 the stereoselective synthesis of quinolyl glycines.<sup>36</sup> Benzo[*b*][1,4]thiazepines, formed by cyclocondensation between 2-aminothiophenol and chiral acetylenic ketones bearing a latent  $\alpha$ -amino acid, undergo sulfur extrusion to yield

the corresponding 2,4-disubstituted quinolines (e.g. QUSZEJ, Scheme 23).



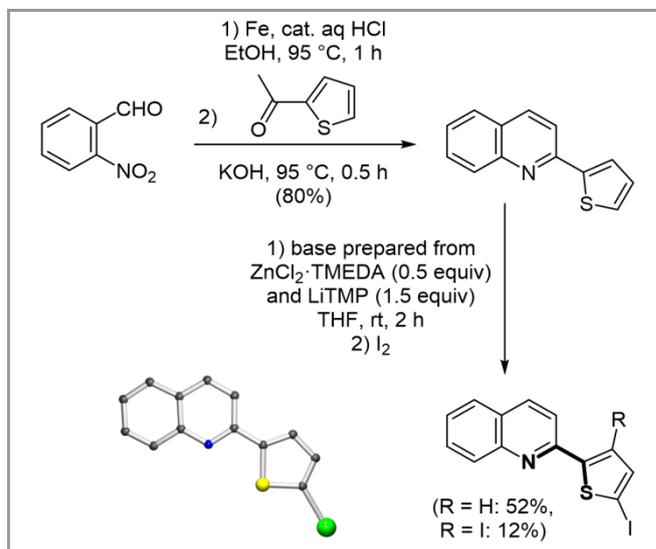
**Scheme 23** Crystal structure (hydrogen atoms are omitted for clarity) and quinoline building (QUSZEJ,  $d_{N-S} = 2.944 \text{ \AA}$ ,  $\phi_{NCCS} = 2.37^\circ$ ) using cyclocondensation followed by sulfur extrusion (PPTS = pyridinium *p*-toluenesulfonate).

In the search of new electron transport materials for organic light-emitting diodes, Jenekhe and co-workers synthesized the tetracyclic compound shown in Scheme 24 (ETILIC) by using the Friedländer condensation reaction from 2-aminobenzophenone and the required 2,2'-bithiophene.<sup>37</sup> The crystal structure shows torsion angles between the thiophene and quinoline moieties below  $18^\circ$ , in relation with the electronic interaction between the unpaired nitrogen electrons and sulfur that lie in the molecular plane.



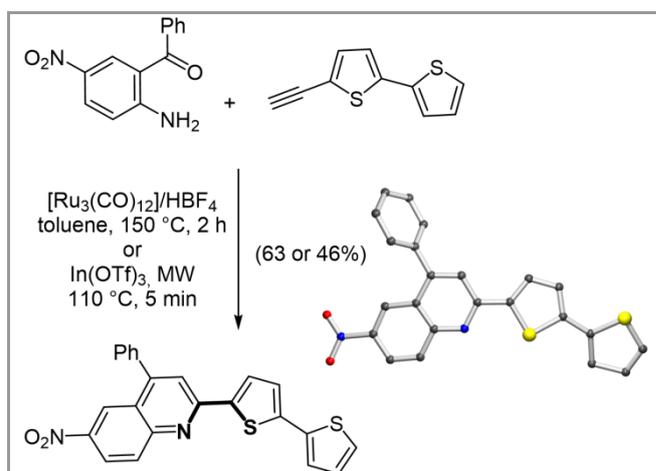
**Scheme 24** Crystal structure (hydrogen atoms are omitted for clarity) and Friedländer synthesis of a (2-thienyl)quinolone (ETILIC,  $d_{N-S} = 2.938$  and  $2.907 \text{ \AA}$ ,  $\phi_{NCCS} = 17.67$  and  $0.07^\circ$ ).

Simplified Friedländer access to 2-substituted quinolines from 2-nitrobenzaldehyde<sup>38</sup> was recently applied to the synthesis of 2-(2-thienyl)quinoline. The latter was functionalized by deprotometalation-iodolysis using a mixed TMP-based lithium-zinc base (Scheme 25);<sup>39</sup> the resulting iodides display coplanarity of the quinoline and thiophene rings, with the N and S atoms lying *syn* to each other.



**Scheme 25** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of 2-(2-thienyl)quinoline and its deprotometalation-iodolysis (DIXHAV,  $d_{N-S} = 2.944 \text{ \AA}$ ,  $\phi_{NCCS} = 0.27^\circ$ ).

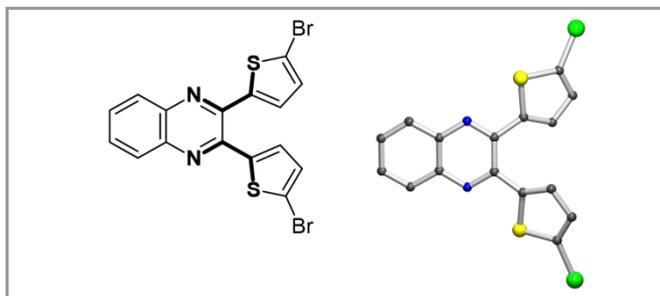
In the search of derivatives for use as efficient and stable organic light-emitting diodes, Slodek and co-workers prepared quinolines derivatives containing the 2,2'-bithiophene motif (the latter being used as electron donor in donor-acceptor systems for intramolecular charge transfer).<sup>40</sup> The 2-(5-(2-thienyl)-2-thienyl)quinoline shown in Scheme 26 (UDIXEM) could be synthesized in one pot reactions from 2-acylaniline and 5-ethynyl-2,2'-bithiophene either under ruthenium catalysis or in the presence of indium triflate under microwave irradiation.



**Scheme 26** Crystal structure (hydrogen atoms are omitted for clarity) and catalyzed syntheses of a 2-(5-(2-thienyl)-2-thienyl)quinoline (UDIXEM,  $d_{N-S} = 2.931 \text{ \AA}$ ,  $\phi_{NCCS} = 3.53^\circ$ ).

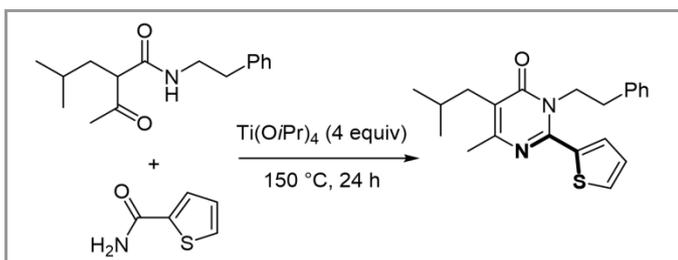
Pyrazine/quinoxaline<sup>41</sup> and pyridazine/phthalazine<sup>42</sup> formation through double condensation has largely been described, and

the presence of a 2-thienyl substituent next to the diazine nitrogen similarly leads to N...S interaction. Because quinoxaline is more electron-deficient than quinoline, its lone pairs are less prone to establishing interaction with C-S  $\sigma^*$  orbitals. When two 2-thienyl groups are present at quinoxaline C2 and C3, coplanarity is hampered but the *s-cis* arrangement adopted by N-C-C-S is kept, as shown in Figure 1 (ETIXAG).<sup>43</sup>



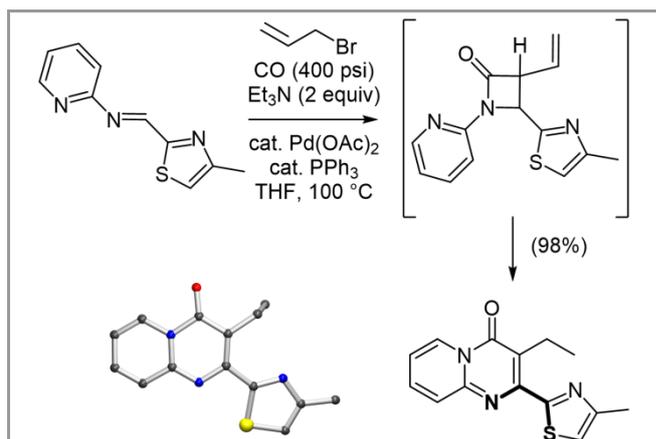
**Figure 1** Crystal structure (hydrogen atoms are omitted for clarity) of a 2,3-di(2-thienyl)quinoxaline (ETIXAG,  $d_{N-S} = 2.864$  and  $2.878$  Å,  $\phi_{NCS} = 20.51$  and  $20.78^\circ$ ).

Ramanjulu and co-workers reported in 2010 a  $Ti(OiPr)_4$ -mediated double condensation for the preparation of tetrasubstituted 4-pyrimidinones from a ketoamide and a primary amide.<sup>44</sup> The relative position of the thiophene ring vs the pyrimidine one is as expected (KOHPOO, Scheme 27).



**Scheme 27** Synthesis of pyrimidone-thiophene (KOHPOO) by diazine building.

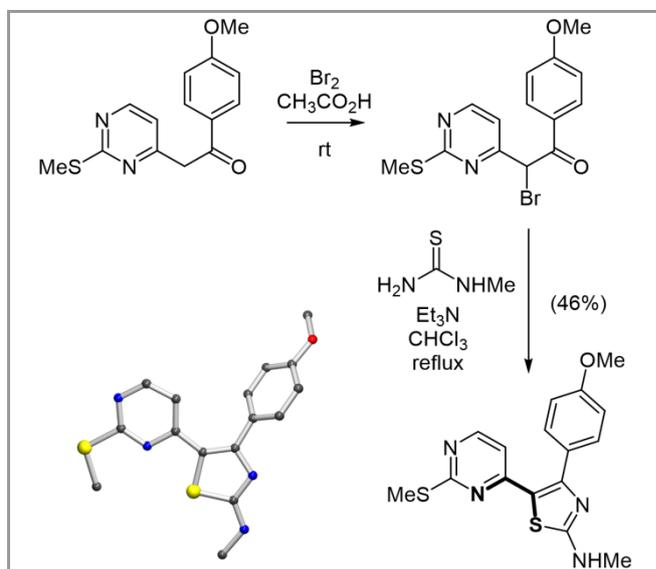
In an attempt to generate  $\beta$ -lactams by palladium-catalyzed [2+2] carbonylative cycloaddition of imines with allyl bromide under CO pressure in the presence of  $Et_3N$ , Troisi and co-workers rather obtained 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, as exemplified in Scheme 28 (QIBNIZ), through a rearrangement (possible two-fold isomerization affording a 2-azetionone, next converted to a ketene and finally to a pyrimidone).<sup>45</sup>



**Scheme 28** Crystal structure (hydrogen atoms are omitted for clarity) and 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (QIBNIZ,  $d_{N-S} = 2.788$  Å,  $\phi_{NCS} = 3.38^\circ$ ) synthesis.

## 7 Heterobiaryl formation by sulfur-containing heterocycle building

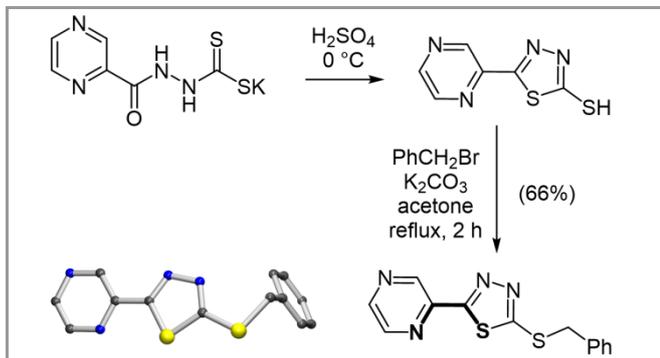
In the course of the synthesis of protein kinase inhibitors, Stanetty and co-workers prepared the pyrimidine-thiazole target shown in Scheme 29 (EHOYUV01). The precursor, obtained by deprotonation of 4-methyl-2-(methylthio)pyrimidine and followed by trapping with Weinreb *N*,4-dimethoxy-*N*-methylbenzamide, was brominated before formation of the thiazole ring using *N*-methylthiourea.<sup>46</sup> The methylthio and methylamino substituents do not hamper the expected conformation for the pyrimidine-thiazole part.



**Scheme 29** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a pyrimidine-thiazole (EHOYUV01,  $d_{N-S} = 2.752$  Å,  $\phi_{NCS} = 6.05^\circ$ ) by thiazole building.

A synthesis of biaryls based on pyrazine and thiaziazole was reported in 2012 by Zhu and co-workers.<sup>47</sup> From pyrazinecarboxylic acid, the corresponding carbohydrazide was obtained by esterification and subsequent reaction with hydrazine monohydrate. Treatment with carbon disulfide in the presence of KOH, and then with concentrated sulfuric acid allowed the thiaziazole ring to be formed. X-ray diffraction data were recorded from the benzylated derivative shown in Scheme

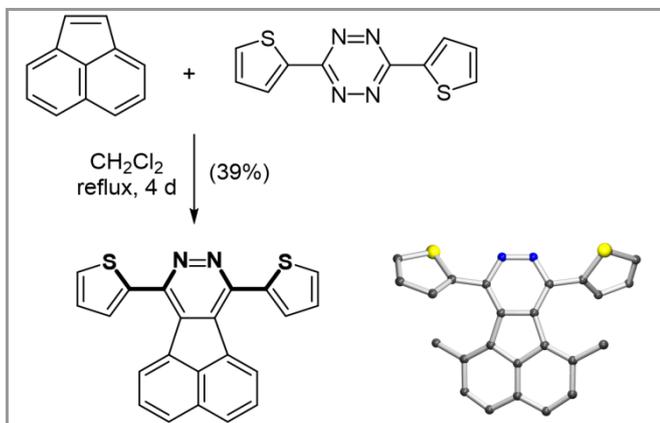
30 (SEWDIJ). As for pyrazine-thiophene bisheterocycle, both rings are close to coplanar, with the N-C-C-S fragment adopting a *s-cis* arrangement.



**Scheme 30** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a pyrazine-thiadiazole (SEWDIJ,  $d_{N-S} = 2.957 \text{ \AA}$ ,  $\phi_{NCCS} = 5.21^\circ$ ) by thiadiazole building.

## 8 Cycloaddition reactions

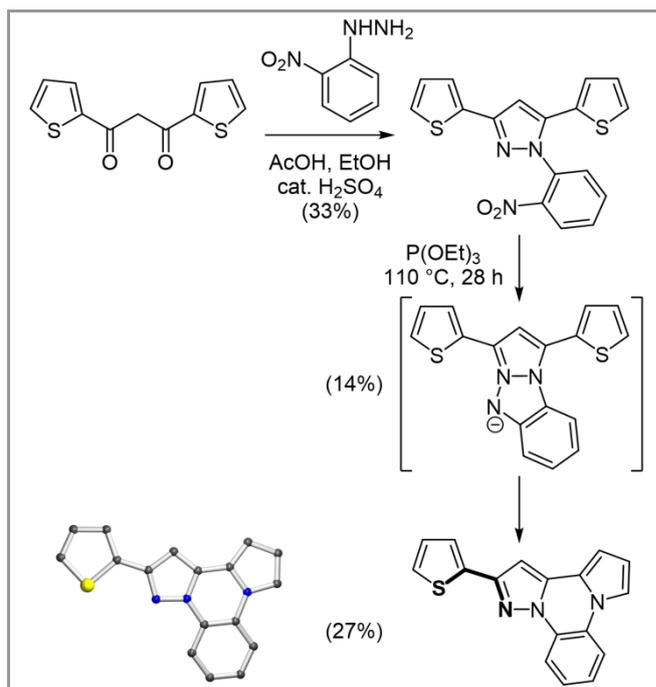
Siegel and co-workers published in 2009 the synthesis of 7,10-disubstituted 8,9-diazafluoranthenes by inverse electron demand [2+4] cycloaddition using 3,6-disubstituted 1,2,4,5-tetrazines.<sup>48</sup> Among the products synthesized, the 7,10-di(2-thienyl) derivative depicted in Scheme 31 (FUBNOG) displays the typical N-C-C-S arrangement, even if coplanarity between rings is not present due to steric hindrance. If 2-thienyls are replaced by 2-thiazolyls, the energy minima also corresponds to a N-C-C-S *cis* arrangement.<sup>49</sup>



**Scheme 31** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a 3,6-di(2-thienyl)pyridazine (FUBNOG,  $d_{S-N} = 3.080 \text{ \AA}$ ,  $\phi_{SCCN} = 45.24^\circ$ ) by cycloaddition.

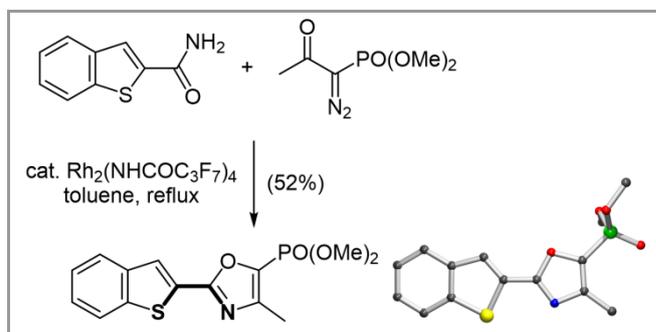
## 9 Other syntheses

In the course of the synthesis of 1,3-di(2-thienyl)pyrazolo[1,2-*a*]benzotriazole, Harrington and Stanforth observed the unexpected formation of 2-(2-thienyl)pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]quinoxaline, a planar molecule, through extrusion of sulfur (SAWYEW, Scheme 32). They rationalized its formation by suggesting a nitrene intermediate formed in the presence of triethylphosphite.<sup>50</sup>



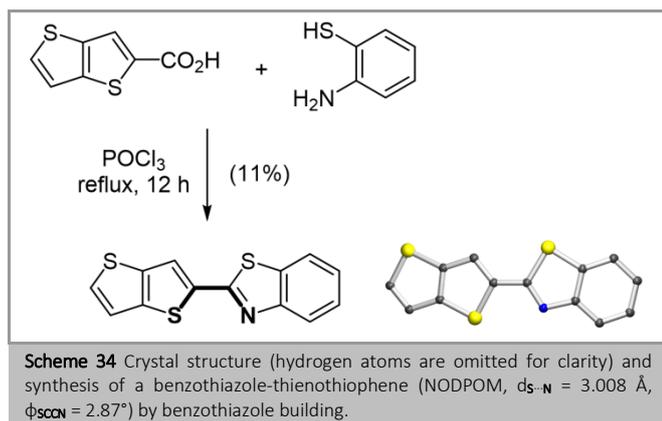
**Scheme 32** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a pyrazole-thiophene (SAWYEW,  $d_{S-N} = 3.083 \text{ \AA}$ ,  $\phi_{SCCN} = 1.20^\circ$ ) by pyrazole building.

Moody and co-workers reported in 2009 a way to form oxazole ring under rhodium catalysis starting from  $\alpha$ -diazo- $\beta$ -ketophosphonates and arenecarboxamides.<sup>51</sup> Using benzothiofene-2-carboxamide led to the oxazole shown in Scheme 33 (SURPAX) in the presence of dirhodium tetrakis(heptafluorobutyramide) as the result of carbene N-H insertion and cyclodehydration.

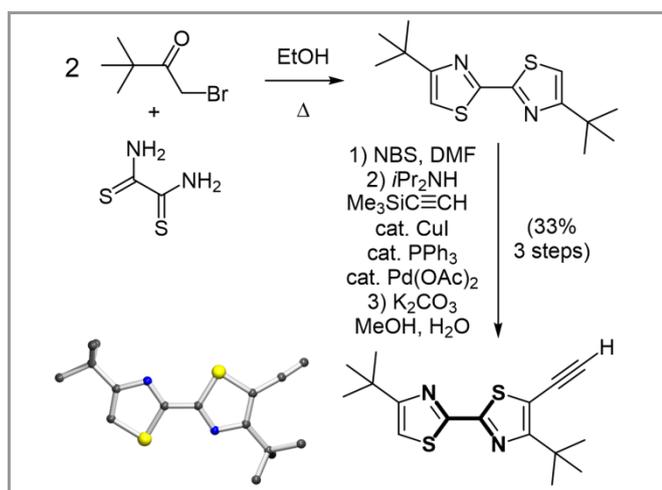


**Scheme 33** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of an oxazole-benzothiofene (SURPAX,  $d_{S-N} = 3.026 \text{ \AA}$ ,  $\phi_{SCCN} = 3.81^\circ$ ) by oxazole building.

In order to reach dipolar compounds alternating electron-rich and electron-deficient units, Lin, Chao and co-workers built the benzothiazole moiety from thieno[3,2-*b*]thiophene-2-carboxylic acid.<sup>52</sup> To this purpose, condensation with 2-aminothiophenol was performed in the presence of  $\text{POCl}_3$  (NODPOM, Scheme 34). The compound is nearly coplanar, with  $\sim 3^\circ$  between the thieno[3,2-*b*]thiophene and benzothiazole rings.

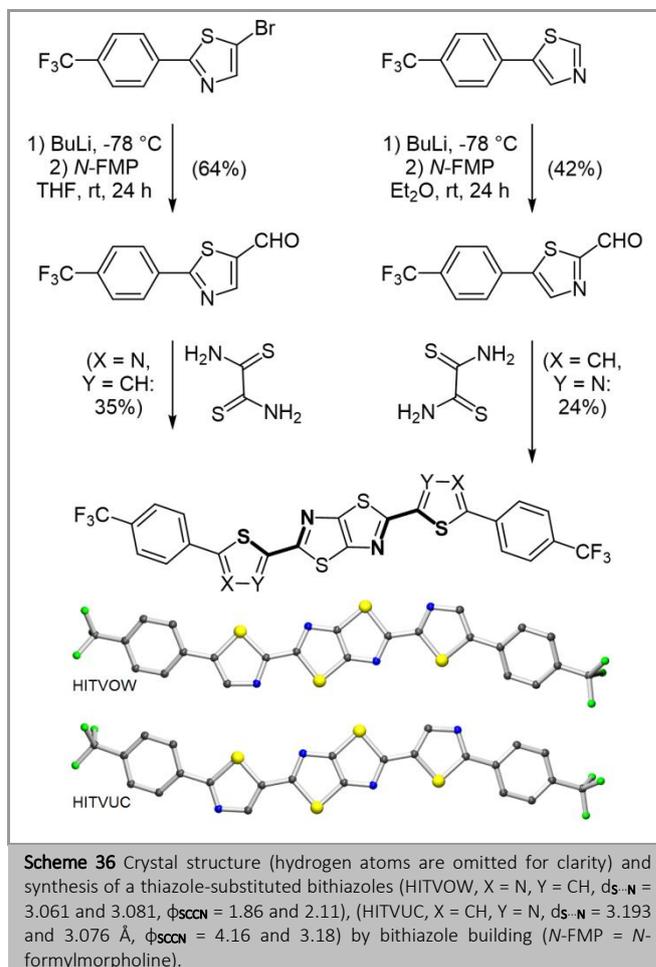


Symmetrical bithiazoles can be synthesized. For example, the 4,4'-di(*tert*-butyl)-2,2'-thiazole shown in Scheme 35 (LEGQUK) can be prepared by reacting 1-bromopinacolone with dithioamide.<sup>53</sup> The crystal structure obtained after monobromination and palladium-catalyzed coupling with trimethylsilylacetylene displays nearly coplanar rings.<sup>54</sup> This arrangement results from dual N to S contacts, as well as dipole-dipole interactions. Because these two N...S contacts are built on the same heterobiaryl junction, the nitrogen and sulfur atoms are relatively distant from one another (~3.1 Å), e.g. when compared with NODPOM (~3.0 Å, Scheme 34).

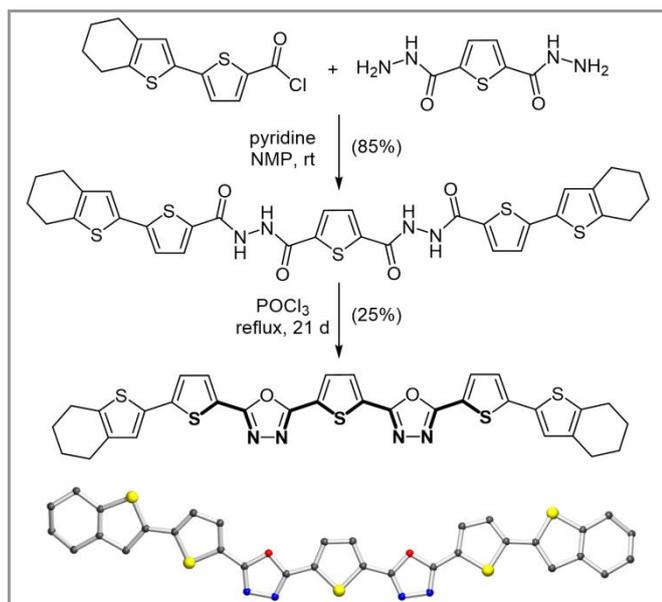


In the search for novel semiconductors, Yamashita and co-workers synthesized the  $\pi$ -conjugated thiazole-substituted bithiazoles shown in Scheme 36 (HITVOW and HITVUC).<sup>55</sup> The left precursor, prepared by Negishi coupling between 4-(trifluoromethyl)phenylzinc chloride and 2-bromothiazole followed by bromination, was debromolithiated and the lithio derivative converted to the aldehyde by subsequent electrophilic trapping. The right precursor, obtained from 2-(trimethylsilyl)thiazole by deprotolithiation next to sulfur, transmetalation to zinc and Negishi coupling with 1-bromo-4-(trifluoromethyl)benzene, was deprotolithiated and the lithio derivative similarly formylated. Both aldehydes were reacted with dithioamide to furnish the targets. The FET (field-effect transistor) characteristics depend on the nitrogen positions: the more planar (HITVUC, Scheme 36, left) derivative with a 2-(4-

trifluoromethylphenyl)thiazole unit affords a higher performance (more efficient  $\pi$ - $\pi$  overlap) than the more twisted (HITVOW, Scheme 36, right) derivative which contains a 4-(4-trifluoromethylphenyl)thiazole.



In order to study their structure-property relationships, Bäuerle and co-workers synthesized mixed oligoheterocycles such as the one shown in Scheme 37 (HOYMEN) by oxadiazole building.<sup>56</sup> To this purpose, acylation of the dihydrazide of thiophene-2,5-dicarboxylic acid was carried out with the required bithienyl acid chloride. Dehydration and cyclization were next performed in boiling phosphoryl chloride. The crystal structure displays practically planar molecules, with the inner three heterocyclic rings exhibiting all-*anti* conformation (65% of the molecules).



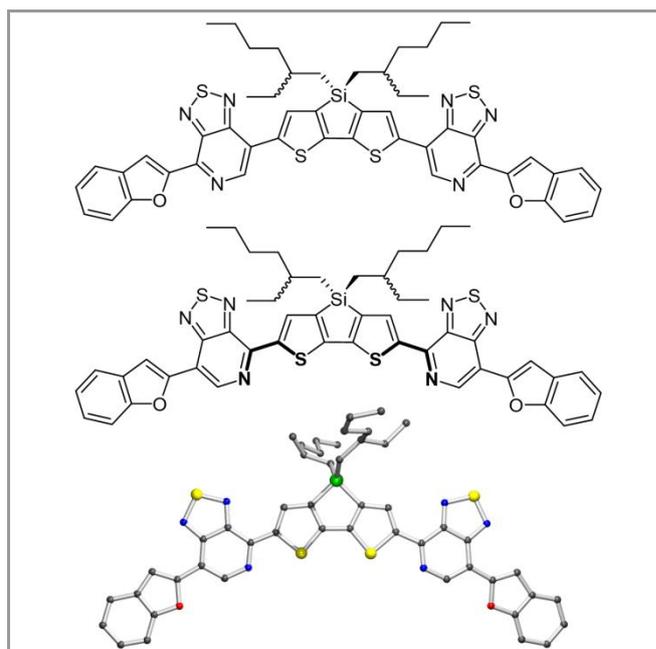
**Scheme 37** Crystal structure (hydrogen atoms are omitted for clarity) and synthesis of a mixed oligoheterocycle (HOYMEN,  $d_{S-N} = 3.115, 3.149, 3.224$  and  $3.231$  Å,  $\phi_{SCCN} = 2.49, 4.54, 2.13$  and  $6.88^\circ$ ) by oxadiazole building (NMP = *N*-methylpyrrolidone).

## 10 Conclusion

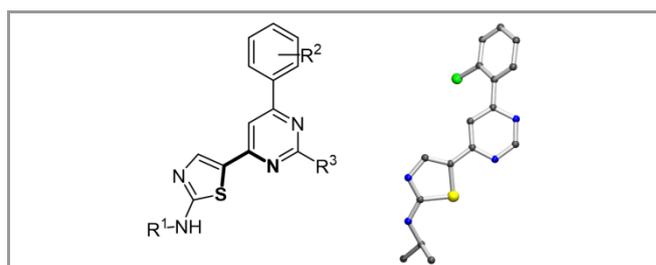
Even if in some examples heterobiaryls containing appropriate N-C-C-S do not exhibit a 1,4 N $\cdots$ S interaction, either because of preferred interactions or for steric reasons,<sup>57</sup> it is a rather general feature. However, if many X-ray diffraction structural data are in accordance with 1,4 N $\cdots$ S inter-ring interaction, few comments are present in the corresponding publications. Thus, the potential of 1,4 N $\cdots$ S inter-ring interaction in the stabilization of specific conformation appears as undervalued.

For example, the two molecules depicted in Figure 2, relevant to the field of organic electronics, and that only differ in the position of two nitrogen atoms, do not display similar molecular shape.<sup>58</sup> Indeed, when the pyridine nitrogen atoms can interact with the thiophene sulfur atoms (CEWWUY, bottom), the bending of the molecular framework into a banana shape is accentuated. Altering molecular shape can impact intermolecular packing and, by this way, change bulk (e.g. crystallographic and optical) properties.

Besides applications at the interface with physics, the impact on a preferred molecular conformation on biological properties has been developed and recently reviewed.<sup>1b</sup> For example, in the course of the design, synthesis and structure-activity relationships of 2-amino-5-thiazolypyrimidines as p38 $\alpha$  MAP kinase inhibitors, Wroblewski and co-workers evidenced the role of N $\cdots$ S intramolecular nonbonding interaction on the stabilization of the conformation required for binding to the p38 $\alpha$  active site (XAJJID, Figure 3).<sup>59</sup>



**Figure 2** Crystal structure (hydrogen atoms are omitted for clarity) (CEWWUY,  $d_{N-S} = 2.891$  and  $2.885$  Å,  $\phi_{NCCS} = 0.74$  and  $0.70^\circ$ ) and impact of the 1,4 N $\cdots$ S inter-ring interaction on the molecular shape.



**Figure 3** Crystal structure (hydrogen atoms are omitted for clarity) (XAJJID, R = *i*Pr,  $d_{S-N} = 2.943$  Å,  $\phi_{SCNN} = 10.58^\circ$ ) and 1,4 N $\cdots$ S inter-ring interaction proposed in the binding mode of 2-amino-5-thiazolypyrimidines with p38 $\alpha$ .

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## Biosketches

	<p>David Tilly graduated as an engineer from ENSC Rennes in 2001 and completed a PhD in Organic Chemistry at University of Le Mans (France) in 2004 working under the supervision of Prof. J. Mortier on directed aromatic C-H lithiations. He was a postdoctoral fellow at University of Queensland Australia for one and a half years with Assoc. Prof. C. Williams working on multistep syntheses of complex natural products until 2006, then with Prof. V. Gevorgyan at University of Illinois Chicago USA for a year working on Palladium catalysed C-H bond functionalisation until 2007. David then joined the ESKITIS Institute for Drug Discovery Australia (Principal Investigator Assoc. Prof. M. Coster) for 3 years to develop anticancer drugs based on natural product scaffolds before returning to Europe in 2011. There, he joined the group of Prof. F. Mongin at University of Rennes 1 (France) for a year to develop mixed lithium-metal bases for applications in synthesis, then the group of Prof. D. Deniaud at University of Nantes (France) for a year in 2012 to develop radioimmunoconjugates of Astatin-211. He was a term Assistant Professor for 2 years at University of Rennes 1 (France) until 2015.</p>
	<p>Floris Chevallier is an Associate Professor at the University of Rennes 1 (Rennes, France). He studied (organic) chemistry at the universities of Orléans and Nantes. He received his Ph.D. in 2004 under the supervision of Prof. Jean-Paul Quintard, where he worked on organotin chemistry. In 2005, he joined the group of Prof. Bernhard Breit at the Albert-Ludwigs-Universität Freiburg (Freiburg, Germany) as a postdoctoral researcher, where he focused on supramolecular catalysis. His current research interests include organometallic methodologies and molecular self-assemblies.</p>
	<p>Florence Mongin obtained her Ph.D. in Chemistry in 1994 from the University of Rouen (France) under the supervision of Prof. Guy Queguiner. After a two-year stay at the Institute of Organic Chemistry of Lausanne (Switzerland) as a postdoctoral fellow with Prof. Manfred Schlosser, she returned to the University of Rouen as an Assistant Professor in 1997 (HDR in 2003). She took up her present position in 2005 as Professor at the University of Rennes (France) and was appointed Junior Member of the Institut Universitaire de France in 2009. Her present scientific interests include the functionalization of aromatic compounds including heterocycles with recourse to mixed lithium-metal bases.</p>