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Gram-scale nucleophilic aromatic substitution of 4,7-dibromo-5,6-difluoro-[2,1,3]-benzothiadiazole for Synthesis of 4,7-dibromo-5,6-BINOL-O-benzo[2,1,3]thiadiazole, and 4,7-dibromo-5,6-dicarbazol-N-ylbenzo[2,1,3]thiadiazole. The Stille coupling reaction and continuous Heck coupling reaction for synthesis of 4,7-bispara-chlorophenyl-5,6-dicarbazol-N-ylbenzo[2,1,3]thiadiazole

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ABSTRACT

In this study, we delveloped a simple and efficient synthetic procedure for the nucleophilic substitution of 4,7-dibromo-5,6-diflourobenzo[2,1,3]thiadiazole with diols, diamines and carbazole to obtain 4,7-dibromo-5,6-dinucleophile-benzo[2,1,3]diadiazole derivatives. The chiral version of BINOL and BINAM, based on (R-/S-) atropisomers of binaphthyl, were employed as nucleophilic reagents under bases (DBU 1,8-diazabicyclo[5.4.0]undec-7-ene and/or K2CO3). The nucleophillic carbazol-N-yl sodium species were synthesized via recrystallized and subsequent treatment in dried DMF and in the presence of strong base as NaH. All three nucleophiles participated successfully in the SnAr reaction, affording excellent yields with BINAM and quantitative yields with carbazole and BINOL.

Introduction

Benzothiadiazole (BTD) is a well-established electron-withdrawing unit featuring versatile modification sites and strong electron affinity, a stable π-conjugated framework, and tunable photophysical properties, making it a valuable building block in applications ranging from phototheranostics and bioimaging to organic photovoltaics (OPVs), field-effect transistors (OFETs), and organic light-emitting diodes (OLEDs)[1-5]. Recently, there has been growing interest in employing BTD derivatives to design advanced fluorophores capable of circularly polarized luminescence (CPL) - a phenomenon critical for emerging technologies such as chiral displays, optical data storage, asymmetric catalysis, and chiral bioimaging (Fig. 1) [6-7]. However, achieving efficient and scalable syntheses of CPL-active materials remains a significant challenge[8]. The structural of these BTD derivatives offer a promising basis for developing organic materials for non-invasive NIR optical sensing technologies.

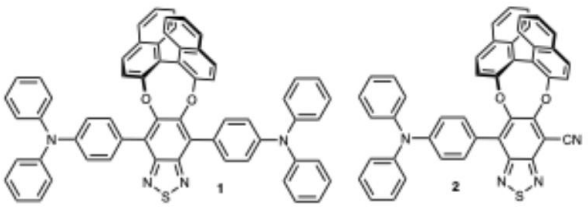

Figure 1: Examples of benzothiadiazole-based CPL-active materials, 1- Kong *et al.* [6], 2- Zhu *et al.* [7]

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To address this, nucleophilic aromatic substitution reactions (SNAr) provide a powerful strategy for precise functionalization of the BTD scaffold. This method enables site-specific modifications that can fine-tune the material's electronic and optical characteristics. Particularly, the use of chiral auxiliaries such as BINOL, BINAM and SPINOL for chirality transfer offers a straightforward route to impart chirality onto otherwise achiral BTD cores, thereby enhancing their chiroptical activity and simplifying synthetic procedures. As a recent example, Kong and co-workers reported an efficient synthesis of a chiral hybridized local and charge-transfer (HLCT) emitter based on a benzothiadizole scaffold though a straightforward two-step strategy combining Suzuki–Miyaura coupling and nucleophilic aromatic substitution to introduce chirality through a chiral perturbation strategy (Fig. 2) [6]. The simplicity, scalability, and use of inexpensive feedstocks highlighted the synthetic practicality of this method.

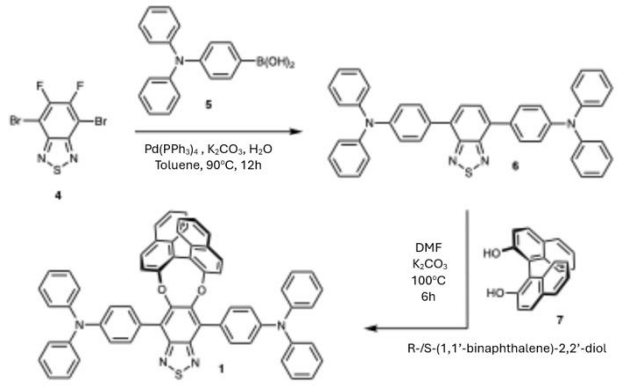

Figure 2. Synthetic procedure of benzothiadiazole-based CPL-active material BBT2TPA by Kong *et al.*

In organic field-effect transistors (OFETs), the benzothiadiazole (BT) unit plays a pivotal role by stabilizing electron transport, tuning energy levels, and promoting ambipolar behavior, thereby enabling high-performance organic semiconductors. Beyond charge transport, BT's strong electron-accepting nature, pronounced optical responsiveness, and donor–acceptor tunability make it especially attractive for multifunctional devices. Its compatibility with thin-film fabrication techniques such as spin-coating further enhances its suitability for scalable sensor technologies. Importantly, these properties position BT-based OFETs as not only valuable in conventional applications such as photodetectors, logic circuits, and memory devices, but also as promising platforms for glucose sensing.

H. Shi *et al.* (2019) reported the successful synthesis of a BT derivative bearing two rigid carbazole units (14), which exhibits efficient red phosphorescence with enhanced triplet stability and suppressed nonradiative decay. Considering the biomedical relevance of red phosphorescence, we further functionalized compound (14) through a one-step Heck cross-coupling reaction. The presence of two bromine atoms in compound (14) provides accessible sites for modification, allowing fine-tuning of absorption, emission, and solubility. These tunable features are particularly significant for the design of next-generation non-invasive blood glucose monitoring devices, where precise optical and electronic control is essential for sensitivity, selectivity, and integration into wearable formats.

In this work, we report a robust, gram-scale synthetic protocols based on SNAr reaction, utilizing 4,7-dibromo-5,6-difluorobenzo [c][1,2,5]thiadiazole as the key precursor. By this approach, we successfully synthesized a series of novel chiral BTD derivatives, including 4,7-dibromo-5,6-BINOL-[2,1,3]-benzothiadiazole, 4,7-dibromo-5,6-SPINOL-[2,1,3]-benzothiadiazole, and 4,7-dibromo-5,6-BINAM-[2,1,3]-benzothiadiazole. Furthermore, an electron-rich carbazole group was introduced using a similar strategy, with optimized base conditions that significantly enhanced the reaction yield compared to previous reports [9].

Experimental

Chemicals and reagents

All chemicals and reagents were used as received from commerical sources without purification unless noted otherwise. 1H and 13C NMR were obtained from a Bruker Advance III-600 MHz (Switzerland). Chemical shifts (Scheme 1) are expressed in parts per million (ppm) relative to tetramethylsilane (TMS).

Synthesis Procedure

Compound 8 (R-/S-):

An 48 mL heavy-walled pressure vessel equipped with a Teflon-coated magnetic stir bar is charged with 4,7-dibromo-5,6-difluorobenzo[c][1,2,5]thia-diazole (5.0 g, 15.15 mmol, 1 equiv.), potassium carbonate (5.23 g, 37.88 mmol, 2.5 equiv.), and enantiopure R-BINOL (7) (4.34 g, 15.15 mmol, 1 equiv.). DMF (50 mL) were then added to the vessel, and the mixture was stirred at 80ºC overnight. After the reaction completion, the mixture was cooled to room temperature and filtered with silica gel to obtain 8, respectively as pale yellow solid (8.2 g, 89%).

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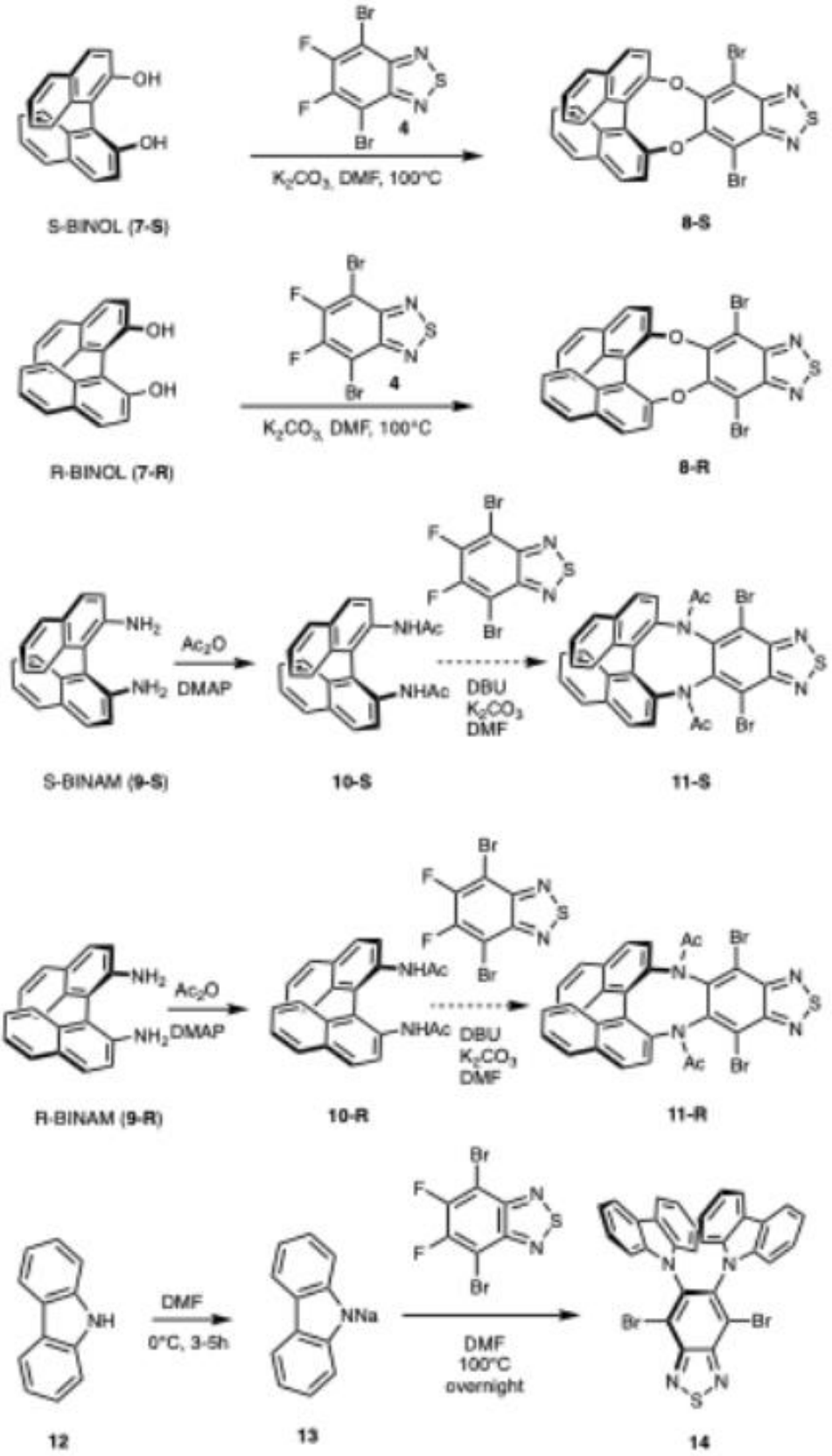
1H-NMR (500 MHz, CDCl3) δ 7.94 (d, J = 8.9 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.8 Hz, 4H), 7.47-7.44 (m, 2H), 7.37-7.34 (m, 2H).



Scheme 1: Nucleophilic armatic substitution in the benzo[2,1,3]thiadiazole core. Note: All the chiral derivatives (both enantiomers) were synthesized using the same procedure albeit with enantiopure (R-/S-) starting material.

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Compound 10 (R-/S-):

A mixture of enaniopure R-BINAM (11) (50 mmol) and dimethoxyaminopyridine (DMAP, 50 mmol) in THF (10 mL) was stirred for 10 min at room temperature. Acetic anhydride (50 mmol) was added dropwise and the resulting mixture was stirred for a further 8 h at room temperature. Water (25 mL) was added and the resulting precipitate was thoroughly washed with ethanol followed by water to remove unreacted acetic anhydride and acetic acid. The desired product was dried at 50 °C under vacuum to yield 12, respectively as a white solid.

1H-NMR (500 MHz, $CDCl_3$) δ 8,32 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7,0 Hz, 2H), 7,26 (t, J = 7,8 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.97 (s, 2H), 1.84 (br s, 6H).

Compound 14:

Dry N,N-dimethylformamide (DMF, 10 mL) was added to a 25 mL pressure tube containing 9H-carbazole (504 mg, 3.02 mmol) and sodium hydride (60% dispersion, 132 mg, 3.01 mmol) under argon. The mixture was stirred at room temperature for 4.5 hours. Subsequently, a solution of 4,7-dibromo-5,6-difluorobenzo[c][2,1,3]thiadiazole (494.91 mg, 1.5 mmol) in dry DMF (8 mL) was slowly introduced, and the reaction was heated at 110 °C for 12 hours, leading to the formation of an orange precipitate. The solid product was isolated by vacuum filtration and washed three times with dichloromethane, affording orange lamellar crystals 14 (886.42 mg, 94% yield).

1H-NMR (500 MHz, CDCl3) δ 7.67 (dd, J = 6 Hz, 2Hz, 4H), 7.02-6.99 (m, 8H), 6.90 (dd, J = 6 Hz, 2Hz, 4H).

13C-NMR signals were not obtained due to poor solubility

Compound 16:

A pressure tube with magnetic stir bar was charged with 15 (1 equiv.), Pd(OAc)2 (0.1 equiv.), 1-bromo-4-chlorobenzene (4 equiv.), and potassium carbonate (48.4 mg, 350 µmol, 5 equiv.). Next, 3 mL of anhydrous DMF was added to the pressure tube, and the mixture was stirred at 100ºC for 24h under argon. After the reaction was complete, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layer was dried over sodium sulfate and then concentrated in vacuo. The residue was purified by column chromatography to afford 16 as an orange solid (37.8 mg, 73.0 % yield).

1H NMR (500MHz, CDCl3) δ 8.58 (d, J = 16.3 Hz, 2H), 7.72 (d, J=7.7 Hz, 4H), 7.13 (d, J=8.4 Hz, 4H), 7.05-6.93 (m, 16H), 6.77 (d, J = 16.3 Hz, 2H).

13C NMR (125 MHz, CDCl3). δ 153.47, 140.33, 137.56, 135.88, 134.99, 134.24, 128.83, 128.76, 128.17, 124.99, 123.26, 121.70, 120.03, 119.64, 110.81.

Results and discussion

Synthesis of 4,7-dibromo-5,6-BINOL-[2,1,3]-benzothiadiazole and 4,7-dibromo-5,6-SPINOL- [2,1,3]-benzothiadiazole

The nucleophilic aromatic substitution (SNAr) of 4,7-dibromo-5,6-difluorobenzo[c][1,2,5]thiadiazole with BINOL was first demonstrated in 2024 by Zhu *et al.* employing Cs_2CO_3 as the base [7]. In our study, we successfully performed the same transformation using K_2CO_3 under otherwise similar conditions, with no observable decrease in yield. This result not only underscores the high reactivity of the benzothiadiazole scaffold but also offers a more practical and cost-effective alternative to cesium carbonate.

Synthesis of 4,7-dibromo-5,6-BINAM- [2,1,3]-benzothiadiazole

We initially tried the direct coupling of BINAM with 4,7-dibromo-5,6-difluorobenzo-[c]-[1,2,5]thiadiazole (4) under S_NAr conditions analogous to those used for BINOL derivatives. However, these reactions resulted in the formation of complex mixtures with numerous by-products and incomplete conversion of the starting materials. This lower reactivity can be attributed to the weaker acidity and lower nucleophilicity of the amino groups in BINAM compared to the hydroxyl groups in BINOL. To overcome this issue, we pursued a strategy involving pre-protection of the amine groups. As summarized in Table 1, several approaches were explored.

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Table 1: Optimization of (R-/S-)-BINAM-protection reaction

Entry	Protecting reagents	Catalyst	Base	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	BnOH	$Pd(dppb)Cl_2$	$NaHCO_3$	neat	24	110°C	Trace
2	BnOH	$Pd(OAc)_2$	KOH	dioxane	24	130°C	Trace
3	BnOH	$Pd(OAc)_2$	KOH	dioxane	48	150°C	15
4	BnBr	-	-	DMF	1	100°C	Trace
5	BnBr	KI	K_2CO_3	DMF	1	100°C	Trace
6	BnBr	-	K_2CO_3	MeCN	24	r.t.	Trace
7	BnBr	KI	Et_3N	DMF	1	100°C	25
8	BnOH	Pyridine	tBuOK	toluene	24	120°C	Trace
9	BnOH	-	NaOH	neat	6	220°C	Trace
10	**Ac_2O**	**DMAP**		**DCM**	**3**	**reflux**	**80**

Palladium-catalyzed N-alkylation [10,11] using benzyl alcohol (Entries 1-3) results in only trace amounts of the desired product, even under elevated temperatures. Hydrogen-borrowing N-alkylation strategies [12] with benzyl alcohol using pyridine-mediated condition (entry 8) also failed to deliver significant product formation. To our surprise, a simple N-acetylation using acetic anhydride and DMAP as catalyst in dichloromethane (entry 10) provided a clean and efficient conversion, affording N,N′-diacetylated product 10 in 80% isolated yield.

Synthesis of 4,7-dibromo-5,6-dicarbazolyl- [2,1,3]-benzothiadiazole

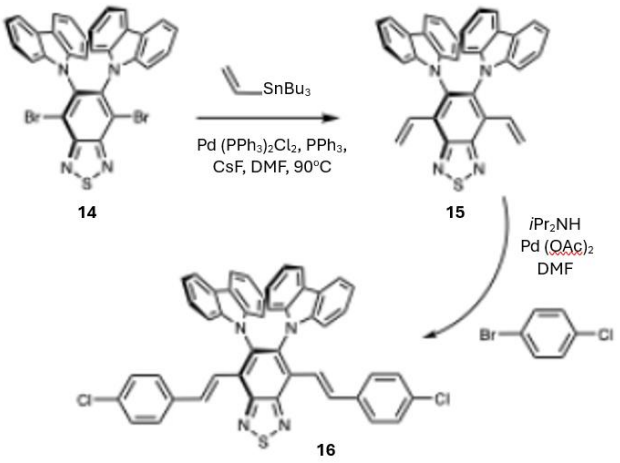
The synthesis of 4,7-dibromo-5,6-dicarbazolyl-[2,1,3]-benzothiadiazole (14) was previously reported by Shi et al. [9] in 2019, employing KOH as a base in dry DMF at 115ºC. Under this condition, the reaction proceeded with a low yield isolated yield of 17.6%, which limited the practicality and scalability of the method for further applications. To overcome this limitation, we revisited the reaction conditions and replaced KOH with sodium hydride (NaH) as the base. NaH, a significantly stronger base, effectively and rapidly deprotonates the N–H bond of carbazole to generate the corresponding carbazolide anion. In our optimized conditions (table 2), using NaH in dry DMF under argon atmosphere at 100°C, the reaction proceeded smoothly and afforded the desired dicarbazolyl-benzothiadiazole 14 in 94% isolated yield. Similarly with previous report, the product precipitated directly from the reaction mixture, enabling isolation by simple filtration. This dramatic improvement in both yield and operational simplicity highlights the critical role of base selection in S_NAr reaction, particularly when weakly acidic N–H nucleophiles such as carbazole are involved.

Table 2: Optimization condition for SnAr reaction of 5,6-difluoro-4,7-dibromobenzo[2,1,3]thiadiazole.

Entry	Base	Temperature (°C)	Yield (%)
1	K_2CO_3[a]	130°C	Trace
2	tBuOK[a]	110°C	15
3	NaH[a]	110°C	51
4	NaH[b]	**110°C**	**94**

[a]Using unrecrystallized Carbazole. [b]Using recrystallized Carbazole.

Moreover, carbazole used for a long time provided less efficient yields than that obtained through recrystallization with ethanol. It should be mentioned that the degradation of carbazole resulted in a lower yield [13]. Surveys such as that conducted by Shotbolt-Brown et al. (1996) showed that carbazole may be degraded by microbial activity. Therefore, carbazole substrate needs to be purified after a period of time.



Scheme 2: Organic transformation of compound 14

Compound 14 was transformated to 4,7-divinylcarbazol-*N*-ylbenzo[2,1,3]thiadiazole (15) via

Stille coupling reaction with 80% yield. Contiuously, the Heck coupling reaction between compound 15 and 1-bromo-4-chlorobenzene to yield compound 16 was worked well with 73% yield. The expasions of many other bromide arenes and photophysical properties are ongoing to do in our laboratory.

Conclusion

The substitution of nucleophiles to aromactic rings was successfull and able to upscale to gram. The reaction of nucleophillic diols (R-/S-BINOL) and 4,7-dibromo-5,6-diflourobenzo[2,1,3]thiadiazole are quantitative yield of 8 (R-/S-) and the purification are just evaporation of DMF, then recrysalization in toluene. The protection of BINAM in the presense of catalyst DMAP and anhydride acetic acid is successful and possible to gram scale synthesis. The reaction of nucleophilic carbazol-N-yl sodium with 4,7-dibromo-5,6-diflourobenzo[2,1,3]thiadiazole are successfull controlled after recrystalization of carbazole and in dried DMF to give 14 with 94% yield. Compound 14 is ready for further organic transformation in order to tune the emission for many potential applications. Functionalized benzothiadiazole derivatives have been synthesized as potential candidates for the development of NIR-active organic materials. Their further organic transformation for integration into optical and electronic layer in OEFT could enhance their value in emerging non-invasive blood-glucose sensing technologies based on near-infrared detection.

Acknowledgments

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