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Pentiptycene Building Blocks Derived from Nucleophilic Aromatic Substitution of Pentiptycene Triflates and Halides

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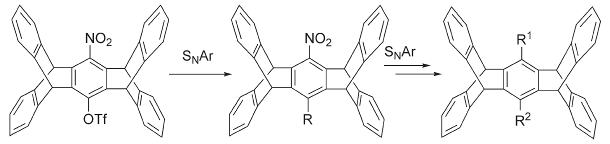


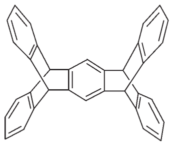
15

18: R = Br
19: R = I

R^1 = Br, I, NH$_2$, NO$_2$
R^2 = Br, I, CN, NH$_2$, SAr

The nucleophilic aromatic substitution (S$_N$Ar) reactions of the nitro-substituted pentiptycene triflate **15** with LiBr and LiI and the resulting halides **18** and **19** with N$_3^-$, CN$^-$, and ArS$^-$ in DMF provide an efficient route toward pentiptycene halides and dihalides and other new pentiptycene building blocks. The reactivity of diaminopentiptycene in Pd-catalyzed C−N coupling reactions is also demonstrated.

The rigid, aromatic, and H-shaped pentiptycene scaffold (**1**)[1] has found many potential applications in molecular and supramolecular chemistry, including fluorescent chemosensors,[2] molecular machines,[3] molecular hosts,[4] supramolecular catalysts,[5] crystal and thin-film engineering,[6,7] and light-emitting π-conjugated oligomers and polymers.[8] The majority of these applications are associated with derivatization of the central phenylene ring. Thus, facile synthesis of the central-ring prefunctionalized pentiptycene building blocks is crucial toward the development of new pentiptycene-derived materials.



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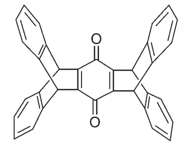

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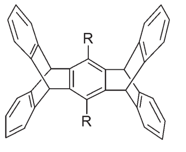
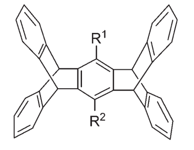


3 R = OH
4 R = CCH
5 R = Br
6 R = I



7 R^1 = OH, R^2 = NH$_2$
8 R^1 = OH, R^2 = NO$_2$
9 R^1 = OH, R^2 = Cl
10 R^1 = OH, R^2 = Br
11 R^1 = OH, R^2 = I
12 R^1 = NH$_2$, R^2 = Br
13 R^1 = NH$_2$, R^2 = I
14 R^1 = Br, R^2 = I

We have shown that the readily prepared pentiptycene quinone **2**[9,10] is an excellent precursor for a variety of central-ring functionalized pentiptycenes, including the symmetrically disubstituted pentiptycene hydroquinone **3**,[7] diacetylene **4**,[9] dibromide **5**, and diiodide **6**,[11] and a series of unsymmetrically disubstituted pentiptycenes such as compounds **7**−**14**.[11,12] While most of the functional-group transformations gave an excellent yield (> 85%) of the desired products, the synthesis of pentiptycene dihalides **5**, **6**, and **14** from pentiptycene triflate **15** has encountered some problems (Scheme 1).[11] For example, the triflate (**15**) to halide (**12** and **13**) transformation was not accomplished in one step but through two individual ones: (i) reduction (detriflate reaction, **15** → **16**) and (ii) oxidation (halogenation, **17** → **12**/**13**) of the central phenylene ring. In addition, the nitro group in **15** must be reduced before carrying out the oxidation step. More importantly, the reduction step has suffered from a small reaction scale (≤0.35 mmol) and low product yield (≤45%). We report herein an alternative route that circumvents these drawbacks and limitations through direct nucleophilic aromatic substitution (S$_N$Ar) of **15** with bromide and iodide ions. This reaction provides not only a solution toward a large-scale synthesis of the pentiptycene dihalides **5**, **6**, and **14** but also an easy access to new pentiptycene building blocks with nitro, amino, and cyano substituents.

The S$_N$Ar reaction of **15** with LiBr and LiI in DMF afforded the halopentiptycenes **18** and **19**, respectively, in

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(1) (a) Hart, H.; Shamouilian, S.; Takehira, Y. *J. Org. Chem.* **1981**, *46*, 4427–4432. (b) Hart, H.; Bashir-Hashemi, A.; Luo, J.; Meador, M. A. *Tetrahedron* **1986**, 1641–1654. (c) Yang, J.-S.; Yan, J.-L. *Chem. Commun.* **2008**, 1501–1512.

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(10) (a) Wiehe, A.; Senge, M. O.; Kurreck, H. *Liebigs Ann./Recl.* **1997**, 1951–1963. (b) Zhu, X.-Z.; Chen, C.-F. *J. Org. Chem.* **2005**, *70*, 917–924.

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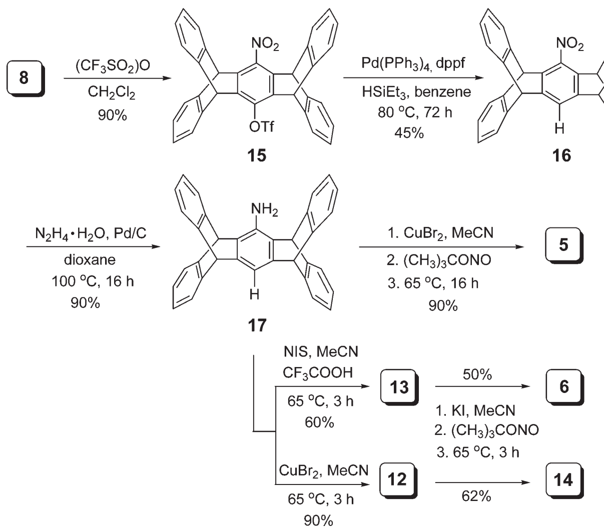
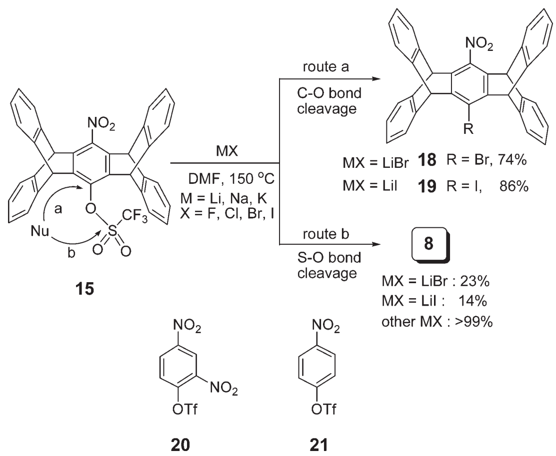
SCHEME 1



SCHEME 2



good yields (the C−O bond cleavage of route a in Scheme 2). The only observed side product is compound **8**, which results from the S−O bond cleavage (route b in Scheme 2). The effect of nucleophiles on the C−O vs S−O bond cleavage of activated aryl triflates (e.g., **20** and **21**) has been well documented.[13−18] The C−O bond cleavage (the S$_N$Ar product) is more favored with nucleophiles of higher polarizability, and the reverse is true for the S−O bond cleavage. This has been attributed to the lower positive charge density on the C (soft) relative to the S (hard) center for nucleophilic attack.[13,14] Potential soft nucleophiles toward S$_N$Ar reactions are amines (e.g., piperidine and morpholine),[15,16] iodide,[17] thiolate,[13] and malonate[18] ions. Although our observation of a higher yield of **19** (Nu = I$^-$) relative to **18** (Nu = Br$^-$) is consistent with this scenario, the S$_N$Ar efficiency of **15** is highly dependent on the reaction conditions. A replacement of the lithium salts LiBr and LiI with the other halogen salts, including NaBr, NaI, KBr, KI, and MCl, and MF (M = Li, Na, and K), or with other potential nucleophiles such as N_3^-, CN$^-$, PhO$^-$, PhS$^-$, piperidine, and morpholine all leads to the S−O bond cleaved product **8** in nearly quantitative yields without any detectable S$_N$Ar products. In the cases of secondary amines and NaN$_3$, the S−O bond cleavage reaction is particularly efficient and proceeds to completion within 5 h at room temperature. In addition, no reaction occurred between **15** and LiBr or LiI when DMF was replaced by other solvents such as THF, acetonitrile, or ethyl acetate under the reflux temperatures. Evidently, the S$_N$Ar reactivity of **15** is significantly lower than **21**, attributable to the steric and electronic perturbations of the iptycene substituents,[19] and its S$_N$Ar reaction in forming **18** and **19** is mainly driven by the novel S$_N$Ar reagents LiBr/DMF and LiI/DMF. To the best of our knowledge, the novel S$_N$Ar reactivity of LiBr or LiI in DMF has not been recognized in the literature.[20−22] We postulated that the observed S$_N$Ar reactivity of **15** is associated with cation−π interactions between Li$^+$ and the pentiptycene phenylene rings. More specifically, the S$_N$Ar reactions require a cooperated effect between an effective cation for activating the phenylene carbon through cation−π interactions and a soft anion for nucleophilic attack on the C rather than the S center. Among the tested halogen salts, Li$^+$ possesses a much larger binding energy with a benzene molecule than Na$^+$ and K$^+$.[23] Among the tested solvents, DMF is superior in dissolving lithium salts into free cations and anions instead of solvated ion pairs or aggregates.[24] A higher reaction temperature in DMF than in THF and acetonitrile might also contribute to the observed S$_N$Ar reactions.

In addition to aryl triflates, activated aryl halides are good candidates for S$_N$Ar reactions.[16,25,26] Indeed, without the

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[14] (a) Zhu, J.; Bigot, A.; Tran Huu Dau, M. E. *Tetrahedron Lett.* **1997**, *38*, 1181–1182. (b) Neuville, L.; Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 7638–7642.

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[19] The homoconjugative interactions of groups through the bicycle-[2.2.2]octane framework has previously been discussed and termed as "hyperconjugative" interactions. See: Kim, Y.; Zhu, Z.; Swager, T. M. *J. Am. Chem. Soc.* **2004**, *126*, 452–453.

[20] The product and yield of a Heck-type reaction between 4-nitrophenyl triflate (**21**) and (*E*)-1,2-bis(trimethylsilyl)ethylene (TMSE) in the presence of LiI in DMF at 110 °C were found to be the same as those between 1-iodo-4-nitrobenzene (INB) and TMSE under the same reaction condition. The same reaction also worked for iodobenzene, but it did not work for phenyl triflate in the presence of LiI. The authors have proposed a four-membered intermediate for the reaction of **21**. See: Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773–1776. Alternatively, INB could be formed in situ through the S$_N$Ar reaction in the case of the activated triflate **21** but not for the nonactivated phenyl triflate. Our preliminary test on the relative reactivity of LiI vs NaI on the S$_N$Ar reaction of **21** showed that a high yield of the product INB was observed with LiI (95%) within 12 h but it requires 24 h to reach a yield of 79% with NaI.

[21] It is known that lithium salts but not sodium and potassium salts facilitate the oxidative addition of vinyl and aryl triflates to the palladium(0) catalyst in Stille coupling ractions. See: Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

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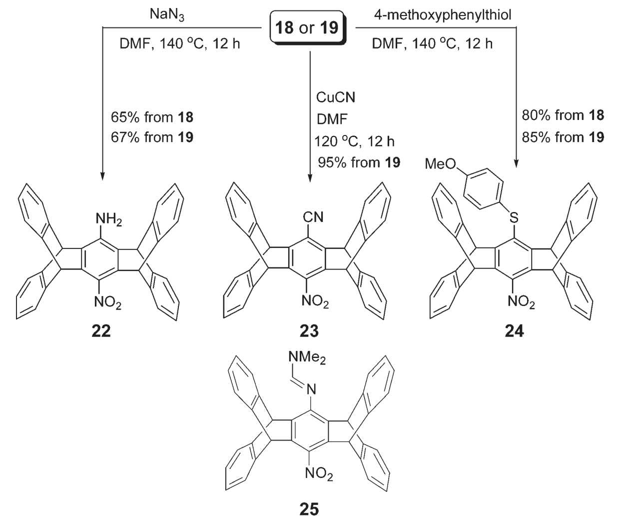
SCHEME 3



complication of the S−O bond cleavage as seen in pentiptycene triflate **15**, the pentiptycene halides **18** and **19** reacted with NaN_3, CuCN, and 4-methoxyphenylthiol to form pentiptycenes **22**, **23**, and **24**, respectively (Scheme 3). The mechanistic aspects of these reactions deserve further comments. In the case of NaN_3, the initially formed azide-substituted product could further react with DMF to form the imine intermediate **25** and then hydrolyzed to form **22** during the aqueous workup according to the literature.[25] For the cyanation of aryl halides (the Rosenmund−von Braun reaction), several different mechanisms, including an S_NAr-like one, have been proposed.[27,28] The crucial role of Cu(I) in the cyanation of **19** is borne out by a failure of the reaction with NaCN but a success with NaCN in the presence of a catalytic amount of CuI.[29] The reaction mechanism between aryl halides and alkyl- or arylthiolate ions could be versatile as well.[25] In addition to the S_NAr mechanism, the radical−chain mechanism $S_{RN}1$ could take place. Nevertheless, there was no evidence of an $S_{RN}1$ mechanism in the reactions of **18** or **19** → **24,** as neither **8** nor **16** was detected[11,12] in the products.

To further convert **18** and **19** to the desired pentiptycene dihalides **5**, **6**, and **14**, the nitro group in **18** and **19** needed to be selectively reduced to form **12** and **13**, respectively, so that the subsequent deaminative halogenation can be conducted. Indeed, this can be achieved with indium metal in the presence of ammonium chloride (Scheme 4).[30] Other reducing agents such as $SnCl_2$/THF, Sn/NH_4Cl, Zn/HCl, and H_2/Pd/C gave a mixture of both the desired products **12** and **13** and the unwanted dehalogenated product **17**, which is hardly separated.

Reduction of the nitro group in **22** and **23** leads to new aminopentiptycenes **26** and **27**, respectively (Scheme 4). This can be conducted simply with $SnCl_2$ to reach an excellent yield. The new compound diaminopentiptycene **26** is particularly interesting, because it was the first proposed precursor[31] for the syntheis of pentiptycene dihalides. The deaminative bromination and iodination of **26** indeed proceed smoothly with *tert*-butyl nitrite and halide salts $CuBr_2$ and KI. The optimum reaction yields toward pentiptycene dihalides from different starting materials **12**, **13**, and **26** are reported in Table 1.

SCHEME 4

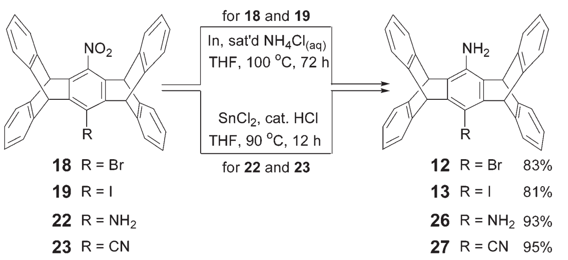
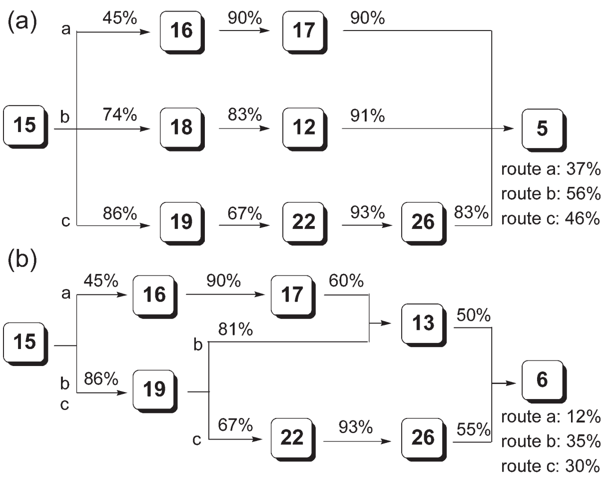


TABLE 1. Optimum Yields of the Pentiptycene Dihalides 5, 6, and 14 from Deaminative Halogenation of Precursors 12, 13, and 26

entry	reactant	halide salt[a]	temp[b] (°C)	product	yield[c] (%)
1	**12**	$CuBr_2$	65	**5**	91
2[d]	**12**	KI	65	**14**	62
3[d]	**13**	KI	65	**6**	50
4	**13**	$CuBr_2$	65	**14**	60
5	**26**	$CuBr_2$	25	**5**	83
6	**26**	KI	25	**6**	55

[a] Solvent is MeCN, another reagent is *tert*-butyl nitrite. [b] Reaction time is 16 h. [c] Isolated yield. [d] From ref 11.

SCHEME 5



Scheme 5 summarizes the possible routes toward pentiptyence dibromide **5** and diiodide **6** from **15**. The S_NAr reaction routes (routes b and c) provide higher yields (46−56% vs 37% for **5** and 30−35% vs 12% for **6**) than the previous method (route a).[11] More importantly, the reaction scale in routes b and c are larger by more than 10-fold than that in route a.

The reactivity of **26** in Pd-catalyzed Buchwald−Hartwig C−N coupling reactions[32] has also been investigated. As shown

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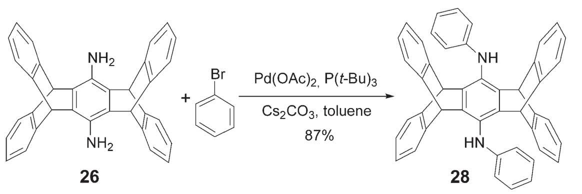
SCHEME 6



in Scheme 6, the reaction with bromobenzene afforded the expected product **28** in a good yield (87%).

In conclusion, the unique S_NAr reactivity of LiBr/DMF and LiI/DMF uncovered in this work expedites the synthesis of the central-ring dihalogenated pentiptycenes as well as other new pentiptycene building blocks. These results should facilitate the progress of pentiptycene-based functional materials.

Experimental Section

The key reactions of this work, which are the S_NAr reaction of **15** to form **18** and **19**, the S_NAr reaction of **18** and **19** to form **22**, and the nitro group reduction of **18** and **19** to form **12** and **13**, are described in the following text. The procedures and characterization data for the other reactions are supplied as Supporting Information.

The S_NAr Reaction of 15. To a stirred solution of **15** (2.01 g, 3.2 mmol) was added LiBr (0.83 g, 9.6 mmol) or LiI (1.29 g, 9.6 mmol) in anhydrous DMF (5.0 mL). It was heated for 24 h at 150 °C and then cooled to room temperature. Water was added to the solution and the resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford crude product. Further purification was carried out with silica gel column chromatography, using CH_2Cl_2/hexane as an eluent. Compound **18**: yield 74%, white solid, mp > 300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (s, 2H), 6.03 (s, 2H), 7.05−7.07 (m, 8H), 7.43−7.45 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.0, 53.7, 119.6, 123.8, 123.9, 125.5, 125.6, 137.0, 142.8, 143.2, 144.2; IR (KBr): 1525, 1351 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{20}BrNO_2$ 553.0677, found 553.0679. Compound **19**: yield 86%, white solid, mp > 300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (s, 2H), 5.96 (s, 2H), 7.03−7.07 (m, 8H), 7.41−7.46 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.1, 59.0, 98.5, 123.6, 123.9, 125.5, 125.6, 135.9, 142.8, 143.4, 147.8; IR (KBr) 1524, 1357 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{20}INO_2$ 601.0539, found 601.0541.

Procedure for the S_NAr Reaction of 18 and 19. This is illustrated with the reaction between **19** and azide. To a stirred solution of **19** (1.02 g, 1.7 mmol) was added sodium azide (0.32 g, 4.99 mmol) in dry DMF (5.0 mL). It was heated for 12 h at 140 °C, and then cooled to room temperature. Water was added to the solution and the resulting precipitate was collected by filtration, washed with water, and dried under vacuum to afford crude product. Purification was carried out with silica gel column chromatography, using CH_2Cl_2/hexane as an eluent to afford compound **22**: yield 67%, yellow solid, mp > 300 ° C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (br, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.99−7.04 (m, 8H), 7.34−7.44 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.9, 49.7, 123.2, 124.3, 125.5, 125.6, 129.8, 136.9, 138.3, 138.8, 144.0, 144.3; IR (KBr) 3487, 3402, 1526, 1350 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{34}H_{22}N_2O_2$ 490.1681, found 490.1683.

General Procedure for Reduction of the Nitro Group in 18 and 19. This is illustrated with the case of compound **19**. To a stirred solution of **19** (0.51 g, 0.85 mmol) was added indium powder (0.28 g, 2.5 mmol) and saturated ammonium chloride (2.0 mL) solution in THF (10.0 mL). It was then refluxed for 72 h at 100 °C, cooled to room temperature, and concentrated under reduce pressure. The reaction mixture was diluted with water, extracted with CH_2Cl_2, and dried under vacuum to afford crude product. Purification was carried out with silica gel column chromatography, using CH_2Cl_2/hexane as an eluent. Characterization data for the resulting products **12** and **13** have been reported.[11]

Acknowledgment. We thank the National Science Council of Taiwan (NSC-98-2119-M-002-002-MY3) and Academia Sinica for financial support.

Supporting Information Available: Experimental procedures and characterization data for **23**, **24**, and **26**−**28** and ^1H and ^{13}C NMR spectra of **18**, **19**, **22**−**24**, and **26**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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