Aromatic Substitution

International Edition: DOI: 10.1002/anie.201503671
German Edition: DOI: 10.1002/ange.201503671

Transition-Metal-Free Synthesis of Carbazoles and Indoles by an S_NAr-Based "Aromatic Metamorphosis" of Thiaarenes[**]

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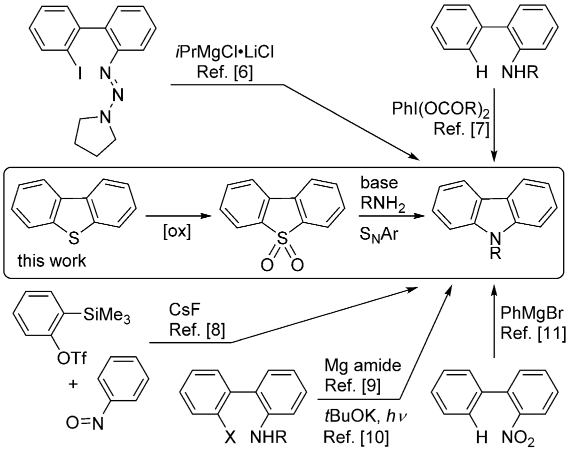
Abstract: *Dibenzothiophene dioxides, which are readily prepared through oxidation of the parent dibenzothiophenes, undergo nucleophilic aromatic substitution with anilines intermolecularly and then intramolecularly to yield the corresponding carbazoles in a single operation. The "aromatic metamorphosis" of dibenzothiophenes into carbazoles does not require any heavy metals. This strategy is also applicable to the synthesis of indoles. Since electron-deficient thiaarene dioxides exhibit interesting reactivity, which is not observed for that the corresponding electron-rich azaarenes, a combination of a thiaarene-dioxide-specific reaction with the S_NAr-based aromatic metamorphosis allows transition-metal-free construction of difficult-to-prepare carbazoles.*

Carbazoles represent an important class of heteroaromatic compounds, many of which find a wide range of applications as biologically active agents in medicinal chemistry[1] and as hole-transport and light-emitting materials in organic electronics.[2] For the last two decades, transition-metal catalysis has been used for constructing a carbazole skeleton by catalytic C–N bond formation, and includes Buchwald–Hartwig or Ullmann-type amination of halobiaryls,[3] oxidative C–H amination of aminobiaryls,[4] or nitrene insertion from azidobiphenyls.[5] Despite the high efficiency and reasonably wide scope, residual transition-metal impurities could adversely affect the biological properties or device performance of the final products.

Transition-metal-free synthesis of carbazoles has therefore undergone a renaissance for the last few years (Scheme 1). Liu and Knochel disclosed that halogen–magnesium exchange of 2-iodo-2′-triazenobiaryls resulted in formation of carbazoles.[6] The groups of Chang and Antonchick reported intramolecular oxidative C–H amination of aminobiaryls with hypervalent iodine reagents.[7] Studer and co-workers invented an interesting approach, that is, reactions of arynes with nitrosoarenes,[8] but the yields were moderate and the regioselectivity was not as well controlled as is typically observed in aryne chemistry. Tokuyama and co-workers developed a base-mediated cyclization of 2-amino-2′-bromobiphenyls via arynes.[9] From similar precursors, photoinduced cyclization occurs by a radical process to yield carbazoles.[10] Kürti and co-workers disclosed facile reductive cyclization of 2-nitrobiaryls by means of PhMgBr.[11] Regardless of these elegant protocols, there still remains ample room to develop novel strategies to prepare carbazoles without recourse to transition-metal catalysts.



Scheme 1. Recent strategies for transition-metal-free synthesis of carbazoles.

Recently, our group has been interested in developing "aromatic metamorphosis", which represents a transformation of an aromatic system into a different one through partial disassembly of the starting aromatic ring.[12–14] Along these lines, herein we report transition-metal-free S_NAr-based aromatic metamorphosis of dibenzothiophenes to carbazoles via dibenzothiophene dioxides.

Our strategy begins with smooth oxidation of dibenzothiophenes with aqueous hydrogen peroxide (see the Supporting Information; Scheme 1).[15] This conventional process is useful as the first step for the aromatic metamorphosis. Although aryl sulfones are known to undergo S_NAr reactions, the scope of the substitution is limited.[16–19] Another difficulty could originate from the second intramolecular S_NAr reaction which would involve formal elimination of K_2SO_2, which is a high-energy compound.[20] The realization of the second, and the last step, sequential inter/intramolecular nucleophilic

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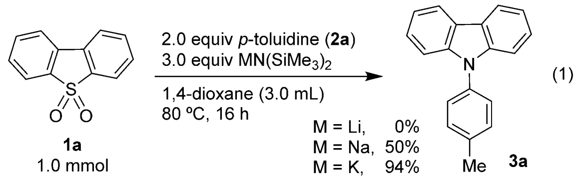
[**] This work was supported by Grants-in-Aid from MEXT (25107002 "Science of Atomic Layers") and from JSPS [24685007 (Young Scientists (A)), 26620081 (Exploratory Research)]. D.V. and K.M. thank JSPS for financial support. H.Y. acknowledges the Japan Association for Chemical Innovation for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503671.

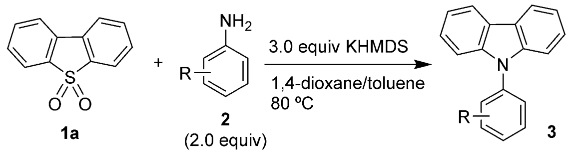
aromatic substitution, required screening of the reaction conditions. We selected the reaction of dibenzo[*b*,*d*]thiophene 5,5-dioxide (**1a**) with *p*-toluidine (**2a**) as a model reaction for optimization [Eq. (1)]. The reaction of **1a** (1.0 equiv) with **2a** (2.0 equiv) by means of lithium hexamethyldisilazide (3.0 equiv) in 1,4-dioxane at 80 °C for 16 hours did not produce the desired carbazole **3a**. Interestingly, **3a** was obtained in 50 % yield when $NaN(SiMe_3)_2$ was employed. To our delight, $KN(SiMe_3)_2$ (potassium hexamethyldisilazide; KHMDS, 0.5 M toluene solution) gave the best result for isolating **3a** in 94 % yield. Other potassium bases such as K_2CO_3, K_3PO_4, KOAc, and KO*t*Bu were totally ineffective. 1,4-Dioxane has proven to be the best cosolvent for toluene from the KHMDS solution. The reactions in 1,2-dimethoxyethane/toluene and in toluene as a sole solvent delivered **3a** in 91 and 61 % yield, respectively. Reducing the amount of **2a** or KHMDS led to lower yields of **3a**.



(1)

With the optimized the reaction conditions in hand, the scope with respect to the amines was examined (Table 1). The reactions proceeded efficiently with both electron-rich and electron-neutral anilines to yield **3b–l** in high yields. The vinyl functionality was tolerated under the reaction conditions to afford **3f** in moderate yield. The TIPS group of **2g** partly survived under the reaction conditions to yield a mixture of the protected **3g** and unprotected **3h** quantitatively in 1:2.6 ratio. Unfortunately, unprotected *p*-aminophenol (**2h**) reacted sluggishly. Despite its steric hindrance, mesitylamine (**2l**) participated in the reaction to give **3l** in high yield. Moderately electron-withdrawing halo groups retarded the reaction and also underwent dehalogenation. The reaction with 4-chloroaniline (**2m**) yielded a 4:1 mixture of the desired **3m** and the hydrodechlorinated byproduct **3b** in 64 % yield. The fluoro analogue **2n** was less reactive and afforded **3n** in 30 % yield. In addition, the fluoro group was substituted with **2n** through an S_NAr reaction to yield *N*-(4-(9-carbazolyl)-phenyl)-4-fluoroaniline (**3n′**) as a byproduct. Alkylamines such as *p*-methoxybenzylamine reacted moderately (34 % yield with *p*-methoxybenzylamine in 18 h), possibly because of the less acidic NH protons. The attempted phenylation of carbazole with diphenyl sulfone under similar reaction conditions resulted in no conversion, probably because of the lower nucleophilicity of potassium carbazolide.

Table 1: Scope with respect to the anilines.

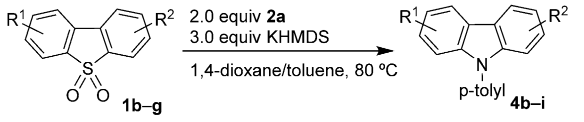


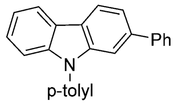
R	*t* [h]	3	Yield [%][a]
H	24	**3b**	77
4-MeO	16	**3c**	94
4-*t*Bu	16	**3d**	92
4-Me_2N	17	**3e**	91
4-$CH_2{=}CH$	17	**3f**	60
4-TIPSO	17	**3g**	28 (72[b])
4-HO	24	**3h**	26[c]
3-MeO	16	**3i**	70
3,5-*t*Bu_2	17	**3j**	98
3,4-OCH_2O	17	**3k**	65
2,4,6-Me_3	16	**3l**	67
4-Cl	18	**3m**	51 (13[d])
4-F	13	**3n**	30[e] (9[f])

[a] Yield of isolated product. [b] The yield of **3h** as a byproduct. [c] 1,4-Dioxane (6.0 mL), 100 °C. [d] The yield of **3b** as a byproduct. [e] 2.0 equiv of KHMDS. [f] The yield of **3n′** as a byproduct. TIPS = triisopropylsilyl.

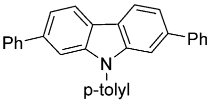
The scope with respect to the dibenzothiophene dioxide derivatives is broad (Table 2). Substituted or π-extended carbazoles were obtained efficiently. Gratifyingly, the sterically demanding **4g**[21] was obtained in high yield. The reactions of substrates bearing bromo and methoxy groups gave slightly complex mixtures, but **4h** and **4i** , respectively, were isolated in moderate yield. Notably, we could synthesize 2,7-diphenyl-9-*p*-tolylcarbazoles (**4c**) in a controlled manner. While electron-rich dibenzothiophene, as well as carbazole, undergoes electrophilic bromination at the 3,6-positions with exclusive regioselectivity, dibenzothiophene dioxide is electron-deficient and delivers the 2,7-dibromo product (Scheme 2).[15a,22] By changing the oxidation state of sulfur, we alter

Table 2: Scope with respect to dibenzothiophenes.

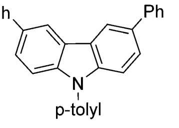




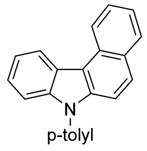
4b, 89% (17 h)



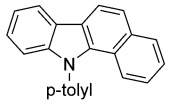
4c, 93% (17 h)



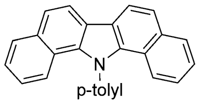
4d, 94% (19 h)



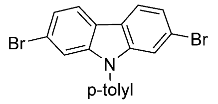
4e, 93% (22 h)



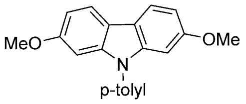
4f, 91% (24 h)



4g, 84% (22 h)

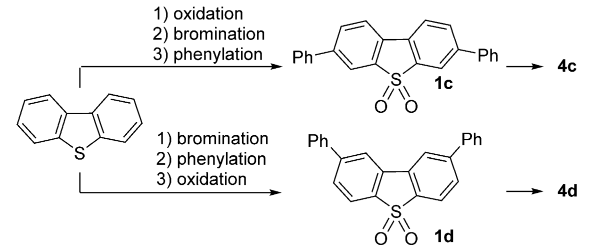


4h, 34% (12 h, 2.0 equiv KHMDS)



4i, 36% (18 h, 100 ºC)

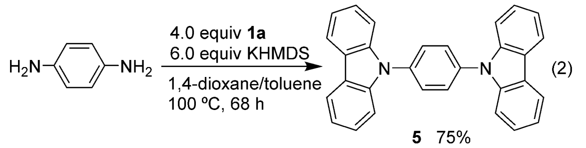
Yield is that of isolated product.



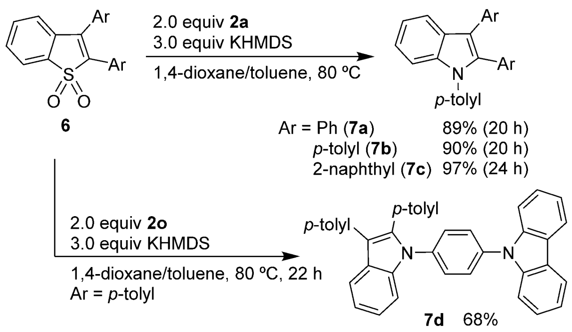
Scheme 2. Selective synthesis of two diphenyl isomers.[15a, 22b]

the positions of the substituents in the final carbazoles **4c** and **4d**.[21]

Benzene-1,4-diamine reacted with **1a** smoothly to afford the bis(carbazolyl)benzene **5**, an important structural unit which has found diverse applications in electronic devices[23] [Eq. (2)]. Usually, bis(carbazolyl)benzenes are obtained in moderate yields through palladium-catalyzed or copper-mediated reactions of 1,4-dihalobenzene with carbazole at 170–200°C.

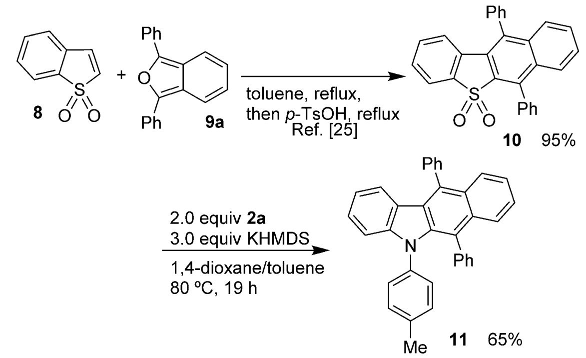


Our S_NAr-based amination was applicable to the synthesis of indoles (Scheme 3). Although 2,3-diaryl groups are necessary to avoid undesired conjugate addition onto the vinyl sulfoxide unit, densely arylated indoles (**7a–c**)[21] were formed in excellent yields. The reaction of **6** with 4-(9-carbazolyl)aniline (**2o**) yielded an unsymmetric indole-carbazole hybrid (**7d**), which will find applications in organic electroluminescence.[24]

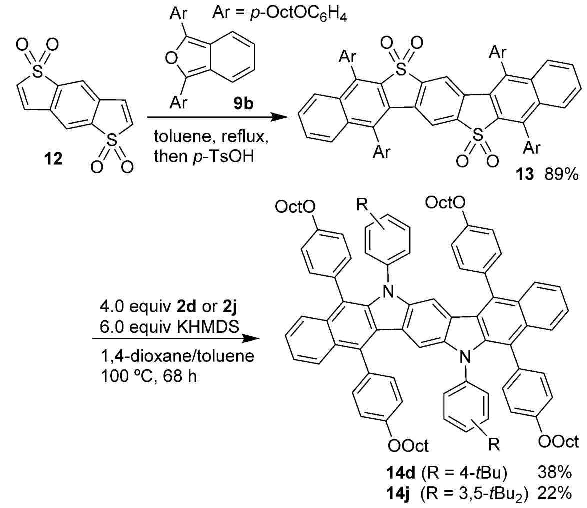


Scheme 3. S_NAr-based synthesis of indoles.

The electron-deficient benzothiophene dioxide **8** showed uniquely high reactivity as a dienophile in the Diels–Alder reaction with isobenzofuran (**9a**),[25] whereas indoles do not react with **9a** (Scheme 4). By taking advantage of the Diels–Alder reaction, we could extend the π-conjugation to form benzonaphthothiophene dioxide (**10**). Eventually, the π-extended benzocarbazole **11** was obtained in good overall yield from commercially available **8**.



Scheme 4. Sequential Diels–Alder reaction/carbazole formation.



Scheme 5. Concise synthesis of π-extended dibenzoindolo[3,2-*b*]carbazoles.

We used this Diels–Alder-based approach to achieve significantly π-extended dibenzoindolo[3,2-*b*]carbazoles (**14**; Scheme 5). The precursor bis(sulfone) **13** was obtained from a rather small aromatic compound (**12**) in 89% yield. Subsequently, expected quadruple C–N bond formations occurred to give **14d** and **14j** in 38 and 22% yield, respectively. In comparison with elegant yet burdensome construction of similar dibenzoindolo[3,2-*b*]carbazoles for OFET devices,[26,27] this overall transformation highlights the synthetic potential of our carbazole synthesis.

Figure 1 shows the UV/visible and fluorescence spectra of **14j** in dichloromethane.[28] The lowest energy absorption maximum was observed at $\lambda = 496$ nm, which is significantly red-shifted compared to typical absorption of indolo[3,2-*b*]carbazoles ($\lambda = 420$–440 nm).[29] The compound **14j** showed bright-green fluorescence which has its intensity maximum at $\lambda = 511$ nm with a fluorescence quantum yield of 34%. Our S_NAr-based approach is thus useful for exploring π-extended carbazoles which show interesting functions.

The most likely mechanism would be the sequential inter/intramolecular S_NAr reactions with highly nucleophilic potassium amides (Scheme 6). The first intermolecular S_NAr reaction would be faster than the second intramolecular

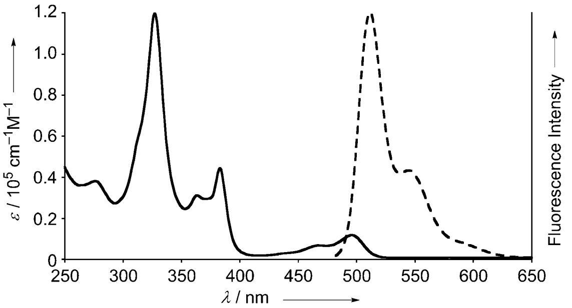
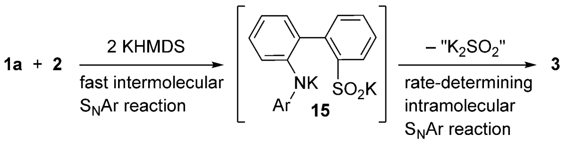
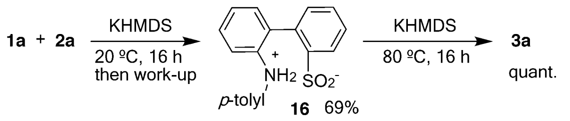


Figure 1. UV/visible (solid line) and fluorescence (dotted line) spectra of **14j** in CH_2Cl_2.



Scheme 6. Plausible mechanism.



Scheme 7. Elucidation of mechanism.

reaction of **15**,[30] and the carbazole formation necessitates a high temperature. The following experiments strongly support the mechanism (Scheme 7): **1a** reacted with **2a** in the presence of KHMDS at room temperature and the zwitterionic **16** was isolate.[21] Subsequent exposure of **16** to KHMDS at 80 °C afforded **3a** quantitatively. Although there are several debatable reaction pathways for aromatic substitution of aryl sulfones,[18] the isolation of **16** strongly indicates the intermediacy of **15** and hence the S_NAr pathway in our case.

In conclusion, we have reported a new powerful and practical strategy to prepare carbazoles without recourse to transition-metal catalysts. Dibenzothiophene dioxide derivatives undergo sequential inter/intramolecular nucleophilic aromatic substitution with anilines in the presence of KHMDS to afford a wide range of carbazoles in a single operation. Considering that dibenzothiophene dioxides are readily available by oxidation of the parent dibenzothiophenes, one can concisely achieve aromatic metamorphosis of dibenzothiophenes to carbazoles. Since electron-deficient thiophene dioxides exhibit reactivity different from that of the corresponding electron-rich azaarenes, coupling a thiaarene-dioxide-specific reaction with the S_NAr carbazole synthesis opens up a new route to difficult-to-access carbazoles. Current efforts are directed toward exploring new aromatic metamorphosis in our laboratory.

Keywords: amination · aromatic substitution · fluorescence · sulfur heterocycles · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10234–10238
Angew. Chem. **2015**, *127*, 10372–10376

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[1] a) H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303; b) H.-J. Knölker, *Chem. Lett.* **2009**, *38*, 8; c) I. Bauer, H.-J. Knölker, *Top. Curr. Chem.* **2012**, *309*, 203; d) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193.

[2] a) P. Strohriegl, J. V. Grazulevicius, *Adv. Mater.* **2002**, *14*, 1439; b) J. V. Grazulevicius, P. Strohriegl, J. Pielichowski, K. Pielichowski, *Prog. Polym. Sci.* **2003**, *28*, 1297; c) N. Blouin, M. Leclerc, *Acc. Chem. Res.* **2008**, *41*, 1110.

[3] Double arylation of primary amines with 2,2′-dihalobiaryls: a) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H.-Z. Tang, M. Fujiki, S. Yamaguchi, K. Tamao, *Angew. Chem. Int. Ed.* **2003**, *42*, 2051; *Angew. Chem.* **2003**, *115*, 2097; b) T. Kitawaki, Y. Hayashi, N. Chida, *Heterocycles* **2005**, *65*, 1561; c) A. Kuwahara, K. Nakano, K. Nozaki, *J. Org. Chem.* **2005**, *70*, 413; d) T. Kitawaki, Y. Hayashi, A. Ueno, N. Chida, *Tetrahedron* **2006**, *62*, 6792; e) T. Q. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, A. Villinger, P. Langer, *Org. Biomol. Chem.* **2014**, *12*, 2596; With cyclic diaryliodonium salts: f) D. Zhu, Q. Liu, B. Luo, M. Chen, R. Pi, P. Huang, S. Wen, *Adv. Synth. Catal.* **2013**, *355*, 2172; g) S. Riedmüller, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2013**, *9*, 1202.

[4] a) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184; b) S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996; c) S. W. Youn, J. H. Bihn, B. S. Kim, *Org. Lett.* **2011**, *13*, 3738; d) Q. Jiang, D. Duan-Mu, W. Zhong, H. Chen, H. Yan, *Chem. Eur. J.* **2013**, *19*, 1903; e) M. Yamamoto, S. Matsubara, *Chem. Lett.* **2007**, *36*, 172.

[5] a) B. J. Stokes, B. Jovanovic, H. Dong, K. J. Richert, R. D. Riell, T. G. Driver, *J. Org. Chem.* **2009**, *74*, 3225; b) B. J. Stokes, K. J. Richert, T. G. Driver, *J. Org. Chem.* **2009**, *74*, 6442.

[6] C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543.

[7] a) Ref. [4b]; b) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; *Angew. Chem.* **2011**, *123*, 8764.

[8] S. Chakrabarty, I. Chatterjee, L. Tebben, A. Studer, *Angew. Chem. Int. Ed.* **2013**, *52*, 2968; *Angew. Chem.* **2013**, *125*, 3041.

[9] T. Noji, H. Fujiwara, K. Okano, H. Tokuyama, *Org. Lett.* **2013**, *15*, 1946.

[10] W. D. Guerra, R. A. Rossi, A. B. Pierini, S. M. Barolo, *J. Org. Chem.* **2015**, *80*, 928.

[11] H. Gao, Q.-L. Xu, M. Yousufuddin, D. H. Ess, L. Kürti, *Angew. Chem. Int. Ed.* **2014**, *53*, 2701; *Angew. Chem.* **2014**, *126*, 2739.

[12] D. Vasu, H. Yorimitsu, A. Osuka, *Angew. Chem.* **2015**, *127*, 7268; *Angew. Chem. Int. Ed.* **2015**, *54*, 7162.

[13] Diels–Alder reactions of five-membered heteroaromatics and azines with either alkenes or alkynes result in aromatic metamorphosis to the corresponding aromatic rings with extrusion of their heteroatomic units. Very recent examples: a) A. Criado, M. Vilas-Varela, A. Cobas, D. Pérez, D. Peña, E. Guitián, *J. Org. Chem.* **2013**, *78*, 12637; b) X. Ding, S. T. Nguyen, J. D. Williams, N. P. Peet, *Tetrahedron Lett.* **2014**, *55*, 7002; c) S. P. J. T. Bachollet, J. F. Vivat, D. C. Cocker, H. Adams, J. P. A. Harrity, *Chem. Eur. J.* **2014**, *20*, 12889; d) S. Suzuki, Y. Segawa, K. Itami, J. Yamaguchi, *Nat. Chem.* **2015**, *7*, 227.

[14] Reviews on catalytic denitrogenative transannulation of triazoles: a) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2012**, *51*, 862; *Angew. Chem.* **2012**, *124*, 886; b) P. Anbarasan, D. Yadagiri, S. Rajasekar, *Synthesis* **2014**, *46*, 3004.

[15] a) Z. Duan, X. Huang, S. Fujii, H. Kataura, Y. Nishioka, *Chem. Lett.* **2012**, *41*, 363; b) S. F. Nelsen, Y. Luo, M. N. Weaver, J. V. Lockard, J. I. Zink, *J. Org. Chem.* **2006**, *71*, 4286; c) G.

Barbarella, L. Favaretto, A. Zanelli, G. Gigli, M. Mazzeo, M. Anni, A. Bongini, *Adv. Funct. Mater.* **2005**, *15*, 664.

[16] Intramolecular Smiles rearrangement is a well-known transformation which includes an S_NAr reaction of aryl sulfones: W. E. Truce, E. M. Kreider, W. W. Brand, *Org. React.* **1970**, *18*, 99.

[17] Some aryl sulfones undergo S_NAr substitution with amines under highly basic conditions. For instance, see: a) W. Bradley, *J. Chem. Soc.* **1938**, 458; b) G. Köbrich, *Chem. Ber.* **1959**, *92*, 2981.

[18] Diphenyl sulfone reacted with fused potassium hydroxide to afford phenol: a) S. Oae, N. Furukawa, *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2260. Dibenzothiophene dioxides reacted with potassium alkoxide or hydroxide at about 160 °C to yield the simple ring-opening product through one S_NAr process: b) T. G. Squires, C. G. Venier, B. A. Hodgson, L. W. Chang, *J. Org. Chem.* **1981**, *46*, 2373; c) T. Aida, T. G. Squires, C. G. Venier, *Tetrahedron Lett.* **1983**, *24*, 3543.

[19] Reactive azaaryl sulfones such as tetrazolyl sulfones are well known to undergo intermolecular S_NAr substitution with a variety of nucleophiles. For instance: a) P. J. Kocienski, A. Bell, P. R. Blakemore, *Synlett* **2000**, 365; b) C. Aïssa, *J. Org. Chem.* **2006**, *71*, 360; c) P. Jankowski, K. Plesniak, J. Wicha, *Org. Lett.* **2003**, *5*, 2789.

[20] K_2SO_2 is an elusive species: a) P. J. Bruna, F. Grein, *J. Phys. Chem. A* **2012**, *116*, 10229; b) D. P. Morales, A. S. Taylor, S. C. Framer, *Molecules* **2010**, *15*, 1265.

[21] X-ray crystallographic analysis unambiguously revealed the structure. For details, see the Supporting Information.

[22] a) L. Zhang, S. Zeng, L. Yin, C. Ji, K. Li, Y. Li, Y. Wang, *New J. Chem.* **2013**, *37*, 632; b) A. Heynderickx, A. Samat, R. Guglielmetti, *Synthesis* **2002**, 213.

[23] a) B. E. Koene, D. E. Loy, M. E. Thompson, *Chem. Mater.* **1998**, *10*, 2235; b) H.-P. Shi, J.-X. Dai, L.-W. Shi, M.-H. Wang, L. Fang, S.-M. Shuang, C. Dong, *Chem. Commun.* **2012**, *48*, 8586; c) Q. Zhang, J. Chen, Y. Cheng, L. Wang, D. Ma, X. Jing, F. Wang, *J. Mater. Chem.* **2004**, *14*, 895.

[24] T. Iwakuma, H. Yamamoto, Y. Hironaka, H. Ikeda, C. Hosokawa, S. Tomita, T. Arakane (Idemitsu Kosan Co., Ltd.), US 8580391 B2, **2013**.

[25] M. Nandakumar, J. Karunakaran, A. K. Mohanakrishnan, *Org. Lett.* **2014**, *16*, 3068.

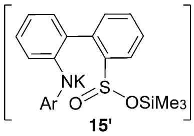
[26] M. T. Levick, I. Grace, S.-Y. Dai, N. Kasch, C. Muryn, C. Lambert, M. L. Turner, D. J. Procter, *Org. Lett.* **2014**, *16*, 2292.

[27] Importance of benzobipyrroles in organic electronics: H. Tsuji, Y. Yokoi, C. Mitsui, L. Ilies, Y. Sato, E. Nakamura, *Chem. Asian J.* **2009**, *4*, 655, and references therein.

[28] The photophysical properties of **14d** are very similar to those of **14j**. For details, see the Supporting Information.

[29] a) J. Simokaitiene, E. Stanislovaityte, J. V. Grazulevicius, V. Jankauskas, R. Gu, W. Dehaen, Y.-C. Hung, C.-P. Hsu, *J. Org. Chem.* **2012**, *77*, 4924; b) K. Kawaguchi, K. Nakano, K. Nozaki, *J. Org. Chem.* **2007**, *72*, 5119.

[30] The elimination of elusive and high-energy K_2SO_2 is unlikely. After many experiments, at this stage we speculate that trimethylsilylation of **15** with HN(SiMe$_3$)$_2$, generated in situ, would take place to afford **15′**, which should undergo a cleaner S_NAr reaction.



15′

Received: April 22, 2015