JOC*Note*

Synthesis and Cross-Coupling Reactions of Substituted 5-Triflyloxyindoles

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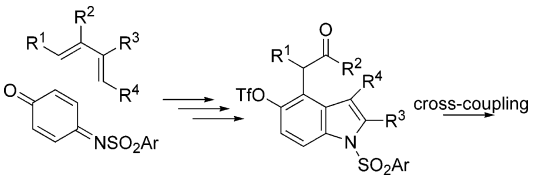
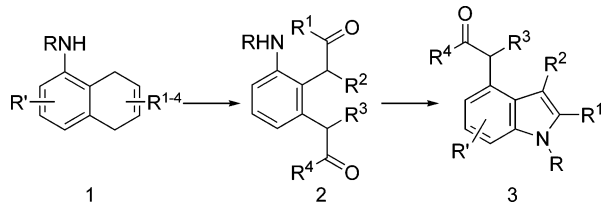


N-Arylsulfonyl quinone monoimines undergo smooth cycloadditions in a [4+2] sense to yield the expected cycloadducts. The crude cycloadducts, when subjected to a short series of simple transformations, produce synthetically useful quantities of 5-triflyloxyindoles in excellent overall yields. Such compounds are excellent participants in cross-coupling chemistry.

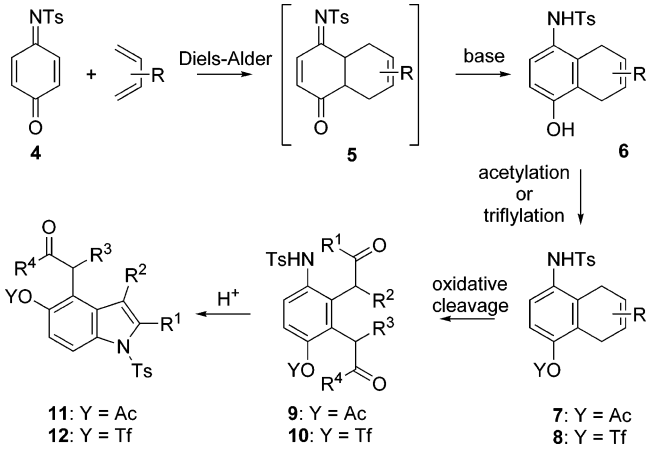
The indole moiety remains probably the most studied of the heteroaromatic compounds. This is due in large part to the huge number of bioactive natural products as well as medicinally important unnatural compounds based on the benzopyrrole skeleton.[1] While the 2- and 3-positions of the indole ring system are relatively easy to functionalize (due to the reactivity of the enamine-like double bond), the preparation of indoles bearing complex functionality on the benzenoid portion of the molecule remains a challenge.

The strategy of converting a 2-aminodihydronaphthalene to a 4-substituted indole (a Plieninger indole synthesis, Scheme 1) has been known for some time[2] but has been scarcely used,[3] owing to the lack of a flexible synthetic approach to the starting material (often by Birch reduction of a 2-aminonaphthalene). Recently, we have reported the preparation of highly substituted 5-methoxy- and 5-alkylindoles by oxidative scission of dihydronaphthalenes, which in turn were prepared by way of a Diels–Alder reaction of a quinoid imine derivative.[4] It occurred to us that use of the tosyl derivatives

SCHEME 1. Plieninger Indole Synthesis



SCHEME 2. Strategy for the Formation of 5-Triflyloxyindoles



of the parent quinone imines could yield 5-hydroxyindoles or, more importantly, 5-triflyloxyindoles. Such compounds could be important partners in cross-coupling reactions for the construction of more sophisticated indole motifs. A survey of the literature reveals only a few references to the synthesis and reactions of 5-triflyloxyindoles (vide infra). Our desire to prepare such compounds is grounded in their potential as starting materials for a series of benzenoid-substituted indole natural products. In fact we have recently reported the synthesis of several such compounds, namely, *cis*-trikentrin B and herbindole B.[5] In this note we report the efficient synthesis and cross-coupling reactions of substituted 5-triflyloxyindoles.

The strategy for the formation of 5-triflyloxyindoles via the Diels–Alder reaction of *p*-benzoquinone monoimines is shown in Scheme 2. Issues for consideration are the regiochemical outcome of the cycloaddition (**4** → **5**), the method of aromatization of the initial adduct to a dihydronaphthalene (**5** → **6**), regioselective triflylation of the resulting phenolic group (**6** → **8**), and subsequent conversion to the indole (**8** → **10** → **12**).

The Diels–Alder reaction of *N*-arylsulfonyl-*p*-benzoquinone monoimines has been reported[6] but scarcely used. It is known that the tosylimino group dictates the regiochemistry in the Diels–Alder reaction; that is, it overrides the carbonyl moiety in terms of stabilization of the LUMO. Table 1 shows the results of the cyclo-

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(5) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215.

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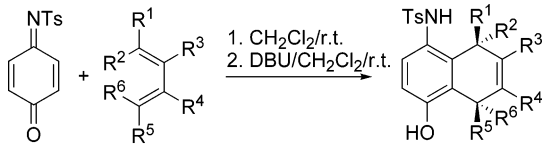
TABLE 1. Diels–Alder/Aromatization Reactions of 4



entry	diene	product (yield)
1	R^1–R^6 = H	**6a** (80%)
2	R^1 = Me, R^2–R^6 = H	**6b** (80%)
3	R^3,R^4 = Me, R^1,R^2,R^5,R^6 = H	**6c** (86%)
4	R^1,R^3 = Me, R^2,R^4,R^5,R^6 = H	**6d** (95%)[a]
5	R^1,R^5 = CH_2CH_2, R^1,R^2,R^5,R^6 = H	**6e** (85%)
6	R^1,R^4=Me, R^2,R^6 = CH_2CH_2, R^3,R^5 = H	**6f** (68%)
7	R^1 = Ph, R^2–R^6 = H	**6g** (80%)
8	R^4 = Me, R^1,R^2,R^3,R^5,R^6 = H	**6h** (66%)[b]

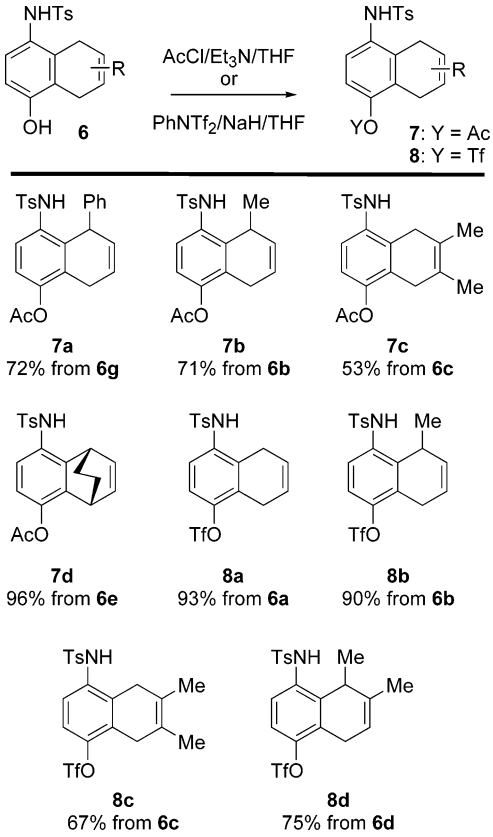
[a] Isolated as a 4:1 mixture of regioisomers. Major regioisomer shown. [b] Isolated as a 2:1 mixture of regioisomers. Major isomer shown.

addition of *N*-*p*-toluenesulfonyl-*p*-benzoquinone monoimine **4**[7] with a variety of dienes with subsequent aromatization. In practice, the cycloaddition was allowed to proceed at ambient temperature until TLC indicated the complete disappearance of starting material. At this time a drop of DBU was added to the reaction mixture and stirred for 10 min to effect tautomerization to the dihydronaphthalene. Several points from the table are worthy of note. In all cases the tosylimino group dictated the regiochemistry. In the case of 1,2-dimethylbutadiene (entry 4) and isoprene (entry 8), a mixture of regioisomers was formed in ratios of 4:1 and 2:1, respectively. The mixture of isomers for adduct **6d** might be expected since the two methyl groups on the diene have contradicting influences in regiocontrol. For the isoprene adduct **6h**, the lack of reasonable selectivity is less clear to us. In all other cases the cycloaddition was very regioselective and follows the literature precedent of Moore.[6a] It is also notable that the aromatization was better effected under basic conditions, which is in contrast to our previous experience with quinone imine ketals.[4a]

We attempted to prepare 5-hydroxyindoles by oxidative cleavage of **6**; however, under conditions required for olefin cleavage, the phenolic compound was oxidized to the quinoid species, in poor yield. We then protected the phenolic group as either the acetoxy or triflyloxy derivatives (**7** and **8**, respectively) under standard conditions. Chart 1 shows the dihydronaphthalene derivatives **7** and **8**, which would serve as substrates for our indole synthesis. In most cases the yields of the desired compounds were excellent; however N-acylation or sulfonylation was always a consideration and had to be carefully avoided.

With dihydronaphthalenes **7** and **8** in hand, attention was turned to formation of the indoles. Treatment of **7** and **8** with catalytic osmium tetroxide in the presence of NMO yielded a diol, which was isolated in crude form and treated with $NaIO_4$ supported on silica gel.[8] The crude dicarbonyl compounds (**9** and **10**) were then treated with several drops of concentrated H_2SO_4 in tetrahydrofuran to effect ring closure to the requisite indoles **11** and

CHART 1. Acetylation/Triflylation of Hydroxydihydronaphthalenes



12 in generally excellent overall yields (Chart 2). Interestingly, in some cases the intermediate hydroxyindoline was observed but was converted to the indole upon prolonged stirring with acid.

To illustrate the utility of the 5-triflyloxyindoles prepared by this method, we selected a typical example (**12a**) and subjected it to a series of cross-coupling experiments. The cross-coupling of 5-triflyloxyindoles has been reported on only several occasions.[9] Furthermore, these types of reactions are typically performed on indoles unsubstituted on the benzenoid portion of the molecule. Scheme 3 shows a variety of coupling reactions performed on an indole derived from **12a**. In these cases typical experimental procedures from the literature were employed without optimization, with the yields ranging from good to excellent. In all cases the presence of the aldehyde in **12a** was problematic and appeared to be participating in the reaction in a manner that remains unknown to

(7) Dienophile **4** was best prepared by oxidation of *N*-*p*-toluenesulfonyl-*p*-hydroxyaniline with $NaIO_4$ supported on silica gel. See Supporting Information for details.

(8) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

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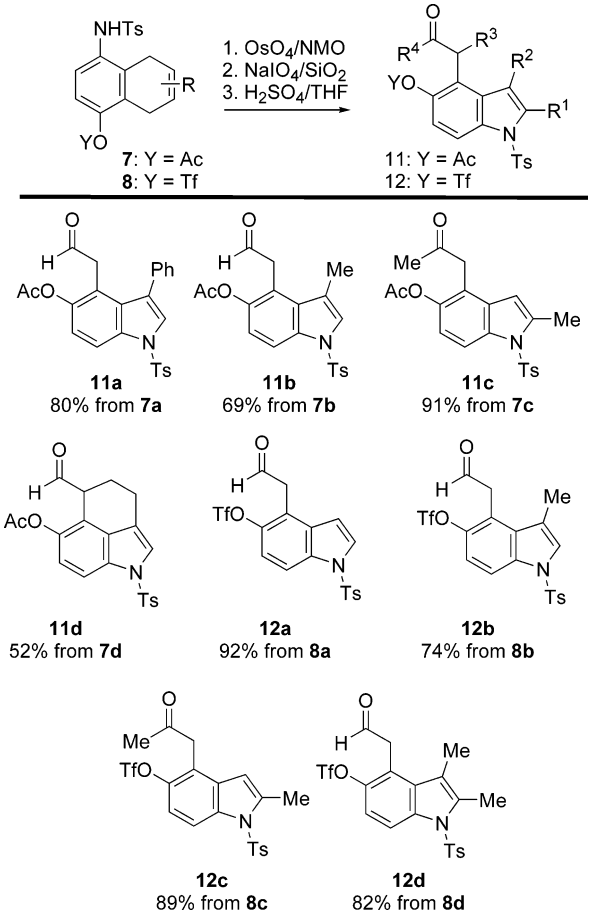
CHART 2. Preparation of 5-Hydroxyindole Derivatives



us. To this end **12a** was reduced and protected as an acetate to furnish a suitable substrate. The addition of lithium chloride to the reaction mixture was crucial to the success of the cross-coupling reactions[10] with the exception of the Heck reaction.

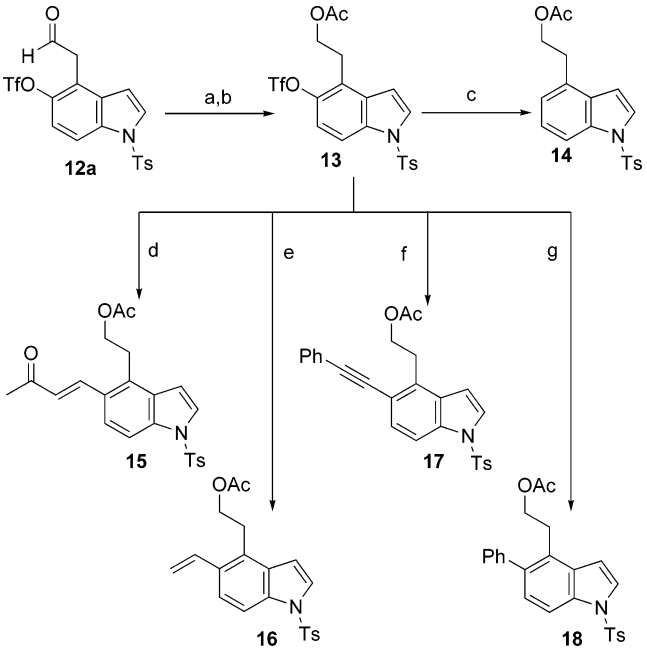
In summary we have reported the Diels–Alder reactions of a quinone monoimine with a variety of 1,3-butadienes to provide, in excellent yields, the expected cycloadducts. The adducts were aromatized and subjected to a series of transformations leading to 5-triflyloxyindoles. The utility of these compounds was illustrated by their participation in cross-coupling chemistry. The use of this chemistry for the synthesis of complex indole-containing natural products will be the subject of forthcoming reports from our laboratory.

Experimental Section

General Procedure for the Diels–Alder Reaction: Preparation of 6a. The *N*-*p*-toluenesulfonyl-*p*-benzoquinone monoimine **4** (7.84 g, 30 mmol) was added to a sealable tube and dissolved in CH_2Cl_2 (30 mL). 1,3-Butadiene (5.68 g, 105 mmol) was condensed into the tube and the reaction purged with argon. The tube was sealed and the reaction stirred at room temperature for 2 days, after which time the reaction mixture was diluted with CH_2Cl_2 and DBU (8 drops) was added. After 10 min, the reaction mixture was partitioned between EtOAc and H_2O.

(10) The use of lithium chloride to facilitate palladium-catalyzed cross-coupling reactions is well documented. See: Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

SCHEME 3. Cross-Coupling of a 5-Triflyloxyindole[a]



[a] Reaction conditions: (a) $NaBH_4$, MeOH, THF; (b) AcCl, Et_3N, THF (98% overall); (c) NH_4CO_2H, LiCl, $Pd(PPh_3)_2Cl_2$, DMF (88%); (d) MVK, $Pd(PPh_3)_4$, Et_3N, DMF (65%); (e) CH_2=$CHSnBu_3$, LiCl, $Pd(PPh_3)_2Cl_2$, DMF (80%); (f) phenylacetylene, Et_3N, CuI, LiCl, $Pd(PPh_3)_2Cl_2$, DMF (95%); (g) $PhB(OH)_2$, LiCl, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DMF (88%).

The organic layer was separated and the aqueous portion extracted several times with EtOAc. The combined organic layers were washed with 5% HCl, followed by H_2O and brine. The organic solution was then dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude solid was purified by trituration with Et_2O to yield 7.57 g (80%) of **6a** as a yellow solid: mp 165 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 9.10 (s, 1H), 7.52 (d, 2H, J = 8.2 Hz), 7.33 (d, 2H, J = 8.0 Hz), 6.47 (AB quartet, 2H), 5.79–5.69 (m, 2H), 3.07 (broad s, 4H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.4, 142.7, 138, 133, 129.4, 126.7, 125.7, 125, 123.6, 123.4, 121.5, 111.6, 25.5, 24.2, 21. IR (thin film): ν_{max} 3428, 3271, 2874, 1595, 1468, 1305, 1155. HRMS: calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0934.

Typical Procedure for the Triflylation of the Diels–Alder Adducts. Synthesis of 8a. A suspension of sodium hydride (1.14 g, 28.5 mmol) in THF (70 mL) was purged with argon and cooled in a flask to 0 °C. The Diels–Alder adduct **6a** (6.00 g, 19 mmol) dissolved in THF (70 mL) was added to this suspension via cannula and allowed to stir for 30 min. *N*-Phenyltriflimide (8.15 g, 22.8 mmol) in THF (70 mL) was then added via cannula, and the reaction mixture was stirred for 30 min at 0 °C, followed by another hour at room temperature. The reaction was partitioned between EtOAc and H_2O. The aqueous layer was extracted several times with EtOAc. The combined organic layers were washed twice with water and once with brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated. The mixture was purified by flash column chromatography on silica (30% EtOAc/hexanes) to yield **8a** (7.9 g, 93%) as an off-white solid, mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 7.9 Hz), 7.25 (d, 1H, J = 9.1 Hz), 7.08 (d, 1H, J = 9.1 Hz), 6.66 (s, 1H), 5.85–5.82 (m, 1H), 5.79–5.75 (m, 1H), 3.37–3.34 (m, 2H), 3.10–3.07 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 144.4, 136.3, 133.9, 130.2, 129.9, 128.8, 127.1, 122.5, 122.2, 121.9, 119.2, 25.6, 24.6, 21.6 (CF_3 quartet not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2. IR (thin film):

ν_{max} 3301, 1597, 1475, 1416, 1331, 1210, 1142. HRMS: calcd for $C_{18}H_{16}F_3NO_5S_2$ 447.0422, found 447.0418.

Typical Procedure for Indole Formation. Synthesis of 12a. The dihydronaphthalene **8a** (3.94 g, 8.8 mmol) was suspended in a 2:1 mixture of THF and H_2O (105 mL). A crystal of osmium tetroxide (<1 mg) was added, and the mixture stirred for 5 min, giving a black solution, after which NMO (1.24 g, 10.56 mmol) was added portionwise. The solution was stirred until starting material was consumed by TLC, at which point Na_2SO_3 (about 12 equiv) was added. The mixture was then stirred for a further 10 min and extracted with EtOAc (3 times). The combined organic layers were then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield the crude diol. The diol was used without further purification and dissolved in CH_2Cl_2. $NaIO_4$ supported on SiO_2 gel (20.7 g, 14.08 mmol)[4] was added to this mixture and stirred vigorously until the starting material was consumed, as indicated by TLC. The mixture was filtered, rinsed with CH_2Cl_2, and concentrated to yield the crude dialdehyde. The dialdehyde was taken up in dry THF, treated with concentrated sulfuric acid (15 drops), and stirred under argon until consumption of the dialdehyde was indicated by TLC. Solid $NaHCO_3$ was then added, and the mixture was stirred for 10 min. Anhydrous $MgSO_4$ was added, and the mixture was stirred for another 10 min. Filtration and concentration yielded the crude indole, which was purified by column chromatography on silica gel using 20% EtOAc/hexanes. The solid was isolated as an off-white solid (3.74 g, 92% overall), mp 83−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, 1H, J = 1.6, 1.6 Hz), 8.0 (d, 1H, J = 9.2 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.71 (d, 1H, J = 3.7 Hz), 7.28 (d, 1H, J = 9.2 Hz), 7.28 (d, 2H, J = 8.0 Hz), 6.62 (d, 1H, J = 3.7 Hz), 3.99 (d, 2H, J = 1.6 Hz), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 145.8, 143.6, 134.8, 133.3, 132.1, 130.2, 128.8, 127, 118.1, 118, 114.1, 106.8, 42.2, 21.6 (CF_3 quartet not observed). ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.9. IR (thin film): ν_{max} 3147, 2927, 1728, 1596, 1476, 1424, 1380, 1214, 1137. HRMS: calcd for $C_{18}H_{14}F_3NO_6S_2$ 461.0215, found 461.0215.

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR, ^{13}C NMR, IR, and MS analysis data for compounds **4**, **6**−**8**, and **11**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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