

Novel Brønsted Acid Catalyzed Three-Component Alkylations of Indoles with *N*-Phenylselenophthalimide and Styrenes

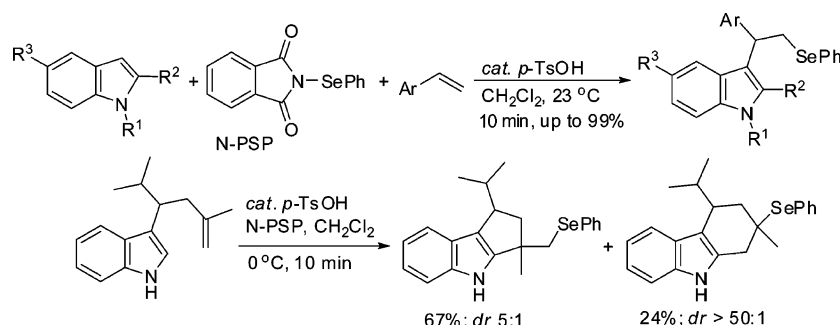
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ABSTRACT



Novel and efficient Brønsted acid (*p*-TsOH) catalyzed inter- and intramolecular Friedel–Crafts alkylations have been developed to synthesize selenated three-component coupling and selenation–cyclization indole derivatives. Chemical removal of the phenylseleno moiety was investigated, and the reaction mechanisms were discussed.

Functionalization of indoles has received more and more attention because the indole moiety is an important structural unit in many bioactive compounds, and indoles have also been used as synthons of complex molecules.¹ Recently, much work has been directed to catalytic Friedel–Crafts reactions of indoles with active carbonyl compounds,² epoxides,³ olefins,^{4–6} imines,⁷ and allyl compounds,⁸ etc. Three-component aza-Friedel–Crafts reactions of indoles,

aldehydes, and amines have also been documented to prepare 3-substituted indole derivatives.^{2,9} Organoselenium compounds are potentially bioactive and have demonstrated versatile utility in main group chemistry,¹⁰ where phenylseleno compounds can be used as valuable synthetic intermediates.¹¹ A phenylseleno group can be introduced to unsaturated substrates by means of *N*-phenylselenophthalimide (N-PSP) or other phenylseleno reagents, and removal of such a phenylseleno moiety results in a saturated or unsaturated functional group in the product.^{12–16} Lewis and Brønsted

(1) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, Germany, 2003.

(2) Li, H.-M.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063.

(3) Kantam, M. L.; Laha, S.; Yadav, J.; Sreedhar, B. *Tetrahedron Lett.* **2006**, *47*, 6213.

(4) Blay, G.; Fernandez, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601.

(5) (a) Liu, C.; Han, X. Q.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700. (b) Zhang, Z. B.; Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 3717.

(6) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.

(7) (a) Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1485.

(8) (a) Westermaier, M.; Mayr, H. *Org. Lett.* **2006**, *8*, 4791. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.

(9) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 4939.

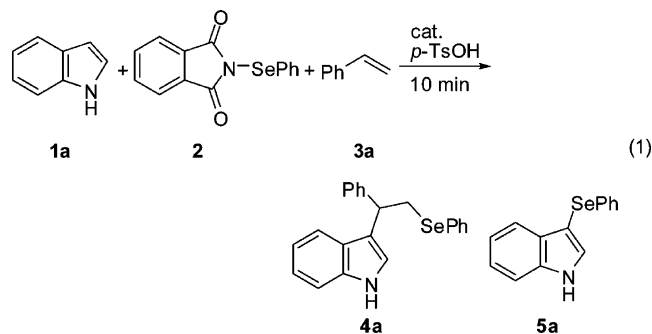
(10) (a) Back, T. G. *Organoselenium Chemistry-A Practical Approach*; Oxford University Press: Oxford, 1999. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255.

(11) (a) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712. (b) Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713.

(12) Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28.

acids BF₃,^{17a} SnCl₄,^{17b} CSA,^{17c} and *p*-TsOH^{17c,d} have been known to promote reactions of phenylseleno reagents with some carbon–carbon unsaturated substrates. Although sulfenylation of indoles has recently been realized by MgBr₂-catalyzed reactions of indoles with *N*-phenylthiophthalimide (N-PTP),¹⁸ reactions of indoles with organoselenium reagents have seldom been investigated.¹⁹ Herein, we report a novel and efficient catalytic route to PhSe-functionalized indoles by catalytic three-component reactions of indoles, N-PSP, and styrenes.

The reaction of indole (**1a**), N-PSP (**2**), and styrene (**3a**) was initially carried out with 10 mol % of *p*-TsOH as catalyst in CH₂Cl₂ at 23 °C (eq 1). The three-component reaction



proceeded rapidly to afford 3-alkylation product **4a** in 80% isolated yield within 10 min. The catalyst loading varied from 5 to 100 mol % to give **4a** in similar yields, but the reaction did not efficiently proceed with <5 mol % of catalyst. With 5 mol % of *p*-TsOH as catalyst, the reaction also efficiently occurred in CH₃CN or DCE, while in THF or Et₂O, 3-phenylselenoindole (**5a**) was formed as the major product. Without a catalyst, the reaction of **1a**, **2**, and styrene proceeded to form **5a** in 82% yield with styrene unreacted (vide infra).

The methodology was extended to substituted and functionalized indoles (Table 1). The reactions of indoles, **2**, and styrenes gave the desired products **4a–d** in 66–82% yields (entries 1–4), while the reactions of *N*-methyl and *N*-benzylindoles, **2**, and styrenes afforded **4e–g** and **4j–m** in excellent yields (88–99%, entries 5–7 and 10–13), and only in the cases using 4- and 2-chlorostyrenes, **4h** and **4i** were obtained in good to moderate yields (83 and 63%, entries 8 and 9). From the reactions of functionalized indoles, **2**, and styrene, the desired products **4n–s** were produced in 80–93% yields (entries 14–19), in which allyl, bromo, and nitro groups can withstand the reaction conditions. Compounds **4**

Table 1. Three-Component Alkylation of Indoles, **2**, and Styrenes

entry ^a	R ¹	R ²	R ³	Ar	product	yield ^b (%)
1	H	H	H	Ph	4a	82
2	H	H	H	4-MeC ₆ H ₄	4b	66
3	H	H	H	2-MeC ₆ H ₄	4c	69
4	H	H	H	4-ClC ₆ H ₄	4d	68
5	Me	H	H	Ph	4e	99
6	Me	H	H	4-MeC ₆ H ₄	4f	97
7	Me	H	H	2-MeC ₆ H ₄	4g	88
8	Me	H	H	4-ClC ₆ H ₄	4h	83
9	Me	H	H	2-ClC ₆ H ₄	4i	63
10	Bn	H	H	Ph	4j	99
11	Bn	H	H	4-MeC ₆ H ₄	4k	89
12	Bn	H	H	2-MeC ₆ H ₄	4l	91
13	Bn	H	H	4-ClC ₆ H ₄	4m	95
14	allyl	H	H	Ph	4n	83
15	H	Me	H	Ph	4o	80
16	Et	Ph	H	Ph	4p	82
17	H	H	Br	Ph	4q	82
18	Bn	H	Br	Ph	4r	93
19	H	H	NO ₂	Ph	4s	81

^a Conditions: indole, 0.5 mmol; indole/N-PSP/styrene = 1:1.2:1.5; *p*-TsOH, 5 mol %; CH₂Cl₂, 3 mL; 23 °C, 10 min. ^b Isolated yields.

were characterized by ¹H, ¹³C{¹H} NMR, and HRMS or elemental analysis, and their molecular structures were further confirmed by the X-ray single-crystal structure of **4r** (Figure 1). In compound **4r**, the PhSe and aryl groups are arranged *anti* to each other. The three-component

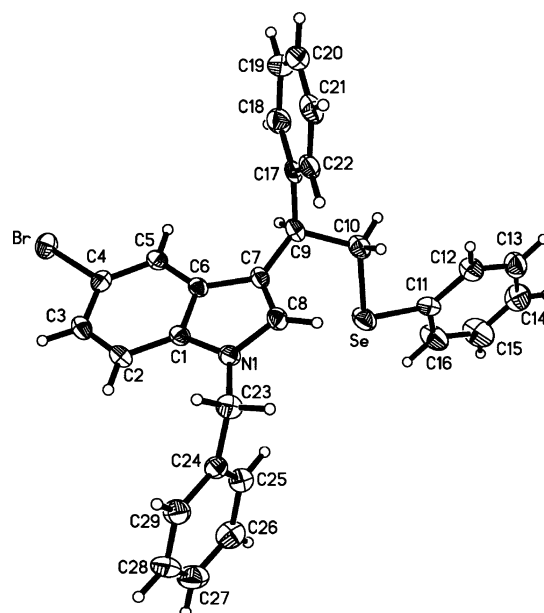
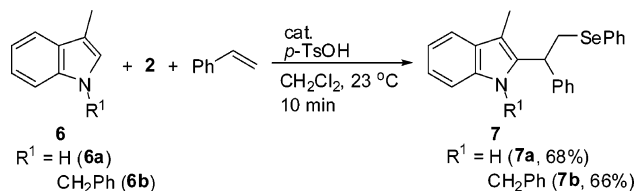


Figure 1. Molecular structure of **4r**.

- (13) Nicolaou, K. C. *Tetrahedron* **1981**, 37, 4097.
 (14) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, 39, 2133.
 (15) Uemura, S.; Fukuzawa, S. I.; Toshimitsu, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1501.
 (16) Woo, S. H. *Tetrahedron Lett.* **1993**, 34, 7587.
 (17) (a) Back, T. G.; Collins, S. *J. Org. Chem.* **1981**, 46, 3249. (b) Chretien, F.; Chapleur, Y. *J. Org. Chem.* **1988**, 53, 3615. (c) Hernández, R.; León, E. I.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1987**, 312. (d) Cossy, J.; Furet, N. *Tetrahedron Lett.* **1993**, 34, 7755.
 (18) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.* **2006**, 8, 565.
 (19) (a) Crich, D.; Huang, X. H. *J. Org. Chem.* **1999**, 64, 7218. (b) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1989**, 30, 4307. (c) Barton, D. H. R.; Lusini, X.; Milliet, P. *Tetrahedron* **1985**, 41, 4727.

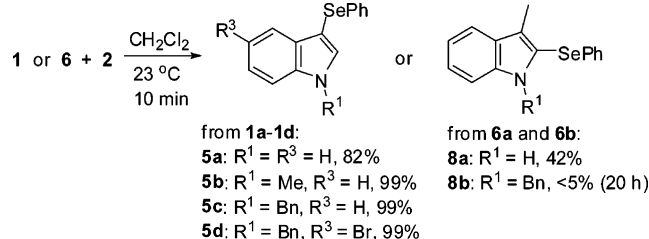
coupling can also take place at the 2-position of 3-substituted indoles. Treatment of 3-methylindoles **6a** and **6b** with **2** and styrene produced 2-alkylation products **7a** and **7b** in 66–68% yields, respectively (Scheme 1). Without a catalyst, the

Scheme 1. Three-Component Alkylation at the 2-Position of Indoles



three-component reaction did not occur, but the direct coupling of indoles and **2** afforded 3- and 2-phenylselenoin-

Scheme 2. Noncatalytic Coupling of Indoles and **2**



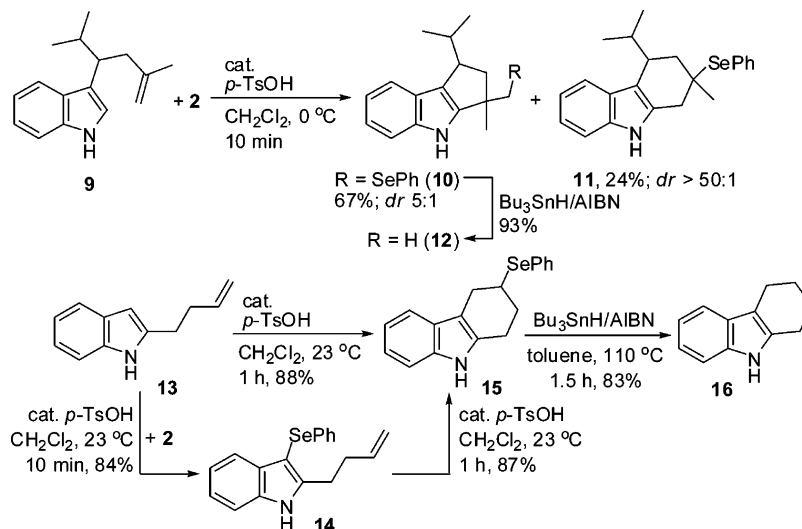
doles **5** and **8**, respectively (Scheme 2). In these two-component coupling reactions, the 2-position of an indole substrate demonstrated much lower reactivity than its 3-position. It should be noted that indole can couple with phenylselenenic anhydride or phenylselenenic acid to form 3-phenylselenoindole.^{19c}

3-Alkenyl indole **9** and **2** efficiently underwent intramolecular selenation–cyclization, generating ring-closure products **10** (67%) and **11** (24%) (Scheme 3). In a similar fashion, reaction of 2-alkenyl indole **13** with **2** exclusively afforded the six-membered ring-closure product **15** in 88% yield. It was found that intermediate **14** was initially formed during the reaction by TLC monitoring and then quickly converted to **15**. Thus **14** was isolated in 84% yield after the reaction was carried out for 10 min, and it was also transformed to **15** in 87% yield (Scheme 3). The selenation–cyclization products were additionally characterized by 2D NMR analysis (see the Supporting Information).

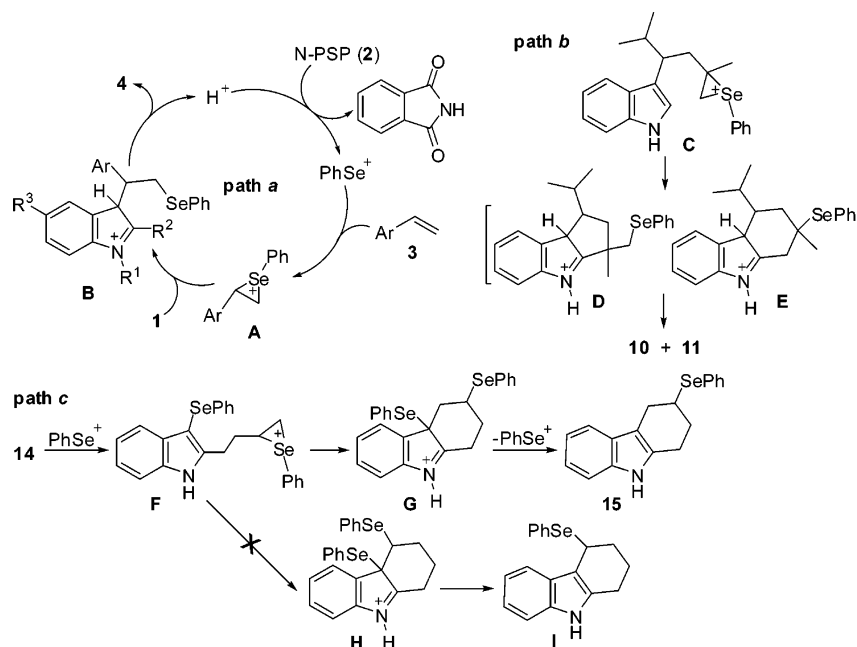
The mechanisms are proposed for formation of the selenation–alkylation products (Scheme 4). As shown in path *a*, the in situ generated cation PhSe^+ from the reaction of catalyst *p*-TsOH and **2** instantly reacts with styrene **3** to form cation **A**^{12–17} which electrophilically attacks indole **1** at its 3-position, producing intermediate **B**, and **B** releases a proton to form the product **4**. Compounds **7**, **10**, and **11** are considered to be formed in the same way, and species **C–E** may be involved in the formation of **10** and **11** (path *b*). Compound **15** is presumably formed via a different route (path *c*). The initially generated intermediate **14** reacts with PhSe^+ to form **F** which further undergoes intramolecular cyclization to form **G** instead of sterically hindered **H**. A PhSe group is deleted from **G** to afford **15**. This type of organocatalytic intramolecular cyclization of indoles is obviously different from those catalyzed by metals^{5,20} but similar to those sulfenium ion-promoted cyclizations.²¹

Treatment of **10**, **15**, **4a**, **4e**, and **4j** with $\text{Bu}_3\text{SnH/AIBN}$ in toluene at the refluxing temperature for 1.5 h efficiently produced alkyl-functionalized indoles **12**, **16**, and **17** in 83–99% yields (Schemes 3 and 5). Oxidation of **4e** with 30% H_2O_2 in THF afforded vinylindole **18** and PhSe -functionalized vinylindole **19** in 44 and 16% yields, respectively, while

Scheme 3. Intramolecular Selenated Alkylation of Indoles

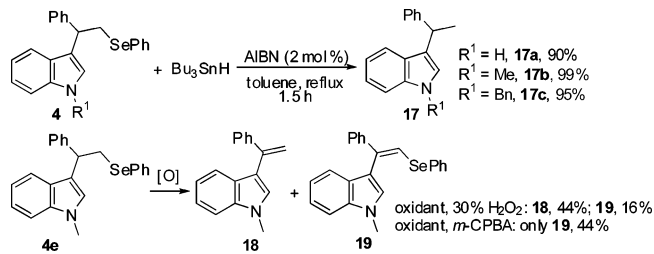


Scheme 4. The Proposed Mechanisms



treatment of **4e** with *m*-CPBA in CH_2Cl_2 exclusively generated **19** in 44% yield. It is noteworthy that *m*-CPBA usually

Scheme 5. Chemical Removal of a Phenylseleno Group



oxidizes PhSe compounds into phenylselenoxide derivatives.^{15,21} **19** can be considered as the intermediate to **18**,

and formation of **19** is a rare example in the oxidation of phenylseleno derivatives by *m*-CPBA.²²

In conclusion, we have developed a novel and efficient organocatalytic route to phenylseleno-functionalized indoles by inter- and intramolecular three-component Friedel–Crafts alkylations.

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Supporting Information Available: Experimental procedures, analytical data, copies of NMR spectra, and X-ray crystallographic data of **4r**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) (a) Kong, A. D.; Han, X. L.; Lu, X. Y. *Org. Lett.* **2006**, *8*, 1339. (b) Han, X. Q.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801. (c) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935.

(21) Edstrom, E. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334.

(22) Saluzzo, C.; Alvernhe, G.; Anker, D.; Haufe, G. *Tetrahedron Lett.* **1990**, *31*, 2127.