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Facile Regio- and Stereoselective Carbon–Carbon Coupling of Phenol Derivatives with Aryl Aziridines

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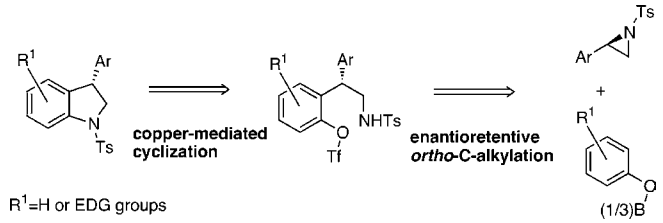
ABSTRACT



A chemo-, regio-, and stereoselective direct carbon–carbon coupling of readily available aryl borates with N-protected aryl aziridines provides a method for the synthesis of new 2-(*o*-hydroxyaryl)-2-aryl ethylamines which can be used, in a novel annulation sequence, to give stereodefined substituted 3-aryl indolines.

Phenol derivatives are of considerable importance for the chemical industry as pharmaceutical and fine chemicals. Hence, the development of a direct regio- and stereoselective C−C coupling reaction of phenols with readily available carbon electrophiles is an important area in organic synthesis. Aziridines are well-known carbon electrophiles capable of undergoing ring-opening reactions with various nucleophiles to give substituted amines.[1] The chemistry of aziridines is enriched with respect to that of epoxides by the presence of an additional valency on the heteroatom, allowing modular reactivity of these strained heterocycles.[2] Although carbanion nucleophilic addition to aziridines is well documented,[3] we are not aware of reactions of any kind of organometallic reagent, derived from ortho metalation of (protected) phenols, with aziridines to give arylated ethylamines. Furthermore, no direct regio- and stereoselective arylation of aziridines with phenol derivatives has been described. Only a few Friedel−Crafts reactions of arenes with activated aziridines to give mixtures of regioisomeric β-arylated ethylamines have been reported so far.[4] Recently, a practical synthesis of a gonanotropin-releasing hormone (GnRH) antagonist based on a regioselective opening of 2-alkyl nosylaziridines by indoles was described by Farr and co-workers. The reaction was mediated by BF_3-Et_2O and in the optimized reaction conditions was completely anti stereoselective.[5] On the other hand, Durst et al. reported that highly substituted aziridines could not be trapped in the C-3 position with highly nucleophilic indoles by the use of common Lewis acid catalysts such as BF_3-Et_2O and $SnCl_4$.[6] Very recently, we have reported a novel intermolecular Friedel−Crafts

(1) For a recent review, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
(2) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
(3) (a) Hassner, A.; Kascheres, A. *Tetrahedron Lett.* **1970**, *N*, 4623. (b) Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153. (c) Baldwin J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852. (d) Stamm, H.; Weib, R. *Synthesis* **1986**, 395. (e) Iwamoto, K.; Chatani, N.; Murai, S. *J. Org. Chem.* **2001**, *66*, 169. (f) Enders, D.; Janeck, C. F.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 3337. (g) Vicario, J. L.; Badia, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.
(4) (a) Stamm, H.; Onistaschenko, A.; Bucholz, B.; Mall, T. *J. Org. Chem.* **1989**, *53*, 193 and references therein. (b) Yadav, J. S.; Subba Reddy, B. V.; Srinivasa Rao, R.; Veerendhar, G.; Nagaiah, K. *Tetrahedron Lett.* **2001**, *42*, 8067.
(5) Farr, R. N.; Alabaster, R. J.; Chung, J. Y. L.; Craig, B.; Edwards, J. S.; Gibson, A. W.; Ho, G.-J.; Humprey, G. R.; Johnson, S. A.; Grabowski, E. J. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3503.
(6) Reddy, R.; Jaquith, J. B.; Neelagiri, V. R.; Saleh-Hanna, S.; Durst, T. *Org. Lett.* **2002**, *4*, 695.

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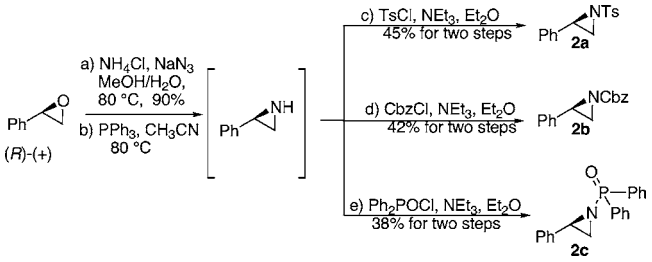
alkylation of phenolic substrates with aryl epoxides, in which, unfortunately, consistent amounts of O-alkylated products and low stereoselectivities were obtained in most cases.[7]

We report here a new carbon−carbon coupling reaction of phenol derivatives with aryl aziridines, proceeding under mild conditions, with a high regioselectivity and a high syn stereoselectivity, without the need for any external transition-metal catalysts or Lewis acids.

After the study of the epoxide ring opening, we hypothesized that the use of different protecting groups on the aziridine nitrogen might cause a different activation of the strained ring in the reaction with the aryl borate, thus causing a different chemo- (C- vs O-alkylation) and stereoselectivity, with respect to the same reaction performed with epoxides. To verify this working hypothesis, three different N-protected enantiomerically pure aziridines **2a**−**c** were prepared from commercially available optically active (*R*)-(+)-styrene oxide (99:1 er) via azidolysis and subsequent phosphine-mediated ring closure of the obtained azido alcohols (Scheme 1). The

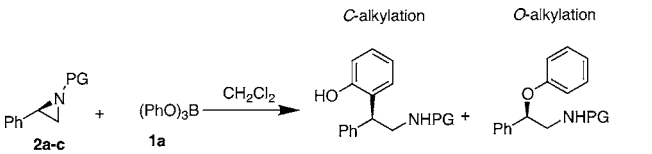
Scheme 1. Synthesis of Enantiomerically Enriched N-Protected Aziridines **2a**−**c**



crude NH aziridines were not isolated but were directly derivatized to give the corresponding protected *N*-tosyl (**2a**), *N*-benzyloxy carbonyl (**2b**), and *N*-diphenyl phosphinyl aziridine (**2c**) with no loss of optical purity.[8]

In preliminary experiments, we found that the reaction of simple triphenyl borate **1a** with optically pure N-protected aziridines **2a**−**c** occurred in CH_2Cl_2 at −78 °C to give an almost equimolar mixture of C- and O-alkylated products of type **3** and **4** (Scheme 2).[9] The new carbon−carbon bond was formed with complete regioselectivity at the benzylic position of the aziridine ring and at the ortho position of the phenol derivative.

Scheme 2. Friedel−Crafts Alkylation of the N-Protected Aziridines **2a**−**c** Derived from (*R*)-(+)-Styrene Oxide (99:1 er) with Triphenyl Borate (**1a**)



2a, PG=Ts	-78 °C, 16 h	**3aa**, 60% (81:19 er)	**4aa**, 40% (82:18 er)
2b, PG=Cbz	-78 °C, 2 h	**3ba**, 50% (87:13 er)	**4ba**, 50% (69:31 er)
2c, PG=P(O)Ph_2	-78 °C, 16 h	**3ca**, 41% (96:4 er)	**4ca**, 59% (85:15 er)

In this reaction, the correct choice of the N-protecting group turned out to be important to determine the extent of epimerization of the C-alkylation process. The lower extent of epimerization (96% er) was found with aziridine **2c**, bearing the *N*-diphenylphosphinyl protecting group described by Sweeney et al.[8]

The use of electron-rich borates such as **1b**−**d** with optically active aziridines **2a**−**c** proved to be particularly fruitful providing a dramatic increase in the C-alkylation pathway and allowing a novel entry to the corresponding optically active unsymmetrical 2,2-diaryl ethylamines of type **3** which are very difficult to obtain by other routes (Table 2).[10] For example, the reactions of aziridines **2a**−**c** with tris-(3,5-dimethylphenyl)borate (**1b**) gave the corresponding C-alkylated products **3ab**, **3bb**, and **3cb**, with good yields and a high chemoselectivity and syn stereoselectivity (entries 1−3, Table 1). Similar results were obtained with the reactions of borates **1c** and **1d** on **2b** (entries 4 and 5). The syn−anti stereoselectivities, demonstrated by cyclization to indolines (vide infra), were determined by HPLC on chiral columns and were particularly high with *N*-diphenylphosphinyl-protected aziridine **2c** (entry 3). On the other hand, the use of *p*-methoxyphenyl borate **1e** gave the corresponding diaryl ethylamine **3be** with a lower chemo- and stereoselectivity (entry 6). In borate **1a**, the *p*-methoxy group reduces the electron density at the reactive ortho position by means of the associated inductive electron-withdrawing effect.[11] In contrast, in borates **1b**−**d** in which the corresponding reactive ortho positions are particularly electron-rich due to inductive or mesomeric effects, a fast chemo- and stereoselective C-alkylation reaction was obtained.

Whereas substituted styrenyl aziridines bearing electron-withdrawing groups (*p*-nitro, *o*-nitro, *o*-bromo) proved to be unreactive, racemic *p*-fluorophenyl aziridine **2d** and *p*-methylaziridine **2e** underwent the reaction under mild conditions and with a high chemo- and regioselectivity (Table 1, entries 7 and 8). The use of disubstituted *trans*-aryl aziridine **2f** gave the corresponding C-alkylated ring-opened product **3fd** with complete syn stereoselectivity and a high yield (entry 9).[12]

As aryl triflates can be readily obtained from the corresponding phenols, they are valuable starting materials in

(7) Bertolini, F.; Crotti, P.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 61.

(8) Osborn, H. M. I.; Sweeney, J. B.; Howson, B. *Synlett* **1994**, 145.

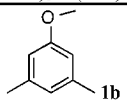
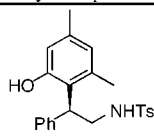
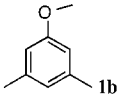
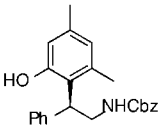
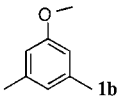
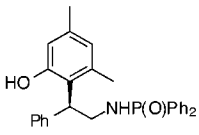
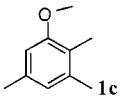
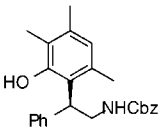
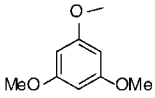
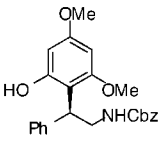
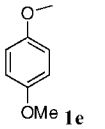
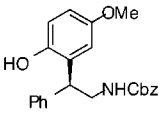
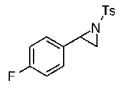
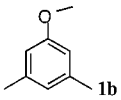
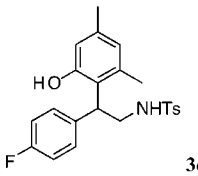
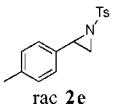
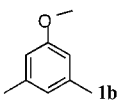
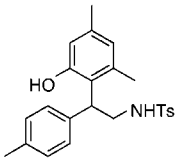
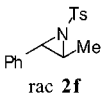
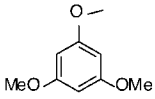
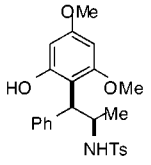
(9) **General Procedure:** A solution of freshly prepared aryl borate **1a**−**e** (1.5 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of aziridine (1.0 mmol) in CH_2Cl_2 (3.0 mL) under Ar. The reaction was followed by TLC and quenched with brine (4.0 mL). The solution was diluted with Et_2O or CH_2Cl_2 (40 mL) and washed with brine. Evaporation of the dried organic solution afforded a crude reaction mixture that was purified by silica gel chromatography to give the corresponding pure products.

(10) For a general approach to 2,2-diaryl ethylamines devoid of the phenolic functionality, see: Maryanoff, B. E.; Nortey, S.; Gardocki, J. F. *J. Med. Chem.* **1984**, *27*, 1067.

(11) Moreover, it should be considered that the electron density on phenolic oxygen is low because of $p_\pi-p_\pi$ back-bonding with the boron atom. For a study of the Lewis acidity of the boron atom in triarylborates, see: (a) Fenwick, J. T. F.; Wilson, J. W. *Inorg. Chem.* **1975**, *14*, 1602. For a recent report on the catalytic activity of borate esters, see: (b) Yasuda, M.; Yoshioka, S.; Yamasaki, S.; Somyo, T.; Chiba, K.; Baba, A. *Org. Lett.* **2006**, *8*, 761.

(12) However, with some disubstituted aziridines and aryl borates, lower yields and stereoselectivities were obtained. For other examples of the use of disubstituted aziridines, see Supporting Information.

Table 1. Synthesis of New Phenolic Ethylamines by Coupling of Protected Aziridines with Electron-Rich Aryl Borates[a]

entry	aziridines	conditions	$(ArO)_3B$ (Ar=)[c]	*C*-alk /*O*-alk[d]	*C*-alkylated product (yield%)[e]	*syn/anti* (%)[f]
1	(*R*)-**2a**[b]	-78 °C, 2 h	 **1b**	94/6	 **3ab** (73)	95/5
2	(*R*)-**2b**[b]	-78 °C, 16 h	 **1b**	>95/<5	 **3bb** (51)	98/2
3	(*R*)-**2c**[b]	-78 °C, 2 h	 **1b**	>95/<5	 **3cb** (70)	>99/<1
4	(*R*)-**2b**[b]	-78 °C, 2 h	 **1c**	>95/<5	 **3bc** (40)	>99/<1
5	(*R*)-**2b**[b]	-78 °C, 1 h	 **1d**	>95/<5	 **3bd** (88)	98/2
6	(*R*)-**2b**[b]	-78 °C, 2 h	 **1e**	73/27	 **3be** (59)	81/19
7	 rac **2d**	-78 °C, 1 h	 **1b**	>95/<5	 **3db** (87)	N/A
8	 rac **2e**	-78 °C, 24 h	 **1b**	>95/<5	 **3eb** (65)	N/A
9	 rac **2f**	-78 °C, 14 h	 **1d**	>95/<5	 **3fd** (85)	>98/<2

[a] All reactions were carried out in accordance with the general procedure.[9] [b] Obtained from (*R*)-(+)-styrene oxide (see Scheme 1). [c] All phenols were treated with BH_3-Me_2S to form the corresponding aryl borates immediately before use (see Supporting Information). [d] Determined by ^1H NMR examination of the crude reaction mixture. [e] Isolated yield after chromatography on silica gel. [f] Determined by chiral HPLC analysis on the basis of the initial enantiomer distribution of the starting aziridine (99:1 er).

many types of metal-catalyzed coupling reactions.[13] We envisaged the possibility of an intramolecular ring closure to give substituted 3-aryl indolines, which are important chiral constituents of a number of biologically active compounds.[14] Despite the outstanding recent progress in *intermolecular* C−N bond-forming reactions using aryl halides and Pd-[15] or Cu-catalyzed catalytic systems,[16] only a few examples of the coupling of amides with aryl triflates

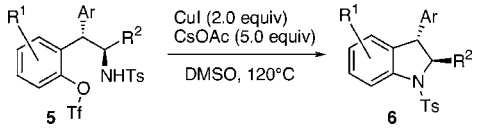
(13) For a review, see: (a) Ritter, K. *Synthesis* **1993**, 735. For recent reports on their preparation, see: (b) Bengston, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, *4*, 1231. (c) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717.

(14) For a recent highly enantioselective synthesis of chiral 3-substituted indolines by catalytic asymmetric hydrogenation of indoles, see: Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213 and pertinent references therein.

(15) For reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

have been disclosed.[17] Moreover, we are aware of only one report on *intramolecular* amination using an aryl triflate.[18] A solution was found in the CuI/CsOAc-mediated intramolecular amination developed by Fukuyama and co-workers for aryl bromides and iodides.[19] In preliminary experiments, the application of the original reaction conditions (DMSO, room temperature or 90 °C) to aryl triflate **5ab** gave the corresponding indoline **6ab** with very low yields (<10%), but a simple increase in the reaction temperature to 120 °C gave complete conversion in 12 h; indoline **6ab** was isolated in 72% yield after chromatographic purification (entry 1, Table 2).

Table 2. Synthesis of 3-Aryl Indolines by Intramolecular Copper-Mediated Ring Closure of Sulfonamidic Aryl Triflates[a]



entry	R^1	R^2	Ar (**N°**)	time (h)	yield (%)[b]
1	3,5-di-Me	H	Ph (**5ab**)	12	72 (**6ab**)
2	4-Me	H	Ph (**5af**)	12	77 (**6af**)
3	H	H	Ph (**5aa**)	12	45 (**6aa**)
4	3,5-di-Me	H	*p*-F-C_6H_4 (**5db**)	12	90 (**6db**)
5	3,5-di-OMe	Me	Ph (**5fd**)	12	22 (**6fd**)

[a] Reactions carried out at 120 °C in accordance with the general procedure reported in the Supporting Information. [b] Isolated yields after chromatographic purification on silica gel.

The optimized reaction conditions were applied to other sulfonamidic triflates of type **5**, giving rapid and versatile access to the corresponding 3-aryl indolines of type **6** (entries 2−4). The application of this procedure to triflate **5fd** derived from the ring opening of a disubstituted aziridine such as **2f** afforded the corresponding *trans* 2,3-substituted indoline **6fd**, albeit with a lower isolated yield (entry 5).[20] By means of copper-mediated intramolecular amidation, it was also possible to establish unequivocally the relative and absolute configuration of the original phenolic 2-aryl ethylamines of type **3** (see Supporting Information for details).

To sum up, an easy regioselective C-functionalization of hydroxy arenes to give 2-(*o*-hydroxyaryl)-2-aryl ethylamines has been realized. The reaction occurs with aryl aziridines at a remarkably low temperature and neutral conditions with retention of configuration at the cleaved center. Starting from readily available aryl borates and activated (enantiomerically enriched) aryl aziridines, it is now possible to access stereodefined substituted 3-aryl indolines by way of a novel and versatile procedure.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a recent mechanistic study of the Goldberg amidation reactions, see: Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120 and references therein.

(17) (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (b) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

(18) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *3*, 1141. In this case, the mitomycin core ring system was obtained in moderate yields by means of a $Pd(OAc)_2$/BINAP catalytic system, but application of this reaction procedure to a compound of type **5** bearing the free amine functionality (Table 2, scheme) proved to be ineffective. Likewise, the use of enhanced versions of the Goldberg amidation reaction developed by Buchwald and co-workers[16] proved to be unsuccessful for the intramolecular ring closure of triflates **5**.

(19) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.

(20) It should be noted that *trans* 2,3-substituted indolines are difficult to obtain by other routes and cannot be obtained by catalytic hydrogenation of the corresponding 2,3-substituted indoles. For an efficient synthesis of 2,3-disubstituted indoles, see: (a) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (b) For a review of indole synthesis, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.