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Nucleophilic Addition of Phenol Derivatives to Methyl 1-Nitrocyclopropanecarboxylates

Olga Lifchits, Dino Alberico, Irina Zakharian, and André B. Charette*

Department of Chemistry, Université de Montréal, P. O. 6128, Station Downtown, Montréal, Quebec, Canada H3C 3J7

andre.charette@umontreal.ca

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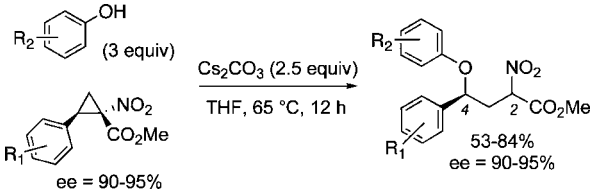
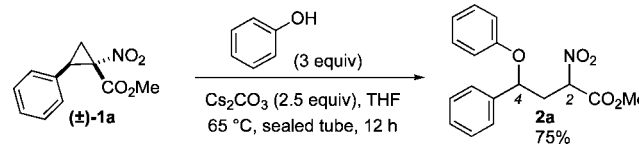


Nucleophilic ring opening of methyl 1-nitrocyclopropanecarboxylates by phenol derivatives in the presence of Cs_2CO_3 is described. The reaction tolerates a variety of substituents on both the aromatic alcohol and the cyclopropane and affords the products in good yields (53−84%) and with complete preservation of the enantiomeric excess at C-4. The methodology was applied in an enantioselective synthesis of the norepinephrine reuptake inhibitor atomoxetine (Strattera).

Activated cyclopropanes have found wide use in organic synthesis as versatile electrophilic or 1,3-zwitterionic synthons.[1–3] In particular, their ring opening by heteroatom nucleophiles can serve as a facile route to 1,3-bifunctional molecules that are present in the core of many small molecules with biological or pharmaceutical activity.[4]

SCHEME 1. Optimized Reaction Conditions for the Nucleophilic Ring Opening of Cyclopropane (±)-1a with Phenol



Our group has recently reported efficient methodologies to generate racemic[5] and enantioenriched[6] 1-nitrocyclopropyl carbonyls, which have been used in the synthesis of cyclopropane α-amino acids[7] and esters,[6,7] and substituted dihydropyrroles and pyrroles.[2c] Most recently, we have shown that these cyclopropanes can undergo Lewis acid catalyzed ring opening by amine nucleophiles with complete preservation of the enantiomeric excess from the cyclopropane.[8] As a further extension of this methodology, we now report the addition of aromatic alcohols[9] to cyclopropanes of type **1** (Scheme 1). The 3-aryl-3-phenoxypropane motif generated in the ring-opened products is present in the core structure of several monoamine reuptake inhibitors (Figure 1).[10,11] These compounds are widely used in the clinical treatment of various psychiatric disorders including attention deficit hyperactivity disorder (ADHD) and anxiety and depression (atomoxetine, fluoxetine),[10] as well as in biochemical research (nisoxetine).[11]

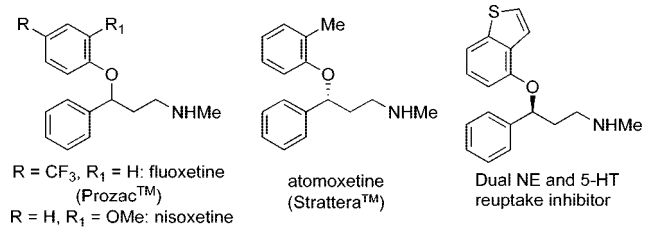


FIGURE 1. Examples of monoamine reuptake inhibitors containing a 3-aryl-3-phenoxypropylamine motif.

We began our studies by examining the nucleophilic ring opening of racemic cyclopropane (±)-**1a** with phenol. Several bases and numbers of equivalents were examined, and Cs_2CO_3 (2.5 equiv) proved to be optimal. By screening solvents and reaction temperatures, we found that stirring the reaction mixture in tetrahydrofuran at 65 °C in a sealed tube for 12 h led to a clean reaction with complete conversion and a good isolated yield of **2a** (Scheme 1).

With the optimal conditions in hand, we examined the scope of the ring opening reaction, first employing the readily

(1) For reviews, see: (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239. (b) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (d) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (e) Burritt, A.; Coron, J. M.; Steel, P. J. *Trends Org. Chem.* **1993**, *4*, 517.

(2) For examples of reactions and reaction cascades involving ring opening of electrophilic cyclopropanes, see: (a) Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709. (b) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017. (c) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (d) Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett.* **2006**, *47*, 647. (e) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992.

(3) For recent examples of [2 + 3]-cycloaddition reactions of cyclopropanes, see: (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (b) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (c) Perreault, C.; Goudreau, S.; Zimmer, L.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (d) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (e) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.

(4) See, for example: (a) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2091. (b) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331. (c) Bose, G.; Langer, P. *Tetrahedron Lett.* **2004**, *45*, 3861.

(5) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327.

(6) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.

(7) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262.

(8) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809.

(9) Few examples of the addition of aromatic alcohols to electrophilic cyclopropanes have been reported and involve only racemic or achiral starting materials: (a) Seebach, D.; Haener, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507. (b) Schweizer, E. E.; Berniger, C. J.; Thompson, J. G. *J. Org. Chem.* **1968**, *33*, 336. (c) Fuchs, P. L. *J. Am. Chem. Soc.* **1974**, *96*, 1607. (d) Stewart, J. M.; Westberg, H. H. *J. Org. Chem.* **1965**, *30*, 1951.

(10) Walter, M. W. *Drug Dev. Res.* **2005**, *65*, 97.

(11) Graham, D.; Langer, S. Z. *Life Sci.* **1992**, *51*, 631.

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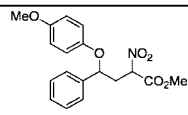
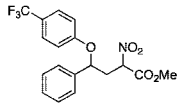
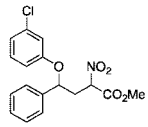
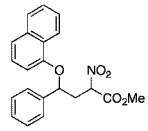
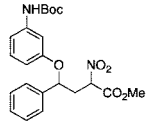
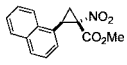
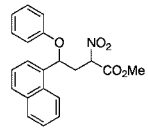
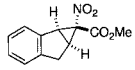
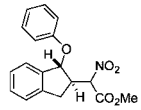
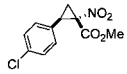
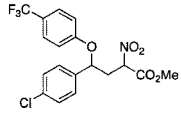
TABLE 1. Scope of the Cyclopropane Ring-Opening Reaction with Phenol Derivatives

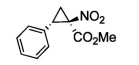
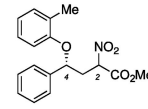
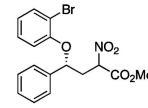
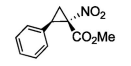
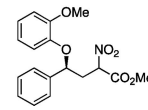
entry	cyclopropane	ArOH	Product		yield (%)[a,b]
1	**(±)-1a**	*p*-MeO-Ph		**2b**	68
2	**(±)-1a**	*p*-CF_3-Ph		**2c**	84[c]
3	**(±)-1a**	*m*-Cl-Ph		**2d**	57
4	**(±)-1a**	1-naphthyl		**2e**	53
5	**(±)-1a**	*m*-NHBoc-Ph		**2f**	72
6	 **1b**	Ph		**2g**	58
7	 **1c**	Ph		**2h**	59
8	 **1d**	*p*-CF_3-Ph		**2i**	74

[a] Reaction conditions: **1** (1 equiv), ArOH (3 equiv), Cs_2CO_3 (2.5 equiv), THF (0.2 M), 65 °C (sealed tube), 12 h. [b] Isolated yield. [c] Reaction performed on 1 g scale under reflux.

synthesized racemic cyclopropanes **1a**−**1d**[5] and various aromatic alcohols (Table 1). Phenol derivatives substituted with both electron-donating (entry 1) and electron-withdrawing (entry 2) substituents were well tolerated. Slightly lower yields were obtained with *m*-chlorophenol (entry 3) and with the bulkier 1-naphthol (entry 4). Phenol bearing a Boc-protected amine group (entry 5) afforded the desired product in good yield. Varying the 2-substituents on the electrophilic cyclopropane to more sterically encumbered naphthyl (entry 6) and indenyl (entry 7) groups resulted in slightly lower but synthetically useful yields. The presence of substituents on both the nucleophile and the electrophile (entry 8) was unproblematic, and the desired functionalized product was obtained in a good yield. In all cases the adducts were isolated as mixtures of interconvertible diastereomers at C-2 in an approximately 1:1 ratio except for **2k** (60:40 dr) and **2l** (70:30 dr).[12] We were pleased to find that the reaction could be easily scaled up: nucleophilic addition of the *p*-(trifluoromethyl)phenol (entry 3) on a 1 g scale under reflux cleanly afforded 1.5 g of **2d**, a potential fluoxetine precursor (84% yield).

(12) Crystalline compound **2h** was furthermore seen to undergo a self-catalyzed enrichment of the diastereomeric ratio at C-2 to 90:10 in the solid state. See Supporting Information for details.

TABLE 2. Ring Opening of Enantioenriched Cyclopropanes

entry	cyclopropane (% ee)	ArOH	product		yield (%),[a,b] (% ee)
1	 (1*R*,2*S*)-**1a** (90)	*o*-Me-Ph		**2j**	76 (90)
2	(1*R*,2*S*)-**1a** (90)	*o*-Br-Ph		**2k**	74 (90)
3	 (1*S*,2*R*)-**1a** (95)	*o*-MeO-Ph		**2l**	78 (95)

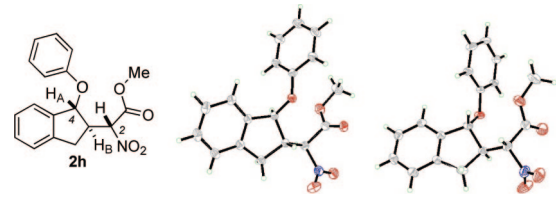
[a] Reaction conditions: **1** (1 equiv), ArOH (3 equiv), Cs_2CO_3 (2.5 equiv), THF (0.2 M), 65 °C (sealed tube), 12 h. [b] Isolated yield.

We next turned our attention to the ring opening of enantioenriched cyclopropanes as a method to access nonracemic adducts. Indeed, ring opening of (1*R*,2*S*)-**1a** (90% ee)[6] with *o*-cresol afforded the product with complete preservation of the enantiomeric excess and an inversion of the absolute configuration at C-4 via an S_N2 pathway (Table 2, entry 1).[13] Similarly, the addition of *o*-bromophenol to (1*R*,2*S*)-**1a** (entry 2) afforded the adduct **2k** in 74% yield and with 90% ee. Ring opening of (1*S*,2*R*)-**1a** (95% ee) with *o*-methoxyphenol (entry 3) gave **2l**, a potential (*R*)-nisoxetine precursor, in a 78% yield and with 95% ee.

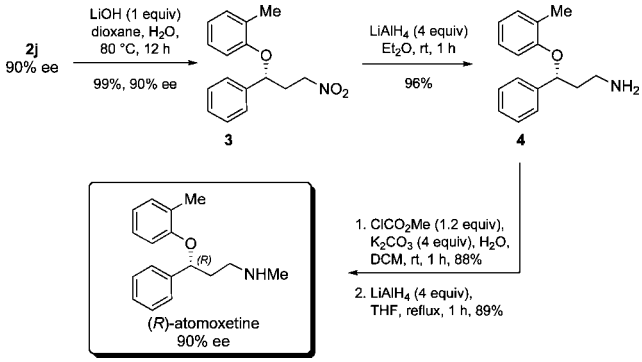
Having established a route to the enantioenriched products, we then applied the methodology to the synthesis of (*R*)-atomoxetine (Strattera), a selective norepinephrine inhibitor used in the treatment of ADHD (Scheme 2).[10] Starting from the enantioenriched adduct **2j** (90% ee), the ester group was saponified and decarboxylated with aqueous LiOH to give the nitropropyl intermediate **3** in 99% yield and without any loss of the optical purity. The nitro group was reduced with $LiAlH_4$ to a primary amine affording compound **4** in 96% yield. Monomethylation of the amine via a carbamate intermediate gave (*R*)-atomoxetine in an overall yield of 74% from **2j** and 90% ee.

In conclusion, we have developed a simple and practical method for the nucleophilic ring opening of methyl 1-nitrocyclopropyl carboxylates with phenol derivatives. The reaction

(13) The absolute configuration of **2j** and hence the S_N2 pathway was established by comparing the optical rotation of the corresponding derivative **6** with the literature value (see Supporting information for data; see ref 6 for the absolute configuration of the starting cyclopropane **1a**). The absolute confiiguration of **2k** and **2l** was assigned by analogy. X-ray diffraction analysis of cocyrstallized enantiomers **2h** confirmed the expected trans-relationship of H_A and H_B, serving as further proof of the S_N2 inversion at C-4 in the ring opening reaction.



SCHEME 2. Enantioselective Synthesis of Atomoxetine



tolerates a variety of substituents on both the aromatic alcohol and the cyclopropane and affords products with complete retention of the enantiomeric excess stemming from the cyclopropane. The methodology was applied to an expedient and high-yielding enantioselective synthesis of the norepinephrine reuptake inhibitor atomoxetine (Strattera).

Experimental Section

General Procedure for Ring Opening of Cyclopropanes 1 with Phenol Derivatives. In an oven-dried 2-mL microwave vial, cyclopropane **1** (0.45 mmol, 1 equiv) was combined with the appropriate phenol derivative (1.36 mmol, 3 equiv), anhydrous Cs_2CO_3 (0.32 g, 1.13 mmol, 2.5 equiv), and anhydrous tetrahydrofuran (2 mL). The vial was sealed with a Teflon cap, and the reaction mixture was stirred at 65 °C in an oil bath for 12 h, quenched with saturated aqueous NH_4Cl (5 mL), and partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (10 mL) three times, and the combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography eluting with 100% benzene afforded the spectroscopically pure product (method A). In the cases in which the remaining excess phenol derivative was difficult to separate by flash chromatography, it was removed by the following aqueous workup (method B): The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the mixture partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (10 mL) three times, and the combined organic layers were washed with 0.1 M NaOH (5 mL) three times, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography eluting with 10−20% EtOAc/hexane afforded the spectroscopically pure product.

On large scale, the reaction was performed in a round-bottom flask equipped with a reflux condenser and heated at reflux in an oil bath for 12 h.

Specific Procedure for Synthesis of Methyl (4*R*)-4-(2-Methylphenoxy)-2-nitro-4-phenylbutanoate (2j). In a 2-mL microwave vial equipped with a stirbar, cyclopropane (1*R*,2*S*)-**1a**[6] (100.0 mg, 0.45 mmol, 1 equiv, 90% ee), *o*-cresol (146.6 mg, 1.36 mmol, 3 equiv), and anhydrous Cs_2CO_3 (317.3 mg, 1.13 mmol, 2.5 equiv) were combined with anhydrous THF (2 mL), and the vial was sealed with a Teflon cap. The reaction mixture was stirred at 65 °C for 12 h, quenched with saturated aqueous NH_4Cl (5 mL), and partitioned between water and diethyl ether. The aqueous layer was extracted with diethyl ether (10 mL) three times, and the combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography eluting with 100% benzene afforded the spectroscopically pure product as a pale yellow solid (112.4 mg, 0.34 mmol, 76%, 50:50 dr, 90% ee). Mp 83−90 °C; R_f = 0.69 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of 2 diastereomers d_1 and d_2) δ 7.41−7.28 (m, 5H), 7.13 (d, J = 7.3 Hz, 1H), 6.99−6.92 (m, 1H), 6.84−6.79 (m, 1H), 6.57 (d, J = 7.6 Hz, 1H^{d1}), 6.52 (d, J = 7.3 Hz, 1H^{d2}), 5.59 (dd, J = 3.5 Hz, 10.5 Hz, 1H^{d1}), 5.37−5.31 (m, 1H^{d2} + 1H^{d1}), 5.25 (dd, J = 3.2 Hz, 9.3 Hz, 1H^{d2}), 3.83 (s, 3H^{d1}), 3.81 (s, 3H^{d2}), 3.08−2.90 (m, 1H), 2.81−2.71 (m, 1H), 2.32 (s, 3H^{d1}), 2.30 (s, 3H^{d2}); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of 2 diastereomers) δ 165.0, 164.7, 155.0, 154.9, 139.5, 139.4, 130.9, 130.8, 129.02, 129.00, 128.4, 128.3, 127.1, 126.9, 126.6, 126.5, 125.8, 125.6, 121.0, 120.9, 112.6, 112.4, 85.1, 75.2, 53.73, 53.72, 39.1, 38.9, 16.4, 16.3; FTIR (neat) 3708, 3680, 2951, 2844, 1754, 1561, 1454, 1235, 1053, 1121, 750, 701 cm^{-1}; HRMS calcd for $C_{18}H_{18}NO_5$ (M − H)$^-$ 328.1191, found 328.1195. SFC (Chiralcel OD-H, 3% MeOH, 2 mL/min, 200 bar, 30 °C) t_R 5.7 min (minor enantiomer, d_1), t_R 6.4 min (minor enantiomer, d_2), t_R 7.0 min (major enantiomer, d_2), t_R 8.5 min (major enantiomer, d_1).

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Supporting Information Available: General information, specific experimental conditions, characterization data for all new compounds, NMR spectra, SFC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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