Synthesis of Polysubstituted Benzenes via the Tandem Addition-Rearrangement Aryne Reaction of Substituted 2-Bromoanisoles and Lithioarenenitriles

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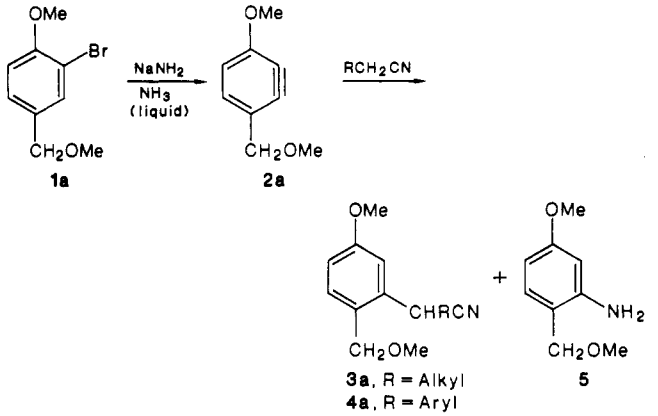
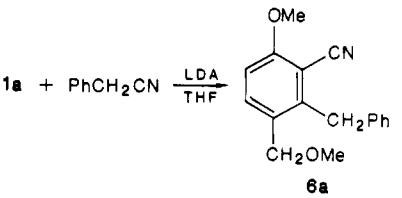
Lithioarenenitriles add regiospecifically to substituted 3-methoxybenzynes generated in situ from the corresponding haloarenes by using lithium diisopropylamide as a base. The addition to methoxybenzynes substituted with an electron-releasing group is followed by rearrangement to substituted 2-cyano-3-(arylmethyl)anisoles. The rearrangement pathway involves cyclization of the initially formed nitrile–aryne adducts to benzocyclobutanone imines which are converted to rearranged products after ring opening and neutralization. In contrast, 3-methoxybenzynes substituted with an electron-attracting group proceed via the usual aryne pathway, yielding products of simple anion addition. Disubstituted 3-methoxybenzynes possessing an electron-releasing group and an electron-attracting substituent yield mixtures of rearranged and typical nitrile products. An explanation in terms of the ability of the substituents to influence the nucleophilicity of the 2-lithio cyclization site of the initially formed nitrile–aryne adduct is presented.

Introduction

We[1] recently reported a synthetic route to 4-alkyl- and 4-aryl-substituted isochroman-3-ones which involved as the key step the synthesis of α-alkyl- and α-aryl-2,5-bis(methoxymethyl)phenylacetonitriles via the addition of anions of alkyl- and arylacetonitriles to the symmetrical 3,6-bis(methoxymethyl)benzyne. In order to extend this method to the synthesis of methoxy-substituted isochroman-3-ones, we[2] examined the addition of the anions of nitriles to the unsymmetrical aryne, 3-methoxy-6-(methoxymethyl)benzyne (**2a**), generated by the action of sodamide on 2-bromo-4-(methoxymethyl)anisole (**1a**) in liquid ammonia. Satisfactory yields (45–50%) of α-alkyl-2-(methoxymethyl)-5-methoxyphenylacetonitriles **3a** were obtained from the reaction of **1a** with alkyl acetonitriles. However, the α-aryl-2-(methoxymethyl)-5-methoxyphenylacetonitriles **4a** were obtained in poor yields (15–25%) when arylacetonitriles were used; the major product in all reactions was 5-methoxy-2-(methoxymethyl)aniline (**5**) (40–60%), resulting from the amination of **2a** by the liquid ammonia solvent.

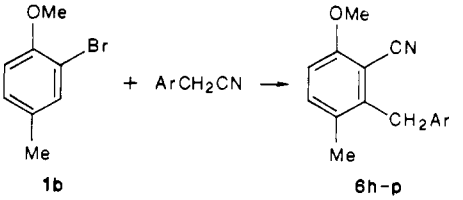


The use of lithium diisopropylamide (LDA) as a base in tetrahydrofuran was investigated in order to improve the yields of **4a**. Interestingly, the preliminary studies[3] on the reaction of **1a** with phenylacetonitrile and LDA did not yield the expected simple anion addition product, α-phenyl-2-(methoxymethyl)-5-methoxyphenylacetonitrile.



Instead, it gave the rearranged nitrile, 2-cyano-3-benzyl-4-(methoxymethyl)anisole (**6a**) in 43% yield. Although this reaction is not appropriate for the synthesis of isochromanones since the cyano and methoxymethyl groups in the rearranged products are not suitably configured for required cyclization, it is still worthy of further study since two groups (cyano and arylmethyl) are introduced simultaneously on to an aromatic ring. To obtain information on the scope and mechanism of this reaction, we[4] studied the reaction of various methyl- and methoxy-substituted 2-bromoanisoles and various aromatic acetonitriles using LDA as base and report the results herein.

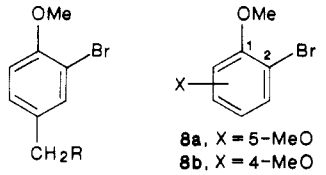
2-Bromo-4-methylanisole (**1b**) was first studied and was found to give in all cases the rearranged products, 3-(arylmethyl)-2-cyano-4-methylanisoles **6h–p**, in good to moderate yields; no detectable amounts of the simple anion addition products were observed. For example, the reaction of **1b** (entry 12) with 3,4-dimethoxyphenylacetonitrile gave 2-cyano-3-(3′,4′-dimethoxybenzyl)-4-methylanisole (**6l**) in 83% yield. The products were identified on the basis of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Additionally, the structure of 2-cyano-3-(3′-methoxy-



(1) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 1333.
(2) Unpublished report presented: Khanapure, S. P.; Biehl, E. R. *Abstract of Papers*, 191st National Meeting of the American Chemical Society, New York, NY; American Chemical Society: Washington, D.C., 1986; ORGN 096.
(3) Crenshaw, L. C. M.S. Thesis, Southern Methodist University, 1988.
(4) A preliminary account of this work was reported at the 194th National Meeting of the American Chemical Society, New Orleans, LA; Khanapure, S. P.; Crenshaw, L.; Reddy, T. R.; Biehl, E. R. *Abstract of Papers*; American Chemical Society: Washington, D.C., 1987; ORGN 0054.

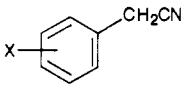
0022-3263/88/1953-4915$01.50/0

Table I. Reaction of Haloarenes 1a,b and 8a,b with Arenenitriles 3a–j

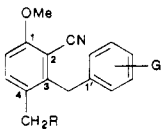
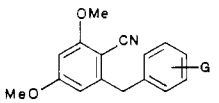


1a, R = OMe
1b, R = H

8a, X = 5-MeO
8b, X = 4-MeO



3a, X = H
3b, X = 2-MeO
3c, X = 3-MeO
3d, X = 4-MeO
3e, X = 3, 4-di-MeO
3f, X = 3,5-di-MeO
3g, X = 3,4,5-tri-MeO
3h, X = 2-F
3i, X = 3-F
3j, X = 4-F

entry	haloarene	arene-nitrile	product[a]	yield,[b] %
				
1	1a	3a	**6a**, R = OMe; G = H	43
2	1a	3b	**6b**, R = OMe; G = 2′-MeO	16
3	1a	3c	**6c**, R = OMe; G = 3′-MeO	48
4	1a	3d	**6d**, R = OMe; G = 4′-MeO	36
5	1a	3g	**6e**, R = OMe; G = 3′,4′,5′-tri-MeO	16
6	1a	3h	**6f**, R = OMe; G = 2′-F	30
7	1a	3j	**6g**, R = OMe; G = 4′-F	18
8	1b	3a	**6h**, R = G = H	65
9	1b	3b	**6i**, R = H; G = 2′-MeO	33
10	1b	3c	**6j**, R = H; G = 3′-MeO	48
11	1b	3d	**6k**, R = H; G = 4′-MeO	34
12	1b	3e	**6l**, R = H; G = 3′,4′-di-MeO	83
13	1b	3g	**6m**, R = H; G = 3′,4′,5′-tri-MeO	26
14	1b	3h	**6n**, R = H; G = 2′-F	23
15	1b	3i	**6o**, R = H; G = 3′-F	26
16	1b	3j	**6p**, R = H; G = 4′-F	35
				
17	8a	3b	**6q**, G = 2′-MeO	35
18	8a	3c	**6r**, G = 3′-MeO	43[c]
19	8a	3d	**6s**, G = 4′-MeO	41[c]
20	8a	3f	**6t**, G = 3′,5′-di-MeO	30

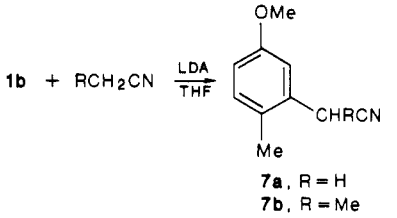
[a] All new compounds have been fully characterized by spectral means and have satisfactory analyses. [b] Yields are based on pure products isolated by flash column chromatography over silica gel. [c] 10–15% simple anion addition product was isolated.

benzyl)-4-methylanisole (**6j**) was determined by X-ray crystallography.[5]

Interestingly, the reaction of **1b** with acetonitrile and propionitrile gave only simple anion addition products **7a** and **7b**, respectively; no rearranged nitriles were detected.

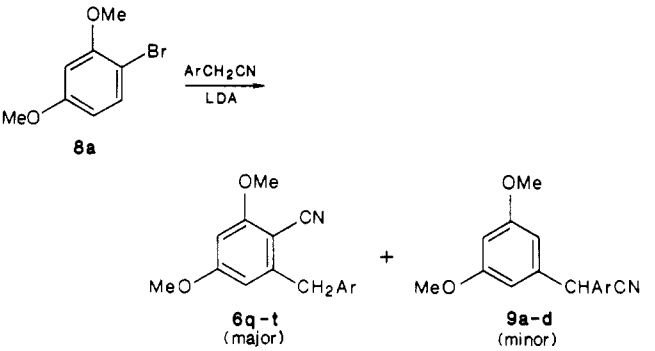
The reaction of two dimethoxybromobenzenes, i.e., 2-bromo-1,5-dimethoxybenzene (**8a**) and 2-bromo-1,4-dimethoxybenzene (**8b**), with arylacetonitriles were studied next. Of these, **8a** gave rearranged compounds (**6q–t**) as

(5) Siriwardane, U.; Khanapure, S. P.; Biehl, E. R. *Acta Crystallogr.*, in press.



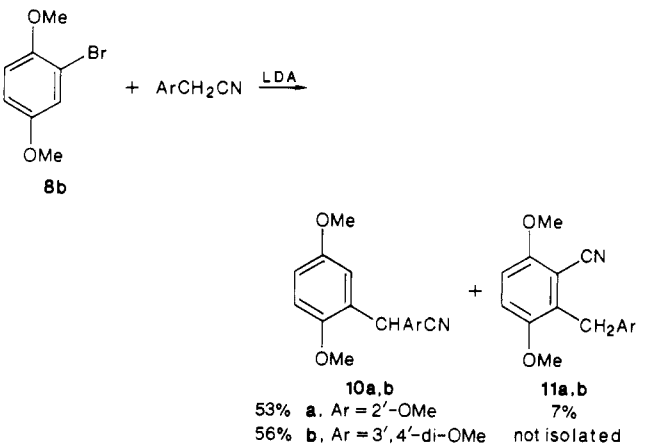
7a, R = H
7b, R = Me

major products; the simple anion addition products **9a–d** were obtained in trace amounts. For example, the reaction



8a **6q–t** (major) **9a–d** (minor)

of **8a** with 3,5-dimethoxyphenylacetonitrile (**3f**) (entry 20) gave 2-cyano-3-(3′,5′-dimethoxybenzyl)-1,5-dimethoxybenzene (**6t**) in 30% yield and α,α-bis(3,5-dimethoxyphenyl)acetonitrile (**9d**) in less than 2% yield. In contrast, **8b** gave predominantly simple anion addition products and only minor amounts of the rearranged products. For example, the reaction of **8b** with 2-methoxyphenylacetonitrile gave α-(2′-methoxyphenyl)-2,5-dimethoxyphenylacetonitrile (**10**) in 53% yield and 2-cyano-3-(2′-methoxybenzyl)-1,4-dimethoxybenzene (**11**) in only 7% yield.



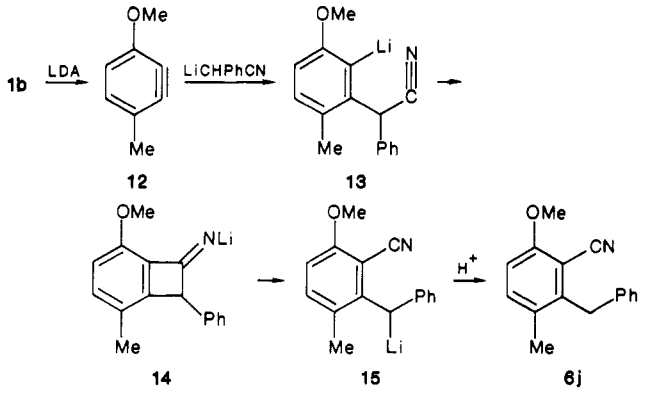
8b

10a,b
53% **a**, Ar = 2′-OMe
56% **b**, Ar = 3′,4′-di-OMe

11a,b
7%
not isolated

A tandem addition–rearrangement mechanism to account for the rearranged nitrile products is outlined in Scheme I using the reaction of **1b** and phenylacetonitrile (**3a**), yielding **6h** as typical example. Accordingly α-lithiophenylacetonitrile adds regioselectively to 3-methoxy-6-methylbenzyne (**12**), affording the aryne–nitrile adduct **13**, which undergoes ring closure to the benzocyclobutenium intermediate **14**. Ring opening of **14** affords the α-lithio intermediate **15** which, after neutralization, gives 3-benzyl-2-cyano-4-methylanisole. The electron-releasing 1-methoxy and 4-methyl groups apparently increase the nucleophilicity of the 2-lithio site to such an extent that **13** is converted to the cyclic intermediate **14** rather than undergoing the usual α-hydrogen atom exchange to give simple anion addition products. The preference of **1a,b** and **8a** for the rearrangement pathway and that of **8b** for the typical aryne pathway are in accord with this mechanism. In the former cases, the nucleophilicity of the 2-

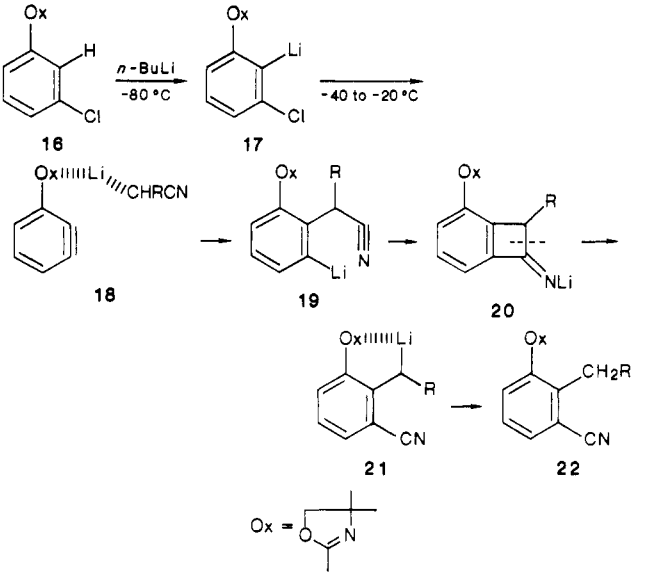
Scheme I



lithio cyclization site is increased by the presence of electron-releasing groups at both ortho and para positions which increases the rate of cyclization to such an extent that the usual α-hydrogen–2-lithio exchange process cannot compete. In the latter case, this effect is partially reduced since the nucleophilic enhancing effect of the electron-releasing *o*-methoxy group is countered by the electron-attraction effect of the *m*-methoxy group. In this instance, the rearrangement pathway available to **8b** cannot compete with usual the α-hydrogen–2-lithio exchange process and thus is converted to simple anion nitrile addition products. Another driving force for the rearrangement pathway observed for arylacetonitriles is the resonance stabilization provided by the aryl substituent of α-lithio intermediates such as **15**. Such stabilization is not available when lithioalkanenitriles are used; in fact, the alkyl group would be expected to destabilize the corresponding α-lithio intermediate.

The tandem addition–rearrangement mechanism proposed here is similar to that proposed by Meyers[6] and co-worker to account for the rearranged products from the addition of lithioalkanenitriles to 3-oxazolylbenzyne (**18**) (see Scheme II). In that study, **18** was generated at −20 °C from lithiated *m*-(chlorophenyl)oxazoline (**17**), prepared by the reaction of *n*-butyllithium and *m*-(chlorophenyl)-oxazoline (**16**) at −78 °C. Because of chelation of the lithio nitrile to oxazoline during the addition step, alkylation occurs at the 2-position of **18** affording **19**. Cyclization of **19** gives the benzocyclobutenimine **20** which, after ring opening to **21**, yields the 2-alkyl-3-cyano derivative **22**, after neutralization. A possible reason for the contrasting behavior toward lithioalkanenitriles between aryne **18** generated by *n*-butyllithium and those methoxyarynes produced by LDA is that only in the former case can ring-opened species such as **21** be further stabilized by chelation. Further, the formation of aryne **18** from **16** by *n*-butyllithium may involve the initial complexation of *n*-butyllithium with oxazoline, thus directing lithiation at the 2-position to give lithio derivative **17**, which upon warming to −20 °C generates aryne **18**. We[7] have observed that when one attempts to generate methoxyarynes from bromoanisoles using *n*-butyllithium, the competing metal–halogen exchange reaction occurred to a greater extent; LDA was found to be a better base for generating methoxyarynes. Finally, since nitrile anions add to 3-methoxyarynes in the usual way,[8] chelation between the methoxy group and the incoming lithio nitrile is not as important as the inductive stabilization of the transition state for nitrile anion addition to the 3-methoxyaryne. This is not an unexpected result since the methoxy group would be expected to exert a stronger inductive effect than the oxazoline group due to the oxygen atom in the former being closer to the developing negative charge in anionic addition to arynes than either the oxygen or nitrogen atoms in the oxazoline.

Scheme II



To our knowledge, the reaction reported herein represents the second example of tandem addition–rearrangement of nitrile anions to arynes and the first illustration of a reaction of lithioarenenitriles and arynes generated from bromoarenes and LDA. The work to explore the scope and limitations of this reaction in the synthesis of natural products is now in progress in our laboratory.

Experimental Section

General Comments. Melting points were determined on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 grating spectrometer. High field (200-MHz) proton and carbon-13 spectra were taken on an IBM-Bruker WP200-SY spectrometer. NMR spectra were run in $CDCl_3$ solutions and chemical shifts were related to Me_4Si. Gas chromatographic analyses and mass spectra (70 eV) were obtained on a Hewlet-Packard Model 5988A spectrometer using a 0.2 mm × 12 m capillary column containing cross-linked methyl silicone of 0.33-μm film thickness. Data reported are the m/z values for the most abundant peaks. Microanalyses were performed on a Carlo ERBA Strumentazione instrument. E. Merck silica gel 9385 (230–400 mesh) was used for flash column chromatography. Tetrahydrofuran (THF) and diisopropylamine were dried and distilled prior to use. Haloarenes and arylacetonitriles were either obtained from Aldrich Chemical Co. or prepared by standard procedures and distilled. *n*-Butyllithium (*n*-BuLi) was obtained from Aldrich Chemical Co. All reactions were carried out in flame-dried flasks under nitrogen atmosphere.

General Procedure for the Reaction of Haloarenes with Arylacetonitriles and LDA in THF. In a flame-dried flask flushed with nitrogen, LDA (15 mmol) was prepared by adding diisopropylamine (18 mmol) in to a −78 °C solution of *n*-BuLi (15 mmol, 2.5M in hexane) in THF (25 mL) under nitrogen atmosphere (using septum cap technique). After stirring the solution for 10 min at −78 °C, the appropriate arylacetonitrile (5 mmol) in THF (25 mL) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 10 min and then allowed to warm to −40 °C. A solution of haloarene (5 mmol) in THF (25 mL) was added dropwise over 20 min at −40 °C. The reaction mixture was stirred further and allowed to warm to room temperature slowly over a period of 2 h. The dark reddish brown

(6) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1984**, *25*, 2941.
(7) Unpublished results.
(8) Roberts, J. D.; Vaughan, C. W.; Carlsmith, L. A.; Semonov, D. A. *J. Am. Chem. Soc.* **1956**, *78*, 611.

solution was then quenced with absolute ethanol, THF was evaporated under reduced pressure, and the residue was extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to provide an oil which was purified by flash column chromatography using a mixture of hexane/EtOAc [19:1 or 9:1, depending on the polarity of the nitrile product] as an eluant.

2-Cyano-3-benzyl-4-(methoxymethyl)anisole (6a): white needles (from CH_2Cl_2–hexane); mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 3.34 (s, 3 H), 3.95 (s, 3 H), 4.31 (s, 4 H), 6.88 (d, J = 8.6 Hz, 1 H), 7.11–7.27 (m, 5 H), 7.55 (d, J = 8.6 Hz, 1 H), ^{13}C NMR ($CDCl_3$) δ 161.38, 144.25, 138.12, 134.77, 129.81, 128.19, 126.36, 121.45, 115.66, 109.01, 103.90, 71.59, 51.18, 56.01, 36.54; IR ($CHCl_3$) 2205 cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.25; H, 6.47; N, 5.39.

2-Cyano-3-(2′-methoxybenzyl)-4-(methoxymethyl)anisole (6b): white needles (from CH_2Cl_2–hexane); mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 3.31 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 4.25 (s, 2 H), 4.26 (s, 2 H), 6.63 (m, 1 H), 6.75–6.91 (m, 3 H), 7.19 (m, 1 H), 7.57 (d, J = 8.6 Hz, 1 H); IR ($CHCl_3$) 2215 cm^{-1}; MS, m/z 297 ($M^{+\cdot}$), 265 (M – CH_3OH). Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.78; H, 6.38; N, 4.67.

2-Cyano-3-(3′-methoxybenzyl)-4-(methoxymethyl)-anisole (6c): white needles (from CH_2Cl_2–hexane); mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 3.35 (s, 3 H), 3.77 (s, 3 H), 3.95 (s, 3 H), 4.3 (s, 2 H), 4.33 (s, 2 H), 6.67–6.76 (m, 3 H), 6.88 (d, J = 8.6 Hz, 1 H), 7.20 (m, 1 H), 7.55 (d, J = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.2, 159.55, 143.82, 139.55, 134.72, 129.66, 129.24, 120.47, 115.56, 114.11, 111.32, 108.93, 103.57, 71.42, 57.99, 55.84, 54.86, 36.31; IR (KBr) 2217 cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.89; H, 6.48; N, 4.65.

2-Cyano-3-(4′-methoxybenzyl)-4-(methoxymethyl)anisole (6d): white crystals (from CH_2Cl_2–hexane); mp 92 °C; ^1H NMR ($CDCl_3$)$_2$ δ 3.34 (s, 3 H), 3.78 (s, 3 H), 3.94 (s, 3 H), 4.24 (s, 2 H), 4.31 (s, 2 H), 6.79–6.89 (m, 4 H), 7.05 (d, J = 8.2 Hz, 1 H), 7.54 (d, J = 8.3 Hz, 1 H); IR ($CHCl_3$) 2215 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 35.75, 56.05, 58.17, 71.69, 109.16, 115.06, 115.48, 115.39, 129.61, 129.78, 133.82, 135.01, 144.19, 161.53, 163.92. Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.53; H, 6.49; N, 4.74.

2-Cyano-3-(3′,4′,5′-trimethoxybenzyl)-4-(methoxymethyl)anisole (6e): white needles (from CH_2Cl_2–hexane); mp 180–182 °C; ^1H NMR ($CDCl_3$) δ 3.34 (s, 3 H), 3.79 (s, 6 H), 3.81 (s, 3 H), 4.16 (s, 2 H), 4.24 (s, 2 H), 6.36 (s, 2 H), 6.8 (d, J = 8.61 Hz, 1 H), 7.32 (d, J = 8.6 Hz, 1 H); IR (KBr) 2217 cm^{-1}; MS, m/z 357 ($M^{+\cdot}$). Anal. Calcd for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.32; H, 6.36; N, 3.88.

2-Cyano-3-(2′-fluorobenzyl)-4-(methoxymethyl)anisole (6f): white needles (from CH_2Cl_2–hexane); mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3 H), 3.97 (s, 3 H), 4.28 (s, 2 H), 4.31 (s, 2 H), 6.85–7.24 (m, 5 H), 7.57 (d, J = 8.5 Hz, 1 H); IR ($CHCl_3$) 2215 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_2NF$: C, 71.57; H, 5.7; N, 4.91. Found: C, 71.83; H, 5.62; N, 4.82.

2-Cyano-3-(4′-fluorobenzyl)-4-(methoxymethyl)anisole (6g): white needles (from CH_2Cl_2–hexane); mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 3.32 (s, 3 H), 3.96 (s, 3 H), 4.28 (s, 2 H), 4.31 (s, 2 H), 6.85–7.2 (m, 5 H), 7.57 (d, J = 8.5 Hz, 1 H); IR ($CHCl_3$) 2217 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_2NF$: C, 71.57; H, 5.7; N, 4.91. Found: C, 71.71; H, 5.66; N, 4.97.

2-Cyano-3-benzyl-4-methylanisole (6h): white needles (from CH_2Cl_2–hexane); mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 3.9 (s, 3 H), 4.21 (s, 2 H), 6.78 (d, J = 8.2 Hz, 1 H), 7–7.31 (m, 6 H); IR ($CHCl_3$) 2221, 1591 cm^{-1}; MS, m/z 237 ($M^{+\cdot}$), 222 (M – CH_3). Anal. Calcd for $C_{16}H_{15}ON$: C, 80.98; H, 6.37; N, 5.9. Found: C, 81.17; H, 6.43; N, 5.98.

2-Cyano-3-(2′-methoxybenzyl)-4-methylanisole (6i): white needles (from CH_2Cl_2–hexane); mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 4.19 (s, 2 H), 6.50 (m, 1 H), 6.78–6.91 (m, 3 H), 7.19 (m, 1 H), 7.32 (d, J = 8.4 Hz, 1 H); IR ($CHCl_3$) 2115 cm^{-1}; MS, m/z 267 ($M^{+\cdot}$), 252 (M – CH_3). Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.71; H, 6.54; N, 5.26.

2-Cyano-3-(3′-methoxybenzyl)-4-methylanisole (6j): white crystals (from EtOAc); mp 151–153 °C; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 3.75 (s, 3 H), 3.89 (s, 3 H), 4.20 (s, 2 H), 6.67–6.75 (m, 3 H), 6.79 (d, J = 8.6 Hz, 1 H), 7.18 (m, 1 H), 7.30 (d, J = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 159.95, 159.58, 143.24, 139.44, 135.54, 129.57, 129.24, 120.47, 116.05, 114.14, 111.19, 109.01, 103.07, 55.80, 54.92, 37.43, 18.72; IR ($CHCl_3$) 2218 cm^{-1}; MS, m/z 267 ($M^{+\cdot}$). Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.64; H, 6.60; N, 5.28.

2-Cyano-3-(4′-methoxybenzyl)-4-methylanisole (6k): white crystals (from CH_2Cl_2–hexane); mp 112 °C; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 4.16 (s, 2 H), 6.81–6.91 (m, 4 H), 7.13 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.5 Hz, 1 H); IR (KBr) 2217 cm^{-1}; MS, m/z 267 ($M^{+\cdot}$), 252 (M – CH_3); ^{13}C NMR ($CDCl_3$) δ 18.90, 36.80, 55.20, 55.96, 108.23, 113.93, 116.29, 129.21, 129.61, 130.08, 135.64, 144.19, 158,10, 160.17. Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.68; H, 6.36; N, 5.20.

2-Cyano-3-(3′,4′-dimethoxybenzyl)-4-methylanisole (6l): white needles (from CH_2Cl_2–hexane); mp 140 °C; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H), 3.84 (s, 6 H), 3.93 (s, 3 H), 4.17 (s, 2 H), 6.61 (dd, J = 8.3 and 1.3 Hz, 1 H), 6.74–6.81 (m, 3 H), 7.31 (d, J = 8.5 Hz, 1 H); IR (KBr) 2222 cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.86; H, 6.57; N, 4.76.

2-Cyano-3-(3′,4′,5′-trimethoxybenzyl)-4-methylanisole (6m): white needles (from CH_2Cl_2–hexane); mp 158–162 °C; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.79 (s, 6 H), 3.81 (s, 3 H), 3.93 (s, 3 H), 4.16 (s, 2 H), 6.36 (s, 2 H), 6.8 (d, J = 8.6 Hz, 1 H), 7.32 (d, J = 8.6 Hz, 1 H); IR ($CHCl_3$) 2215 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 18.96, 37.79, 55.95, 56.13, 60.74, 103.25, 105.71, 109.16, 116.20, 129.66, 133.72, 135.67, 136.78, 143.58, 153.23, 160.19. Anal. Calcd for $C_{19}H_{21}O_4N$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.91; H, 6.39; N, 4.21.

2-Cyano-3-(2′-fluorobenzyl)-4-methylanisole (6n): white needles (from CH_2Cl_2–hexane); mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 3.94 (s, 3 H), 4.23 (s, 2 H), 6.83 (d, J = 8.5 Hz, 1 H), 6.99–7.12 (m, 4 H), 7.33 (d, J = 8.5 Hz, 1 H); IR (KBr) 2214 cm^{-1}. Anal. Calcd for $C_{16}H_{14}NOF$: C, 75.28; H, 5.53; N, 5.49. Found: C, 75.21; H, 5.57; N, 5.53.

2-Cyano-3-(3′-fluorobenzyl)-4-methylanisole (6o): white needles (from CH_2Cl_2–hexane); mp 92 °C; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H), 3.94 (s, 3 H), 4.22 (s, 2 H), 6.74–6.94 (m, 4 H), 7.21–7.26 (m, 1 H), 7.34 (d, J = 8.6 Hz, 1 H); IR ($CHCl_3$) 2218 cm^{-1}. Anal. Calcd for $C_{16}H_{14}NOF$: C, 75.27; H, 5.53; N, 5.49. Found: C, 75.35; H, 5.64; N, 5.47.

2-Cyano-3-(4′-fluorobenzyl)-4-methylanisole (6p): white needles (from CH_2Cl_2–hexane); mp 115 °C; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 3.93 (s, 3 H), 4.19 (s, 2 H), 6.81 (d, J = 8.6 Hz, 1 H), 6.95 (m, 2 H), 7.07 (m, 2 H), 7.32 (d, J = 8.5 Hz, 1 H); IR ($CHCl_3$) 2218 cm^{-1}; MS, m/z 255 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{14}ONF$: C, 75.27; H, 5.53; N, 5.49. Found: C, 75.58; H, 5.47; N, 5.41.

2-Cyano-3-(2′-methoxybenzyl)-1,5-dimethoxybenzene (6q): white crystals (from EtOAc–hexane); mp 106–108 °C; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 4.13 (s, 2 H), 6.31–6.32 (d, J = 2.07 Hz, 1 H), 6.35–6.36 (d, J = 2.1 Hz, 1 H), 6.91 (m, 2 H), 7.18 (dd, J = 7.36 Hz and 1.2 Hz, 1 H), 7.26 (d, J = 7.1 Hz, 1 H); IR ($CHCl_3$) 2215 and 1593 cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.04; N, 4.94. Found: C, 72.23; H, 6.13; N, 4.83.

2-Cyano-3-(3′-methoxybenzyl)-1,5-dimethoxybenzene (6r): white crystals (from EtOAc–hexane); mp 104–106 °C; ^1H NMR ($CDCl_3$) δ 3.78 (s, 6 H), 3.87 (s, 3 H), 4.08 (s, 2 H), 6.35 (m, 2 H), 6.79–6.83 (m, 3 H), 7.22 (m, 1 H); IR (KBr) 2217, 1593 cm^{-1}; MS, m/z 283 ($M^{+\cdot}$). Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.11; H, 6.04; N, 4.94. Found: C, 72.18; H, 6.09, N, 4.97.

2-Cyano-3-(4′-methoxybenzyl)-1,5-dimethoxybenzene (6s): white solid, mp 103–105 °C; ^1H NMR ($CDCl_3$) δ 3.77 (s, 6 H), 3.87 (s, 3 H), 4.07 (s, 2 H), 6.32 (m, 2 H), 6.87 (m, 2 H), 7.05 (m, 2 H); IR (KBr) 2218, 1590 cm^{-1}; MS, m/z 283 ($M^{+\cdot}$). Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.11; H, 6.04; N, 4.94. Found: C, 72.23; H, 6.12; N, 4.91.

2-Cyano-3-(3′,5′-dimethoxybenzyl)-1,5-dimethoxybenzene (6t): white crystals (from hexane/EtOAc); mp 109–110 °C; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 3.77 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.26 (s, 2 H), 6.28 (s, 1 H), 6.32 (s, 1 H), 6.42 (s, 3 H); IR (KBr) 2217 and 1593 cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 66.87; H, 6.09; N, 4.43.

α-(2′-Methoxyphenyl)-2,5-dimethoxyphenylacetonitrile (10a): white solid (from EtOAc); mp 122–124 °C; ^1H NMR

($CDCl_3$) δ 3.76 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 5.73 (s, 1 H), 6.84–6.98 (m, 5 H), 7.28–7.32 (m, 2 H); IR (KBr) 2239, 1593 cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_3N$: C, 72.06, H, 6.04; N, 4.94. Found: C, 72.17; H, 6.09; N, 4.86.

α-(3′,4′-Dimethoxyphenyl)-2,5-dimethoxyphenylacetonitrile (10b): colorless thick oil; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.77 (s, 3 H), 3.82 (s, 6 H), 5.46 (s, 1 H), 6.80–6.91 (m, 6 H); IR 2240, 1595 cm^{-1}.

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Synthesis of 1-(2-Hydroxyaryl)-1,2,3-propanetriol and 1-(2-Hydroxyaryl)-2-amino-1,3-propanediol Derivatives of either *threo* or *erythro* Configuration[1]

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The title arylglycerols **3A** and **4A** and arylaminopropanediols **3B** and **4B**, in either optical series (D or L) and with either configuration (*threo* or *erythro*), were prepared in optically pure form by direct arylation of 2,3-*O*-isopropylidene-D- or -L-glyceraldehyde (**2A**) and *N*-*t*-Boc-2,3-*N*,*O*-isopropylidene-D- or -L-serinal (**2B**) with Mg-based or Ti-based phenolates **1** in a highly diastereodivergent manner.

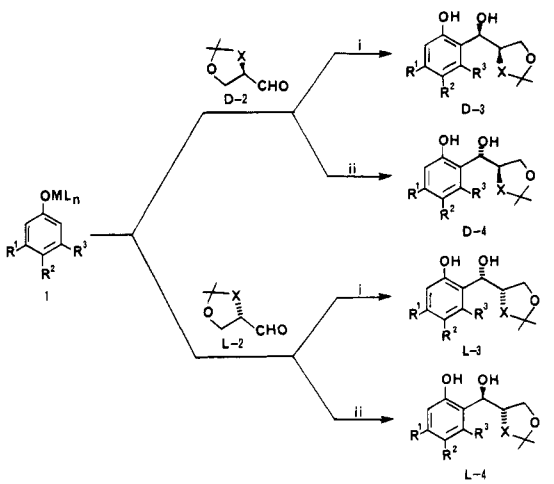
The regiospecific ortho-arylation of carbonyl compounds having chiral centers by means of metal phenolates, investigated recently in our laboratory, has proven to be a promising route to homochiral multifunctional aromatics.[1,3] Very high, often complete, stereodivergence has been achieved via metal tuning, thus allowing different stereochemical arrangements of the emerging molecules to be generated.

As an extension of this work, we now report a practical synthesis of all four possible stereoisomers of the ring-hydroxylated 1-aryl-1,2,3-propanetriols **3A** and **4A** and 1-aryl-2-amino-1,3-propanediol acetonides **3B** and **4B** via regio- and diastereoselective arylation of isopropylidene-blocked D- and L-glyceraldehyde (**2A**)[4] and D- and L-*N*-*t*-Boc-serinal (**2B**)[5] with bromomagnesium or triisopropoxytitanium phenolates [**1**; ML_n = $MgBr^+$ or $Ti(O\text{-}i\text{-}Pr)_3^+$] in apolar media.

Results and Discussion

Synthesis of Arylglycerols. We first investigated the reaction between the bromomagnesium salt of 4-*tert*-butylphenol (**1a**, ML_n = $MgBr^+$) and D-glyceraldehyde acetonide (D-**2A**) under the conditions we generally used for regiocontrolled arylation of carbonyl compounds.[3] In the event, by using anhydrous ethanol-free methylene dichloride as solvent at ambient temperature and magnetically stirring the resulting slurry, a mixture of D-*threo*- and D-*erythro*-arylglycerols D-**3Aa** and D-**4Aa** was obtained in 32% combined yield with a diastereoselectivity in favor of *threo* derivative D-**3Aa** as moderate as 85:15 (60% diastereoisomeric excess) (Scheme I).

Scheme I[a]



[a] **A**, X = O; **B**, X = *N*-*t*-Boc; (i) ML_n = $MgBr^+$, CH_2Cl_2; (ii) ML_n = $Ti(O\text{-}i\text{-}Pr)_3^+$, toluene.

To improve the reactant conversion and the selectivity, we turned toward ultrasound. The use of sonication in organic chemistry as a tool for improving reaction rates and modifying the physicochemical state of the reaction components is well-documented.[6] In the reaction above (homogeneous conditions at 0 °C), this simple expedient improved both the yield and diastereoselectivity significantly, so that D-**3Aa** was obtained in 70% isolated yield and 92% de.

The extension of this reaction and improved procedure (CH_2Cl_2; 0 °C) to a variety of ring-substituted phenols and both enantiomers of **2A** was successful. The complete

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