= 6 Hz, 4 H), 2.43 (t, J = 6 Hz, 4 H). The other isomer showed the following ^{1}H NMR signals: ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz), 1.26 (m), 1.57 (m).

Acknowledgment. We thank David N. Whittern for conducting the INADEQUATE and the 2D NMR analyses on a Varian XL-200 spectrometer (NSF Grant CHE-8004246). We also thank the Purdue University Biochemical Magnetic Resonance Laboratory for the use of NT-470 NMR spectrometer (NIH Grant RR-01077). The financial assistance from the National Institutes of Health (GM-10937-20) and the National Science Foundation (Grant CHE 79-18881) is gratefully acknowledged.

Registry No. 1, 280-64-8; 6, 5626-20-0; 7, 4480-56-2; 8, 60579-50-2; 9, 60579-58-0; 10, 94-65-5; 11, 1126-18-7; 12, 32362-97-3; 13, 3313-59-5; 14, 16556-72-2; BMS, 13292-87-0; 1,7-heptanediol, 629-30-1; 1,5-heptanediol, 60096-09-5; cyclooctanone, 502-49-8; 2-ethylcyclohexanone, 4423-94-3; 1,8-octanediol, 629-41-4; 1,6-octanediol, 4066-76-6; 1,9-nonanediol, 3937-56-2; 1,5-nonanediol, 13686-96-9; 1,10-decanediol, 112-47-0; 1,5-decanediol, 4203-48-9; 1,14-tetradecanediol, 19812-64-7; cyclopentadecanone, 502-72-7; *B*-methoxy-2-propylborinane, 60579-70-6; *B*-methoxy-2-butylborinane, 88703-65-5; *B*-methoxy-2-pentylborinane, 88703-66-6; *B*-methoxy-2-heptylborinane, 88729-57-1; *B*-methoxy-2-nonylborinane, 88703-67-7; 1,3-butadiene, 106-99-0; 1,5-hexadiene, 592-42-7; 1,6-heptadiene, 3070-53-9; 1,7-octadiene, 3710-30-3; 1,8-nonadiene, 4900-30-5; 1,9-decadiene, 1647-16-1; 1,11-dodecadiene, 5876-87-9; 1,13-tetradecadiene, 21964-49-8; 1,4-butanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-68-8; 1,5-pentanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 81547-70-8; 1,6-hexanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-69-9; 1,7-heptanediyl-*B*,*B*′-bis(9-borabicyclo[3.3.1]nonane), 88703-70-2; BH_3, 13283-31-3.

Ortho Metalation Directed by α-Amino Alkoxides

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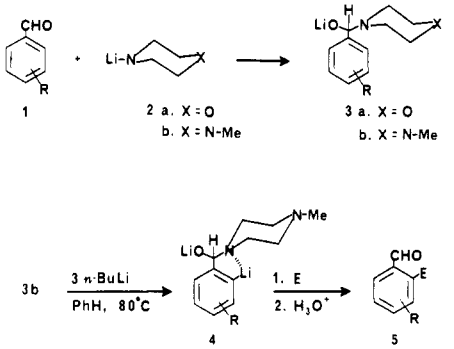
Received August 2, 1983

The addition of aromatic aldehydes to certain lithium dialkylamides in benzene or tetrahydrofuran gave α-amino alkoxides which were ortho lithiated with excess *n*-butyllithium. Subsequent alkylation and hydrolysis provided ortho-substituted aromatic aldehydes via a one-pot reaction. The ortho metalation of α-amino alkoxides derived from 1- and 2-naphthaldehyde and various substituted benzaldehydes was examined. When *N*,*N*,*N*′-trimethylethylenediamine was used as the amine component of the α-amino alkoxide, metalation could be carried out at lower temperatures. This rate increase is due to an intramolecular TMEDA-like assisted metalation. The synthetic utility of this ortho metalation, including how varying the amine component of the α-amino alkoxide affects the regiochemistry and metalation rate, is discussed.

In recent years there has been considerable interest in the area of ortho metalation.[1] A variety of ortho-directing groups have been utilized on various aromatic rings to direct regiospecific metalation in the ortho position. Carbonyl-derived directing groups include $CONR_2$,[2] CONHR,[3] oxazolines,[4] α-amino alkoxides[5] (prepared from tertiary amides and RLi), $CH(OR)_2$,[6] imidazolidines,[7] cyclohexylimines,[8] and α-amino alkoxides[9] (prepared from aromatic aldehydes and lithium *N*-methylpiperazide). We recently reported an in situ protection of aromatic and aliphatic aldehydes in high yield via the formation of α-amino alkoxides.[10] The α-amino alkoxides **3** are prepared



by the addition of an aromatic aldehyde (1) to certain

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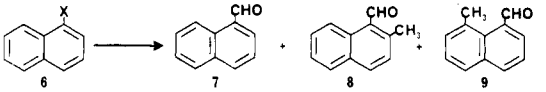
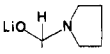
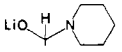
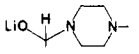
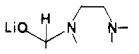
Table I



entry	x	metalation conditions	yield (GC) 7	8	9
a		3 *n*-BuLi, 3 TMEDA, ether, room temp, 7 h	15.1	5.7	12.4
b		1 *t*-BuLi, ether, −78 → 0 °C	38.5	12.5	26.5
c		1.1 *n*-BuLi, THF, −78 °C, 15 min	0	0	0
d		3 *n*-BuLi, benzene, reflux, 10 h	32	32.6	1.6
e		3 *n*-BuLi, benzene, reflux, 10 h	5	30	2.8
f		3 *n*-BuLi, benzene, reflux, 10 h	55.7	19.4	1
g		3 *n*-BuLi, benzene, reflux, 10 h	9.3	42.7	1.6
h		3 *n*-BuLi, THF, −20 °C, 24 h	27.9	51.3	4.9

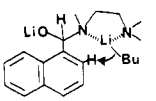
amide bases such as lithium morpholide (**2a**) or lithium *N*-methylpiperazide (**2b**). The in situ formed α-amino alkoxide protects the formyl group toward organometallic reagents. For example, the α-amino alkoxide **3b** can be treated with 3 equiv of *n*-BuLi in relfuxing benzene for several hours with only minor decomposition resulting. In fact, under these conditions the α-amino alkoxide functions not only as a protecting group, but also as an ortho-directing group for ortho metalation. Ortho lithiation of α-amino alkoxides **3b** gives dianions **4** which can be alkylated with various electrophiles. Quenching the reactions with water or aqueous acid provides ortho-substituted aromatic aldehydes (**5**) via a one-pot reaction.[9]

The convenience and synthetic potential of this reaction have prompted us to investigate its scope. This paper is a report on our continuing studies of ortho metalation directed by α-amino alkoxides.[11]

Results and Discussion

Ortho Metalation of 1- and 2-Naphthaldehyde. We have investigated the ortho alkylation of 1- and 2-naphthaldehyde by using α-amino alkoxides and other aldehyde derivatives as ortho-directing groups. The amine component of the α-amino alkoxide was varied to determine its effect on the regioselectivity of the metalation step. The results of this study using 1-naphthaldehyde are given in Table I.

The metalated 1-naphthaldehyde derivatives were alkylated with methyl iodide and hydrolyzed with dilute hydrochloric acid. The crude product was analyzed (GC) for 1-naphthaldehyde, 2-methyl-1-naphthaldehyde, and 8-methyl-1-naphthaldehyde. When an imidazolidine was used as the ortho-directing group (entry a), a low yield of methylated products was obtained with the 8-methyl-1-naphthaldehyde predominating. The analogous reaction with the dimethyl acetal derivative (entry b) gave a similar result. Reaction of the cyclohexylimine of 1-naphthaldehyde with *n*-butyllithium (entry c) gave only addition of the lithium reagent to the aromatic ring and no products derived from ortho metalation were detected. The α-amino alkoxides direct ortho lithiation mainly to the 2 position of the 1-naphthaldehyde ring. The yields of methylated products ranged from 20–57% depending on the structure of the amine component. Although varying the amine component of the α-amino alkoxide did affect the yield of methylated products, it had little effect on the regioselectivity of the metalation step. The α-amino alkoxides derived from diethylamine, pyrrolidine, piperidine, and *N*-methylpiperizine (entries d–g) were metalated with 3 equiv of *n*-butyllithium in refluxing benzene (10 h). These conditions were necessary to effect metalation in high yield. The α-amino alkoxide derived from *N,N,N'*-trimethylethylenediamine completely decomposed under these conditions. It was subsequently discovered, however, that metalation of this α-amino alkoxide could be effected at room temperature in benzene or at −20 °C in tetrahydrofuran (entry h). It is well-known that tetramethylethylenediamine (TMEDA) accelerates metalation reactions.[12] The rate enhancement discussed above is undoubtedly due to an *intramolecular* TMEDA-like assisted metalation as shown below.



In contrast, the analogous reaction using *N*-methyl-

(11) Comins, D. L.; Brown, J. D.; Mantlo, N. B. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, Washington, March 20–25, 1983; American Chemical Society: Washington, D.C.; Abstr. ORGN 117. Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465–5468.

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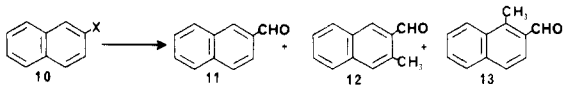
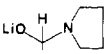
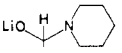
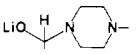
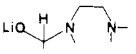
Table II

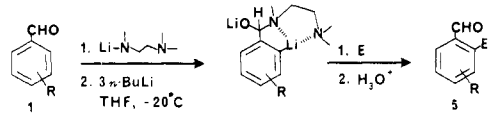


entry	x	metalation conditions	yield (GC) 11	12	13
a		3 *n*-BuLi, 3 TMEDA, ether, room temp, 7 h	25.6	31.2	8.2
b		1 *t*-BuLi, ether, −78 → 0 °C	21	13.5	9.8
c		1.1 *n*-BuLi, THF, −78 °C, 15 min	0	0	0
d		3 *n*-BuLi, benzene, reflux, 10 h	2.1	51.4	6.2
e		3 *n*-BuLi, benzene, reflux, 10 h	3.4	33.7	5.9
f		3 *n*-BuLi, benzene, reflux, 10 h	1	41	4.7
g		3 *n*-BuLi, benzene, reflux, 10 h	4.9	49.6	7.6
h		3 *n*-BuLi, benzene, room temp, 3 h	10.8	51	15.4

piperazine as the amine component gave less than 5% metalation (THF, −20 °C, 3 *n*-BuLi, 24 h).

A similar study was performed with 2-naphthaldehyde and the results are given in Table II. The crude product mixtures were analyzed for 3-methyl-2-naphthaldehyde, 1-methyl-2-naphthaldehyde, and 2-naphthaldehyde. In all examples studied, 3-methyl-2-naphthaldehyde was the major product. In general, α-amino alkoxides (entries d–h) gave better yields and product ratios than the corresponding imidazolidine and dimethyl acetal derivatives (entries a–b). Attempted metalation–alkylation of the cyclohexylimine of 2-naphthaldehyde gave mainly decomposition (entry c). The α-amino alkoxide derived from 2-naphthaldehyde and *N,N,N'*-trimethylethylenediamine again showed a rate enhancement during the metalation step. This allowed the metalation to occur at room temperature in benzene (3 h). Subsequent methylation provided a 66% yield of ortho-substituted products (entry h), the highest yield of all examples studied.

Low-Temperature Ortho Lithiation of α-Amino Alkoxides Derived from *N,N,N'*-Trimethylethylenediamine and Aryl Aldehydes. The discovery that α-amino alkoxides derived from 1- or 2-naphthaldehyde and the lithium salt of *N,N,N'*-trimethylethylenediamine could be metalated at low temperature (−20 °C) prompted us to reinvestigate our earlier work.[9] We felt that the milder



metalation conditions, for metalation of aryl α-amino alkoxides derived from *N,N,N'*-trimethylethylenediamine, would allow for higher overall yields than we obtained originally for the one-pot ortho alkylation reaction. In addition, the milder metalation conditions should allow for more functional groups to be present on the aromatic ring during this substitution reaction. The results of this study are given in Table III.

The yields of the first three examples, utilizing benzaldehyde as starting material, are 8–21% higher than the yields from our earlier work using *N*-methylpiperazine as the amine component of the α-amino alkoxides. The higher yields are indicative of less decomposition during the metalation step. A chlorine substituent activates the aromatic ring toward metalation.[1] The α-amino alkoxide from *o*- or *p*-chlorobenzaldehyde was ortho lithiated in only 3 h at −20 °C. The analogous reaction with *m*-chlorobenzaldehyde gave benzyne formation at −42 °C. Since the benzyne **6** forms in the presence of excess *n*-butyllithium and the diamine of the α-amino alkoxide, we anticipated addition of the lithium reagent to the benzyne **6** with some regioselectivity.[28] However, regioselectivity

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(22) Tanaka, A. K.; Kobayashi, A.; Yamashita, K. *Agr. Biol. Chem.* **1973**, *37*, 669–674.
(23) Lovie, J. C.; Tomson, R. H. *J. Chem. Soc.* **1961**, 485–487.
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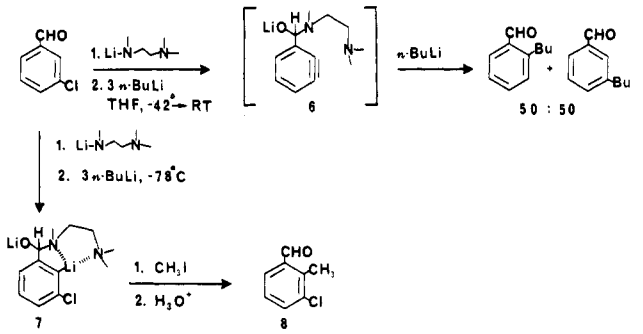
(25) An aryllithium has been chlorinated with carbon tetrachloride: Carlson, J., Sterling-Winthrop Research Institute, Rensselaer, New York, unpublished results. For the reaction of carbon tetrachloride with ester enolate anions, see: Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687–3689.
(26) Alper, H.; Root, W. G. *J. Am. Chem. Soc.* **1975**, *97*, 4251–4257.
(27) Mao, C. L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 475–482.

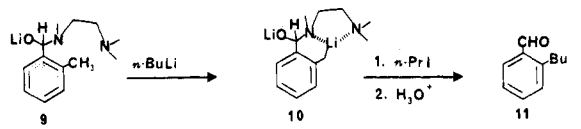


did not occur and a 50:50 mixture of 2- and 3-butylbenzaldehyde resulted. Metalation of *m*-chlorobenzaldehyde was carried out at −78 °C without benzyne formation, and the resulting dianion **7** was alkylated with methyl iodide to give 3-chloro-2-methylbenzaldehyde (**8**) in good yield.

We next investigated the ortho alkylation of methoxybenzaldehydes. *p*-Methoxybenzaldehyde gave only ortho metalation–alkylation at the position ortho to the aldehyde function. This result demonstrated that the α-amino alkoxide, derived from *N,N,N′*-trimethylethylenediamine, is a better ortho director than the methoxy group. However, when the amine component of the α-amino alkoxide is changed from *N,N,N′*-trimethylethylenediamine to *N*-methylpiperazine, the regioselectivity is reversed and metalation ortho to the methoxy group occurs. This useful regiochemical control is discussed in detail in the next section.

The α-amino alkoxides of *m*-methoxybenzladehyde, 3,4,5-trimethoxybenzaldehyde, and piperonal are doubly activated toward ortho metalation, so clean alkylation at the 2-position was anticipated. The ortho alkylation of *o*-methoxybenzaldehyde failed as only decomposition occurred; however, the α-amino alkoxide formed from *o*-methoxybenzaldehyde and lithium *N*-methylpiperazide is more stable and can be metalated ortho to the methoxy group with *n*-BuLi/TMEDA (see Table IV).

An electron-donating methyl group on the aromatic ring should decrease the metalation rate. This proved to be true; however, *m*- and *p*-tolualdehyde were ortho lithiated in high yield by using longer metalation time (48 h) at −20 °C. The ortho alkylation of *m*-tolualdehyde was highly regioselective for the less hindered 6 position. The α-amino alkoxide **9** prepared from *o*-tolualdehyde underwent lateral

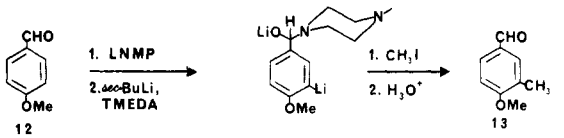


metalation at the methyl group, rather than ortho metalation, to give the dianion **10** in high yield. This is not unusual, for ortho methyl aryl oxazolines, *N,N*-diethyl amides, and imidazolidines all metalate in this manner.[1,7] Alkylation of **10** with *n*-propyl iodide gave **11** in 85% yield.

Regioselective Metalation Controlled by Varying the Amine Component of the α-Amino Alkoxide. Since the directing power of an α-amino alkoxide could be altered by simply varying the amine component, it appeared that regioselective control during the metalation of a diactivated benzene ring was feasible. We examined the ortho metalation-methylation of various methoxybenzaldehydes and the results are shown in Table IV.

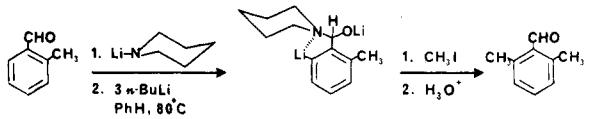
(28) Regioselective addition of organolithium reagents to the benzyne formed from 2-(*m*-chlorophenyl)-2-oxazoline has been reported. Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935–4938. Meyers, A. I.; Rieker, W. F. *Ibid.* **1982**, *23*, 2091–2094.

p-Anisaldehyde (**12**) was treated with lithium *N*-



methylpiperazide (LNMP) followed by 2 equiv of *sec*-BuLi/TMEDA in THF (−20 °C) for 24 h. After methylation and workup, 4-methoxy-3-methylbenzaldehyde (**13**) was isolated *as the sole product* in 73% yield. This is in sharp constrast to the analogous reaction using *N,N,N′*-trimethylethylenediamine as the amine component, where 4-methoxy-2-methylbenzaldehyde was produced in 90% yield (Table III). When the same strategy was utilized, *m*-anisaldehyde was methylated in the 4-position in moderate yield; only a trace of 2-substituted product was detected. The 3,5- and 2,4-dimethoxybenzaldehydes were alkylated between the methoxy groups in excellent yield as indicated in the table; when *N,N,N′*-trimethylethylenediamine was used as the amine component for these examples, a mixture of products resulted.

In light of the above results, metalation of the α-amino alkoxide derived from *o*-tolualdehyde was reexamined. As



mentioned earlier, when *N,N,N′*-trimethylethylenediamine was used as the amine, lateral metalation occurred in high yield (see Table III). However, use of lithium piperidide to form the α-amino alkoxide effected ortho metalation–alkylation at the 6-position to provide 2,6-dimethylbenzaldehyde (50%).

Conclusion

This work significantly extends the scope of ortho metalation. The method is convenient and allows for the one-pot ortho alkylation of aromatic aldehydes. Remarkable regioselective control can be obtained by simply changing the amine component of the α-amino alkoxide, a novel versatility which should be useful in synthesis.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Benzene, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), *N,N,N′*-trimethylethylenediamine, *N*-methylpiperazine, piperidine, diethylamine, and pyrrolidine were distilled from calcium hydride and stored over 4-Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-360 spectrometer and IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Gas-liquid chromatography (GC) was performed with a Hewlett-Packard Model 5880 A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-17.

1,3-Dimethyl-2-(1-naphthyl)imidazolidine. Using the procedure for the preparation of 1,3-dimethyl-2-phenylimidazolidine,[7] 4.3 mL (32 mmol) of 1-naphthaldehyde and 4.1 mL (38 mmol) of *sym*-dimethylethylenediamine gave, after Kugelrohr distillation (bp 130–140 °C (0.75 mm)), 6.97 g (96%) of a clear oil: ^1H NMR (CCl_4) δ 9.2–8.8 (m, 1 H), 8.0–7.3 (m, 6 H), 3.9 (s, 1 H), 3.45 (m, 2 H), 2.55 (m, 2 H), 2.1 (s, 6 H); IR (neat) 2775, 1450, 1240 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.73; H, 8.03; N, 12.40.

Table III. Low-Temperature Ortho Lithiation of Aryl α-Amino Alkoxides

aryl aldehyde 1	metalation[a] conditions	E	product[b] 5	yield[c]	mp, °C[f] (Lit. mp, °C)
benzaldehyde	-20 °C, 24 h	Me_3SiCl	2-trimethylsilylbenzaldehyde	82	g
		MeI	o-tolualdehyde	75[d]	g
		n-BuI	2-butylbenzaldehyde	68	g
		CCl_4[25]	2-chlorobenzaldehyde	68	g
		PhCHO	1,3-dihydro-3-phenyl-1-isobenzofuranol	85	lactone 102-104 (103-104.5)[26]
		PhC(=O)Ph	1,3-dihydro-3,3-diphenyl-1-isobenzofuranol		lactone 115.5-117 (116-117)[27]
4-chlorobenzaldehyde	-20 °C, 3 h	MeI	4-chloro-2-methylbenzaldehyde	80	acid 166-167 (167-169)[13]
3-chlorobenzaldehyde	-78 °C, 7 h	MeI	3-chloro-2-methylbenzaldehyde	62	acid 155-157 (158)[14]
2-chlorobenzaldehyde	-20 °C, 3 h	MeI	2-chloro-6-methylbenzaldehyde	70	acid 98-100 (102)[15]
4-methoxybenzaldehyde	-20 °C, 24 h	MeI	4-methoxy-2-methylbenzaldehyde	90	acid 175-177 (176-177.5)[16]
3-methoxybenzaldehyde	-20 °C, 10 h	MeI	3-methoxy-2-methylbenzaldehyde	80	acid 145-147 (148-149)[17]
3,4,5-trimethoxybenzaldehyde	-20 °C, 3 h	MeI	2-methyl-3,4,5-trimethoxybenzaldehyde	90	DNP 189-190[6a]
piperonal	-20 °C, 3 h	MeI	2-methylpiperonal	90	72-74 (73-74.5)[8a]
p-tolualdehyde	-20 °C, 48 h	MeI	2,4-dimethylbenzaldehyde	80	g
m-tolualdehyde	-20 °C, 48 h	MeI	2,5-dimethylbenzaldehyde	60[d,e]	g
o-tolualdehyde	-20 °C, 1.5 h	n-PrI	2-butylbenzaldehyde	85	g

[a] The reactions were performed on a 3 mmol scale using N,N,N'-trimethylethylenediamine as the amine component. The metalation was carried out in THF using 3 equiv of n-BuLi. [b] All products gave the expected IR and ^1H NMR spectra. [c] Yield of purified product obtained from preparative layer chromatography (silica gel, acetone-hexanes). [d] Yield determined by GC. [e] 2,3-Dimethylbenzaldehyde (10%) was present in the crude product (by GC). [f] The lactones and carboxylic acids were prepared by Jones oxidation. DNP = 2,4-dinitrophenylhydrazone. [g] The product was identical with an authentic sample.

Table IV. Regioselective Alkylation of Methoxybenzaldehydes

aryl aldehyde	metalation[a] conditions	product[b]	yield[c]	mp, °C[d] (Lit. mp, °C)
4-methoxybenzaldehyde	2-sec-BuLi, 2 TMEDA, -20 °C, 24 h	4-methoxy-3-methylbenzaldehyde	73	DNP 234-236 (235-237)[18]
3-methoxybenzaldehyde	3 sec-BuLi, 3 TMEDA, -20 °C, 12 h	3-methoxy-4-methylbenzaldehyde	66	DNP 238-240 (241)[19]
2-methoxybenzaldehyde	3 n-BuLi, 3 TMEDA, -20 °C, 48 h	2-methoxy-3-methylbenzaldehyde	63	45-46 (44-46)[20]
3,5-dimethoxybenzaldehyde	3 n-BuLi, -20 °C, 24 h	3,5-dimethoxy-4-methylbenzaldehyde	95	90-91 (89-90)[21]
2,4-dimethoxybenzaldehyde	3 n-BuLi, -20 °C, 24 h	2,4-dimethoxy-3-methylbenzaldehyde	95	52-54 (54)[22]
2,3-dimethoxybenzaldehyde	3 n-BuLi, 3 TMEDA, -20 °C, 48 h	2,3-dimethoxy-4-methylbenzaldehyde	62	acid[e] 124-125 (125)[23]

[a] The reactions were performed on a 3 mmol scale using N-methylpiperazine as the amine component. The metalation was carried out in THF. [b] All products gave the expected IR and ^1H NMR spectra. [c] Yield of purified product obtained from preparative layer chromatography (silica gel, acetone-hexanes). [d] DNP = 2,4-dinitrophenylhydrazone. [e] Prepared by Jones oxidation.

1,3-Dimethyl-2-(2-naphthyl)imidazolidine. Following the above procedure, 2-naphthaldehyde and *sym*-dimethylethylenediamine gave the product as a clear oil (91%) after Kugelrohr distillation (bp 125–140 °C (0.75 mm)): ^1H NMR (CCl_4) δ 8.2–7.3 (m, 7 H), 3.4 (m, 3 H), 2.5 (m, 2 H), 2.15 (s, 6 H); IR (neat) 2840, 2770, 1450, 1240 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.49; H, 8.16; N, 12.41.

1-Naphthaldehyde Cyclohexylimine. The imine was prepared from 1-naphthaldehyde (1.0 equiv), cyclohexylamine (1.2 equiv, distilled), and a catalytic amount of *p*-toluenesulfonic acid in benzene solution by azeotropic removal of water. The crude product was purified by Kugelrohr distillation (bp 130–140 °C (0.3 mm)) to give a clear oil (89%): ^1H NMR (CCl_4) δ 9.2 (m, 1 H), 8.85 (s, 1 H), 8.0–7.3 (br m, 6 H), 3.2 (br s, 1 H), 2.2–1.1 (br m, 10 H); IR (neat) 2920, 2840, 1635, 1440 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.13; H, 8.07; N, 5.95.

2-Naphthaldehyde Cyclohexylimine. Following the above procedure, 2-naphthaldehyde and cyclohexylamine gave the imine as a white solid (65%) after recrystallization from methanol: mp 86.5–87 °C; ^1H NMR (CCl_4) δ 8.4 (s, 1 H), 8.3–7.3 (m, 7 H), 3.2 (br s, 1 H), 2.2–1.1 (br m, 10 H); IR (KBr) 2919, 2840, 1635, 1450 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.32; H, 8.27; N, 5.95.

Ortho Lithiation–Methylation of the Imidazolidines, Dimethyl Acetals, and Cyclohexylimines of 1- and 2-Naphthaldehyde. The lithiation–alkylation of these naphthaldehyde derivatives was carried out according to published procedures for the analogous reaction with 1,3-dimethyl-2-phenylimidazolidine,[7] the dimethyl acetal of benzaldehyde,[6] and piperonal cyclohexylimine.[8] After hydrolysis with dilute hydrochloric acid, the crude product was isolated and subjected to GC analysis using 2,3-dimethylnaphthalene as an internal standard. See Tables I and II.

Ortho Methylation of 1- and 2-Naphthaldehyde via α-Amino Alkoxide Intermediates. General Procedure (See Tables I and II, Entries d–g). To a stirred solution of the secondary amine (3.3 mmol) in 8 mL of dry benzene under nitrogen was added *n*-butyllithium (3.3 mmol, in hexane solution). After 15 min, the naphthaldehyde (3 mmol) was added slowly

dropwise, and the mixture was stirred at room temperature for 15 min. A hexane solution of *n*-butyllithium (9 mmol) was added slowly dropwise and the resulting mixture was heated at reflux for 10 h. THF (10 mL) was added and the mixture was cooled to −42 °C (CH_3CN–dry ice) followed by the addition of methyl iodide (18 mmol). After stirring for 30 min at −42 °C, the cooling bath was removed and stirring was continued at room temperature (30 min). The mixture was poured into cold stirred 10% hydrochloric acid (50 mL) and extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The crude oil obtained on concentration was subjected to GC analysis using 2,3-dimethylnaphthalene as an internal standard.

Low-Temperature Ortho Lithiation–Alkylation of α-Amino Alkoxides Derived from *N,N,N'*-Trimethylethylenediamine and Aryl Aldehydes. General Procedure. To a solution of 0.41 mL (3.2 mmol) of *N,N,N'*-trimethylethylenediamine in 8 mL of THF at −20 °C was added 3.1 mmol of *n*-BuLi dropwise. After 15 min, the aryl aldehyde (3.0 mmol) was added, the mixture was stirred for 15 min, and *n*-BuLi (9 mmol) was added via syringe. After the reaction mixture was stirred (or placed in a refrigerator) for the designated time (−20 °C), the electrophile (18 mmol) was added (−42 °C). The mixture was stirred for the designated time, poured into cold stirred 10% hydrochloric acid, extracted with ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product. Purification by preparative layer chromatography (SiO_2, acetone–hexanes) gave the desired known aldehydes, or lactols, which were characterized as described in the tables.

Regioselective Metalation Controlled by Varying the Amine Component of the α-Amino Alkoxide. General Procedure. To a solution of 0.35 mL (3.2 mmol) of *N*-methylpiperazine in 8 mL of THF at −20 °C was added 3.1 mmol of *n*-BuLi dropwise. After 15 min, the aryl aldehyde (3.0 mmol) was added, the mixture was stirred for 15 min, TMEDA (6–9 mmol) and *n*-BuLi or *sec*-BuLi (6–9 mmol) were added, and the mixture was placed in a freezer (−20 °C) for the designated time (12–24 h). Methyl iodide (1.1 mL, 18 mmol) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The workup and purification were as described above. All products were known compounds which were characterized as described in Table IV.

***o*-Butylbenzaldehyde from *o*-Tolualdehyde.** The α-amino alkoxide was prepared in THF from *o*-tolualdehyde (3 mmol) and the lithium amide of *N,N,N'*-trimethylethylenediamine as described above. A hexane solution of *n*-BuLi (9 mmol) was added at −20 °C, and the mixture was stirred (−20 °C) for 1.5 h. After cooling to −78 °C, *n*-propyl iodide (1.7 mL, 18 mmol) was added, the cooling bath was removed, and the mixture was stirred at room temperature for 30 min. The workup and purification were as described above. This compound was identical with an authentic sample prepared from *o*-bromobenzaldehyde, lithium morpholide, and *n*-butyliodide via lithium–halogen exchange.[10]

2,6-Dimethylbenzaldehyde from *o*-Tolualdehyde. The α-amino alkoxide was prepared in benzene (room temperature) from *o*-tolualdehyde (3 mmol) and lithium piperidide (3.1 mmol). A hexane solution of *n*-butyllithium (9 mmol) was added slowly dropwise, and the resulting mixture was heated at reflux for 15 h. Methylation and workup were the same as described above. Purification by preparative layer chromatography (silica gel, acetone–hexanes) gave 200 mg (50%) of 2,6-dimethylbenzaldehyde as a clear oil: mp (2,4-DNP) 248–250 °C (lit.[24] mp 250–252 °C); ^1H NMR (CCl_4) δ 10.6 (s, 1 H), 7.5–6.9 (m, 3 H), 2.53 (s, 6 H); IR (neat) 2975, 1700, 1200 cm^{-1}.

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Registry No. 1,3-Dimethyl-2-(1-naphthyl)imidazolidine, 88802-84-0; 1-(dimethoxymethyl)naphthalene, 33250-32-7; 1-naphthaldehyde cyclohexylimine, 4323-24-4; lithium α-(diethylamino)-1-naphthylmethoxide, 88802-85-1; lithium α-pyrrolidino-1-naphthylmethoxide, 88802-86-2; lithium α-piperidino-1-naphthylmethoxide, 88802-87-3; lithium α-(4-methylpiperazino)-1-naphthylmethoxide, 88802-88-4; lithium α-(trimethylethylenediamino)-1-naphthylmethoxide, 88802-89-5; 1-naphthaldehyde, 66-77-3; 2-methyl-1-naphthaldehyde, 35699-44-6; 8-methyl-1-naphthaldehyde, 6549-57-1; 1,3-dimethyl-2-(2-naphthyl)imidazolidine, 88802-90-8; 2-(dimethoxymethyl)-naphthalene, 77196-31-7; 2-naphthaldehyde cyclohexylimine, 3525-72-2; lithium α-(diethylamino)-2-naphthylmethoxide, 88802-91-9; lithium α-pyrrolidino-2-naphthylmethoxide, 88802-92-0; lithium α-piperidino-2-naphthylmethoxide, 88802-93-1; lithium α-(4-methylpiperazino)-2-naphthylmethoxide, 88802-94-2; lithium α-(trimethylethylenediamino)-2-naphthylmethoxide, 88802-95-3; 2-naphthaldehyde, 66-99-9; 3-methyl-2-naphthaldehyde, 17893-94-6; 1-methyl-2-naphthaldehyde, 35699-45-7; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1; 3-chlorobenzaldehyde, 587-04-2; 2-chlorobenzaldehyde, 89-98-5; 4-methoxybenzaldehyde, 123-11-5; 3-methoxybenzaldehyde, 591-31-1; 3,4,5-trimethoxybenzaldehyde, 86-81-7; piperonal, 120-57-0; *p*-tolualdehyde, 104-87-0; *m*-tolualdehyde, 620-23-5; *o*-tolualdehyde, 529-20-4; 2-methoxybenzaldehyde, 135-02-4; 3,5-dimethoxybenzaldehyde, 7311-34-4; 2,4-dimethoxybenzaldehyde, 613-45-6; 2,3-dimethoxybenzaldehyde, 86-51-1; 2-(trimethylsilyl)benzaldehyde, 17887-55-7; 2-butylbenzaldehyde, 59059-42-6; 1,3-dihydro-3-phenyl-1-isobenzofuranol, 65184-67-0; 1,3-dihydro-3-phenyl-1-isobenzofuranone, 5398-11-8; 1,3-dihydro-3,3-diphenyl-1-isobenzofuranol, 69621-97-2; 1,3-dihydro-3,3-diphenyl-1-isobenzofuranone, 596-29-2; 4-chloro-2-methylbenzaldehyde, 40137-29-9; 4-chloro-2-methylbenzoic acid, 7499-07-2; 3-chloro-2-methylbenzaldehyde, 874-27-1; 3-chloro-2-methylbenzoic acid, 7499-08-3; 2-chloro-6-methylbenzaldehyde, 1194-64-5; 2-chloro-6-methylbenzoic acid, 21327-86-6; 4-methoxy-2-methylbenzaldehyde, 52289-54-0; 4-methoxy-2-methylbenzoic acid, 6245-57-4; 3-methoxy-2-methylbenzaldehyde, 56724-03-9; 3-methoxy-2-methylbenzoic acid, 55289-06-0; 2-methyl-3,4,5-trimethoxybenzaldehyde, 74327-91-6; 2-methyl-3,4,5-trimethoxybenaldehyde DNP, 88802-96-4; 2-methylpiperonal, 58343-46-7; 2,4-dimethylbenzaldehyde, 15764-16-6; 2,5-dimethylbenzaldehyde, 5779-94-2; 4-methoxy-3-methylbenzaldehyde, 32723-67-4; 4-methoxy-3-methylbenzaldehyde DNP, 32723-68-5; 3-methoxy-4-methylbenzaldehyde, 24973-22-6; 3-methoxy-4-methylbenzaldehyde DNP, 53581-85-4; 2-methoxy-3-methylbenzaldehyde, 67639-61-6; 3,5-dimethoxy-4-methylbenzaldehyde, 1011-27-4; 2,4-dimethoxy-3-methylbenzaldehyde, 7149-92-0; 2,3-dimethoxy-4-methylbenzaldehyde, 75889-47-3; 2,3-dimethoxy-4-methylbenzoic acid, 77869-39-7; *sym*-dimethylethylenediamine, 110-70-3; *N,N,N'*-trimethylethylenediamine, 142-25-6; *N*-methylpiperazine, 109-01-3.