Effect of the Substitution Pattern on Reactions of Methoxylated Araldehyde 2,4-Dimethylpent-3-ylimines with Organolithium Reagents†

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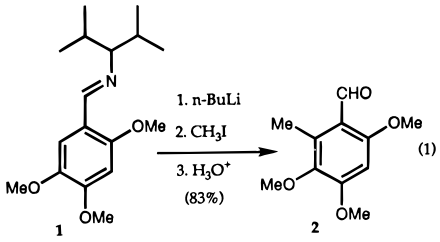
Introduction

Araldimines are versatile araldehyde equivalents that may direct selective aromatic ring metalation,[3] lateral metalation,[4] or nucleophilic aromatic substitution (S_NAr)[5] reactions depending on the choice of imine structure and reaction conditions. Araldehyde 2,4-dimethylpent-3-ylimines containing a suitably positioned nucleofugic group are particularly useful substrates for S_NAr reactions with a variety of organolithium reagents;[5] however, it was recently observed that treatment of 2,4,5-trimethoxybenzaldehyde 2,4-dimethylpent-3-ylimine, **1**, with *n*-BuLi or PhLi (ether−hexane; −78 → +20 °C) followed by workup with aqueous NH_4Cl, afforded only unchanged starting material rather than the expected nucleophilic aromatic substitution products.[6] This result prompted us to conduct a more detailed study of imine **1** and the general effect of substitution pattern on the reactions of methoxylated araldehyde 2,4-dimethylpent-3-ylimines with selected organolithium reagents.

Results and Discussion

Closer scrutiny has revealed that imine **1** undergoes facile ortho-directed lithiation at C-6 with *n*-BuLi; thus, reaction of the imine with *n*-BuLi (ether−hexane) followed by a methyl iodide quench to probe for metalation processes gave, after acid hydrolysis, aldehyde **2** in 83% isolated yield (eq 1).



Although the C-5 methoxy group might be expected to attenuate S_NAr-reactivity at C-2 of imine **1**, it is remarkable that ring metalation was the exclusive reaction pathway and occurred only at C-6 with this substrate.

Scheme 1

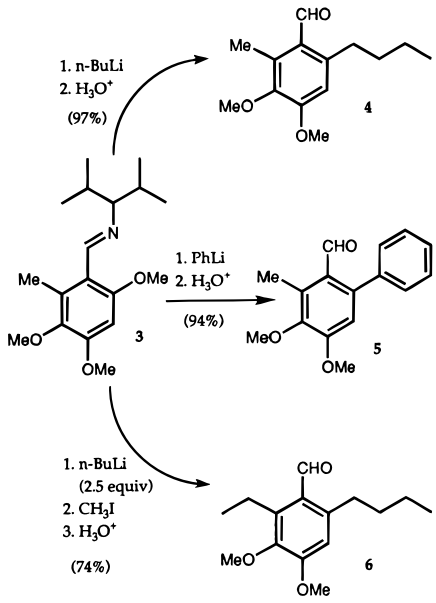
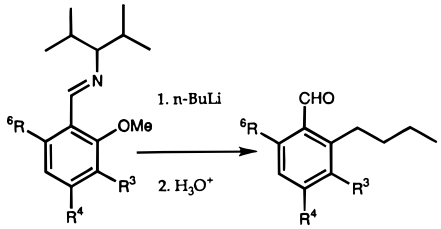


Table 1. S_NAr Reactions of Araldimines with *n*-BuLi



entry	imine	R^3	R^4	R^6	reaction[a]	product[b] (%)
1	**7**	H	H	H	A	**8** (70)[c]
2	**9**	MeO	H	H	A	**10** (94)[c]
3	**11**	H	MeO	H	B	**12** (88)
4	**13**	H	H	MeO	A	**14** (73)[c]
5	**15**	MeO	MeO	H	A	**16** (69)

[a] Method A: (1) *n*-BuLi (2) H_3O^+. Method B: (1) *n*-BuLi, (2) CH_3I (to detect possible metalation), (3) H_3O^+. [b] Yields are for isolated products. [c] Reference 5c.

Reaction of imine **3** with *n*-BuLi (Scheme 1) could potentially lead to lateral metalation of the C-6 methyl group, ring metalation at the unsubstituted C-3 position, or S_NAr replacement of the C-2 methoxy substituent. In an initial experiment to probe this question imine **3** reacted with 1.2 equiv of *n*-BuLi to give a red solution which was quenched with excess methyl iodide and hydrolyzed to give a 4:1 ratio of aldehydes **4** and **6**. When the methyl iodide quench was replaced with a simple hydrolytic workup the reaction of *n*-BuLi with imine **3** gave aldehyde **4** exclusively and in high yield. Similarly, phenyllithium reacted smoothly with imine **3** to give aldehyde **5**. A convenient one-pot S_NAr reaction−lateral metalation−electrophilic capture sequence was demonstrated using imine **3**: Treatment of the imine with 2.5 equiv of *n*-BuLi gave a deep magenta solution that was quenched with excess methyl iodide. The crude product was hydrolyzed and purified by flash chromatography to give aldehyde **6** in 94% yield (Scheme 1).

Simple araldimines containing a C-2 methoxy group generally reacted with *n*-BuLi exclusively via a nucleophilic aromatic substitution pathway (Table 1).

However, imine **17**, which in common with imines **1** and **3** contains methoxy groups at both the C-2 and C-5

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

(1) Syntex Student Intern, 1993.

(2) Roche Bioscience Student Intern, 1994.

(3) (a) Flippin, L. A.; Muchowski, J. M.; Carter, D. S. *J. Org. Chem.* **1993**, *58*, 2463. (b) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067. (c) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.*, **1976**, *41*, 1564.

(4) (a) Flippin, L. A.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 2631. (b) Forth, M. A.; Mitchell, M. B.; Smith, S. A. C.; Gombatz, K.; Snyder, L. *J. Org. Chem.* **1994**, *59*, 2616.

(5) (a) Flippin, L. A.; Carter, D. S.; Dubree, N. J. P. *Tetrahedron Lett.* **1993**, *34*, 3255. (b) Reuter, D. C.; Flippin, L. A.; McIntosh, J.; Caroon, J. M.; Hammaker, J. *Tetrahedron Lett.* **1994**, *35*, 4899.

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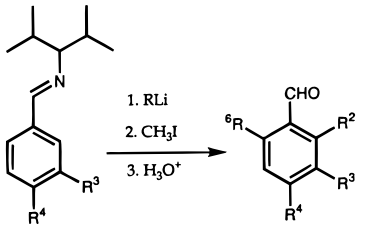
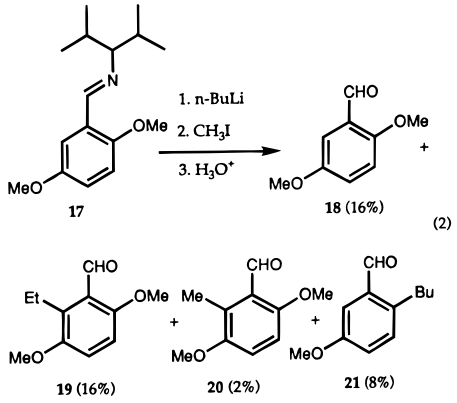
Table 2. Directed Ortho-Metalation of Araldimines



entry	imine	R^3	R^4	reaction[a]	product	R^2	R^3	R^4	yield[b] (%)
1	22	MeO	H	A			no reaction		
2	22			B	23	H	MeO	Me	44
					24	Me	MeO	H	24
3	25	H	MeO	B	26	Me	H	MeO	56
4	27	MeO	MeO	A	28	Me	MeO	MeO	73

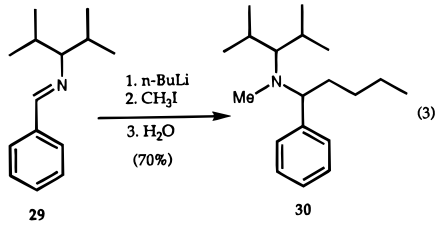
[a] A: (1) *n*-BuLi, (2) CH_3I (3) H_3O^+. B: (1) *s*-BuLi/TMEDA, (2) CH_3I, (3) H_3O^+. [b] Yield of isolated product.

positions, gave a complex mixture upon treatment with *n*-BuLi followed by quenching with excess methyl iodide to assure efficient capture of any metalated intermediates. The crude imine products were hydrolyzed with aqueous acid and the initial distribution of aldehyde products was determined by ^{1}H NMR analysis of the crude reaction mixture before chromatographic separation. The distribution of aldehydes in the crude hydrolysis mixture was **18**:**19**:**20**:**21** = 7:8:1:4, nearly identical to the distribution of isolated aldehydes (eq 2).

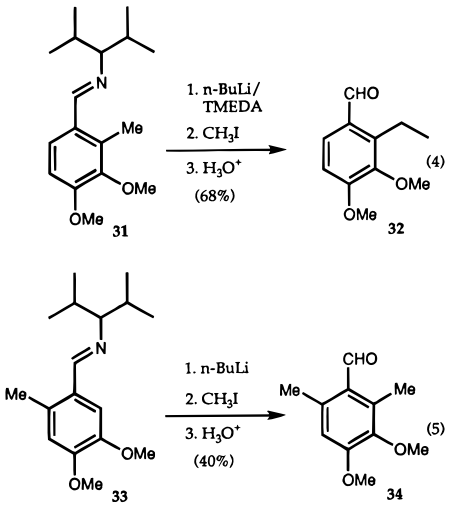


The reactions of simpler comparators **7** and **22** are not readily predictive of the complex behavior of imine **17**. Thus, imine **7** undergoes facile S_NAr replacement of the C-2 methoxy group with *n*-BuLi with no evidence of competitive ring metalation (entry 1, Table 1). Imine **22**, having no viable S_NAr pathway available, is also quite resistant toward ring metalation with *n*-BuLi (entry 1, Table 2), although more forcing conditions (*s*-BuLi-TMEDA),[7] led to poorly selective metalation at C-4 and C-2 (entry 2, Table 2). In contrast, metalation at C-6 is the predominant reaction course for imine **17**, accounting for almost 70% of the new products (**19** + **20**/**19** + **20** + **21** × 100%). It is likely that electron donation from the C-2 methoxy group increases the Lewis basicity and ortho-directing ability of the C-5 methoxy.[8] Concomitant electron donation from the C-5 methoxy should attenuate the rate of S_NAr attack at C-2 in imine **17**; the relatively minor amount of S_NAr product **21** seems to confirm this effect.[9]

The general utility of the 2,4-dimethylpent-3-ylimino group for directed metalation reactions is limited by occasional side reactions, low selectivity or reactivity in some examples, and unpredictability.[3a] For example, benzaldehyde 2,4-dimethylpent-3-ylimine **29** suffers nucleophilic addition of *n*-BuLi to the C=N bond under typical metalation conditions (eq 3).



In unexpected contrast to the results with imine **22**, imine **25** was easily metalated at C-2 using n-BuLi. A methyl iodide quench of the metalation reaction mixture and acid hydrolysis gave aldehyde **26** in modest isolated yield; however, ^{1}H NMR analysis of the crude hydrolysis mixture showed that **26** was the exclusive new reaction product (entry 3, Table 2). Similarly, imine **27** was metalated at the C-2 position using n-BuLi (entry 4, Table 2). Isomeric imines **31** and **33**, both of which contain potentially acidic aromatic ring positions and C-2 methyl groups, showed contrasting behavior under metalation conditions (eqs 4 and 5). Imine **31** was unreactive



with *n*-BuLi alone; however, *n*-BuLi−TMEDA gave selective lateral metalation to afford, after methyl iodide quench and hydrolysis, aldehyde **32** in fair yield (eq 4). In contrast, imine **33** underwent highly selective ortho-metalation at C-6 with *n*-BuLi (eq 5).

In the latter instance, ^{1}H NMR analysis of the crude hydrolysis mixture showed the presence of three trace aldehydic products (total = *ca.* 10 mol %) which were not isolated.

(7) For a discussion of the sometimes dramatic TMEDA effect on regioselectivity of directed ortho-metalation, see: Khaldi, M; Chretien, F.; Chapleur, Y. *Tetrahedron Lett.* **1994**, *35*, 401.

(8) For a discussion of the effect of Lewis basicity (coordinative potential) of substitutents on directed ortho-metalation, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(9) The rate-lowering effect of electron-donating substitutents situated para to the nucleofuge in S_NAr reactions is well known. See: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley Interscience: New York, 1992; Chapter 13 and references therein.

Experimental Section

Reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried with standard drying agents[10] and distilled before use. Melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature on $CDCl_3$ solutions. Imines **1**, **3**, **7**, **9**, **11**, **13**, **15**, **17**, **22**, **25**, **27**, **31**, and **33** were prepared from the corresponding aldehyde and 3-amino-2,4-dimethylpentane (Acros Organics, NJ) as described elsewhere.[3a,5a] Flash column chromatography[11] purification of aldehydes was performed on silica gel 60 (230−400 mesh).

Directed Metalation of Imines. 2-Methyl-3,4,6-trimethoxybenzaldehyde (2). To a −78 °C solution of 554 mg (1.9 mmol) of imine **1** in 15 mL of ether was added 1.3 mL of a 1.6 M solution of *n*-BuLi in hexane over 5 min. After addition was complete the reaction mixture was allowed to warm to room temperature for 1 h. The solution was recooled to −78 °C, methyl iodide (0.4 mL; 6.4 mmol) was added in one portion, and the reaction mixture was allowed to warm to room temperature over 30 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with ether to give crude imine **3**. Recrystallization of the crude product from hexane gave 538 mg (92%) of pure imine **3**: mp 74.5−75 °C; ^{1}H NMR δ 8.40 (s, 1H), 6.37 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H) 3.72 (s, 3H), 2.48 (s, 3H), 2.43 (t, J = 6 Hz, 1H), 2.03 (octet, J = 6 Hz, 2H), 0.88 (d, J = 6 Hz, 12H); ^{13}C NMR δ 157.3, 156.2, 153.7, 141.6, 132.9, 117.8, 94.6, 85.0, 60.4, 56.3, 55.8, 29.3, 20.4, 18.4, 13.7. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.60; H, 9.54; N, 4.55.

Imine **3** (369 mg; 1.2 mmol) was dissolved in 10 mL of THF. Aqueous 4 M HCl (1.5 mL) was added, and the mixture was refluxed for 1 h. The crude product was isolated by ether extraction and recrystallized from hexane to give 228 mg (83% yield from imine **1**) of aldehyde **2**: mp 99−100 °C (lit.[12] mp 103−104.5 °C); ^{1}H NMR δ 10.49 (s, 1H), 6.37 (br s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.71 (s, 3H), 2.59 (s, 3H). **2,4-DNP derivative**: mp 223−224 °C. Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.65; N, 14.35. Found: C, 52.45; H, 4.58; N, 14.56.

Using *s*-BuLi−TMEDA, the following compound was similarly prepared from imine **25**:

4-Methoxy-2-methylbenzaldehyde[13] **(26):** yield 56%; ^{1}H NMR δ 9.86 (s, 1H), 7.72 (dd, J = 8.2, 2 Hz, 1H), 7.69 (m, 1H), 3.92 (s, 3H), 2.27 (s, 3H). **2,4-DNP derivative:** mp 227−228 °C. Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.96. Found: C, 54.56; H, 4.32; N, 16.84.

Using *n*-BuLi, the following compound was similarly prepared from imine **27**:

3,4-Dimethoxy-2-methylbenzaldehyde (28):[14] yield 73%; mp 49.9−50.6 °C (lit.[14a] mp 47−49 °C); ^{1}H NMR δ 10.11 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 2.56 (s, 3H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.99; H, 6.80.

Using *n*-BuLi−TMEDA, the following compound was similarly prepared from imine **31**:

2-Ethyl-3,4-dimethoxybenzaldehyde[15] **(32):** yield 68%; ^{1}H NMR δ 10.11 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.10 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 3 Hz, 3H). **2,4-DNP derivative:** mp 193−194 °C. Anal. Calcd for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.67; H, 4.89; N, 14.91.

Using *n*-BuLi, the following compound was similarly prepared from imine **33**:

3,4-Dimethoxy-2,6-dimethylbenzaldehyde (34): yield 40%; mp 54.8−55.5 °C; ^{1}H NMR δ 10.47 (s, 1H), 6.61 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.60 (s, 3H), 2.54 (s, 3H); ^{13}C NMR δ 192.1, 156.3, 139.2, 135.7, 112.5, 60.4, 55.7, 20.9, 11.9. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.21; H, 7.38.

Directed-Metalation of Imine 22. A stirred solution of 610 mg (2.6 mmol) of imine **3** and 470 mg (3.1 mmol) of TMEDA in 25 mL of ether was cooled to −72 °C, and 2.4 mL (3.1 mmol) of a 1.3 M solution of *s*-BuLi in cyclohexane was added dropwise to give a yellow solution. The reaction mixture was kept at −72 °C for 1 h, and 250 mg (3.9 mmol) of CH_3I was added in one portion. The reaction mixture was warmed to room temperature and quenched with water. The crude reaction products were extracted with ether, dried over K_2CO_3, and concentrated with a rotary evaporator to give 670 mg of a yellow oil. The oily product was hydrolyzed in a refluxing solution of 3:1 THF−10% aqueous HCl (2 h), and the aldehyde products were isolated by flash chromatography to give 174 mg (44%) of **23** and 94 mg (24%) of **24**.[3a]

3-Methoxy-4-methylbenzaldehyde (23):[16] mp 40.4−40.8 °C (lit.[16a] mp 40−41 °C); ^{1}H NMR δ 9.93 (s, 1H), 7.4−7.3 (m, 3H), 3.90 (s, 3H), 2.30 (s, 3H).

Reaction of Imine 17 with n-BuLi−CH_3I. To a −70 °C solution of 501 mg (1.9 mmol) of imine **17** in 25 mL of ether was added 1.4 mL of a 1.6 M solution of *n*-BuLi in hexane over 5 min. The reaction mixture was warmed to room temperature for 1 h, recooled to −65 °C, and quenched rapidly with 0.6 mL (9.5 mmol) of methyl iodide. The mixture was allowed to stand at room temperature for 1 h and diluted with water, and the layers were separated. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated to give 622 mg of a yellow oil. The crude oil was dissolved in 25 mL of 4:1 THF−water containing 3.6 mL of 1 M aqueous HCl, and the mixture was refluxed for 1.5 h. The reaction mixture was extracted with ether to give 399 mg of a viscous yellow syrup. Flash chromatography (100:1 hexane−EtOAc) gave 51 mg (16%) of 2,5-dimethoxybenzaldehyde **18** and three additional product aldehydes:

3,6-Dimethoxy-2-ethylbenzaldehyde (19): 59 mg (16%); ^{1}H NMR δ 10.58 (s, 1H), 7.01 (d, J = 9 Hz, 1H), 6.77 (d, J = 9 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.98 (q, J = 7.4 Hz, 2H), 1.13 (t, J = 7.4 Hz, 3H); MS (m/z) 194 (M^+, 98), 193 (16), 179 (36), 164 (18).

3,6-Dimethoxy-2-methylbenzaldehyde[17] **(20):** 7 mg (2%); ^{1}H NMR δ 10.61 (s, 1H), 7.02 (d, J = 9 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 2.46 (s, 3H).

2-*n*-Butyl-5-methoxybenzaldehyde (21): 29 mg (8%); ^{1}H NMR δ 10.30 (s, 1H), 7.35 (d, J = 3 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.4, 3 Hz, 1H), 3.84 (s, 3H), 2.95 (m, 2H), 1.58 (m, 2H), 1.40 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); MS (m/z) 192 (M^+, 76), 177(10), 163 (30), 159 (40), 149 (100), 135 (40), 121 (96).

S_NAr Reactions of Imines. 2-*n*-Butyl-4-methoxybenzaldehyde (12). Imine **11** (500 mg; 1.9 mmol) was dissolved in 10 mL of ether, and the stirred solution was cooled to −60 °C. *n*-BuLi (1.4 mL of a 1.6 M solution in hexane; 2.3 mmol) was added dropwise to the imine solution, and the reaction mixture was allowed to warm to 20 °C over 1 h. The reaction mixture was again cooled to −60 °C, and 0.6 mL (9.5 mmol) of methyl iodide was added in one portion. (Note: The methyl iodide quench step in this example served as a probe for metalation processes; accordingly, this step can be eliminated from reaction sequences where no metalation is observed or there is no preparative value in capturing metalated intermediates). The reaction mixture was warmed to 20 °C, quenched with water, and extracted with ether to give 560 mg of a crude imine. A mixture of 462 mg (1.7 mmol) of the crude imine and and 25 mmol of HCl in 1:1 THF−water was refluxed for 2 h. The acidic reaction mixture was diluted with 50 mL of water and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 320 mg of a yellow oil. Column chromatography afforded 281 mg (88%) of colorless **12**: oil; ^{1}H NMR δ 10.14 (s, 1H), 7.8 (d, J = 8.6 Hz, 1H), 6.84 (dd, J = 8.6, 2.5 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H), 3.87 (s, 3H), 3.00 (m, 2H), 1.60 (m, 2H), 1.41 (sextet, J = 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 190.6, 163.7,

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148.4, 134.1, 127.3, 116.0, 111.5, 55.3, 34.2, 32.4, 22.5, 13.8; MS (*m*/*z*) 192 (M^+, 52), 191 (35), 163 (100), 150 (20), 149 (30), 121 (28, 91 (40). **2,4-DNP derivative:** mp = 159−160 °C. Anal. Calcd for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.00; H, 5.39; N, 15.11.

2-*n*-Butyl-3,4-dimethoxybenzaldehyde (16). Imine **15** (344 mg; 1.2 mmol) was dissolved in 10 mL of ether. The stirred solution was cooled to −78 °C, and 0.8 mL (1.3 mmol) of a 1.6 M solution of *n*-BuLi in hexane was added dropwise over 3 min. The reaction mixture was allowed to warm to 20 °C over 1 h and quenched with saturated NH_4Cl. The organic product was extracted with ether, dried (Na_2SO_4), and concentrated with a rotary evaporator to give a crude imine. The imine was hydrolyzed with 3 mL of 1 M HCl in 10 mL of THF (reflux, 1 h), and the crude aldehyde was extracted with ether. Purification of the crude aldehyde by column chromatography gave 180 mg (69%) of colorless **16**: oil; ^{1}H NMR δ 10.11 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.05 (m, 2H), 1.6−1.4 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 191.0, 157.4, 147.1, 140.1, 129.1, 127.9, 109.4, 60.9, 55.8, 34.3, 24.6, 23.0, 13.9. 2,**4-DNP derivative:** mp 142−143 °C. Anal. Calcd for $C_{19}H_{22}N_4O_6$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.75; H, 5.42; N, 14.08.

The following compound was similarly prepared from imine **3**:

6-*n*-Butyl-3,4-dimethoxy-2-methylbenzaldehyde (4): yield 97%; ^{1}H NMR δ 10.43 (s, 1H), 6.60 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 2.92 (t, J = 7.7 Hz, 2H), 2.53 (s, 3H), 1.58 (m, 2H), 1.41 (sextet, J = 7.4 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 191.8, 156.2, 145.5, 144.5, 135.3, 125.6, 111.6, 60.2, 55.6, 34.8, 33.4, 22.6, 13.8, 12.2; MS (*m*/*z*) 236 (M^+, 100), 207 (52), 193 (54), 179 (28), 165 (33). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.23; H, 8.80. **2,4-DNP derivative**: mp 163.6−163.7 °C.

Using phenyllithium, the following compound was similarly prepared from imine **3**:

3,4-Dimethoxy-2-methyl-6-phenylbenzaldehyde (5): yield 74%; mp 103.4−103.6 °C; ^{1}H NMR δ 9.83 (s, 1H), 7.44 (m, 3H), 7.34 (m, 2H), 6.75 (s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 2.61 (s, 3H); ^{13}C NMR δ 193.4, 155.6, 146.9, 145.3, 139.0, 134.5, 129.9, 128.2, 127.8, 126.4, 111.5, 60.4, 55.8, 12.9; MS (*m*/*z*) 256 (M^+, 100), 241 (25), 225 (18). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.15; H, 6.17.

6-*n*-Butyl-2-ethyl-3,4-dimethoxybenzaldehyde (6). To a −70 °C solution of 1.00 g (3.25 mmol) of imine **3** in 40 mL of ether was added 5.1 mL of 1.6 M *n*-BuLi in hexane over 10 min. The magenta reaction mixture was warmed to room temperature for 2 h and recooled to −70 °C, and 1.0 mL (16 mmol) of methyl iodide was added in one portion. The light yellow reaction mixture was allowed to stand at room temperature for 30 min and quenched with water. The mixture was extracted with additional ether, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give 1.209 g of a yellow oil. The crude product was dissolved in 50 mL of 4:1 THF−water, and 5.2 mL of aqueous 1 M HCl was added. The mixture was refluxed for 45 min and diluted with 100 mL of ether, and the aqueous layer was discarded. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil. Flash chromatography of the crude material gave 765 mg (94%) of aldehyde **5**: oil; ^{1}H NMR δ 10.40 (s, 1H), 6.61 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.03 (q, J = 7.5 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 1.56 (m, 2H), 1.43 (sextet, J = 7.3 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 191.8, 156.1, 145.0, 144.4, 141.9, 124.9, 111.9, 60.8, 55.6, 34.7, 33.7, 22.7, 18.9, 16.1, 13.9; MS (*m*/*z*) 250 (M^+, 100), 221 (87), 207 (80), 193 (55), 179 (45), 91 (45). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.20; H, 8.71.

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