Directed Metalation of Aromatic Aldimines with Lithium 2,2,6,6-Tetramethylpiperidide†

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Received September 17, 1992 (Revised Manuscript Received January 27, 1993)

N-Cyclohexyl aromatic aldimines are ortho-lithiated or *o*-methyl-lithiated with 2 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF solution at −15 °C. The lithiated intermediates generally reacted with alkyl halides or CO_2 to provide ortho-functionalized aldimine products which could be readily converted to the corresponding aldehydes by hydrolysis with aqueous 4 M HCl. Aromatic aldimines derived from (±)-*trans*-2-methylcyclohexylamine or 3-amino-2,4-dimethylpentane are resistant toward C=N addition with 1 equiv of n-BuLi at 0 °C in THF solution; however, they are also surprisingly resistant toward directed metalation reactions with either LTMP or n-BuLi. Exceptions to the ortho-directing and *o*-methyl-directing effects of the aldimine group were observed in a reaction of 3-methylthiophene-2-carboxaldehyde cyclohexylimine (**7**) with LTMP, followed by CH_3I, which gave a 9:1 mixture of 3,5-dimethylthiophene-2-carboxaldehyde cyclohexylimine (**22**) and 5-ethyl-3-methylthiophene-2-carboxaldehyde cyclohexylimine (**23**), and a reaction of *p*-tolualdehyde 2,4-dimethylpent-3-ylimine (**11**) with either n-BuLi or LTMP, followed by CH_3I, which gave *p*-ethylbenzaldehyde 2,4-dimethylpent-3-ylimine (**25**).

Introduction

A synthetic method for directed metalation of protected aromatic aldehydes that is both convenient and broadly applicable has proved elusive despite several impressive efforts toward this goal. In the course of their seminal investigations of directed metalation of aromatic aldimines Ziegler and Fowler[1] demonstrated that 3,4-(methylenedioxy)benzaldehyde cyclohexylimine can be efficiently lithiated on the aromatic ring at C(2) with n-BuLi in THF solution at −78 °C; however, this reaction does not appear to be very general, instead leading to n-BuLi addition at the C=N bond in most examples of aromatic aldimines which lack a 3,4-methylenedioxy group. The same workers reported that lithium diisopropylamide only partially effected the lithiation of 3,4-(methylenedioxy)benzaldehyde cyclohexylimine.[1] Gschwend[2] showed that aryloxazolines can be ortho-lithiated and trapped with electrophiles; the resulting products can subsequently be converted by a three-step procedure to the corresponding benzaldehyde derivatives. The ortho-lithiation of arylimidazolidines has been demonstrated by Harris.[3] However, even though the imidazolidine group is a potentially useful form of protected aldehyde (requiring mild acid hydrolysis to liberate the CHO group) it has not yet proved to be a widely accepted directed-metalation group, possibly due to inconvenient metalation conditions. Rodrigo[4] has shown that aromatic acetals can in some instances be ortho-lithiated by the use of alkyllithium reagents. While aromatic acetals can be easily transformed into the corresponding aldehydes by acid hydrolysis, the acetal functionality is apparently a poor metalation-directing group and has enjoyed only limited utility in that role. Comins' method[5] of conversion of aromatic aldehydes to α-aminoalkoxides followed in the same reaction vessel by ortho-lithiation, functionalization with an electrophile, and hydrolytic workup has found useful application in a variety of interesting synthetic problems. Nevertheless, the Comins procedure sometimes requires lengthy reaction times and intricate control of reaction conditions to ensure complete metalation. Einhorn and Luche[6] have described an ultrasound-accelerated Bouvealt reaction which produces a "Comins α-aminoalkoxide" in tetrahydropyran solution; they report that the directed metalation step is somewhat more facile in this medium than in the solvents usually employed for the Comins procedure.

In this paper we describe a simple and potentially general protocol for directed lithiation of *N*-cyclohexyl aromatic aldimines with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF solution.[7] The lithiated aldimines can be functionalized with a variety of electrophiles, and mild acid hydrolysis of the resulting products affords substituted aromatic aldehydes in good to excellent yield.

† Contribution No. 861 from the Institute of Organic Chemistry. This paper is dedicated to Dr. John A. Edwards on the occasion of his retirement from Syntex Discovery Research. This work was presented in part at the 203rd ACS National Meeting, San Francisco, Organic Division paper no. 67.

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(7) We found no products indicative of α-lithiotetrahydrofuran formation when LTMP was preformed in THF solution with n-BuLi at −10 to −15 °C. In a control experiment, an LTMP solution prepared at −10 °C and aged for 1 h was quenched at −10 °C with an excess of freshly purified benzaldehyde. No evidence for the formation of an α-lithiotetrahydrofuran adduct with benzaldehyde could be detected by ^1H NMR. For alternative methods of preparing LTMP in THF solution and evidence of the formation of stable α-lithiotetrahydrofuran under some conditions, see: (a) Eaton, P. E.; Higuchi, H.; Milikan, R. *Tetrahedron Lett.* **1987**, *28*, 1055. (b) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T. *J. Org. Chem.* **1987**, *52*, 2100.

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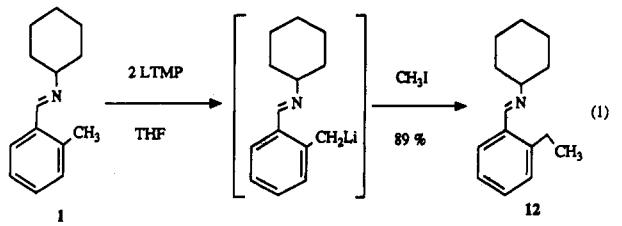
Results and Discussion

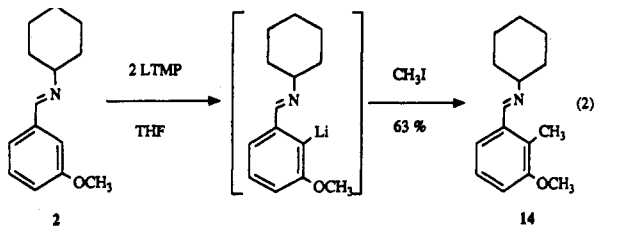
The attempted metalation of imines 1 or 2 with 1 equiv of an alkyllithium reagent (n-BuLi or t-BuLi, THF, −78 °C) gave products exclusively derived from addition of the alkyllithium reagents to the C=N bond. Lithium diisopropylamide gave incomplete metalation of imine 1 under a variety of reaction conditions.

On the other hand, o-tolualdehyde cyclohexylimine (1) reacted with 2 equiv of LTMP in THF solution at −15 °C to give a deep purple solution of 2-(lithiomethyl)benzaldehyde cyclohexylimine. After 1 h at −15 °C, the reaction mixture was quenched rapidly with an excess of CH_3I to give 2-ethylbenzaldehyde cyclohexylimine (12) in 89% isolated yield (eq 1). The use of either 1 equiv or 1.5 equiv



of LTMP under otherwise identical conditions gave incomplete metalation of imine 1 (approximately 50% and 75% completion, respectively, based on the ratios of imine 12/imine 1 observed in the crude product mixtures).

Imine 2 was effectively lithiated under reaction conditions identical to those found suitable for imine 1; again, less than 2 equiv of LTMP gave incomplete metalation. Solutions containing 2-lithio-3-methoxybenzaldehyde cyclohexylimine were cooled to −60 °C before they were quenched in one portion with CH_3I. Recrystallization of the crude product from a typical reaction of imine 2 afforded 3-methoxy-2-methylbenzaldehyde cyclohexylimine (14) in 63% yield (eq 2).

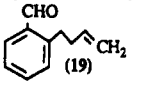
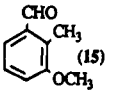
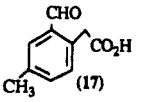
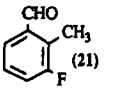
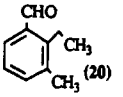
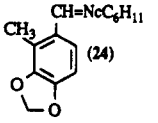
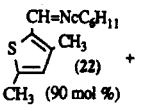
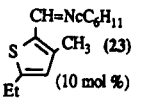


If the CH_3I quench was carried out slowly or at the same temperature as metalation (−15 to −10 °C) the crude product was usually contaminated with significant amounts (ca. 10%) of 2-ethyl-3-methoxybenzaldehyde cyclohexylimine.

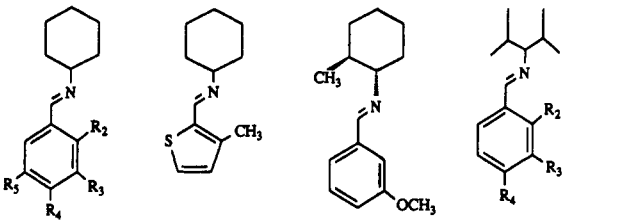
The facile lithiation of aldimines 1 and 2 under identical, mild reaction conditions represents a simple and potentially general solution to the problem of directed metalation of aromatic aldehyde derivatives; thus, we explored several additional examples of aromatic aldimine lithiation with LTMP. Aldimines 1–11 were prepared from commercially available aldehydes.

Following metalation and functionalization of the *N*-cyclohexyl aldimines, the products were conveniently hydrolyzed to corresponding aldehydes by hydrolysis with 4 M HCl (25 °C, 12 h). The results of synthetically useful directed lithiation–functionalization reactions of selected *N*-cyclohexyl aromatic aldimines are given in Table I.

Table I. Metalation–Functionalization of Aromatic Aldimines

starting aldimine	electrophile	final product	% yield[a]
1	CH_3I	2-ethylbenzaldehyde (13)	81
1	1-iodopentane	2-hexylbenzaldehyde (16)	88
1	allyl bromide	 (19)	69
2	CH_3I	 (15)	59
3	CO_2	 (17)	40
4	CH_3I	 (21)	78
5	CH_3I	 (20)	80
6	CH_3I	 (24)	97[b]
7	CH_3I	 (22) (90 mol %) +  (23) (10 mol %)	91[b]

[a] Isolated yield. [b] Crude yield.



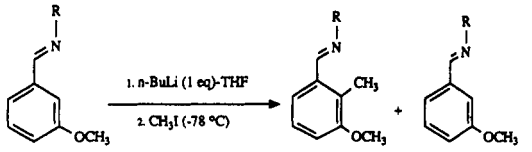
1: R_2=CH_3;R_3=R_4=R_5=H
2: R_3=CH_3O;R_2=R_4=R_5=H
3: R_2=R_5=CH_3;R_3=R_4=H
4: R_3=F;R_2=R_4=R_5=H
5: R_2=R_3=CH_3;R_4=R_5=H
6: R_3, R_4=OCH_2O;R_2=R_5=H

9: R_3=CH_3O;R_2=R_4=H
10: R_2=CH_3;R_3=R_4=H
11: R_4=CH_3;R_2=R_3=H

While the cyclohexylimine moiety clearly functions as a directed metalation group in the benzenoid aromatic aldimines that we studied, it failed to induce lithiation at the C(3) methyl group of thiophene derivative 7 giving instead only products from metalation at C(5) (Table I).

When benzaldehyde cyclohexylimine (26) was lithiated with 2 equiv of LTMP followed by a CH_3I quench only 18 mol % of o-tolualdehyde cyclohexylimine was detected in the crude reaction mixture; the remainder was starting material. In an experiment wherein imine 26 was added to 1 equiv of preformed LTMP in THF at −15 °C, followed by slow addition of a second equivalent of n-BuLi at −20 °C (total metalation time = 1 h), quenching with CH_3I gave a crude product comprised of 40 mol % of imine 1

Table II. Metalation–Functionalization of Imine 8



R = (±)-trans-2-methylcyclohexyl

condns, temp (°C) (time (h))	products (% yield)	
−20 (1.3)	trace	95
0 (1)	50	50
0 (2)	67	33

and 60 mol % of starting imine **26**. However, we felt that if we could find a general way to metalate aromatic aldimines with a single equivalent of an alkyllithium reagent perhaps we could overcome the problem of incomplete LTMP-induced metalation of benzaldehyde imines and also avoid potential side reactions of some electrophiles with the excess base that is normally required for LTMP metalation procedures. In an attempt to discover if we could effectively shield the imine C=N bond from unwanted addition reactions, we prepared novel aromatic aldimines **8–11** and studied their reactions with alkyllithium reagents or LTMP, followed by a quench of the reaction mixtures with CH_3I. Aldimines **8–11** all showed satisfactory resistance toward C=N addition reactions of n-BuLi in THF solution even up to 0 °C. The results of ortho-lithiation of imine **8** with n-BuLi are shown in Table II.

Aldimines **9** and **10** were surprisingly inert toward metalation with n-BuLi or LTMP, respectively. For example, **9** was treated with 1.1 equiv of n-BuLi (THF, 0 °C, 1 h) followed by CH_3I to give a 17:1 mixture of starting imine and the expected 2-methyl derivative. After treatment with 2 equiv of LTMP (THF, 0 °C, 1 h) followed by CH_3I, imine **10** gave a 93:7 mixture of starting material and the expected 2-ethyl derivative. On the other hand, aldimine **11** reacted with 1.0 equiv of n-BuLi (THF, −10 → 0 °C, 30 min) followed by a CH_3I quench to give 4-ethyl derivative **25** as a 3:1 admixture with starting material. Aldimine **11** was more efficiently lithiated with 2 equiv of LTMP to give, after reaction with CH_3I, pure 4-ethylbenzaldehyde 2,4-dimethylpentan-3-ylimine (**25**) in 69% yield.

Experimental Section

General. NMR spectra were measured on $CDCl_3$ solutions containing internal TMS using a spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. Commercial cyclohexylamine and 2,2,6,6-tetramethylpiperidine (TMP) were distilled from CaH_2 and stored under a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium–benzophenone under a nitrogen atmosphere immediately before use.

Preparation of Aldimines. Aldimine starting materials were prepared from the corresponding aldehyde (1.0 equiv) and 1.2 equiv of cyclohexylamine, (±)-*trans*-2-methylcyclohexylamine, or 3-amino-2,4-dimethylpentane in the presence of *p*-toluenesulfonic acid by azeotropic removal of water. The aldimines were isolated by distillation at reduced pressure or recrystallization from hexane in 70–90% yield (see also supplementary material).

***o*-Tolualdehyde Cyclohexylimine, 1.** Bp (1.5 Torr) = 115–120 °C. Mp = 30–31 °C. ^1H NMR: δ 8.65 (s, 1 H); 7.90 (dd, *J* = 7.6, 1.7 Hz, 1 H); 7.30–7.10 (m, 3 H); 3.23 (m, 1 H); 2.52 (s, 3 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 157.1; 137.3; 134.6; 130.7; 129.9; 127.4; 126.2; 70.5; 34.5; 25.7; 24.8; 19.3.

3-Methoxybenzaldehyde Cyclohexylimine,[1] 2. Bp (0.8 Torr) = 135–140 °C. ^1H NMR: δ 8.31 (s, 1 H); 7.35–7.20 (m, 3 H); 7.0–6.9 (m, 1 H); 3.87 (s, 3 H); 3.22 (m, 1 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 159.8; 158.5; 138.1; 129.5; 121.2; 116.9; 111.8; 70.0; 55.4; 34.3; 25.6; 24.8.

2,5-Dimethylbenzaldehyde Cyclohexylimine, 3. Bp (0.4 Torr) = 119–121 °C. ^1H NMR: δ 8.63 (s, 1 H); 7.72 (br s, 1 H); 7.15–6.95 (m, 2 H); 3.22 (m, 1 H); 2.46 (s, 3 H); 2.35 (s, 3 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 157.3; 135.7; 134.3; 130.8; 130.6; 127.4; 70.6; 34.5; 25.7; 24.9; 20.9; 18.7.

3-Fluorobenzaldehyde Cyclohexylimine, 4. Bp (0.4 Torr) = 95–100 °C. ^1H NMR: δ 8.30 (s, 1 H); 7.54–7.30 (m, 3 H); 7.10 (m, 1 H); 3.23 (m, 1 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 163.1 (d, *J* = 246 Hz); 157.2 (d, *J* = 3 Hz); 139.0 (d, *J* = 7 Hz); 130.0 (d, *J* = 8 Hz); 124.1 (d, *J* = 2 Hz); 117.2 (d, *J* = 21 Hz); 114.2 (d, *J* = 22 Hz); 69.9; 34.3; 25.6; 24.7.

3-Methylthiophene-2-carboxaldehyde Cyclohexylimine, 7. Bp (0.4 Torr) = 110–115 °C. ^1H NMR: δ 8.49 (s, 1 H); 7.28 (d, *J* = 5.1 Hz, 1 H); 6.85 (d, *J* = 5.1 Hz, 1 H); 3.17 (m, 1 H); 2.39 (s, 3 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 150.6; 139.6; 136.1; 130.6; 127.5; 70.1; 34.4; 25.6; 24.9; 13.8.

2,3-Dimethylbenzaldehyde Cyclohexylimine, 5. Bp (1.0 Torr) = 124–128 °C. Mp = 42–43 °C. ^1H NMR: δ 8.67 (s, 1 H); 7.68 (br d, *J* = 7.5 Hz, 1 H); 7.18 (m, 1 H); 7.11 (t, *J* = 7.5 Hz, 1 H); 3.20 (m, 1 H); 2.37 (s, 3 H); 2.29 (s, 3 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 157.9; 137.0; 135.8; 134.9; 131.5; 125.7; 125.5; 70.5; 34.6; 25.7; 25.1; 20.4; 14.7.

3,4-(Methylenedioxy)benzaldehyde Cyclohexylimine,[1] 6. Mp = 60–63 °C. ^1H NMR: δ 8.17 (s, 1 H); 7.34 (d, *J* = 1.5 Hz, 1 H); 7.07 (dd, *J* = 8.1, 1.5 Hz, 1 H); 6.79 (d, *J* = 8.1 Hz, 1 H); 5.96 (s, 2 H); 3.13 (m, 1 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 157.6; 149.5; 148.2; 131.5; 124.0; 108.0; 106.7; 101.3; 69.7; 34.5; 25.7; 24.8.

3-Methoxybenzaldehyde (±)-*trans*-2-Methylcyclohexylimine, 8. Bp (0.2 Torr) = 85–90 °C. ^1H NMR: δ 8.26 (s, 1 H); 7.42–7.28 (m, 2 H); 7.02–6.95 (m, 1 H); 3.87 (s, 3 H); 2.73 (m, 1 H); 2.0–1.0 (m, 9 H); 0.81 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR: δ 159.9; 159.1; 138.1; 129.5; 121.2; 116.9; 112.0; 77.2; 55.4; 37.6; 34.5; 33.9; 26.1; 25.2; 19.7.

3-Methoxybenzaldehyde 2,4-Dimethylpent-3-ylimine, 9. Bp (0.4 Torr) = 80–90 °C. ^1H NMR: δ 8.09 (s, 1 H); 7.35–7.22 (m, 2 H); 7.0–6.9 (m, 1 H); 3.85 (s, 3 H); 2.47 (t, *J* = 6.0 Hz, 1 H); 2.06 (octet, *J* = 6.6 Hz, 2 H); 0.87 (d, *J* = 6.6 Hz, 6 H); 0.86 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR: δ 159.9; 159.2; 138.2; 129.5; 121.1; 116.5; 112.3; 83.4; 55.3; 29.4; 20.5; 18.5.

***o*-Tolualdehyde 2,4-Dimethylpent-3-ylimine, 10.** Bp (0.2 Torr) = 80–90 °C. ^1H NMR: δ 8.39 (s, 1 H); 7.80 (dd, *J* = 7.2, 2.0 Hz, 1 H); 7.30–7.10 (m, 2 H); 2.49 (s, 3 H); 2.47 (t, *J* = 6.0 Hz, 1 H); 2.06 (octet, *J* = 6.6 Hz, 2 H); 0.89 (d, *J* = 6.3 Hz, 6 H); 0.87 (d, *J* = 6.3 Hz, 6 H). ^{13}C NMR: δ 158.5; 137.2; 134.8; 130.6; 129.6; 128.1; 126.0; 84.0; 29.4; 20.4; 19.6; 18.4.

***p*-Tolualdehyde 2,4-Dimethylpent-3-ylimine, 11.** Bp (0.2 Torr) = 80–90 °C. Mp = 36–37 °C. ^1H NMR: δ 8.08 (s, 1 H); 7.64 (d, *J* = 8.0 Hz, 2 H); 7.20 (d, *J* = 8.0 Hz, 2 H); 2.45 (t, *J* = 6.0 Hz, 1 H); 2.37 (s, 3 H); 2.05 (octet, *J* = 6.5 Hz, 2 H); 0.87 (d, *J* = 6.7 Hz, 6 H); 0.86 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR: δ 159.3; 140.3; 134.0; 129.2; 128.1; 83.5; 29.5; 21.4; 20.4; 18.4.

Benzaldehyde Cyclohexylimine, 26. Bp (0.5 Torr) = 95–100 °C. ^1H NMR: δ 8.29 (s, 1 H); 7.75–7.65 (m, 2 H); 7.40–7.30 (m, 3 H); 2.90 (m, 1 H); 1.90–1.15 (m, 10 H). ^{13}C NMR: δ 158.6; 136.6; 130.4; 128.6; 128.1; 70.1; 34.4; 25.7; 24.9.

2-Ethylbenzaldehyde Cyclohexylimine, 12. To a three-neck round-bottom flask equipped with a magnetic stirrer, internal thermometer, and nitrogen inlet was added 1.50 g (11.0 mmol) of 2,2,6,6-tetramethylpiperidine in 25 mL of dry THF. The solution was cooled to −15 °C, and 8.0 mL of 1.3 M s-BuLi (cyclohexane solution) was added over 3 min. After 10 min, 1.00 g (5.0 mmol) of imine **1** was added dropwise to give a deep purple solution. After 1 h, 1.0 mL of CH_3I was added in one portion (immediate decoloration, temperature rise: −15 → +5 °C). The reaction mixture was poured into aqueous NH_4Cl and extracted with ether. The ether solution was washed several times with water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 1.17 g of a yellow oil. The oil was distilled with a Kugelrohr apparatus to give 0.96 g (89%) of colorless **12**. Bp (1.5 Torr) = 120–125 °C. ^1H NMR: δ 8.63 (s, 1 H); 7.87 (dd, *J*

= 6.1, 1.4, 1 H); 7.35–7.10 (m, 3 H); 3.20 (m, 1 H); 2.85 (q, J = 7.6 Hz, 2 H); 1.90–1.10 (m, 10 H), 1.22 (t, J = 7.6 Hz, 3 H). ^{13}C NMR: δ 156.9; 143.6; 134.2; 130.2; 129.2; 127.7; 126.3; 70.5; 34.6; 25.9; 25.8; 24.9; 16.3.

Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.57; H, 10.05; N, 6.29.

2-Ethylbenzaldehyde,[8] **13.** Imine **12** (0.50 g; 2.3 mmol) was stirred vigorously at room temperature with 5 mL of 4 M aqueous HCl and 1 mL of ether for 12 h. The mixture was extracted with ether; the ether solution was washed with several portions of water, dried ($MgSO_4$), filtered, and concentrated at room temperature with a rotary evaporator. The residue was distilled with a Kugelrohr device to give 0.28 g (91%) of 2-ethylbenzaldehyde. Bp (1.0 Torr) = 60–70 °C. ^{1}H NMR: δ 10.3 (s, 1 H); 7.85 (dd, J = 7.7, 1.6 Hz, 1 H); 7.54 (td, J = 7.7, 1.6 Hz, 1 H); 7.40–7.25 (m, 2 H); 3.09 (q, J = 7.6 Hz, 2 H); 1.30 (t, J = 7.6 Hz, 3 H).

2,4-Dinitrophenylhydrazone. Mp = 181–182 °C (ethanol).

3-Methoxy-2-methylbenzaldehyde Cyclohexylimine, 14. TMP (3.00 g; 21.0 mmol) was dissolved in 50 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −15 °C, and 13.1 mL of 1.6 M n-BuLi (hexane solution) was added over 5 min. After 20 min 2.00 g (9.2 mmol) of imine **2** was added dropwise to give a pale green solution. The reaction mixture was maintained between −15 and −10 °C for 55 min and cooled to −60 °C, and 2.4 mL (39 mmol) of CH_3I was added rapidly in one portion with vigorous stirring. The reaction mixture was allowed to warm to room temperature, poured into saturated NH_4Cl solution, and extracted with ether. The ether solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 1.89 g of a yellow, waxy solid. Recrystallization of the crude product from hexane gave 1.33 g (63%) of imine **14**. Mp = 67–68 °C. ^{1}H NMR: δ 8.66 (s, 1 H); 7.48 (d, J = 7.5 Hz, 1 H); 7.17 (t, J = 7.5 Hz, 1 H); 6.87 (d, J = 7.5 Hz, 1 H); 3.83 (s, 3 H); 3.20 (m, 1 H); 2.34 (s, 3 H); 1.90–1.20 (m, 10 H). ^{13}C NMR: δ 157.7; 157.3; 135.9; 126.4; 126.3; 119.6; 111.5; 70.5; 55.7; 34.5; 25.7; 24.8; 10.8.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.56; H, 9.03; N, 5.48.

3-Methoxy-2-methylbenzaldehyde,[5] **15.** Imine **14**, 0.50 g (2.2 mmol), was dissolved in 1 mL of ether, and the solution was stirred with 10 mL of 4 M HCl at room temperature for 16 h. The mixture was extracted with ether; the ether solution was washed with several portions of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator. The residue was distilled with a Kugelrohr apparatus to give 0.31 g (94%) of colorless **15**. Bp (1.5 Torr) = 95–105 °C. ^{1}H NMR: δ 10.35 (s, 1 H); 7.45 (d, J = 7.8 Hz, 1 H); 7.33 (t, J = 7.8 Hz, 1 H); 7.09 (d, J = 7.8 Hz, 1 H); 3.89 (s, 3 H); 2.56 (s, 3 H). ^{13}C NMR: δ 192.8; 158.1; 135.1; 129.7; 126.6; 123.0; 115.3; 55.9; 10.5.

2-Hexylbenzaldehyde, 16. TMP (1.50 g; 10.0 mmol) was dissolved in 25 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −15 °C, and 8.0 mL of 1.3 M s-BuLi (cyclohexane solution) was added over 3 min. After 15 min 1.00 g (5.0 mmol) of imine **1** was added dropwise to give a purple solution. The solution was maintained at −15 to −10 °C for 1 h, and 1.3 mL (10.0 mmol) of 1-iodopentane was added in one portion. The reaction mixture was allowed to warm to room temperature and poured into saturated NH_4Cl solution. The usual extractive workup (ether) gave 1.46 g of crude oily product which was hydrolyzed (4 M HCl, room temperature, 12 h) without further purification. The crude aldehyde was distilled with a Kugelrohr apparatus to give 0.84 g (88%) of colorless **16**. Bp (0.6 Torr) = 100–110 °C. ^{1}H NMR: δ 10.30 (s, 1 H); 7.83 (dd, J = 7.6, 1.2 Hz, 1 H); 7.50 (dd, J = 7.6, 1.2 Hz, 1 H); 7.35 (t, J = 7.3, 1.0 Hz, 1 H); 7.27 (d, J = 7.3 Hz, 1 H); 3.02 (t, J = 7.8 Hz, 2 H); 1.61 (m, 2 H); 1.45–1.15 (m, 6 H); 0.88 (t, J = 7.0 Hz, 3 H). ^{13}C NMR: δ 192.4; 145.9; 133.8; 131.3; 131.0; 126.4; 34.6; 32.5; 31.7; 29.2; 22.6; 14.1.

2,4-Dinitrophenylhydrazone. Mp = 128–129 °C (ethanol).

Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.32; H, 5.98; N, 14.74.

(8) Maitte, P. *Ann. Chim. (Paris)* **1954**, *9*, 431.

2-Formyl-4-methylphenylacetic Acid, 17. TMP (3.00 g; 21.0 mmol) was dissolved in 30 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −15 °C, and 13.1 mL of 1.6 M n-BuLi (hexane solution) was added. After 15 min 2.00 g (9.3 mmol) of imine **3** was added dropwise to give a purple solution. After 45 min, dry CO_2 was bubbled into the reaction mixture to give a clear yellow solution. A 50-mL portion of 2 M HCl was added, and the reaction mixture was stirred at room temperature for 4 h. The mixture was extracted with ethyl acetate; the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 0.86 g of yellow solid. Recrystallization of the crude material from ethanol–ether gave 0.67 g (40%) of unstable, white solid **17**. Mp = 126–128 °C. ^{1}H NMR: δ 10.08 (s, 1 H); 7.70 (br s, 1 H); 7.42 (br d, J = 7.7 Hz, 1 H); 7.27 (d, J = 7.7 Hz, 1 H); 3.96 (s, 2 H); 2.38 (s, 3 H).

2-(1-Buten-4-yl)benzaldehyde Cyclohexylimine, 18. TMP (1.50 g; 10.0 mmol) was dissolved in 25 mL of dry THF under a nitrogen atmosphere. At −15 °C 8.0 mL of 1.3 M s-BuLi was added to the solution over 5 min. After 10 min 1.00 g (5.0 mmol) of imine **1** was added dropwise to the solution. After 45 min, 0.90 mL (10.0 mmol) of allyl bromide was added in one portion. The usual extractive workup gave 1.16 g of a yellow oil which was distilled with a Kugelrohr device to give 1.01 g (84%) of colorless **18**. Bp (0.8 Torr) = 110–120 °C. ^{1}H NMR: δ 8.60 (s, 1 H); 7.84 (dd, J = 7.6, 1.6 Hz, 1 H); 7.35–7.15 (m, 3 H); 5.95–5.75 (m, 1 H); 5.10–4.95 (m, 2 H); 3.20 (m, 1 H); 2.93 (dd, J = 8.0, 7.0 Hz, 2 H); 2.34–2.25 (m, 2 H); 1.90–1.15 (m, 10 H).

2-(1-Buten-4-yl)benzaldehyde, 19. Hydrolysis of imine **18** (0.420 g; 1.7 mmol) with 4 M HCl (room temperature, 13 h) gave 0.224 (82%) of distilled, colorless **19**. Bp (1.0 Torr) = 95–105 °C. ^{1}H NMR: δ 10.18 (s, 1 H); 7.75 (dd, J = 7.6, 1.5 Hz, 1 H); 7.43 (td, J = 7.6, 1.5 Hz, 1 H); 7.29 (br t, J = 7.3 Hz, 1 H); 7.19 (br d, J = 7.0 Hz, 1 H); 5.85–5.70 (m, 1 H); 5.00–4.88 (m, 2 H); 3.04 (dd, J = 8.0, 7.8 Hz, 2 H); 2.32–2.20 (m, 2 H). ^{13}C NMR: δ 192.4; 144.6; 137.4; 133.8; 133.7; 132.1; 131.1; 126.6; 115.5; 36.0; 32.1.

2,4-Dinitrophenylhydrazone. Mp = 162–163 °C.

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 60.00; H, 4.74; N, 16.46. Found: C, 59.99; H, 4.74; N, 16.26.

2-Ethyl-3-methylbenzaldehyde, 20. TMP (3.00 g; 21.0 mmol) was dissolved in 35 mL of dry THF under a nitrogen atmosphere. At −20 °C 8.0 mL of 2.5 M n-BuLi (hexane solution) was added over 10 min. After 15 min, 2.00 g (9.3 mmol) of imine **5** was added dropwise to give a dark purple solution. The reaction mixture was maintained between −20 and −15 °C for 45 min and quenched with 4.0 mL of CH_3I in one portion (decoloration; temperature rise: −15 ° → +20 °C). The reaction mixture was worked up in the usual way to give 1.84 g of a yellow oil. Acid hydrolysis of the crude product gave an oily residue which was distilled with a Kugelrohr apparatus to afford 1.17 g (80%) of colorless **20**. Bp (1.0 Torr) = 75–85 °C. ^{1}H NMR: δ 10.32 (s, 1 H); 7.71 (dd, J = 7.6, 1.0 Hz, 1 H); 7.41 (d, J = 7.4 Hz, 1 H); 7.28 (t, J = 7.5 Hz, 1 H); 3.09 (q, J = 7.5 Hz, 2 H); 2.41 (s, 3 H); 1.23 (t, J = 7.5 Hz, 3 H). ^{13}C NMR: δ 192.8; 145.4; 137.3; 136.0; 129.7; 126.0; 21.2; 19.0; 15.2.

2,4-Dinitrophenylhydrazone. Mp = 190–191 °C (ethanol).

Anal. Calcd for $C_{16}H_{15}N_4O_4$: C, 58.71; H, 4.62; N, 17.12. Found: C, 58.83; H, 4.90; N, 17.14.

3-Fluoro-2-methylbenzaldehyde, 21. TMP (3.00 g; 21.0 mmol) was dissolved in 50 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −15 °C, and 8.5 mL of 2.5 M n-BuLi (hexane solution) was added over 5 min. The solution was kept at −15 °C for 15 min, and 2.10 g (10.0 mmol) of imine **4** was added dropwise to give a deep red solution. The reaction mixture was maintained at −15 °C for 45 min and cooled to −60 °C, and 3.0 mL of CH_3I was added in one portion. The solution was allowed to warm to 0 °C over 20 min and poured into saturated NH_4Cl solution. The reaction mixture was extracted with ether to give 1.93 g of a dark oil which appeared to be a 9:1 mixture of 3-fluoro-2-methylbenzaldehyde cyclohexylimine and 3-fluoro-2-methylbenzaldehyde. The crude mixture was hydrolyzed in the usual way to give an oil which was distilled to give 1.08 g (78%) of colorless **21**. Bp (1.0 Torr) = 55–60 °C. ^{1}H NMR: δ 10.25 (d, J = 1.0 Hz, 1 H); 7.61 (dd, J = 7.3, 1.0 Hz, 1 H); 7.39–7.23 (m, 2 H); 2.57 (d, J = 2.0 Hz, 3 H). ^{13}C NMR:

δ 191.8; 161.4 (d, J = 246 Hz); 135.9 (d, J = 4.3 Hz); 127.6 (d, J = 3.0 Hz); 127.1 (d, J = 8.3 Hz); 120.5 (d, J = 23.7 Hz); 9.9 (d, J = 5.9 Hz).

2,4-Dinitrophenylhydrazone. Mp = 212–213 °C (ethanol).

Anal. Calcd for $C_{14}H_{10}FN_4O_4$: C, 53.00; H, 3.18; N, 17.66. Found: C, 53.29; H, 3.50; N, 17.06.

Lithiation/Methylation of 3-Methylthiophene-2-carboxaldehyde Cyclohexylimine. TMP (3.00 g; 21.0 mmol) was dissolved in 35 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −15 °C, and 8.0 mL of 2.5 M n-BuLi (hexane solution) was added dropwise over a 5 min. The solution was maintained between −15 and −10 °C for 20 min, and 2.10 g (10.0 mmol) of imine **7** was added dropwise to give a bright orange solution. The reaction mixture was maintained at −10 °C for 1 h, cooled to −50 °C, and quenched with 4.0 mL of CH_3I. Ether extraction provided 2.00 g of a yellow oil which consisted of a 9:1 mixture of 3,5-dimethylthiophene-2-carboxaldehyde cyclohexylimine (**22**) and 5-ethyl-3-methylthiophene-2-carboxaldehyde cyclohexylimine (**23**). The mixture was not separated for the purpose of ^1H NMR analysis.

Imine 22. ^1H NMR: δ 8.38 (s, 1 H); 6.51 (br s, 1 H); 3.10 (m, 1 H); 2.42 (d, J = 0.7 Hz, 3 H); 2.28 (s, 3 H); 1.90–1.15 (m, 10 H).

Imine 23. ^1H NMR: δ 8.39 (s, 1 H); 6.57 (br s, 1 H); 3.10 (m, 1 H); 2.69 (q, J = 7.6 Hz, 2 H); 2.33 (s, 3 H); 1.90–1.15 (m, 10 H); 1.20 (t, J = 7.6 Hz, 3 H).

2-Methyl-3,4-(methylenedioxy)benzaldehyde Cyclohexylimine,[1] 24. TMP (13.65 g; 91.2 mmol) was dissolved in 130 mL of dry THF under a nitrogen atmosphere. The solution was cooled to −10 °C, and 57.0 mL of 1.6 M n-BuLi (hexane solution) was added over 15 min. The solution was kept at −10 to −15 °C for 10 min, and 10.0 g (43.2 mmol) of imine **6** in 50 mL of THF was added dropwise. After addition was complete the solution was maintained at −15 °C for 1 h and cooled to −78 °C, and 15.0 mL of CH_3I was added rapidly in one portion (temperature rise: −78 → −50 °C). The reaction mixture was allowed to warm to room temperature and poured into saturated NH_4Cl solution. The mixture was extracted with ether to give 10.3 g (97%) of an oily product which was identical (^1H and ^{13}C NMR) to a sample of imine **24** prepared independently by the method of Zeigler and Fowler.[1]

4-Ethylbenzaldehyde 2,4-Dimethylpent-3-ylimine, 25. TMP (0.735 g; 5.2 mmol) was dissolved in 3 mL of dry THF under a nitrogen atmosphere. At −15 °C, 3.3 mL of 1.6 M n-BuLi (hexane solution) was added dropwise. After 15 min, 0.500 g (2.6 mmol) of imine **11** in 1 mL of THF was added to give an orange solution; the solution turned brown after 30 min at −15 °C. The reaction mixture was cooled to −40 °C and quenched with 2.0 mL of CH_3I. Extractive workup of the reaction mixture and distillation of the residue with a Kugelrohr apparatus provided 0.420 g (69%) of **25**. ^1H NMR: δ 8.09 (s, 1 H); 7.66 (d, J = 8.2 Hz, 2 H); 7.23 (d, J = 8.2 Hz, 2 H); 2.67 (q, J = 7.6 Hz, 2 H); 2.45 (t, J = 6.0 Hz, 1 H); 2.04 (octet, J = 7.6 Hz, 2 H); 1.24 (t, J = 7.6 Hz, 3 H); 0.86 (d, J = 6.6 Hz, 6 H); 0.85 (d, J = 6.6 Hz, 6 H). ^{13}C NMR: δ 159.3; 146.7; 129.2; 128.3; 128.0; 83.5; 29.5; 28.9; 20.5; 18.4; 15.5.

Supplementary Material Available: ^1H NMR spectra for compounds **1–5, 7–11, 26, 17, 18, 22, 23,** and **25** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.