(*E*)-3-Butyl-4-(*tert*-butyldimethylsilyl)but-3-en-2-one (10). To a dry three-necked flask equipped with magnetic stirrer and nitrogen inlet were added methylene chloride (25 mL), aluminum chloride (1.33 g, 10 mmol), and acetyl chloride (0.71 mL, 10 mmol). The mixture was chilled to 0 °C and 1-butyl-1-(trimethylstannyl)-2-(*tert*-butyldimethylsilyl)ethene (3.61 g, 10 mmol) was added via syringe. The mixture was allowed to warm to ambient temperature and stir 30 min; then it was poured onto ice (300 mL) with stirring and the organics were extracted with methylene chloride (3 × 40 mL). The combined organic layer was washed with brine, dried through a cone of calcium sulfate, and concentrated. The residue was flash chromatographed on silica gel (3 × 8 in., 100-mL fractions, hexane eluent) to give 1400 mL, 20 mg unidentified oil. Continued elution with 10% ether/hexane gave 1000 mL, nil. Further elution with 10% ether/hexane (800 mL) and 20% ether/hexane (400 mL) gave 1.67 g (69%) of product as a yellow oil: NMR (360 MHz) 6.38 (s, 1 H), 2.36 (br t, J = 8 Hz, 2 H), 2.0 (s, 3 H), 1.23–1.07 (m, 4 H), 0.71 (partially obscured t, J = 7 Hz, 3 H), 0.69 (s, 9 H), –0.08 (s, 6 H); IR (neat) 2960, 2930, 2859, 1688, 1573, 1470, 1462, 1360 (m), 1350, 1250, 1175, 835, 825, 810, 770. Irradiation of the vinyl proton gave a strong NOE enhancement to the acetyl methyl protons, thus demonstrating that the product had the *E* configuration.

Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 70.28; H, 11.83.

Preparation of 11. To a dry three-necked flask equipped with magnetic stirrer and nitrogen inlet were added methylene chloride (25 mL), aluminum chloride (1.33 g, 10 mmol), and cyclohexanecarboxylic acid chloride (1.34 mL, 10 mmol). After chilling to 0 °C, 1-butyl-1-(trimethylstannyl)-2-(*tert*-butyldimethylsilyl)ethene (3.61 g, 10 mmol) was added via syringe. The mixture was allowed to warm to ambient temperature and stirred 30 min; then it was poured onto ice (300 g) with stirring and the organics were extracted with methylene chloride (3 × 40 mL). The combined organic layer was washed with brine, dried through a cone of calcium sulfate, and concentrated. The residue was flash chromatographed on silica gel (2 × 10 in., 100-mL fractions, hexane eluent) to give 4000 mL, nil. Continued elution with 1.5% ether/hexane gave 900 mL, 0.15 g, of the minor isomer of the product; 500 mL, 0.2 g, of a mixture of both isomers of the product; 700 mL, 1.98 g (64%) of the major isomer of the product: NMR (360 MHz) 6.4 (s, 1 H), 2.53 (t, J = 7.5 Hz, 2 H), 2.36 (m, 1 H), 1.88–1.74 (m, 4 H), 1.71–1.63 (m, 1 H), 1.42–1.19 (m, 9 H), 0.90 (s, with partially obscured t, 12 H), 0.12 (s, 6 H); IR (neat) 2960, 2930, 2860, 1684, 1575 (m), 835, 825; ^{13}C NMR 203.36, 163.04, 134.58, 51.42, 32.86, 32.11, 28.50 (Si coupling of 65 Hz), 26.85, 25.94, 25.78, 23.38, 17.24, 13.89, –6.20. The silicon coupling to a methylene carbon proves that the double bond has migrated. It is not clear if the major product has the *Z* or *E* configuration.

Anal. Calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.76. Found: C, 73.94; H, 11.77.

Registry No. **1a**, 16393-88-7; **1b**, 97877-91-3; **1c**, 17955-46-3; **1d**, 103731-39-1; **1e**, 103731-36-8; **1f**, 103731-29-9; **2b**, 97877-94-6; **2c**, 103731-37-9; **2d**, 103731-38-0; **2e**, 97877-95-7; **2f**, 97877-96-8; **2g**, 97877-97-9; **2h**, 103731-40-4; *cis*-**2i**, 103731-26-6; *trans*-**2i**, 103731-27-7; *cis*-**2j**, 103731-34-6; *trans*-**2j**, 103731-35-7; **2k**, 103731-28-8; **2m**, 103731-30-2; **2n**, 103731-32-4; **3**, 103731-41-5; **4**, 103731-42-6; *cis*-**5**, 103731-43-7; *trans*-**5**, 103731-44-8; **8a**, 103731-45-9; *cis*-**8b**, 103731-46-0; *trans*-**8b**, 103731-47-1; **9**, 103731-49-3; **10**, 103731-50-6; *cis*-**11**, 103731-51-7; *trans*-**11**, 103731-52-8; $Cl(CH_2)_3C{\equiv}CH$, 14267-92-6; $THPOCH_2CH_2C{\equiv}CH$, 40365-61-5; $Cl(CH_2)_3(SnBu_3)C{=}CH(SiMe_3)$, 103731-31-3; $HO(CH_2)_3C{\equiv}CH$, 5390-04-5; $HO(CH_2)_2(SnBu_3)C{=}CH(SiMe_3)$, 103731-33-5; $HOCH_2CH_2C{\equiv}CH$, 927-74-2; *i*-$PrC{\equiv}CH$, 598-23-2; *t*-$BuC{\equiv}CH$, 917-92-0; $NC(CH_2)_3C{\equiv}CH$, 14918-21-9; $(CH_3)_2C(OAc)C{\equiv}CH$, 1604-29-1; $Me_3SnSnMe_3$, 661-69-8; *t*-$BuMe_2SiCl$, 18162-48-6; Me_3SnH, 1631-73-8; $PhC{\equiv}CH$, 536-74-3; $(Ph_3P)_4Pd$, 14221-01-3; $Me_3SiC{\equiv}CH$, 1066-54-2; $HC{\equiv}CH$, 74-86-2; $BrCH_2C{\equiv}CH$, 106-96-7; cyclohexanecarboxylic acid chloride, 2719-27-9; benzaldehyde, 100-52-7; 1-hexyne, 693-02-7; *N*-fluoro-*N*-norbornyl-*p*-toluenesulfonamide, 103731-48-2.

Directed Lithiation of Tertiary β-Amino Benzamides

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Received February 6, 1986

The directed ortho-lithiation–alkylation of several tertiary β-amino benzamides was studied. The ortho-substituted β-amino benzamides were hydrolyzed directly with 6 N hydrochloric acid, or by a three-step, one-pot reaction involving methylation, elimination, and treatment with aqueous acid. *o*-Toluic acid, 2-*n*-butylbenzoic acid, 2-methoxy-6-methylbenzoic acid, and 4-methoxy-2-methylbenzoic acid were prepared by using this ortho-metalation–hydrolysis methodology. Ortho-lithiation and reaction with benzaldehyde or dimethylformamide followed by hydrolysis with aqueous acid gave lactones in good yield. Methanolysis of *N*-(4-methoxy-2-methylbenzoyl)-*N'*-methylpiperizine with sulfuric acid/methanol gave methyl 4-methoxy-2-methylbenzoate in 71% yield. The conversion of tertiary benzamides into ketones and aldehydes was examined. Treatment of certain tertiary benzamides with alkyllithium reagents gave ketones, while reaction with a modified aluminum hydride reagent gave aldehydes.

Directed metalation reactions of aromatic compounds continue to be of considerable interest.[1] A variety of ortho-directing groups have been utilized on various aromatic rings to direct metalation in the ortho or ortho-benzylic positions. Carboxylic acid derived directing groups[1] include tertiary amides, secondary amides, thioamides, and oxazolines. As was pointed out in a recent review,[1d] the advantages of the tertiary amide include ease of preparation, priority over other directors during the metalation step, utility in polysubstituted aromatic systems, and resistance to nucleophilic attack. The resistance to nucleophilic attack can be a problem if one wishes to convert the tertiary amide group into another functionality. In fact, the main disadvantage of the *N*,*N*-dialkylamide as an ortho-metalation directing group is its resistance to hydrolysis.[1d]

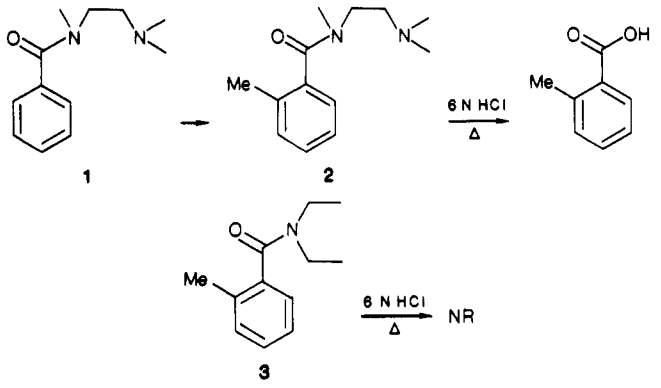
During a recent study involving ortho-metalation directed by α-amino alkoxides,[2] we had the opportunity to investigate an ortho-lithiation–methylation of *N*-[2-(di-

(1) For reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1–360. (b) Omae, I. *Chem. Rev.* **1979**, *79*, 287–321. (c) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676. (d) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312. (e) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95–106.

(2) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465–5468. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078–1083. Comins, D. L.; Brown, J. D. Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979–3982. Comins, D. L.; Brown, J. D. *Ibid.* **1981**, *22*, 4213–4216.

0022-3263/86/1951-3566$01.50/0

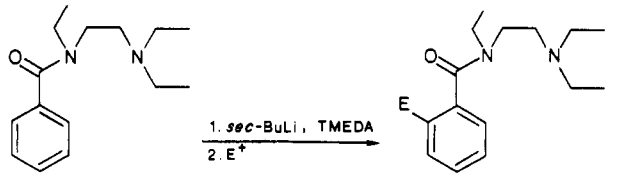
methylamino)ethyl]-*N*-methylbenzamide (1). We discovered that the *o*-methyl derivative **2** was hydrolyzed to *o*-toluic acid with refluxing 6 N hydrochloric acid, whereas the analogous *N,N*-diethylbenzamide **3** was not. This observation prompted us to investigate the scope of this reaction with the objective of complimenting existing methodology by developing a tertiary amide ortho-metalation directing group which is *not* resistant to hydrolysis.



1 2 3

Results and Discussion

Ortho-Metalation Studies. We had little success in expanding the scope of our original ortho-lithiation reaction of *N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide (1). The yields were frequently low due to self-condensation[3] and other side reactions. This forced us to examine the more sterically hindered tertiary β-amino benzamide **4**. *N,N,N'*-Triethylethylenediamine is commercially available and reacts with benzoyl chloride, using a Schotten–Baumann procedure, to provide *N*-[2-(diethylamino)ethyl]-*N*-ethylbenzamide (**4**) conveniently and in high yield. The benzamide **4** was ortho-lithiated by using

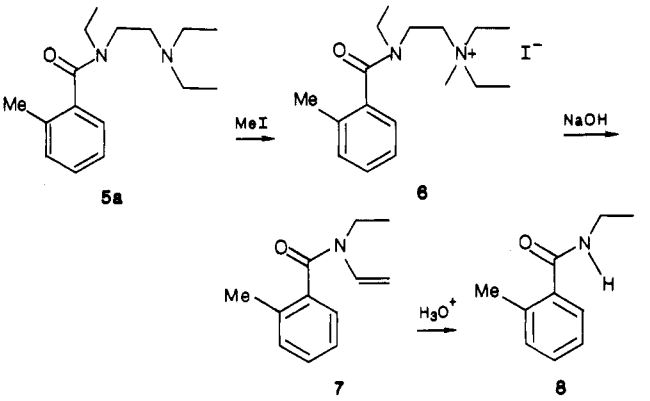


4 5

Beak's conditions (*sec*-BuLi, TMEDA, −78 °C)[4] and treated with electrophiles to give the ortho-substituted benzamides **5** in good yield (MeI, 76%; MeSiCl, 75%; MeSSMe, 56%). The products **5** were isolated by using an acid–base extraction and further purified by chromatography on silica gel.

Hydrolysis Studies. The stability obtained by changing from the *N,N,N'*-trimethyl benzamide **1** to the triethyl derivative **4** worked against us during the hydrolysis step. The *o*-methylbenzamide **5a** was not hydrolyzed under the same conditions (6 N HCl, reflux) that converted benzamide **2** to *o*-toluic acid. This prompted us to examine other hydrolysis conditions.

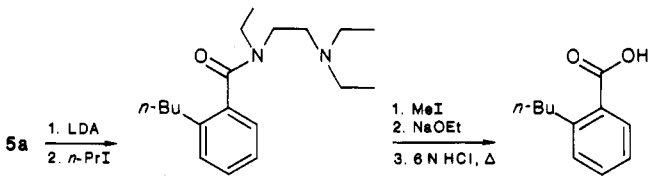
Taking advantage of the amine functionality, we treated benzamide **5a** with methyl iodide to form the quaternary salt **6**, which on heating with 10% aqueous sodium hydroxide gave enamide **7** in high yield. The crude enamide **7** was then treated with aqueous 10% hydrochloric acid to provide the secondary benzamide **8** in 80% overall yield from **5a**. These results and the fact that secondary benzamides hydrolyze more readily than tertiary benzamides prompted us to develop a one-pot hydrolysis of benzamide **5a**.



5a 6 7 8

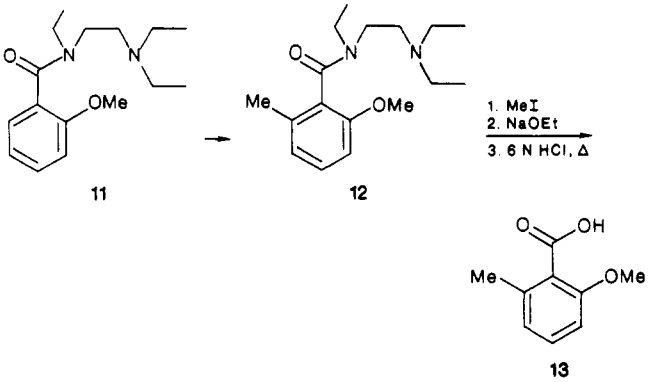
Benzamide **5a** was treated with excess methyl iodide in refluxing tetrahydrofuran and then concentrated. The residue was heated with sodium ethoxide in ethanol to form the enamide and again concentrated. To the residue was added 6 N hydrochloric acid and the mixture was heated at reflux for 24 h to give *o*-toluic acid in 82% yield from **5a**. To determine if this hydrolysis procedure would be effective with a larger ortho substituent present, we performed the following reaction sequence.

Lateral metalation[4b,8] and alkylation of **5a** gave benzamide **9**, which was subjected to the one-pot hydrolysis procedure described above. Although the acid hydrolysis of the intermediate secondary amide was slow, the desired 2-butylbenzoic acid (**10**) was obtained in 53% overall yield from **5a**.



9 10

Since 2-methoxy-6-methylbenzoic acid (**13**) is a useful starting material for natural product synthesis,[5] we explored a synthesis of **13** using our ortho-metalation



11 12 13

(3) Beak, P.; Brubaker, G. R.; Farney, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 3621–3627.

(4) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823–1824. (b) Beak, P.; Brown, R. A. *Ibid.* **1982**, *47*, 34–46.

(5) (a) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814–815. (b) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Ibid.* **1980**, 72–74, and references therein.

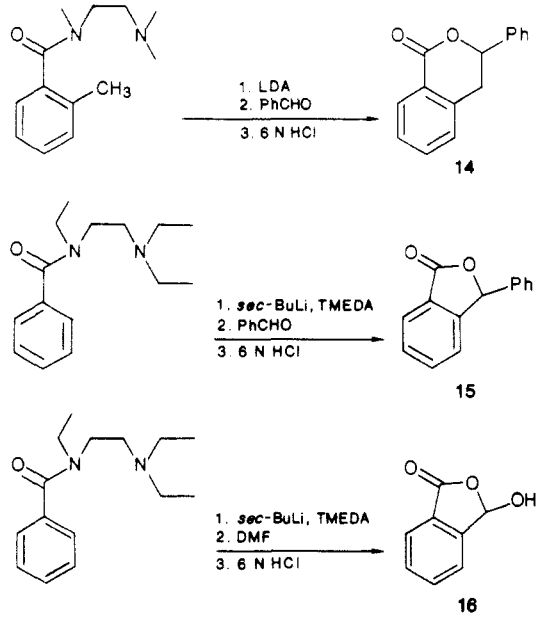
(6) It is likely that the ease of hydrolysis of β-amino benzamides in acid is partially due to their high solubility in the aqueous reaction medium; however, electronic effects of the protonated amine function probably also play a role.

(7) In the analogous one-pot hydrolysis of benzamide **17**, the enamide and secondary benzamide intermediates, corresponding to **19** and **20**, were isolated and their structures confirmed by ^{1}H NMR.

(8) Ludt, R. E.; Griffiths, J. S.; McGrath, K. N.; Hauser, C. R. *J. Org. Chem.* **1973**, *38*, 1668–1674.

methodology. The 2-methoxybenzamide **11** was ortho-lithiated and methylated to give **12** in 82% yield. The one-pot hydrolysis of **12** gave the desired acid **13** in 77% yield.

Beak and Brown[4] demonstrated that lithiated *N,N*-diethylbenzamides were useful in reactions with carbonyl compounds. Snieckus and co-workers[1c] found that reaction with benzaldehydes followed by acid-catalyzed cyclization provided phthalides in good yield. The cyclization step was carried out with *p*-toluenesulfonic acid in refluxing toluene. We were curious if the analogous reactions would occur using a β-amino benzamide, and, because of the presence of the amine functionality, if the cyclization step could be effected by using an aqueous acid hydrolysis. To this end we performed the reactions depicted below. The

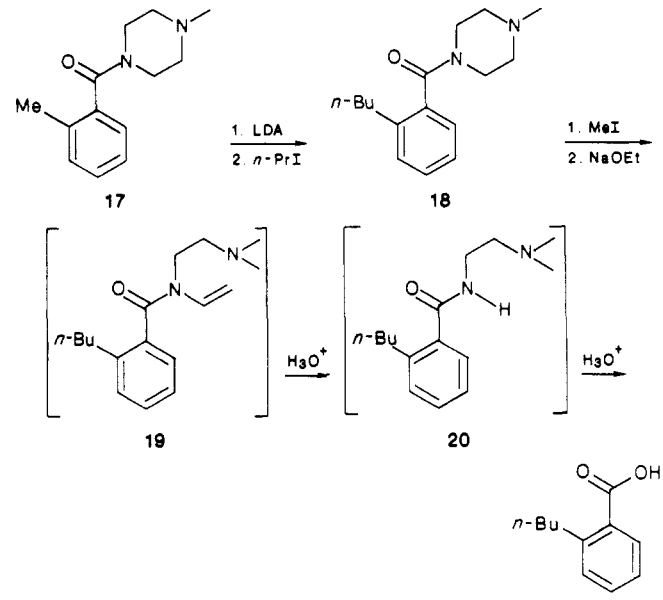


lactones **14** and **15** were conveniently prepared via one-pot reactions. Aqueous hydrochloric acid at reflux was used to effect cyclization. The analogous reactions using *N,N*-diethylbenzamides gave no lactones under these conditions. A synthesis of 3-hydroxyphthalide (**16**) was carried out in a similar manner by first formylating the lithiated benzamide and then hydrolyzing with aqueous hydrochloric acid.

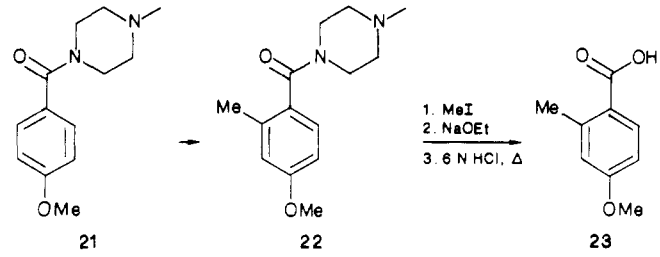
Since tertiary β-amino benzamides and secondary benzamides hydrolyze more readily in aqueous acid than most tertiary benzamides, it stands to reason that a secondary β-amino benzamide would hydrolyze faster than most secondary benzamides.[6] With this in mind, we searched for a tertiary benzamide that could be degraded in situ to a secondary β-amino benzamide, which then could be hydrolyzed with aqueous acid.

N-(*o*-Toluoyl)-*N'*-methylpiperazine (**17**) was laterally lithiated–alkylated and the crude product **18** was hydrolyzed by using the one-pot procedure. A 72% overall yield of the desired 2-butylbenzoic acid was obtained after a relatively short hydrolysis time. Two of the intermediates of this hydrolysis reaction are presumed to be enamide **19** and secondary benzamide **20**.[7]

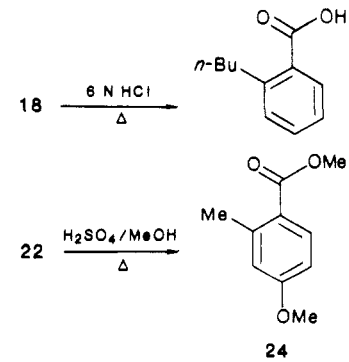
The attractiveness of this novel hydrolysis of **18** was diminished somewhat when we attempted to ortho-lithiate and alkylate *N*-benzoyl-*N'*-methylpiperazine. Extensive self-condensation[3] occurred, indicating that the ortho-lithiated intermediate is not synthetically useful. However, a *p*-methoxy group stabilizes the benzamide carbonyl toward nucleophilic attack, allowing the ortho-lithiation–methylation of benzamide **21** to proceed in 73% yield.



Hydrolysis of **22**, using the one-pot procedure, gave the aryl acid **23** in 51% yield.

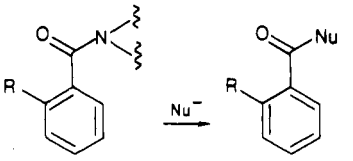


Subsequent to the above study, we discovered that *N*-benzoyl-*N'*-methylpiperazines could be hydrolyzed directly with 6 N hydrochloric acid. For example, benzamide **17** was heated at reflux in 6 N hydrochloric acid for 12 h to give a 90% yield of *o*-toluic acid. A similar reaction with *o*-butylbenzamide **18** gave a 53% yield of 2-butylbenzoic acid. It is interesting that these benzamides, derived from *N*-methylpiperazine, hydrolyze more readily than any of the tertiary β-amino benzamides we have studied so far. Taking advantage of this unusual reactivity, we were able to perform a methanolysis of amide **22** to give ester **24** in 71% yield.

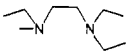
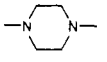
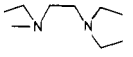
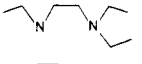
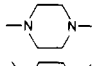
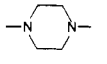


Conversion of Tertiary Benzamides into Aldehydes and Ketones. Hauser and co-workers have shown that meta- and para-substituted *N,N*-diethyltoluamides undergo predominantly addition to the carbonyl with *n*-butyllithium in tetrahydrofuran/hexane and that *N,N*-diethyl-*o*-toluamide undergoes mainly side-chain metalation with *n*-butyllithium.[8] Since conversion of an ortho-substituted tertiary benzamide to an aryl ketone or aldehyde would be synthetically useful, we decided to investigate possibilities for these transformations.

Table I



25

benzamide	R		Nu	conditions[a,e]	product[b]	yield,[d] %
25a	Me		MeMgCl	1.1 equiv, THF, reflux, 12 h	ketone	56
25b	Me		MeMgCl	1.2 equiv, PhH, reflux, 12 h	ketone	38
25c	Me		MeMgCl	1.1 equiv, THF, reflux, 12 h	ketone	0
25a	Me		MeLi	1.5 equiv, PhH, RT, 30 min	ketone	82
25c	Me		MeLi	1.5 equiv, PhH, RT, 30 min	ketone	72
25a	Me		*n*-BuLi	1.5 equiv, PhH, RT, 30 min	ketone	80
25c	Me		*n*-BuLi	1.5 equiv, PhH, RT, 30 min	ketone	61
25a	Me		SMEAH[9]	1.1 equiv, THF, RT, 12 h	aldehyde	80
25c	Me		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	0
25d	Me		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	57
25b	Me		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	0
25e	*n*-Bu		MeLi	1.5 equiv, PhH, RT, 3 h	ketone	77
25f	*n*-Bu		MeLi	1.5 equiv, PhH, RT, 3 h	ketone	55
25e	*n*-Bu		*n*-BuLi	1.5 equiv, PhH, RT, 3 h	ketone[c]	70
25f	*n*-Bu		*n*-BuLi	1.5 equiv, PhH, RT, 3 h	ketone	62
25g	*n*-Bu		*n*-BuLi	1.5 equiv, PhH, RT, 3 h	ketone	64
25h	*n*-Bu		*n*-BuLi	1.5 equiv, PhH, RT, 3 h	ketone	58
25e	*n*-Bu		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	51
25f	*n*-Bu		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	0
25h	*n*-Bu		SMEAH	1.1 equiv, THF, RT, 12 h	aldehyde	0

[a] The reactions were performed on a 2-mmol scale. [b] Unless indicated, products were identical with authentic samples. [c] Product gave the expected IR and ^{1}H NMR spectra and satisfactory analytical data; see Experimental Section. [d] Yield of purified product obtained from preparative layer chromatography (silica gel, ethyl acetate–hexanes). [e] RT = room temperature.

Tertiary benzamides **25** were treated with various organometallics and the results are given in Table I. To our satisfaction the use of benzene in place of tetrahydrofuran for the reaction of an alkyllithium with **25** suppressed lateral metalation, and good yields of the ortho-substituted aryl ketones were obtained. Although the *N,N*-diethylbenzamides **25c** and **25f** undergo this reaction, yields were higher when using the β-amino benzamides. Indeed, the β-amino benzamides **25a** and **25b** even gave the ketone on reaction with methylmagnesium chloride, although the reaction with Grignard reagents appears to be of limited scope. We were successful in converting β-amino benzamides **25a**, **25d**, and **25e** into aryl aldehydes using a modified aluminum hydride reagent (SMEAH).[9] This reaction fails with the analogous *N,N*-diethylbenzamides and again demonstrates the versatility of the tertiary β-amino amide ortho-metalation directing group.

Summary

Our results compliment previous contributions in the area of directed lithiation of aromatic tertiary amides. The use of β-amino tertiary amides in place of the *N,N*-diethyl

(9) Tokoroyama, T.; Kanazawa, R. *Synthesis* **1976**, 526–527.

or *N,N*-diisopropyl amides allows for more versatility in manipulating the directing group after ortho substitution has been effected. The β-amino benzamides can be transformed to benzoic acid derivatives or converted to aryl aldehydes and ketones by using the appropriate organometallic reagent. This versatility can only enhance the potential of ortho-metalated benzamides in synthesis.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under an 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,N,N'*-triethylethylenediamine, and *N*-methylpiperazine 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 Varian EM-360 or JEOL FX-90-Q spectrometers and IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Radial preparative layer chromatography was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA). Combustion analyses were performed by M.H.W. Laboratories, Phoenix, AZ.

***N*-[2-(Diethylamino)ethyl]-*N*-ethylbenzamide (4). General Procedure for the Preparation of Tertiary β-Amino Benzamides.** To a stirred mixture (5 °C) of *N,N,N'*-triethylethylenediamine (3.6 mL, 20 mmol), 1 N sodium hydroxide (20 mL), and 10 mL of methylene chloride was added dropwise a solution of benzoyl chloride (2.3 mL, 20 mmol) in 10 mL of methylene chloride. The mixture was stirred at room temperature for 5 h and then poured into 20 mL of 5% hydrochloric acid. The organic layer was extracted with two 20-mL portions of 5% hydrochloric acid. The combined acid extracts were washed with methylene chloride, cooled, made basic with 25% sodium hydroxide, and extracted with three 30-mL portions of methylene chloride. The combined organic layer was washed with brine, dried (K_2CO_3), and concentrated. The residue was bulb-to-bulb distilled (135–145 °C/1.5 mm) to give 4.3 g (87%) of **4** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.47 (s, 5 H), 3.5 (br m, 4 H), 2.57 (br m, 6 H), 1.07 (br m, 9 H); IR (neat) 2885, 2810, 1615, 1430 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.71; H, 9.56; N, 11.40.

***o*-Methyl-*N*-[2-(diethylamino)ethyl]-*N*-ethylbenzamide (5a). General Procedure for the Ortho-Lithiation–Alkylation of *N,N,N'*-Triethylbenzamide 4.** To a stirred solution of *sec*-BuLi (2.2 mmol) and 0.33 mL (2.2 mmol) of TMEDA in 10 mL of THF at −78 °C was added dropwise benzamide **4** (498 mg, 2.0 mmol) in 3 mL of THF. After 1 h at −78 °C, 0.24 mL (4 mmol) of methyl iodide was added and the mixture was stirred for 2 h at −78 °C. The cooling bath was removed and stirring was continued for an additional 10 min. The mixture was poured into 5% hydrochloric acid, and the organic layer was extracted with 5% hydrochloric acid (2 × 10 mL). The combined acid extracts were washed with ether, cooled, made basic with 25% sodium hydroxide, and extracted with ether. The combined ether extracts were washed with brine, dried over K_2CO_3, filtered, and concentrated to give the crude product as an oil. Purification by radial preparative layer chromatography (silica gel, 1–10% $MeOH/CH_2Cl_2$) gave 398 mg (76%) of **5a** as a clear oil. This amide was identical with an authentic sample prepared from *N,N,N'*-triethylethylenediamine and *o*-toluoyl chloride.

Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.14; H, 10.11; N, 10.90.

***o*-Methyl-*N*-ethyl-*N*-vinylbenzamide (7).** A solution of 472 mg (1.9 mmol) of benzamide **5a** and 0.23 mL (3.6 mmol) of methyl iodide in 5 mL of tetrahydrofuran was heated under reflux for 4 h. The solution was concentrated under reduced pressure, and to the residue was added 4 mL of tetrahydrofuran and 5 mL of aqueous 10% sodium hydroxide. The mixture was heated at reflux for 7 h, poured into water, and extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated to give the crude product as an oil. Purification by radial preparative layer chromatography (silica gel, EtOAc–hexanes) gave 304 mg (89%) of **7** as a clear oil: ^1H NMR ($CDCl_3$) δ 7.2 (br s, 4 H), 6.37 (dd, 1 H, *J* = 12, 8), 4.5 (d, 1 H, *J* = 12), 4.18 (d, 1 H, *J* = 8), 3.88 (q, 2 H), 2.28 (s, 3 H), 1.28 (t, 3 H); IR (neat) 2900, 1665, 1625, 1090 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.00; H, 7.85; N, 7.34.

***o*-Methyl-*N*-ethylbenzamide (8) from Hydrolysis of 7.** A mixture of enamide **7** (89 mg, 0.47 mmol) in 10 mL of aqueous 10% hydrochloric acid was heated at reflux for 4 h, poured into water, and extracted with methylene chloride. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 71 mg (93%) of crude **8** as a white solid. Purification by radial preparative layer chromatography (silica gel, EtOAc/hexane) gave 69 mg (90%) of **8** as white crystals: mp 60–61 °C (water). This amide was identical with an authentic sample prepared from ethylamine and *o*-toluoyl chloride.

***o*-Toluic Acid from a One-Pot Hydrolysis of 5a.** A solution of 525 mg (2.0 mmol) of benzamide **5a** and 0.25 mL (4.0 mmol) of methyl iodide in 8 mL of THF was heated under reflux for 4 h. The solution was concentrated under reduced pressure, and to the residue were added 10 mL of absolute ethanol and 272 mg (4.0 mmol) of sodium ethoxide. The mixture was heated at reflux for 7 h and concentrated under reduced pressure. To the residue was added 15 mL of 6 N HCl, and the resulting mixture was heated at reflux for 24 h. The mixture was extracted with methylene chloride and the organic extract was extracted with 1 N sodium hydroxide solution (3 × 20 mL). The basic aqueous extracts were acidified with 6 N hydrochloric acid and extracted with methylene chloride. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give the crude product. Purification by recrystallization from water gave 223 mg (82%) of *o*-toluic acid as white crystals: mp 103–104 °C (lit.[10] mp 103–104 °C).

***o*-*n*-Butyl-*N*-[2-(diethylamino)ethyl]-*N*-ethylbenzamide (9).** To a solution of lithium diisopropylamide at −78 °C, prepared from diisopropylamine (0.81 mL, 5.8 mmol) and *n*-butyllithium (5.3 mmol) in 10 mL of THF, was added dropwise 1.26 g (4.8 mmol) of benzamide **5a** in 5 mL of THF. After 1 h at −78 °C, 0.94 mL (9.6 mmol) of *n*-propyl iodide was added, the cooling bath was removed, and the mixture was stirred at room temperature for 30 min. The mixture was poured into 10% hydrochloric acid and the organic layer was extracted with 10% hydrochloric acid. The combined acid extracts were washed with ether, cooled, made basic with 25% sodium hydroxide, and extracted with ether. The combined ether extracts were washed with brine, dried over K_2CO_3, filtered, and concentrated to give the crude product as an oil. Purification by radial preparative layer chromatography (silica gel, $MeOH/CH_2Cl_2$) gave 1.34 g (92%) of **9** as a clear oil: ^1H NMR ($CDCl_3$) δ 7.2 (m, 4 H), 3.6 (bm, 2 H), 3.1 (t, 2 H), 2.8–2.1 (m, 8 H), 1.8–0.7 (m, 16 H); IR (neat) 2880, 1640, 1430, 1300 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}N_2O$: C, 74.95; H, 10.59; N, 9.20. Found: C, 74.71; H, 10.60; N, 9.32.

***o*-*n*-Butylbenzoic Acid from a One-Pot Hydrolysis of 9.** The one-pot hydrolysis was performed as described above for the synthesis of *o*-toluic acid from **5a**, with the exception that the mixture of the residue and 6 N HCl was heated at reflux for 10 days. The mixture was extracted with methylene chloride. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 189 mg (53%) of **9**. Recrystallization from petroleum ether (bp 35–60 °C) gave white crystals: mp 36–38 °C (lit.[11] mp 38–38.5 °C).

***o*-Methoxy-*N*-[2-(diethylamino)ethyl]-*N*-ethylbenzamide (11).** This compound was prepared from *o*-anisoyl chloride and *N,N,N'*-triethylethylenediamine by the method described for the preparation of **4**. Purification by radial preparative layer chromatography (silica gel, 2% $MeOH/CH_2Cl_2$) gave 1.26 g (76%) of **11** as a clear oil: ^1H NMR (CCl_4) δ 7.1 (m, 4 H), 3.84 (s, 3 H), 3.7–2.85 (bm, 4 H), 2.8–2.1 (bm, 6 H), 1.4–0.65 (bm, 9 H); IR (neat) 2990, 2825, 1625, 1460 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.14; H, 9.62; N, 10.15.

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2-Methoxy-6-methyl-*N*-[2-(diethylamino)ethyl]-*N*-ethylbenzamide (12). This compound was prepared from benzamide **11** by using the ortho-lithiation–methylation procedure described for the synthesis of **5a**. The reaction mixture was poured into 10% aqueous sodium hydroxide and extracted with ether. The organic extracts were washed with brine, dried (K_2CO_2), and concentrated to give 910 mg of an oil. Purification by radial preparative layer chromatography (silica gel, 2% MeOH/CH_2Cl_2) gave 743 mg (82%) of **12** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.1 (d, 1 H), 6.74 (t, 2 H), 3.9–3.2 (m, 3 H), 3.75 (s, 3 H), 3.1 (t, 2 H), 2.8–2.25 (m, 5 H), 2.23 (s, 3 H), 1.32–0.7 (m, 9 H); IR (neat) 2890, 1640, 1600, 1280 cm^{-1}.

Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.65; N, 9.58. Found: C, 69.69; H, 9.47; N, 9.56.

2-Methoxy-6-methylbenzoic Acid (13). Benzamide **12** was hydrolyzed by using the one-pot procedure described above for the hydrolysis of **9**. The reflux time in 6 N hydrochloric acid was 7 days. Recrystallization from benzene gave 202 mg (77%) of **13** as white crystals: mp 138–140 °C (lit.[5a] mp 139–141.5 °C).

Preparation of 3-Phenyl-3,4-dihydroisocoumarin (14). To a solution of lithium diisopropylamide at −78 °C, prepared from 0.28 mL (2.0 mmol) of diisopropylamine and *n*-butyllithium (1.87 mmol) in 8 mL of THF, was added dropwise 0.4 g (1.7 mmol) of benzamide **2** in 3 mL of THF. After 1 h at −78 °C, 0.26 mL (2.55 mmol) of benzaldehyde was added, the cooling bath was removed, and the mixture was stirred at room temperature for 30 min and concentrated. To the residue was added 6 N hydrochloric acid and the solution was refluxed for 12 h. The mixture was poured into water and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purification by radial preparative layer chromatography (silica gel, EtOAc/hexanes) gave 0.325 g (62%) of a yellow oil, which crystallized from ether giving 0.20 g (53%) of **14** as white crystals: mp 89–91 °C (lit.[12] mp 90–91 °C).

Preparation of 3-Phenyl-1(3*H*)-isobenzofuranone (15). To a stirred solution of *sec*-butyllithium (3.3 mmol) and 0.5 mL (3.3 mmol) of TMEDA in 10 mL of THF at −78 °C was added dropwise benzamide **4** (0.745 g, 3.0 mmol) in 3 mL of THF. After 1 h at −78 °C, 0.34 mL (3.3 mmol) of benzaldehyde was added and the mixture was warmed to room temperature over 30 min. The solvent was removed by reduced pressure and 20 mL of 6 N hydrochloric acid was added. This mixture was refluxed for 12 h and poured into ether, and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered and concentrated to give 0.412 g of a yellow solid. Purification by recrystallization from ether–hexanes gave 0.319 g (50%) of **15** as a light yellow solid: mp 114–115 °C (lit.[4b] mp 115–115.5 °C).

Preparation of 3-Hydroxyphthalide (16). To a stirred solution of *sec*-butyllithium (3.6 mmol) and 0.54 mL (3.6 mmol) of TMEDA in 10 mL of THF at −78 °C was added dropwise benzamide **4** (0.745 g, 3.0 mmol) in 3 mL of THF. After 1 h at −78 °C, 0.46 mL (6.0 mmol) of DMF was added and the cooling bath was removed. Stirring was continued for an additional 10 min. The mixture was poured into water and extracted with ether. The combined ether extracts were washed once with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Purification by radial preparative layer chromatography (silica gel, 1–20% MeOH/CH_2Cl_2) gave 0.658 g (80%) of a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.3 (s, 1 H), 7.6 (br m, 4 H), 4.0–2.1 (br m, 10 H), 1.6–0.7 (br m, 9 H).

The oil from above was mixed with 20 mL of 6 N hydrochloric acid and the mixture was refluxed for 48 h. The resulting solution was poured into brine and extracted with ether. The organic extracts were washed once with brine and dried ($MgSO_4$). The ethereal solution was filtered and concentrated under reduced pressure to give 0.333 g of a light brown solid, which was recrystallized from water to give 0.279 g (62%) of **16** as clear crystals: mp 97–98 °C (lit.[13] mp 97 °C).

***o*-*n*-Butylbenzoic Acid from Benzamide 17.** The benzamide **17** (437 mg, 2 mmol) was treated with LDA and *n*-propyl iodide according to the procedure described for the synthesis of **9**. The mixture was concentrated under reduced pressure and the residue was subjected to the one-pot hydrolysis described above for the hydrolysis of **9**. The reflux time in 6 N hydrochloric acid was 24 h. The mixture was extracted with methylene chloride. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 257 mg (72%) of *o*-*n*-butylbenzoic acid. Recrystallization from petroleum ether (bp 35–60 °C) gave white crystals: mp 36–38 °C (lit.[11] mp 38–38.5 °C).

Preparation of Benzamide 22. Benzamide **21** was prepared according to the procedure for the synthesis of **4**, using *p*-anisoyl chloride and *N*-methylpiperazine. To a stirred solution of *sec*-BuLi (3.63 mmol) and 0.55 mL (3.63 mmol) of TMEDA in 10 mL of THF at −78 °C was added dropwise benzamide **21** (0.77 g, 3.3 mmol) in 4 mL of THF. After 1 h at −78 °C, 0.45 mL (7.3 mmol) of methyl iodide was added and the mixture was stirred for 2 h at −78 °C. The cooling bath was removed and stirring was continued for an additional 10 min. The mixture was poured into 5% hydrochloric acid, and the organic layer was extracted with 5% hydrochloric acid (2 × 10 mL). The combined extracts were washed with ether, cooled, made basic with 25% sodium hydroxide, and extracted with ether. The combined ether extracts were washed with brine, dried over K_2CO_3, filtered, and concentrated to give 0.795 g of a yellow oil. Purification by radial preparative layer chromatography (silica gel, 2% MeOH/CH_2Cl_2) gave 0.598 g (73%) of **22** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.1 (d, 1 H), 6.8 (br s, 2 H), 3.8 (s, 5 H), 3.3 (m, 2 H), 2.7–2.1 (m containing s at 2.3, 10 H); IR (neat) 2960, 2820, 1640, 1440 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 67.72; H, 8.12; 11.28. Found: C, 67.70; H, 7.93; N, 11.02.

4-Methoxy-2-methylbenzoic Acid (23). Benzamide **22** was hydrolyzed by using the one-pot procedure described above for the hydrolysis of **9**. The reflux time in 6 N hydrochloric acid was 24 h. Recrystallization from benzene gave 0.184 g (51%) of **23** as white crystals: mp 175–177 °C (lit.[14] mp 176–177.5 °C).

Methyl 4-Methoxy-2-methylbenzoate (24). Benzamide **22** (0.34 g, 1.37 mmol) was dissolved in 15 mL of dry methanol, and 0.75 mL of concentrated sulfuric acid was added dropwise to this solution. The mixture was heated at reflux for 12 h and was then poured slowly into a stirred saturated $NaHCO_3$ solution. The resulting solution was extracted with ether (3 × 20 mL). The ether extracts were washed once with brine and dried over $MgSO_4$. Concentration gave a light yellow oil which was purified by radial preparative layer chromatography (silica gel, EtOAc/hexanes) to give 0.175 g (71%) of **24** as a clear oil. This compound was identical with an authentic sample.

Preparation of *o*-*n*-Butylvalerophenone. General Procedure for the Addition of Alkyllithium Reagents to Ortho-Substituted Benzamides. To a solution of 0.472 g (1.55 mmol) of benzamide **25** in 8 mL of benzene cooled to 5 °C (ice/water) was added dropwise a hexane solution (2.17 mmol) of *n*-butyllithium. Upon addition of the *n*-butyllithium the solution turned a violet color. The solution was warmed to room temperature. After 30 min at room temperature, the orange solution was poured into a stirred aqueous solution of 10% hydrochloric acid. The mixture was extracted with ether and the combined ethereal extracts were washed with brine and dried ($MgSO_4$). Concentration gave 0.376 g of a yellow oil, which was purified by radial preparative layer chromatography (silica gel, 30% EtOAc–hexanes) to give 0.216 g (64%) of *o*-*n*-butylvalerophenone as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.3 (br m, 4 H), 2.8 (t, 2 H), 2.2–0.8 (br m, 16 H); IR (neat) 2975, 2890, 1690, 1480 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.33, H, 10.02.

Preparation of *o*-Tolualdehyde from Benzamide 25d. General Procedure. To a stirred solution of benzamide **25d** (0.40 g, 1.87 mmol) in 10 mL of THF at room temperature was added 2.0 mmol of modified aluminum hydride reagent (SMEAH).[9] This solution was stirred at room temperature for 12 h and then poured into a stirred solution of 10% hydrochloric acid. The mixture was extracted with ether and the combined ether extracts were washed with brine and dried over $MgSO_4$. Filtration and con-

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centration gave the crude product, which was purified by radial preparative layer chromatography (silica gel, 20% EtOAc–hexanes) to give 0.125 g (57%) of *o*-tolualdehyde. This compound was identical with an authentic sample.

Registry No. 1, 20916-85-2; 2, 56635-61-1; 3, 2728-04-3; 4, 103562-84-1; 5a, 103562-85-2; 7, 103562-86-3; 8, 57056-81-2; 9, 103562-87-4; 10, 54887-23-9; 11, 103562-88-5; 12, 103562-89-6; 13, 6161-65-5; 14, 2674-44-4; 15, 5398-11-8; 16, 16859-59-9; 17, 56635-66-6; 18, 103562-93-2; 21, 67023-02-3; 22, 103562-90-9; 23, 6245-57-4; 24, 35598-05-1; 25e, 103562-91-0; 25f, 103590-64-3; *o*-$CH_3C_6H_4CO(CH_2)_3CH_3$, 20359-56-2; *o*-$CH_3(CH_2)_3C_6H_4CO(CH_2)_3CH_3$, 103562-92-1; *N,N,N'*-triethylenediamine, 105-04-4; benzoyl chloride, 98-88-4; *o*-toluic acid, 118-90-1; *n*-propyl iodide, 107-08-4; *o*-anisoyl chloride, 21615-34-9; benzaldehyde, 100-52-7; *o*-methylacetophenone, 577-16-2; *o*-tolualdehyde, 529-20-4; *o*-butylacetophenone, 58632-85-2; *p*-anisoyl chloride, 100-07-2; *N*-methylpiperazine, 109-01-3; *o*-butylbenzaldehyde, 59059-42-6.

Synthetic Applications of the 1-Cyclobutenyltriphenylphosphonium Salt. Synthesis and Reactions of 1,2-Difunctionalized Cyclobutanes

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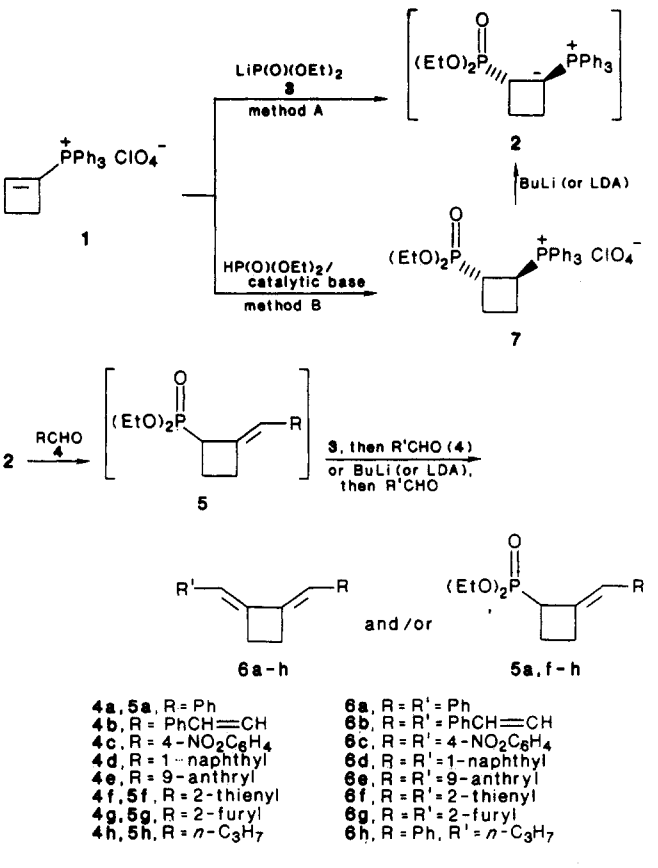
Symmetrical and unsymmetrical 1,2-bis(ylidene)cyclobutanes **6a–g** and **6h** were synthesized in good or moderate yields by the double Wittig reaction of a [2-(diethoxyphosphinyl)cyclobutyl]triphenylphosphonium ylide with aldehydes. The 1,2-bis(ylidene)cyclobutane **6a** readily underwent sequential Diels–Alder reactions with various dienophiles **8a–d** and **15** to give fused bicyclic compounds in good yields. Oxidation and hydrogenation of some 1,2-bis(ylidene)cyclobutanes were studied.

Although the preparation of 1,2-bis(methylene)cyclobutane and its synthetic applications have been well studied,[1] the synthesis of 1,2-bis(ylidene)cyclobutanes and their utilization have been little reported.[2] We have been interested in developing versatile reagents that are applicable to the synthesis of cyclobutanes bearing functionality. We have recently reported preparation of the 1-cyclobutenyltriphenylphosphonium salt **1** and its utilization for the synthesis of functionalized cyclobutanes.[3] In an earlier communication,[4] we described a new synthesis of 1,2-bis(ylidene)cyclobutanes by the reaction of a [2-(diethoxyphosphinyl)cyclobutyl]phosphonium ylide **2** with aromatic aldehydes. In this paper, we report on the reaction of the ylide **2** with various aldehydes and some reactions of the resulting 1,2-bis(ylidene)cyclobutanes.

Results and Discussion

Synthesis of 1,2-Bis(ylidene)cyclobutanes. Since the carbon–carbon double bond of **1** is strongly activated by the phosphonium group,[3a] the salt **1** could be a good Michael acceptor toward diethyl lithiophosphonate (**3**) producing the ylide **2**. So, when the ylide **2**, generated in situ from **1** and 1 equiv of **3** in tetrahydrofuran (THF)–dimethylformamide (DMF) (5:1), was treated with benzaldehyde (**4a**) at room temperature for 24 h, the expected product, diethyl (2-benzylidenecyclobutyl)phosphonate was not obtained, but (*E,E*)-1,2-dibenzylidenecyclobutane (**6a**) was isolated in 50% yield. The reaction using 2 mol equiv of **3** and **4a** to **1**, under similar conditions, led to **6a** in 70% yield.

Scheme I



4a, 5a, R = Ph
4b, R = PhCH=CH
4c, R = 4-$NO_2C_6H_4$
4d, R = 1-naphthyl
4e, R = 9-anthryl
4f, 5f, R = 2-thienyl
4g, 5g, R = 2-furyl
4h, 5h, R = *n*-C_3H_7

6a, R = R' = Ph
6b, R = R' = PhCH=CH
6c, R = R' = 4-$NO_2C_6H_4$
6d, R = R' = 1-naphthyl
6e, R = R' = 9-anthryl
6f, R = R' = 2-thienyl
6g, R = R' = 2-furyl
6h, R = Ph, R' = *n*-C_3H_7

These results can be reasonably accounted for by reaction of the phosphonate carbanion, generated from the

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