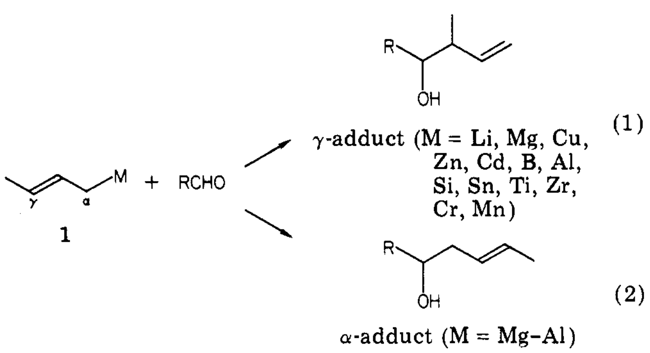
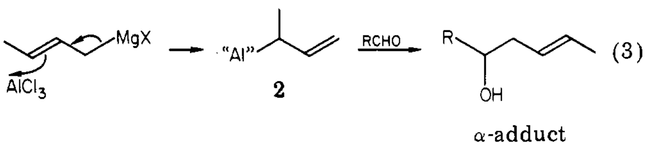
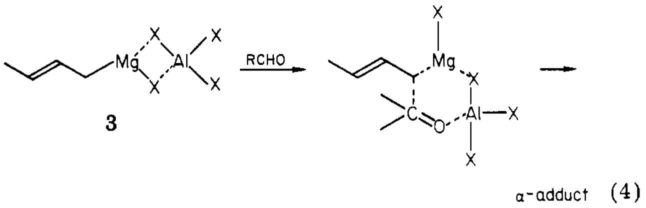


On the other hand, despite great potential importance of the regioreversed addition (shown in eq 2), such a transformation with unhindered carbonyl compounds appears totally unprecedented[13] and this problem has been one of long-standing concerns in organic chemistry. In this communication, we report that the Mg-Al system provides, for the first time, a solution to this problem. The results are summarized in the Table I.

The following procedure for the synthesis of 1-phenylpent-3-en-1-ol is representative. In a 50-mL flask equipped with a magnetic stirrer and maintained under N_2 was placed crotylmagnesium chloride in ether (1.1 mmol, 0.25 M) at −78 °C, and then $AlCl_3$ in ether (3 mmol, 2 M) was slowly added at this temperature. After 5–10 min, benzaldehyde (1 mmol, 0.1 mL) was added. The resulting mixture was allowed to warm to 0 °C and quenched with saturated NH_4Cl solution. The isomer ratio indicated in the Table I was obtained by the GLC examination of this reaction mixture. The usual workup followed by simple Kugelrohr distillation gave the mixture of α- and γ-adduct in 92% yield. Further purification through a column of silica gel with hexane–ether (20:1) as an eluant gave the desired isomer.

As is apparent from Table I, α-adduct is obtained with 83–94% regioselectivity regardless of the structure of aldehydes and the procedure is also applicable to ketones. Usually ether is used as a solvent. THF solvent causes slight decrease of α-adduct but produces the *E* isomer with greater stereoselectivity. Lewis acids other than $AlCl_3$ were also examined, but $TiCl_4$, $SnCl_4$, and $SnCl_2$ gave γ-adduct exclusively. $EtAlCl_2$ and BF_3 afforded α-adduct as a major product, though the degree of the regioselectivity was lower than that with $AlCl_3$. While the discussion of the mechanism of this regioselective C–C bond formation would be premature at this time, the following two routes may be conceivable: (i) the transmetalation of crotylmagnesium reagent to aluminum reagent via S_E2' process[14] followed by rapid S_E2' reaction of the resulting α-metallylaluminum reagent (2) with carbonyl compounds (eq 3); (ii) formation of the Mg–Al-bridged species (3)[15] followed by the coordination of carbonyl group to aluminum atom to produce α-adduct through a six-membered cyclic transition state (eq 4). The intermediate, 2 or 3, is presumably stable only at low temperature and must undergo a facile rearrangement into crotylaluminum reagent at higher temperature. Actually, when the mixture of crotylmagnesium chloride and $AlCl_3$ was temporarily kept at 0 °C and then treated with an aldehyde at −78 °C, γ-adduct was produced quantitatively. Irrespective of the precise mechanism, it is now possible to carry out a previously unavailable organic transformation through crotylmagnesium chloride. The reaction of the Mg–Al system with other substrates and the reaction of other allylic organometallics–Al systems are being pursued.





Registry No. C_6H_5CHO, 100-52-7; CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $CH_3(CH_2)_2CHO$, 123-72-8; $CH_3(CH_2)_3CHO$, 110-62-3; $CH_3(CH_2)_8CHO$, 112-31-2; $(CH_3)_2CHCHO$, 78-84-2; $(CH_3)_2CHCH_2CHO$, 590-86-3; $C_6H_5C(O)CH_3$, 98-86-2; $AlCl_3$, 7446-70-0; (*E*)-1-phenyl-3-penten-1-ol, 75851-77-3; (*Z*)-1-phenyl-3-penten-1-ol, 75851-76-2; (*E*)-4-hexen-2-ol, 54560-70-2; (*Z*)-4-hexen-2-ol, 65709-88-8; (*E*)-5-hepten-3-ol, 64884-87-3; (*Z*)-5-hepten-3-ol, 64884-86-2; (*E*)-6-octen-4-ol, 60340-29-6; (*Z*)-6-octen-4-ol, 60340-30-9; (*E*)-7-nonen-5-ol, 85355-76-6; (*Z*)-7-nonen-5-ol, 85355-77-7; (*E*)-12-tetradecen-10-ol, 85355-78-8; (*Z*)-12-tetradecen-10-ol, 85355-79-9; (*E*)-2-methyl-5-hepten-3-ol, 66248-77-9; (*Z*)-2-methyl-5-hepten-3-ol, 75851-75-1; (*E*)-2-methyl-6-octen-4-ol, 75851-71-7; (*Z*)-2-methyl-6-octen-4-ol, 75851-70-6; (*E,E*)-2,6-octadien-4-ol, 85355-80-2; (*E,Z*)-2,6-octadien-4-ol, 85355-81-3; (*E*)-1-(2-butenyl)cyclopentanol, 85355-82-4; (*Z*)-1-(2-butenyl)cyclopentanol, 85355-83-5; (*E*)-1-(2-butenyl)cyclohexanol, 85355-84-6; (*Z*)-1-(2-butenyl)cyclohexanol, 85355-85-7; (*E*)-2-phenyl-4-hexen-2-ol, 85355-86-8; (*Z*)-2-phenyl-4-hexen-2-ol, 85355-87-9; (*E*)-2-butenal, 123-73-9; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; crotyl chloride, 591-97-9.

Yoshinori Yamamoto,* Kazuhiro Maruyama
Department of Chemistry, Faculty of Science
Kyoto University, Kyoto 606, Japan

Received February 10, 1983

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(12) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134.

(13) (η^3-1,1-Dimethylallyl)nickel bromide reacts with benzil to give 1,2-diphenyl-2-hydroxy-5-methylhex-5-en-1-one predominantly but does not react with ordinary substrates such as cyclohexanone and cyclohexenone (Hegedus, L. S.; Wagner, S. D.; Waterman, E. L.; S-Hansen, K. *J. Org. Chem.* **1975**, *40*, 593). For the reaction of π-allyl and (π-2-methylallyl)nickel complexes with carbonyl compounds, see: Semmelhack, M. F. *Org. React.* (N.Y.) **1972**, *19*, 115. Crotyltrimethylsilane reacts with butanal in the presence of F^- to produce α-adduct together with γ-adduct, and the regioselectivity is not great (Hosomi, A.; Sirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043). See also: Chan, T. H.; Kang, G. J. *Ibid.* **1982**, *23*, 3011.

(14) Usually such a transformation from Mg to Si, Sn, Zn, Cd, or Hg takes place without any allylic rearrangement.[1] See also: Hosomi, A.; Iguchi, H.; Sakurai, H. *Chem. Lett.* **1982**, 223.

(15) For Mg-Al-bridged species and metal exchange, see: Matteson, D. S. "Organometallic Reaction Mechanisms of the Nontransition Element"; Academic Press: New York, 1974.

Directed Metalation of Tertiary Benzamides. Silicon Protection of Ortho Sites and Ortho Methyl Groups

Summary: Metalation of 2-trimethylsilyl or 2-bis(trimethylsilyl)methyl benzamides occurs selectively at the 6-position, providing regiospecific routes to various trisubstituted benzenes.

Sir: The directed ortho metalation[1] of aromatic tertiary amides,[2] secondary amides,[3] and 2-oxazolines[4] (1) provides

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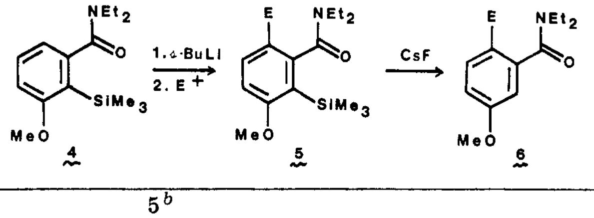
(1) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1.

(2) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Snieckus, V. *Heterocycles* **1980**, *14*, 1649.

(3) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853.

0022-3263/83/1948-1565$01.50/0

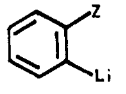
Table I. Synthesis of 3-Methoxy-6-Substituted Benzamides (6)



	5^b		6^b	
electrophile^a	E (yield, %)^c	mp, °C	E (yield, %)^c	bp,^{d} °C
Me_3SiCl	$SiMe_3$ (80)	74-75 (Et_2O-hexane)		
MeI	Me (74)	68-68.5 (hexane)	Me (85)^e	76-80 (0.01 mm)
DMF	CHO (88)	87-87.5 (Et_2O)	CHO (82)	98-104 (0.02 mm)
PhNCS	CSNHPh (89)	144-145 (Et_2O-hexane)	*f*	
$ClCONEt_2$	$CONEt_2$ (89)	75-76 (hexane)	$CONEt_2$ (84)	106-110 (0.01 mm)

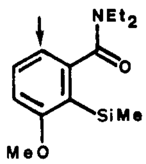
[a] Usually excess (5-10 equiv) of electrophile was used. [b] All new compounds show analytical and spectral (IR, NMR, MS) data consistent with their assigned structures. Products 5 showed diagnostic AB ^1H NMR aromatic spectral patterns. [c] Yields are based on isolated, purified (chromatographed or distilled) material. [d] Temperature of Kugelrohr oven bulb-to-bulb distillation. [e] Based upon recovered starting material. [f] Not obtained under the general desilylation conditions.

a useful strategy for the regiospecific preparation of polysubstituted benzene derivatives.[5] We now report a systematic study of directed metalation combined with silicon protection[6] to effectively mask (a) the more reactive site ortho to a carboxamide **2** and (b) the ortho methyl in an *o*-toluamide **3** to metalation reactions.[7] Using this concept, we demonstrate metalation and attendant electrophile introduction into the alternative ortho positions (arrows in **2**, **3**). We further show possibilities for iterative

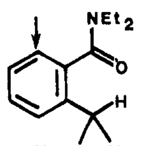


1

Z = CONR$_2$
= CON$^-$R
= 2-oxazolino



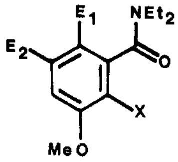
2



3

directed metalation (**7**, **9**) and for electrophilic substitution (**19**, **20**, **22**, **24**) of the silylated benzamides. In view of the ready attachment[7,8] and removal[9] of silyl groups and the broad scope and reliability of the directed metalation method,[1] these concepts augment the methodology for regiospecific construction of diversely functionalized, polysubstituted aromatics.

The sequence **4** → **5** → **6** (Table I) illustrates the use of silicon protection to metalation of the preferred 2-site in deriving 1,2,5-trisubstituted aromatic patterns. Lithiation of **4**[10] under standard conditions (*s*-BuLi/TMEDA/THF/−78 °C)[11] followed by quenching with selected electrophiles leads to benzamides **5** in excellent yields. In cases where the electrophiles introduced are themselves ortho-metalation directors, sequential metalation is feasible, as shown by the further transformation of **5**, E = $CONEt_2$ into the triamide **7**[10] (1. *s*-BuLi, standard conditons; 2. $ClCONEt_2$) in 60% yield and the one-pot conversion of **4** into the pentasubstituted aromatic **9**[10] (1. *s*-BuLi, standard conditions; 2. PhNCS; 3. *s*-BuLi; 4. excess MeI) in 63% yield. Desilylation is achieved by using CsF in DMF/H_2O (10:1) at reflux for 8–20 h, leading to functionally useful benzene derivatives **6** in good yields. Likewise, desilylation of **7** with CsF afforded **8**[10] (70%).



7 X = SiMe$_3$, E$_1$ = E$_2$ = CONEt$_2$
8 X = H, E$_1$ = E$_2$ = CONEt$_2$
9 X = SiMe$_3$, E$_1$ = CSNHPh, E$_2$ = Me

The observation of Beak and co-workers that 2-isopropyl-*N*,*N*-diethylbenzamide undergoes ortho rather than benzylic deprotonation (evidenced by D_2O quench)[12] suggested that an analogous result would be obtained by using the *α*,*α*-bis(trimethylsilyl)-*o*-toluamide (**10**) (Table II). Indeed compound **10**[13] is smoothly deprotonated

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(4) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008. Meyers, A. I.; Mihelich, E. D. *Ibid.* **1975**, *40*, 3158.

(5) Attested by recent use in total synthesis. $CONEt_2$: Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531; Watanabe, M.; Snieckus, V. *Ibid.* **1980**, *102*, 1457. CON$^-$R: Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799; Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. 2-Oxazoline: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Wizenberg, K. N. *Ibid.* **1982**, *104*, 4015; Edgar, K. J.; Bradsher, C. K. *J. Org. Chem.* **1982**, *47*, 1585; Newman, M. S.; Hussain, N. S. *Ibid.* **1982**, *47*, 2837.

(6) In spite of a large body of literature concerning the synthesis of aryl- and heteroaryl silanes (ref 7), silicon protection to metalation has been only briefly and unsuccessfully explored in a thiophene system, and this prior to knowledge of modern methods of desilylation (Slocum, D. W.; Gierer, P. L. *J. Org. Chem.* **1973**, *38*, 4189). However, silicon activation of thiophene ring opening has been effectively used for stereospecific synthesis of enynes: Karlsson, J. O.; Gronowitz, S.; Frejd, T. *J. Org. Chem.* **1982**, *47*, 374 and references therein.

(7) Aryl silanes are known to be generally stable to alkyllithium reagents: Habich, D.; Effenberger, F. *Synthesis* **1979**, 841.

(8) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, 47, 34. (b) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099.

(9) Reiffen, M.; Hoffmann, R. W. *Tetrahedron Lett.* **1978**, 1107.

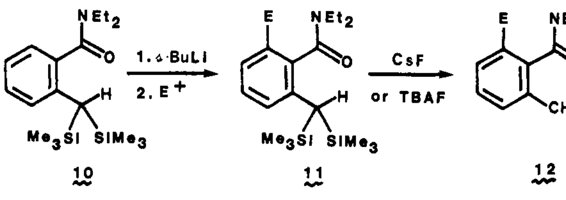
(10) New compound, shows analytical and spectral data in agreement with the given structure.

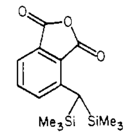
(11) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

(12) Beak, P.; Tse, A.; Hawkins, J.; Chen, C.-W.; Mills, S. *Tetrahedron*, in press. We are indebted to Professor Beak for a preprint of this paper.

(13) (a) Readily prepared in 92% yield in a one-pot sequence as follows: 1. 1 equiv *s*-BuLi/TMEDA/−78 °C/45 min; 2. 1 equiv Me_3SiCl/−78 °C/45 min; 3. 1 equiv *s*-BuLi/TMEDA/−78 °C/45 min; 4. 2 equiv Me_3SiCl/−78 °C → rt/8 h. (b) The monosilylated intermediate (**18**)[10] may be isolated, if desired, after the second step (excess Me_3SiCl) in 87% yield.

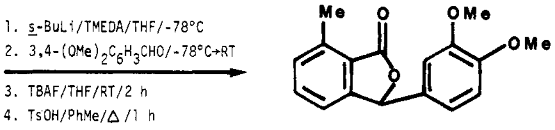
Table II. Synthesis of 6-Substituted-2-Methyl Benzamides (12)



	11^b		12^b	
electrophile[a]	E (yield, %)[c]	mp (bp),[d] °C	E (yield, %)[c]	bp,[d] °C
Me_3SiCl	$SiMe_3$ (94)	69.5-70.5 (CH_2Cl_2-hexane)	$SiMe_3$ (83)	124-125 (0.05 mm)
MeI	Me (91)	(110-111/ 0.03 mm)	Me (81)	106-108 (0.02 mm)
DMF	CHO (95)	(132-134/ 0.01 mm)	CHO (85)	86-88 (0.01 mm)
CO_2		57-58 (hexane)	e	
$(MeS)_2$	SMe (76)	(136-138/ 0.05 mm)	SMe (95)	86-90/ 0.01 mm

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. Compounds 11 showed characteristic ABC ^1H NMR patterns in the aromatic region. [c] See footnote *c*, Table I. [d] See footnote *d*, Table I. [e] See footnote *f*, Table I.

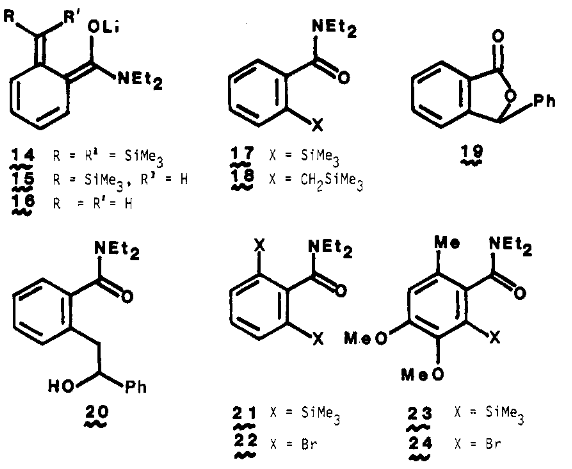
under the standard conditions[11] to give an intense burgundy solution of the 6-lithiated species. Addition of electrophiles results in the discharge of this color to provide, after workup, products **11** (Table II). Cesium fluoride or tetrabutylammonium fluoride[9] mediated double desilylation proceeds rapidly to give the 2,6-disubstituted benzamides **12** in high overall yields. The net conversion *N,N*-diethylbenzamide → **12** cannot be achieved by a conventional directed metalation sequence and constitutes an advantageous approach to contiguously trisubstituted aromatics with functionality at different oxidation states.[14] An example of potential value for the synthesis of 1-methylanthraquinone natural products[15] is the conversion of **10** into the 7-methylphthalide **13**[10] in 65% yield without isolation of intermediates. As proposed by Beak for 2-isopropylbenzamide,[12] ortho rather than benzylic lithiation in **10** may be a consequence of the inability of the intermediate carbanion (or transition state leading to it) to accommodate the steric congestion (**14**), a situation that need not arise in the corresponding anions derived from α-(trimethylsilyl)-*o*-toluamide (**15**) and *o*-toluamide (**16**).



13

The ultility of silylated amides **17** and **18** (Chart I) for carbon–carbon bond formation under conditions *not* involving highly basic alkyllithium reagents was tested by using recent literature precedents.[17] Thus treatment of **17**[10] with benzaldehyde (1.0 equiv of *t*-BuOK/DMF/room temp/11 h)[17a] followed by *p*-toluenesulfonic acid catalyzed cyclization (PhH/reflux/7 h) afforded phthalide **19** (48%) while fluoride-induced condensation of **18**[10] with benzaldehyde (TBAF/THF/room temp/5 min)[17b] gave the amide alcohol **20** (79%).

Chart I



The ready accessibility of silylated benzamides also permits electrophilic ipso desilylation, a method that has had limited application.[18] For example, bromination with bromine in CCl_4 of **21**[10,19] (reflux/4 h) and **23**[10,19] (0 °C/5 min) yields compounds **22**[10] (75%) and **24**[10] (42%), respectively.

The tactic of silicon protection of benzamide ortho sites and ortho methyl functions that are normally deprotonated by strongly basic alkyllithium reagents considerably expands the scope of the directed metalation reaction for the synthesis of polysubstituted aromatics. In view of the numerous groups that promote directed metalation,[1,2]

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(14) Cursory examination of classical syntheses for compounds 12 indicates that the metalation route is competitive or more efficient, e.g., the carboxylic acid of 12, E = CHO, was obtained from commercial 2,6-dimethylaniline in 11% overall yield (Newman, M. S.; Leegwater, A. L. *J. Am. Chem. Soc.* **1968**, *90*, 4410).

(15) Thomson, R. H. "Naturally Occurring Anthraquinones", 2nd ed., Academic Press: New York, 1971.

(16) The slow formation of the benzylic lithiated species and its rapid rearrangement to the ortho-lithiated intermediate cannot be ruled out.

(17) (a) Spiegler, W.; Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 265. (b) Ricci, A.; Degl'Innocenti, A.; Fiorenza, M.; Taddei, M.; Spartera, M. A.; Walton, D. R. M. *Tetrahedron Lett.* **1982**, *23*, 577.

(18) Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981; p 125.

(19) Compound 21 was obtained by sequential metalation–silylation of *N,N*-diethylbenzamide under standard conditions. Compound 23 was similarly prepared from the corresponding 3,4-dimethoxybenzamide.

broad synthetic utility of these concepts may be envisaged.

Acknowledgment. Initial experimental work of J. N. Reed and enlightening correspondence with Dr. C. Carlson are gratefully acknowledged. We are indebted to Professor P. Beak for continuing stimulating exchange of research results. This work was made possible by the financial support of the Natural Sciences and Engineering Research Council of Canada.

Registry No. **4**, 85370-85-0; **5** (E = $SiMe_3$), 85370-74-7; **5** (E = Me), 85370-75-8; **5** (E = CHO), 85370-76-9; **5** (E = CSNHPh), 85370-77-0; **5** (E = $CONEt_2$), 85370-78-1; **6** (E = Me), 85370-62-3; **6** (E = CHO), 85370-63-4; **6** (E = $CONEt_2$), 85370-64-5; **7**, 85370-84-9; **8**, 85370-68-9; **9**, 85370-69-0; **10**, 85370-86-1; **11** (E = $SiMe_3$), 85370-79-2; **11** (E = Me), 85370-80-5; **11** (E = CHO), 85370-81-6; **11** (E = SMe), 85370-83-8; **12** (E = $SiMe_3$), 85370-65-6; **12** (E = Me), 57806-77-6; **12** (E = CHO), 85370-66-7; **12** (E = SMe), 85370-67-8; **13**, 85370-70-3; **17**, 62924-92-9; **18**, 85370-87-2; **19**, 5398-11-8; **20**, 85370-71-4; **21**, 85370-88-3; **22**, 85370-72-5; **24**, 85370-73-6; 4-[bis(trimethylsilyl)methyl]phthalic anhydride, 85370-82-7.

Supplementary Material Available: Spectral data for new compounds (1 page). Ordering information is given on any current masthead page.

R. J. Mills, V. Snieckus*

Guelph-Waterloo Centre for
Graduate Work in Chemistry
University of Waterloo
Waterloo, Ontario, Canada N2L 3G1

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