Metalation of 2,4,6-Trimethylacetophenone Using Organozinc Reagents: The Role of the Base in Determining Composition and Structure of the Developing Enolate

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The new mixed lithium−zinc enolate compounds [(TMEDA)$_2$Li$_2$Zn{OC(=CH$_2$)Mes}$_4$] (**2**) and [{TMP(H)}$_2$Li$_2$Zn{OC(=CH$_2$)Mes}$_4$] (**3**) were prepared by reaction of the sterically demanding ketone 2,4,6-trimethylacetophenone (**1**) with the all-amido homoleptic zincate [LiZn(TMP)$_3$] (TMP = 2,2,6,6-tetramethylpiperidide). X-ray crystallographic studies revealed that these compounds adopt a trinuclear Li···Zn···Li chain arrangement with enolate O bridges. In contrast, the metalation of **1** with heteroleptic [(TMEDA)LiZn(TMP)Me$_2$] afforded the dimeric lithium enolate [(TMEDA)$_2$Li$_2${OC(=CH$_2$)Mes}$_2$] (**4**) as a crystalline solid, which has been characterized in the solid state by X-ray crystallography, and Me$_2$Zn·TMEDA and TMP(H) as coproducts, showing that the dimethylamido zincate behaves as an amide base. The homoleptic zinc enolate [(TMEDA)Zn{OC(=CH$_2$)Mes}$_2$] (**5**) was obtained by reaction of **1** with the zinc amide Zn(TMP)$_2$, and its structure was determined by X-ray crystallography. **5** adopts a rarely observed monomeric arrangement where the two enolate groups bind terminally to the zinc. New enolates **2**−**5** have also been characterized by ^{1}H, ^{13}C, and ^{7}Li NMR spectroscopy in C$_6$D$_6$ solution. DFT studies of the metalation of **1** by Zn(TMP)$_2$ and Et$_2$Zn revealed that the former amide has a much greater kinetic basicity than the latter alkyl reagent.

Introduction

Selective deprotonation of ketones to afford metal enolate intermediates is a cornerstone reaction in synthesis. Anionic enolates play an essential role in a rich variety of fundamental organic reactions involving the formation of new C−C bonds such as Michael additions, acylations, alkylations, or aldol additions.[1] Among this family of compounds zinc enolates are attracting special interest, as they combine a poweful nucleophilicity with a greater functional group tolerance than analogous alkali-metal enolates.[2] Thus, zinc enolates can participate in additions to carbonyl compounds,[3] transition-metal-catalyzed reactions with carbon electrophiles,[4] or catalyzed acrylate polymerizations.[5] However, despite their many synthetic applications only a select few zinc enolate structures have been elucidated. The first structural elucidation of a series of zinc enolates derived from simple ketones was reported by Hagadorn as recently as 2006.[6] The following year we reported the first examples of mixed alkali-metal−zinc enolates derived from the sterically demanding ketone 2,4,6-trimethylacetophenone (**1**) prepared by the reaction of 3 molar equiv with the sodium or potassium trisamido zincate [MZn(HMDS)$_3$] (M = Na, K; HMDS = 1,1,1,3,3,3-hexamethyldisilazide).[7] Zinc enolates can be prepared generally by three different routes: these are insertion of activated zinc metal into an α-halogen-substituted ketone,[8] deprotonation of a ketone by an organolithium reagent such as LDA followed by metathesis with ZnX$_2$,[9] and direct metalation of a ketone with a suitable reactive organozinc reagent.[10] The main drawback of the third approach is the low kinetic reactivity of most of the common commercially available organozinc reagents such as the alkyl Me$_2$Zn or the Grignard equivalent EtZnCl due to the strong carbophilic character of zinc, which reduces the leaving ability of attached C-nucleophiles.[11] An alternative to this problem is to employ zinc amide reagents due to the presence of the more reactive, easier-cleaved Zn−N bonds in these compounds.[12] Thus, although known for a few years, only very recently Zn(TMP)$_2$ (TMP = 2,2,6,6-tetramethylpiperidide) has been reported as a highly efficient

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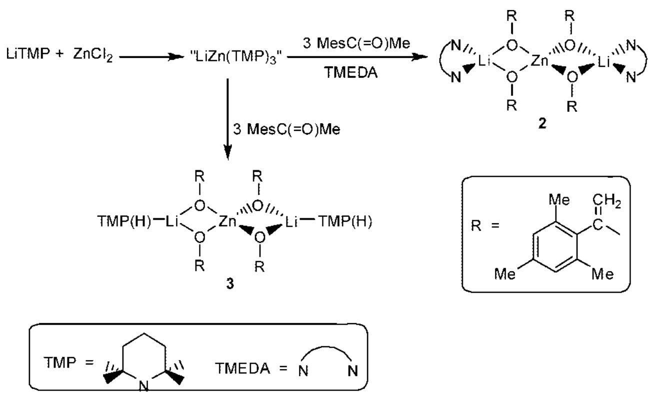
10.1021/om800658s CCC: $40.75

Scheme 1



reagent to metalate a wide range of substrates, including ketones, under very mild conditions.[13] Alkali-metal zincates containing bulky amido ligands have also revealed themselves as highly selective reagents for deprotonation reactions.[14] Herein we explore the reactivity of the homoleptic "inorganic" zincate [LiZn(TMP)$_3$][15] with **1** and report the synthesis and characterization of the dilithium−monozinc tetraanionic enolates [(TMEDA)$_2$Li$_2$Zn{OC(=CH$_2$)Mes}$_4$] (**2**) and [{TMP(H)}$_2$Li$_2$Zn{OC(=CH$_2$)Mes}$_4$] (**3**), which are to the best of our knowledge the first reported examples of lithium−zinc enolate compounds. In addition the structure of the first simple monomeric zinc enolate [(TMEDA)Zn{OC(=CH$_2$)Mes}$_2$] (**5**), obtained by reaction of Zn(TMP)$_2$ with **1**, has been elucidated. The reaction of the heteroleptic zincate [(TMEDA)LiZn(TMP)Me$_2$] toward **1** was also studied, affording the homometallic lithium enolate [(TMEDA)$_2$Li$_2${OC(=CH$_2$)Mes}$_2$] (**4**). A comparative theoretical study of the energies involved in the reactions of **1** with Zn(TMP)$_2$ and ZnEt$_2$ was carried out, from which it can be surmised that the formation of these new zinc enolate compounds is dictated by the kinetics of the reaction.

Results and Discussion

Synthesis. New mixed metal enolate **2** was prepared according to the reaction sequence shown in Scheme 1. First the trisamido zincate [LiZn(TMP)$_3$] was prepared in situ by reaction of 3 molar equiv of the lithium amide with ZnCl$_2$ in ether solution.[15] After removal of deposited LiCl by filtration, the addition of 3 equivalents of **1** and 1 equiv of TMEDA produced compound **2** as colorless crystals in reasonably good isolated yields (35−40%: note that the maximum possible yield from this reaction is 50%; see below). The [Li$_2$Zn(enolate)$_4$] stoichiometry of **2** contrasts with previous results found for the reaction of related tris(amido) zincates [MZn(HMDS)$_3$][16] (M = Na, K) with **1**, which afforded the relevant inverse crown compounds [M$_2$Zn$_2$(enolate)$_6$],[7] having the same stoichiometry (1M:1Zn:3 enolate) as that employed in the reaction mixture. The formation of **2**, whose stoichiometry is different from that in the reaction mixture, could be explained by a disproportionation process whereby an intermediate similar to the Na/Zn or K/Zn enolates is initially formed but subsequently leads to **2** via elimination of Zn(enolate)$_2$ (eq 1). An equilibrium between the three enolate species could be ocurring in solution, which could be favoring the precipitation (crystallization) of **2** due to its lower solubility in hexane solution.

$$(\mathrm{TMEDA})_2\mathrm{Li}_2\mathrm{Zn}_2(\mathrm{enolate})_6 \rightleftharpoons (\mathrm{TMEDA})_2\mathrm{Li}_2\mathrm{Zn}(\mathrm{enolate})_4 + \mathrm{Zn}(\mathrm{enolate})_2 \quad (1)$$

Recently Mongin has demonstrated that the metalation activity of [LiZn(TMP)$_3$] is dramatically dependent on the Lewis basicity of the solvent system employed.[15a] Therefore, we next carried out the reaction using neat hexane as a solvent in the absence of TMEDA. Colorless crystals of the mixed-metal enolate **3** (Scheme 1) were obtained where the lithium centers are now solvated by the secondary amine TMP(H), the coproduct of this metalation reaction. These results show not only that the metalation of **1** is not TMEDA-activated but also that the suggested disproportionation process in eq 1 is not favored nor induced by the presence of the diamine, though a donor solvent (even a poor sterically restricted one such as TMP(H) in **3**) is needed to support the lithium coordination.

For comparative purposes the reaction of **1** with the heteroleptic zincate [(TMEDA)LiZn(TMP)Me$_2$][17] was subsequently performed. This mixed-metal reagent belongs to the family of dialkyl(TMP) zincates, which have been found to be excellent chemoselective bases for direct zincation of a broad range of aromatic substrates.[14] So far, all of the metalated intermediates isolated and structurally characterized from such reactions have shown that these zincates behave overall as monoalkyl bases.[18] The reaction of **1** with the dimethylamido zincate afforded an insoluble white solid that dissolved in toluene on the addition of an extra molar equivalent of TMEDA. On cooling, this solution deposited colorless crystals of the zinc-free lithium enolate **4**. In order to gain more understanding of this reaction, isolated crystals of the starting material [(TMEDA)LiZn(TMP)Me$_2$] were dissolved in deuterated benzene solution and a stoichiometric amount of **1** was added. A white solid precipitated. The ^{1}H NMR analysis of the filtrate revealed that Me$_2$Zn·TMEDA and TMP(H) were the other products of the reaction. This allowed us to suggest the reaction pathway shown in Scheme 2, where the zincate behaves as an amido base to form the putative intermediate [(TMEDA)LiZn(OR)Me$_2$] (**A**), which then disproportionates into the insoluble unsolvated lithium enolate and the zinc alkyl complex Me$_2$Zn·TMEDA. This reaction was also attempted with 3 molar equiv of **1**; however, the lithium enolate **4** was the only metalated product obtained, and unreacted ketone and Me$_2$Zn·TMEDA could be observed in the ^{1}H NMR spectrum of the filtrate. Thus, these results permit a comparison to be made between the reactivity of the all-amido zincate [LiZn(TMP)$_3$] and the dialkyl(amido) zincate [(TMEDA)LiZn(TMP)Me$_2$], showing that for the former the three basic "arms" (or ligands) can react with **1**, whereas for the latter only one of the "arms" (the amide ligand) is

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(16) The same synthetic methodology could not be employed to prepare a lithium analogue since Li(HMDS) and Zn(HMDS)$_2$ fail to form a mixed-metal base.

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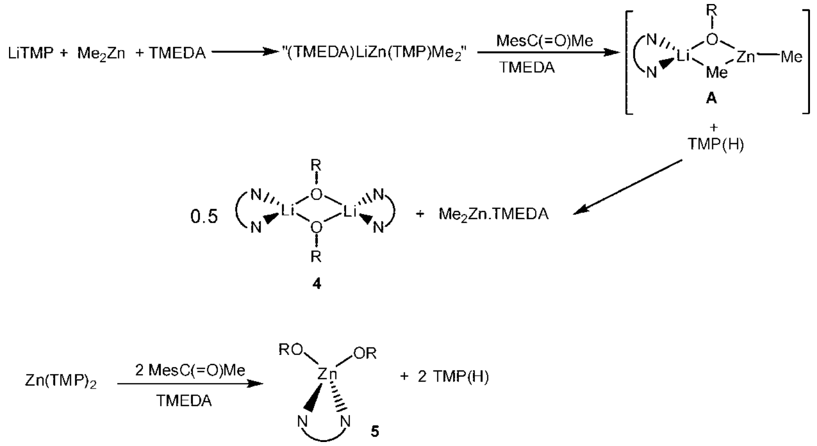
(18) For two exceptions where [LiZn(TMP)*t*Bu$_2$] behaves as a dual alkyl-amido base see: (a) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *43*, 2374. (b) Kondo, Y.; Morey, J. V.; Morgan, J. C.; Naka, H.; Nobuto, D.; Raithby, P. R.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Soc.* **2007**, *129*, 12734.

Scheme 2



reactive enough to metalate **1** and the methyl groups remain coordinated to zinc and act only as spectators. This difference in reactivity illustrates the concept of the lower kinetic reactivity of the Zn−C bonds in comparison to Zn−N bonds. In addition, this is the first example of a metalation reaction using a lithium TMP-dialkyl zincate where the metalated intermediates have been characterized and show that the mixed-metal reagent has behaved exclusively as an amido base with the concomitant loss of TMP(H).[19] The completely different nature of the metalated products obtained from these reactions should also be mentioned. Whereas **2** is a mixed lithium−zinc enolate, where each enolate anion is bridged between the two distinct metals (see below), in **4** the enolate ligands are bonded solely to lithium. This could have a pronounced effect when more complicated ketones containing functionalization are employed since a lithium enolate such as **4** will possess a very limited functional group tolerance in comparison with a mixed lithium−zinc enolate such as **2** or **3**. Moreover, the nature of the enolate nucleophile, whether it be lithium- or zinc-bonded, can have a dramatic influence if the metalated intermediate is to be involved in subsequent organic transformations such as transition metal cross-coupled reactions.

As aforementioned, Hagadorn has recently reported the application of $Zn(TMP)_2$ as an effective metalating reagent under mild conditions.[13] Thus, following this methodology homometallic enolate **5** could be prepared by reaction of 2 molar equiv of **1** with $Zn(TMP)_2$ in the presence of TMEDA at room temperature (Scheme 2). Here, TMEDA seems to merely aid crystallization of **5** since the neutral zinc amide can metalate **1** in an almost quantitative yield in the absence of the diamine, as shown when the reaction was carried out in C_6D_6 solution and monitored by ^1H NMR.

Solid-State Structures. The molecular structures of compounds **2**−**5** were successfully characterized by X-ray diffraction studies. Figures 1 and 2 show that of mixed-metal enolates **2** and **3**, respectively.

The structure of **2** can be described as a ion-contacted aggregate of two oppositely disposed $[Li(TMEDA)]^+$ cations coordinated to the tetrahedral anion $Zn(OR)_4^{2-}$ giving rise to a trimetallic Li···Zn···Li chain arrangement in which the metals are connected through enolate ligands. Compound **3** adopts the same structural motif with the lithium centers solvated by a molecule of the secondary amine TMP(H)[20] instead of being chelated by TMEDA ligands as in **2**. Unfortunately due to a large amount of motion within the TMP(H) ligands, the structure is disordered, which prevents further discussion of the bond lengths and bond angles. The molecule in **2** is centrosymmetric, containing two orthogonal fused {LiOZnO} four-membered rings. Both rings are planar, as evidenced by the sum of the internal angles (360.00°), and the arrangement of the three metals is virtually linear, as shown by the Li···Zn···Li angle [179.99(2)°]. Each metal center in **2** is tetracoordinated in a distorted tetrahedral geometry. Each lithium center is bound to two oxygens and two nitrogens from the enolate and TMEDA ligands, respectively, whereas zinc is bound to four oxygens from the enolate ligands. The Li−O bond distance [1.954(2) Å] is within the average range found for other lithium enolates such as the dimer $[(TMEDA)_2Li_2\{OC({=}CHCH_3)O^tBu\}_2]$ (average Li−O length 1.925 Å).[21] The Zn−O bond length [1.9542(9) Å] is similar to those found in the homometallic ketone enolates $[Br_2Zn_2\{O({=}CH_2)Mes\}_2(dmf)_2]$ [1.954 Å][22] and $[^{Me}LZn_2\{OC({=}CMe_2)^iPr\}_2]$ ($^{Me}L^{2-}$ is a bis(amidoamine)ligand) [1.979 Å].[6] The linear metal motif of **2** contrasts with the inverse crown cyclic structures found for the related mixed-metal trianionic zincates $[Na_2Zn_2\{OC({=}CH_2)Mes\}_6\{OC(CH_3)Mes\}_2]$ (**6**) and $[K_2Zn_2\{OC({=}CH_2)Mes\}_6(CH_3Ph)_2]$ (**7**)[7] (Figure 3).

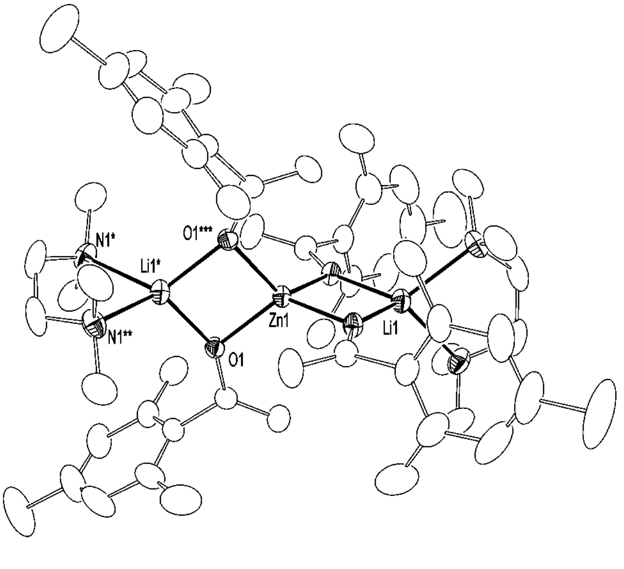


Figure 1. Molecular structure of **2** showing selected atom labeling and with hydrogen atoms omitted for clarity.

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[19] The preferred kinetic amido basicity toward alkyl basicity for TMP-dialkyl zincates has been the subject of several theoretical studies; see for example: (a) Uchiyama, M., M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748. (b) Uchiyama, M.; Matsumoto, Y.; Usui, S.; Hashimoto, Y.; Morokuma, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 926. (c) Garcia, F.; McPartlin, M.; Morey, J. V.; Nobuto, D.; Kondo, Y.; Naka, H.; Uchiyama, M.; Wheatley, A. E. H. *Eur. J. Org. Chem.* **2008**, 644.

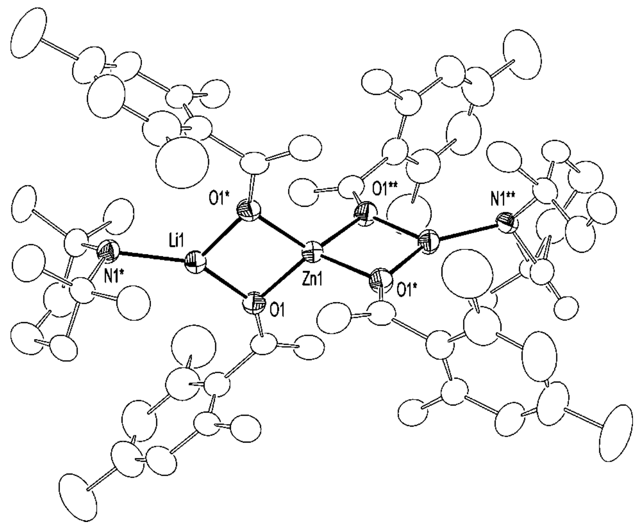

Figure 2. Molecular structure of **3** showing selected atom labeling and with hydrogen atoms and disorder component omitted for clarity.

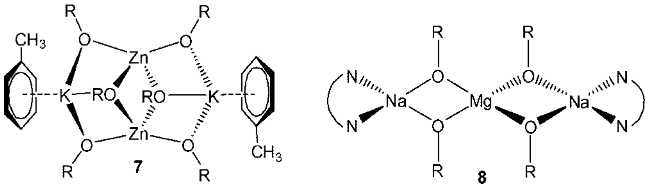

Figure 3. ChemDraw representations of $[K_2Zn_2\{OC(=CH_2)Mes\}_6(CH_3Ph)_2]$ (**7**) and $[(TMEDA)_2Na_2Mg\{OC(=CH_2)Mes\}_4]$ (**8**).

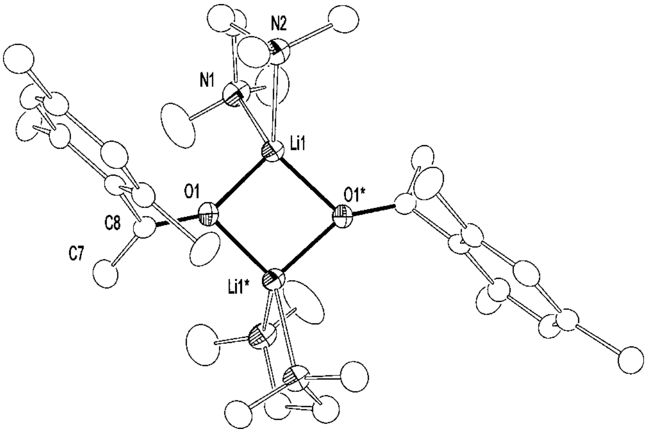

Figure 4. Molecular structure of **4** showing selected atom labeling and with hydrogen atoms omitted for clarity.

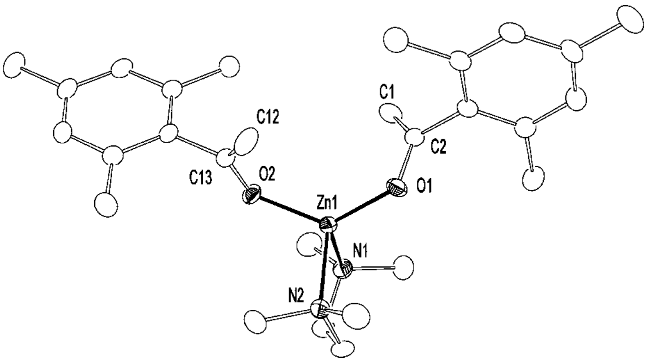

Figure 5. Molecular structure of **5** showing selected atom labeling and with hydrogen atoms omitted for clarity.

To the best of our knowledge **2** represents the first example of a mixed-metal lithium zinc enolate and the first tetraanionic zincate characterized where the anionic ligands around zinc are enolates. The closest precedent to **2**, apart from the Na−Zn and K−Zn enolates aforementioned, is the Na−Mg enolate $[(TMEDA)_2Na_2Mg\{OC(=CH_2)Mes\}_4]$ (**8**),[23] which also adopts an approximately linear Na···Mg···Na arrangement [Na···Mg···Na angle 167.70(5)°], where the metals are connected by four enolate bridges.

Lithium enolate **4** exhibits a dimeric centrosymmetric structure forming a {LiOLiO} four-membered ring where each lithium is externally solvated by a molecule of the chelating diamine TMEDA (Figure 4). The four-membered ring adopts an almost planar disposition (sum of the internal angles is 357.38°). Having a distorted tetrahedral geometry, the lithium coordination is made up of two nitrogens from the TMEDA ligand and two oxygens from the enolate ligands. This structural motif has been previously reported by Seebach for other lithium ester enolates solvated by TMEDA.[21] The Li−O distance in **4** [1.879(2) Å] is modestly shorter than that found in the mixed-metal lithium−zinc enolate **2** [1.954(2) Å]. Previously we have reported the structure of the congeneric sodium-TMEDA-solvated enolate[23] derived from **1**, which is structurally similar to **4**. In this compound the sodium center forms additional interactions due to π-engaging with the olefinic carbons of the enolate ligands. These types of interactions are absent in **4** (the closest Li···C contact is 2.906(4) Å, which is too long to suggest any significant π-interaction) probably due to the harder character, smaller size, and thus easier satisfied coordination of lithium in comparison to that of sodium.[24]

Zinc enolate **5** adopts a simple monomeric structure where zinc occupies a distorted tetrahedral geometry bonded to two nitrogens and two oxygens from the TMEDA and the enolate ligands, respectively (Figure 5). Surprisingly,to the best of our knowledge this is the first example of a homoleptic zinc enolate that has been characterized in the solid state. As previously mentioned, the first examples of zinc enolates derived from simple ketones isolated and structurally characterized were reported by Hagadorn.[6] These compounds exhibit a dimeric arrangement where each zinc binds to two bridging enolate ligands and a sterically hindered bidentate bis(amidoamine) ligand. The same group has recently reported a new series of ketone enolates of formula $[Br_2Zn_2\{OC(=CR_2)R'\}_2(dmf)_2]$ (where dmf is dimethylformamide), which also adopt dimeric structures.[22] Thus **5** is also the first simple monomeric zinc enolate to be structurally characterized. As expected, the Zn−O bond distances in **5** [1.8952(16) Å] are shorter than those found in the aforementioned dimeric compounds (Zn−O bond lengths

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(20) A search of the CCDB showed there are only 19 examples of compounds where TMP(H) acts as a donor ligand, and of those only two contain lithium: (a) Garcia-Alvarez, J.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E. *Chem. Commun.* **2007**, *23*, 2402. (b) Braun, U.; Habereder, H.; Noth, H. *Eur. J. Inorg. Chem.* **2004**, *18*, 3629.

(21) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

(22) Greco, J. F.; McNevin, M. J.; Shoemaker, R. K.; Hagadorn, J. R. *Organometallics* **2008**, *27*, 1948.

(23) Hevia, E.; Henderson, K. W.; Kennedy, A. R.; Mulvey, R. E. *Organometallics* **2006**, *25*, 1778.

(24) For examples of metal−π-arene interactions see: (a) Gokel, G. W.; De Wall, S. L.; Meadows, E. S. *Eur. J. Org. Chem.* **2000**, 2967. (b) Forbes, G C.; Kennedy, A. R.; Mulvey, R. E.; Roberts, B. A.; Rowlings, R. B. *Organometallics* **2002**, *21*, 5115.

Table 1. Key Bond Lengths (Å) and Bond Angles ($^{\rm deg}$) within the Structures of 2, 4, and 5

	For **2**		
Li1*−O1	1.954(2)	O1−C2	1.3443(17)
Zn1−O1	1.9546(9)	C1−C2	1.331(2)
Li1−N1	2.145(3)	C2−C3	1.497(2)
N1−Li1−N1*	85.52(13)	Zn1−O1−Li1	90.29(7)
O1***−Li1−O1**	89.72(14)	C5−C4−C3	119.14(18)
O1*−Zn1−O1	89.70(5)	C5−C4−C9	119.59(18)
O1*−Zn1−O1**	118.22(5)	C9−C4−C3	121.25(14)
	For **4**		
Li1−O1	1.879(4)	O1−C8	1.325(3)
Li1−O1*	1.923(4)	C7−C8	1.338(4)
Li1−N2	2.146(5)	C8−C9	1.508(4)
Li1−N1	2.236(5)	O1*−Na1−N1	107.58(13)
O1*−Li1−O1	93.74(19)	Li1−O1−Li1*	84.95(19)
N1−Li1−N2	82.70(16)	C8−O1−Li1	148.75(18)
	For **5**		
Zn1−O1	1.8952(16)	C1−C2	1.338(3)
Zn1−O2	1.9019(15)	C2−C3	1.498(3)
Zn1−N1	2.1036(19)	O2−C13	1.336(2)
Zn1−N2	2.0902(14)	C12−C13	1.324(4)
O1−C2	1.327(3)	C13−C14	1.504(3)
O1−Zn1−O2	129.72(7)	O2−Zn1−N2	108.39(8)
N2−Zn1−N1	87.64(8)	O1−Zn1−N1	114.59(7)
O1−Zn1−N2	106.66(10)	O2−Zn1−N1	101.81(7)

Table 2. ^{1}H NMR Chemical Shifts (*δ* in ppm) for the Enolate Ligands in Compounds 2−5 in C_6D_6 Solution

compound	*δ*(*m*-H)	*δ*(=CHH′)	*δ*(*o*-CH_3)	*δ*(*p*-CH_3)
2	6.79	5.07, 4.10	2.77	2.21
3	6.77	5.00, 4.18	2.76	2.18
4	6.84	4.10, 3.83	2.72	2.21
5	6.94	4.61, 4.16	2.79	2.27

Table 3. Selected ^{13}C NMR Chemical Shifts (*δ* in ppm) for the Enolate Ligands in C_6D_6 Solution

compound	*δ*(C−O)	*δ*(=CH_2)	Δ*δ*
2	163.76	86.10	77.66
3	162.75	85.34	77.41
4	167.53	80.86	86.67
5	166.71	83.14	83.57
$[(TMEDA)_2Na_2Mg\{O(=CH_2)Mes\}_4]$	165.17	83.91	81.26
$[(TMEDA)_2Na_2\{O(=CH_2)Mes\}_2]$	169.94	79.60	90.34
$[(toluene)_4K_4\{O(=CH_2)Mes\}_4]$	171.23	74.58	96.65

range from 1.952(5) to 2.047(2) Å) or in the mixed-metal lithium−zinc enolate **2** [1.9542(9) Å].

Solution-State Studies. The new enolate compounds **2**−**5** show good solubilities in arene solvents, and therefore their ^{1}H, ^{7}Li, and ^{13}C NMR spectra were recorded from C_6D_6 solutions. Tables 2 and 3 compare the most distinct chemical shifts in the ^{1}H and ^{13}C NMR spectra respectively of compounds **2**−**5**. As observed from Table 2 the chemical shifts of the relevant signals for the *ortho* and *para* methyl groups in compounds **2**−**5** show little change in the ^{1}H NMR spectrum, while the aromatic and olefinic protons show significant variations. Thus, the aromatic protons in the mixed-metal Li−Zn enolates **2** and **3** (6.79 and 6.77 ppm, respectively) appear further upfield than those corresponding to the monometallic lithium enolate **4** (6.84 ppm). This can be attributed largely to the more electropositive nature of lithium, which increases the polarization of the Li−O bonds. Therefore the metal−oxygen bond will be more polarized in **4**, where each enolate is bound to two lithium atoms, whereas in **2** and **3** the ligands bind to lithium and the more covalent zinc. Surprisingly the most deshielded aromatic protons are those corresponding to the homometallic zinc enolate **5** (6.94 ppm) probably due to the fact that the two enolate ligands are terminal, bound solely to a zinc. For the olefinic protons, the resonances of the lithium enolate **4** are further upfield (4.10 and 3.83 ppm) than those found for the mixed-metal Li−Zn enolates (5.07, 4.10 ppm for **2** and 5.00, 4.18 ppm for **3**). In addition, the relative positioning of the TMEDA signals in the ^{1}H NMR spectrum[25] shows that in compounds **2** and **5** the chelating diamine remains coordinated to the metal (lithium in **2** and zinc in **5**), suggesting that the structures found in the solid state for these compounds should be maintained in benzene solution. In contrast when the lithium enolate **4** is dissolved in C_6D_6 solution, the TMEDA ligands appear as free, which suggests a different structure in solution than in the solid state, where the lithium centers are probably interacting with the arene solvent instead of the chelating diamine. For compound **3**, the chemical shifts of the corresponding TMP(H) resonances (1.40, 1.10, 0.85, and 0.15 ppm) are slightly further upfield to those found for the free amine (1.53, 1.22, 1.06, and 0.30 ppm) in the same deuterated solvent, indicating that TMP(H) remains coordinated to the lithium atoms.

As recently reported, the difference between the chemical shifts in the ^{13}C NMR spectrum of the C−O and =CH_2 resonances of the enolato ligand can be considered a good indicator of the degree of polarization of the C=C bonds and the nucleophilicity of the enolate ligand.[6] Table 3 summarizes the values found for the new enolates **2**−**5** and compares them with those previously reported for the related enolates derived from **1**, namely, homometallic $[(TMEDA)_2Na_2\{O(=CH_2)\text{-}Mes\}_2]$[23] and $[(toluene)_4K_4\{O(=CH_2)Mes\}_4]$[26] and the heterometallic Na−Mg enolate $[(TMEDA)_2Na_2Mg\{OC(=CH_2)\text{-}Mes\}_4]$[23] in the same deuterated solvent. The Δ*δ* values for the Li−Zn enolates **2** and **3** are remarkably lower (by an average of 9.10 ppm) than that found in the homometallic lithium enolate **4**. This can be rationalized in terms of the reduced polarization of the M−O bonds in **2** and **3** (as previously discussed). Following the same trend, a comparison between the Δ*δ* values of the homometallic lithium (**4**), sodium, and potassium enolates shows that the more electropositive the metal, the more polarized are the M−O bonds. The mixed-metal Na−Mg enolate, isostructural with **2** as previously mentioned, possesses a higher value of Δ*δ* probably due to the combined effect of magnesium (with a less covalent character than zinc) and sodium (more electropositive than lithium). Surprisingly zinc enolate **5** has a Δ*δ* value significantly greater than those found for Li−Zn enolates **2** and **3** and closer to the lithium enolate **4**. This is consistent with the monomeric structure of **5**, where the terminal enolate ligands form more polarized (and therefore reactive) Zn−O bonds, in comparison with **2** and **3**, where all the enolate ligands are acting as bridges.

Theoretical Studies. As alluded to previously, dialkyl zinc reagents are rarely used in deprotonative metalations due to their low kinetic basicity as a consequence of the high covalency of the Zn−C bonds. An efficient synthetic alternative is the use of zinc amides, as Zn−N bonds are presumed to be easier to break. In order to shed some light on the kinetic/thermodynamic reactivity of zinc reagents, we carried out a theoretical study using DFT calculations at the B3LYP/6-311G** level. The reactions of Et_2Zn and $Zn(TMP)_2$ with 2 equiv of **1** to afford the enolate $[Zn\{O(=CH_2)Mes\}_2]$ were modeled in a two-step mechanism, where initially one molecule of the ketone coordinates to the organozinc reagent (**CP1**) followed by deprotonation to afford the alkyl-enolate or amide-enolato intermediate

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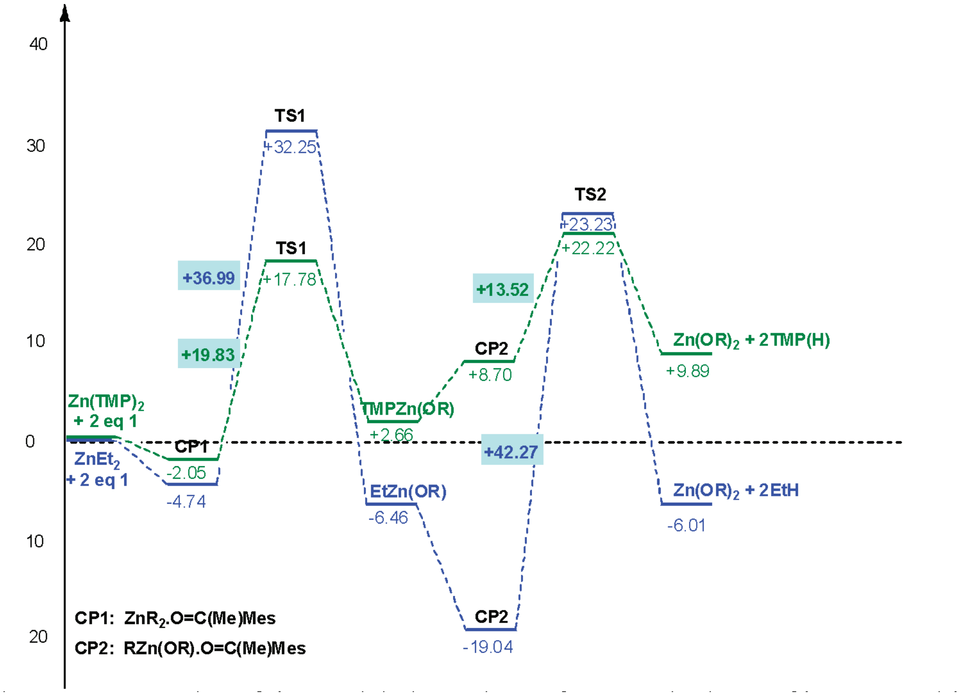

Figure 6. Energetics of the modeled reactions of 2 equiv of ketone **1** with $ZnEt_2$ (blue) or $Zn(TMP)_2$ (green). Energy changes are shown in kcal/mol.

[RZn(OR)] via a transition state (**TS1**). The second equivalent of the ketone then coordinates to this intermediate (**CP2**), and the second metalation takes place to yield the desired zinc enolate $Zn(OR)_2$ and the relevant coproduct (ethane or the amine TMPH) via a second transition state, **TS2** (Figure 6). As observed, from a strictly thermodynamic point of view Et_2Zn should be a better base since the overall reaction to form the bis(enolato) product is exothermic by −6.01 kcal/mol. However this reaction sequence involves two distinct transition states (**TS1** and **TS2**) with extremely high activation barriers (36.99 and 42.27 kcal/mol, respectively). On the other hand the reaction of **1** with the zinc amide $Zn(TMP)_2$ is overall endothermic (+9.89 kcal/mol); however the activation energies of the transition states **TS1** and **TS2** are considerably lower (19.83 and 13.52 kcal/mol). In addition the reaction of $Zn(OR)_2$ with TMEDA to afford enolate **5** is exothermic by 39.14 kcal, which makes the reaction of $Zn(TMP)_2$ with **1** favored not only kinetically but also thermodynamically (−29.25 kcal/mol). Thus these calculations illustrate the greater kinetic basicity of $Zn(TMP)_2$ in comparison with $ZnEt_2$, which makes the former an efficient and versatile base for accomplishing ketone metalations.

Conclusions

The metalation of the highly sterically demanding ketone **1** has been investigated with three different organozinc reagents. When the homoleptic inorganic zincate $[LiZn(TMP)_3]$ is employed, the mixed-metal lithium−zinc enolates $[(L)_2Li_2Zn\{O({=}CH_2)Mes\}_4]$ (L= TMEDA, **2**; TMPH, **3**) were obtained where the three amido groups of the base react with the ketone. In contrast to this ligand-efficient process, when the heteroleptic alkyl-amido zincate $[(TMEDA)LiZn(TMP)Me_2]$ reacts with **1**, only the amido group is basic enough to metalate **1**, affording the lithium enolate $[(TMEDA)_2Li_2\{O({=}CH_2)Mes\}_2]$ (**4**) and releasing $Me_2Zn \cdot TMEDA$ and TMP(H) as coproducts. Enolates **2**−**4** exhibit similar structural motifs, where the metals are connected through enolate bridges. $Zn(TMP)_2$ can successfully metalate **1** to yield the simple monomeric zinc enolate $[(TMEDA)Zn\{OC({=}CH_2)Mes\}_2]$ (**5**). A theoretical study of the reactions of **1** with $Zn(TMP)_2$ and $ZnEt_2$ quantifies the greater kinetic reactivity of the Zn−N bonds in comparison with Zn−C bonds.

Experimental Section

General Procedures. All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. Hexane and toluene were dried by heating to reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. *n*BuLi and Me_2Zn, were purchased from Aldrich Chemicals and used as received. $Zn(TMP)_2$[27] and $[(TMEDA)LiZn(TMP)Me_2]$[17] were prepared following literature procedures. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.13 MHz for ^1H, 150.32 MHz for ^7Li, and 100.62 MHz for ^{13}C.

X-ray Crystallography. Single-crystal diffraction data were measured with a Nonius Kappa CCD diffractometer (compounds **2** and **5**) or an Oxford Diffraction Xcalibur S instrument (samples **3** and **4**) using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were refined by full-matrix least-squares and against F^2 to convergence using the SHELXL-97 program.[28] Specific crystallographic data and refinement parameters are given in Table 4.

Synthesis of $[(TMEDA)_2Li_2Zn\{OC({=}CH_2)Mes\}_4]$ (2). To a solution of LiTMP [6 mmol, prepared in situ by reaction of BuLi (3.75 mL of a commercial 1.6 M solution in hexane, 6 mmol) with TMPH (1.01 mL, 6 mmol)] in hexane cooled at 0 °C was added $ZnCl_2$ (2 mL of a commercial 1 M solution in ether, 2 mmol). A white precipitate (LiCl) was formed instantaneously. The reaction mixture was allowed to stir at room temperature overnight and filtered through Celite, and TMEDA was added (0.3 mL, 2 mmol),

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[28] Sheldrick, G. M. *SHELXL-97, program for crystal structure refinement*; University of Göttingen: Germany, 1997.

Table 4. Key Crystallographic and Refinement Parameters for Compounds 2−5

	2	3	4	5
empirical formula	$C_{56}H_{84}Li_2N_4O_4Zn$	$C_{62}H_{90}Li_2N_2O_4Zn$	$C_{34}H_{58}Li_2N_4O_2$	$C_{28}H_{42}N_2O_2Zn$
mol wt	956.52	1006.61	568.72	504.01
cryst syst	orthorhombic	orthorhombic	orthorhombic	monoclinic
space group	*Fddd*	*Fddd*	*Pnn*2	$P2_1$
a/Å	17.8650(5)	20.948(5)	16.4657(8)	9.4749(3)
b/Å	24.3175(7)	20.964(5)	12.1496(6)	12.6708(3)
c/Å	21.4188(7)	27.849(8)	8.7833(5)	11.6753(3)
β/deg	90	90	90	98.4680(10)
V/Å^3	11911.6(6)	12230(6)	1757.11(16)	1386.39(7)
Z	8	8	2	2
T/K	123(2)	173(2)	150(2)	123(2)
indep reflns	3409	3912	2280	5511
goodness-of-fit on F^2	1.061	0.982	0.865	1.026
R1 [$I > 2\sigma(I)$]	0.0342	0.0454	0.0395	0.0283
wR2	0.0804	0.1186	0.0840	0.0650

affording a pale yellow solution. Then 1.00 mL of **1** (6 mmol) was introduced, and the mixture was allowed to stir for 30 min, affording a white solid. Toluene (5 mL) was added at this stage, and the mixture was gently heated until all the white solid had dissolved, affording a pale orange solution. Allowing this solution to cool slowly to room temperature produced a crop of colorless crystals (0.68 g, 36%). ^{1}H NMR (400 MHz, 25 °C, d_6-benzene): 6.79 (s, 8H, *m-H* Mes), 5.07 (s br, 4H, C*H*H′), 4.10 (s br, 4H, CH*H*′), 2.77 (s, 24H, *o*-CH_3, Mes), 2.21 (s, 12H, *p*-CH_3, Mes), 1.50 (s, 8H, CH_2 TMEDA). $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, d_6-benzene): 163.76 (O*C*=CH_2), 142.49 (C_{ipso}, Mes), 136.35 (C_{ortho}, Mes), 135.31 (C_{para}, Mes), 127.88 (C_{meta}, Mes), 86.10 (OC=*C*H_2), 56.27 (CH_2 TMEDA), 45.20 (CH_3 TMEDA), 20.84 (*p-C*H_3, Mes). 20.16 (*o-C*H_3, Mes). ^{7}Li NMR (155.50 MHz, C_6D_6 reference LiCl in D_2O at 0.00 pppm): 0.07.

Synthesis of [{TMP(H)}$_2$Li$_2$Zn{OC(=CH$_2$)Mes}$_4$] (3). Compound **3** was prepared following the procedure described for **2** with the exclusion of TMEDA. A white solid was obtained. Addition of toluene and gently heating afforded a pale orange solution, which deposited crystals after cooling slowly at room temperature (0.42 g, 46%). ^{1}H NMR (400 MHz, 25 °C, d_6-benzene): 6.77 (s, 8H, *m-H* Mes), 5.00 (s br, 4H, C*H*H′), 4.18 (s br, 4H, CH*H*′), 2.76 (s, 24H, *o*-CH_3, Mes), 2.18 (s, 12H, *p*-CH_3, Mes), 1.40 (s br, 4H, H_γ, TMPH), 1.10 (s br, 8H, H_β, TMPH), 0.85 (s br, 24H, C*H*$_3$, TMPH), 0.14 (s br, 2H, N*H*, TMPH). $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, d_6-benzene): 162.75 (O*C*=CH_2), 142.20 (C_{ipso}, Mes), 135.84 (C_{ortho}, Mes), 135.48 (C_{para}, Mes), 128.36 (C_{meta}, Mes), 85.34 (OC=*C*H_2), 49.68 (C_α, TMPH), 36.06 (C_β, TMPH), 31.08 (*C*H_3, TMPH), 20.25 (*p-C*H_3, Mes), 20.12 (*o-C*H_3, Mes), 17.33 31.08 (C_γ, TMPH). ^{7}Li NMR (155.50 MHz, C_6D_6 reference LiCl in D_2O at 0.00 pppm): 0.59.

Synthesis of [(TMEDA)$_2$Li$_2${OC(=CH$_2$)Mes}$_2$] (4). A 0.36 g (1 mmol) amount of [(TMEDA)LiZn(TMP)Me$_2$] was dissolved in hexane. **1** (0.33 mL, 1mmol) was then introduced. A white solid precipitated instantaneously. TMEDA (0.15 mL, 1 mmol) was added, affording a colorless solution, which was placed in the freezer at −28 °C. A crop of colorless crystals were deposited overnight (0.19 g, 67%). ^{1}H NMR (400 MHz, 25 °C, d_6-benzene): 6.84 (s, 2H, *m-H* Mes), 4.10 (s, br, 1H, C*H*H′), 3.83 (s, br, 1H, CH*H*′), 2.72 (s, 6H, *o*-CH_3, Mes), 2.26 (s, C*H*$_2$, TMEDA), 2.21 (s, 3H, *p*-CH_3, Mes), 2.09(s, C*H*$_3$, TMEDA). $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, d_6-benzene): 167.53 (O*C*=CH_2), 142.38 (C_{ipso}, Mes), 135.19 (C_{ortho}, Mes), 128.70 (C_{para}, Mes), 127.64 (C_{meta}, Mes), 80.86 (OC=*C*H_2), 57.96 (*C*H_2, TMEDA), 45.79 (*C*H_3, TMEDA), 20.87 (*p-C*H_3, Mes), 20.68 (*o-C*H_3, Mes). ^{7}Li NMR (155.50 MHz, C_6D_6 reference LiCl in D_2O at 0.00 pppm): 0.57.

Synthesis of [(TMEDA)Zn{OC(=CH$_2$)Mes}$_2$] (5). 1 (0.67 mL, 4 mmol) was added to a solution of freshly prepared Zn(TMP)$_2$ (0.62 g, 2 mmol) in hexane (10 mL). The solution changed from colorless to pale yellow. TMEDA (0.3 mL, 2 mmol) was then introduced, affording a white suspension. Toluene was introduced at this stage (2 mL), and the mixture was gently heated until all the solid had dissolved, affording a pale orange solution. Allowing this solution to cool slowly at room temperature afforded a crop of colorless crystals (0.35 g, 42% isolated crystalline yield, NMR analysis of the filtrate showed the reaction is almost quantitative). ^{1}H NMR (400 MHz, 25 °C, d_6-benzene): 6.94 (s, 4H, *m-H* Mes), 4.61 (s br, 2H, C*H*H′), 4.16 (s br, 2H, CH*H*′), 2.79 (s, 12H, *o*-CH_3, Mes), 2.27 (s, 6H, *p*-CH_3, Mes), 2.03 (s, 12H, C*H*$_3$, TMEDA), 1.51 (s, 4H, C*H*$_2$, TMEDA). $^{13}C\{^1H\}$ NMR (100.63 MHz, 25 °C, d_6-benzene): 166.71 (O*C*=CH_2), 142.38 (C_{ipso}, Mes), 135.64 (C_{ortho}, Mes), 134.94 (C_{para}, Mes), 128.71 (C_{meta}, Mes), 83.14 (OC=*C*H_2), 55.87 (*C*H_2, TMEDA), 45.65 (*C*H_3, TMEDA), 20.45 (*p-C*H_3, Mes), 20.11 (*o-C*H_3, Mes).

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Supporting Information Available: CIF file giving crystal data, computational details, and NMR spectra are available free of charge via the Internet at http://pubs.acs.org.

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