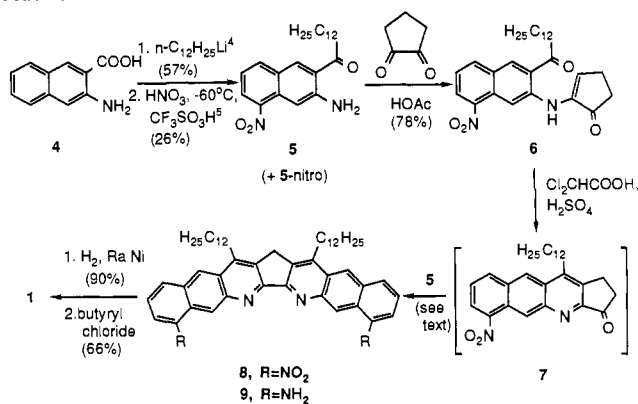Scheme I

10b and 3c, which are, respectively, ~0.7 Å too short and ~0.5 Å too long for a "perfect" fit indicates (i) that hydrogen bond lengths are more adaptable than expected, (ii) that binding of 10b and 3c induces changes in the shape of 1 (the two N–H's of 1 can be regarded as being at the extremes of two long lever arms extending from a central fulcrum), or (iii) that in complex 2c, 3c is tilted[18] relative to the plane of 1 are questions which remain unanswered. X-ray crystallography of complexes 2c and 11 would shed light on these questions, but, despite considerable effort,[19] neither 2c nor 11 has yet been induced to crystallize. Further studies are in progress.[20]

(17) Indeed, the modicum of flexibility [e.g., rotation around the Ar–butyramide bond] incorporated in 1 may be advantageous: i, the very rigid nine-ring nominal isostere of 1, exhibits no detectable binding with either 10b or 3c in either DMSO or 1:1 (v/v) CH₂Cl₂/toluene (because of the poor solubility of i only $K_{dissoc} \leq \sim 10^{-3}$ could have been detected with CH₂Cl₂/toluene). Compound i was prepared by condensation (50%) of 9 with ii followed by cyclization (44%) in refluxing diphenyl ether (Cassis, R.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* 1985, *15*, 125–133).
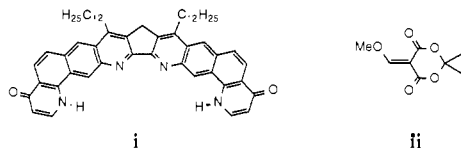
(18) For a study of the directionality of hydrogen bonds, see: Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* 1983, *105*, 5761–5766. Hydrogen bonds tolerate modest deviations from linearity: Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman: New York, 1985; p 297.

(19) Complex 11 is more soluble in nonpolar solvents than its constituents, presumably (in part) because binding attenuates the polarity of the four hydrogen bonding sites present in both 1 and 10b. Thus, addition of hexane to a CHCl₃ solution of 11 results in desolubilization of 1 and/or 10b; as noted above, addition of MeOH to a CHCl₃ solution of 11 disrupts the complex.

(20) All compounds gave spectral data in agreement with the structures assigned; satisfactory combustion analyses were obtained for most new compounds. ¹H NMR data and [mp's] for selected compounds: 1 [224–227 °C, dec] δ (CDCl₃) 0.87 (6 H, t, *J* = 6.8), 1.15–1.48 (38 H, m), 1.57 (4 H, m), 1.78 (4 H, m), 1.98 (4 H, m), 2.68 (4 H, br t, *J* = 7.5), 3.18 (4 *H*, br t, *J* = 7.5), 3.97 (2 H, s), 7.28 (2 H, br apparent t, *J* ~8.2), 7.64 (2 H, br d, *J* = 8.4), 8.08 (2 H, br d, *J* = 8.1), 8.15 (2 H, br s), 8.32 (2 H, s), 9.00 (2 H, s); 3c [170~180 °C, dec] δ (DMSO-d₆) 2.91 (2 H, m), 3.42 (2 H, m), 7.17–7.41 (15 H, m), 10.78 (1 H, br s), 11.75 (2 H, br s); 5 [110–111 °C] δ (CDCl₃) 0.88 (3 H, t, *J* = 6.9), 1.22–1.48 (18 H, m), 1.78 (2 H, apparent pentet, *J* = 7.2), 3.11 (2 H, t, *J* = 7.4), 6.35 (2 H, br s), 7.20 (1 H, t, *J* = 7.8), 7.88 (1 H, br s), 8.00 (1 H, br d, *J* = 7.8), 8.35 (1 H, dd, *J* = 7.8, 1.2), 8.40 (1 H, br s); 8 [189–191 °C] δ (CDCl₃) 0.86 (6 H, t, *J* = 6.8), 1.20–1.42 (32 H, m), 1.46–1.58 (4 H, m), 1.64–1.76 (4 H, m), 3.11 (4 H, br t, *J* = 7.5), 4.13 (2 H, br s), 7.39 (2 H, dd, *J* = 8.1, 7.5), 7.94 (2 H, br d, *J* = 8.1), 8.09 (2 H, s), 8.30 (2 H, dd, *J* = 7.5, 1.2), 9.48 (2 H, s); 10b [269–271 °C] δ (CDCl₃) 0.89 (6 H, m), 1.24–1.48 (12 H, m), 1.73 (4 H, m), 3.58 (2 H, br t, *J* = 7.2), 3.80 (2 H, br t, *J* = 7.2), 7.72 (1 H, s), 12.14 (1 H, br s), 14.85 (1 H, br s).

The First Practical Niobium(III) Reagent in Organic Synthesis. A Convenient Route to 2-Amino Alcohols via the Coupling of Imines with Aldehydes or Ketones Promoted by NbCl₃(DME)

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The application of low-valent early transition metals as two electron reductants in organic synthesis has centered around titanium and zirconium complexes,[1] with recent attention being focused on the metallocene derivatives of these metals (i.e., "Cp₂Ti"[2] and "Cp₂Zr"[3] which are generated in situ by reduction of the corresponding Cp₂MX₂). We have been interested in using Nb(III)Cl₃Lₙ reagents with the anticipation that such species should exhibit markedly different reaction chemistry from the group IV metallocenes. These differences would arise from the enhanced Lewis acidity of the niobium–chloride complexes and the potential for substitution of the chlorides with other ligands (e.g., chiral ligands). Prior to this work the primary soluble sources of "NbCl₃" were the well-known series of dimers, Nb₂Cl₆L₃,[4] (e.g., L = tetrahydrothiophene (THT), Me₂S, Cl⁻), which have exhibited a rich inorganic and organometallic chemistry.[5] However, large scale syntheses of these materials (e.g., >50 g) are not convenient for practical applications in stoichiometric organic reactions. Herein, we report a new and convenient synthesis of 2-amino alcohols via the cross coupling of an imine with an aldehyde or ketone by using a readily available niobium reagent, NbCl₃(DME) (1).

NbCl₃(DME) (1) is prepared by the addition of NbCl₅ to a solution of tributyltin hydride in dimethoxyethane (DME) at –78 °C (eq 1).[6] The NbCl₃(DME) precipitates from the reaction

$$NbCl_5 + 2 Bu_3SnH \xrightarrow{\text{DME}} NbCl_3(DME) + 2 Bu_3SnCl + H_2 \quad (1)$$

allowing for easy separation from the tributyltin chloride that is generated. The isolated brick-red solid is then simply stored (under an inert atmosphere) and used when desired. At this time, we do not know the molecular structure of 1 due to its lack of solubility in any solvent with which it does not react. The *empirical* formula shown is based on repeated elemental analyses[7] and the reaction of 1 with tetrahydrothiophene which produces the known complex Nb₂Cl₆(THT)₃ in high yield (88%). No hydrogen was evolved from this reaction indicating that 1 is not a niobium(IV) hydride.

(1) For reviews, see: (a) McMurry, J. E. *Acc. Chem. Res.* 1983, *16*, 405. (b) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Wiley: New York, 1983; Vol. 3. (c) Lai, Y. H. *Org. Prep. Proc. Int.* 1980, *112*, 361. (d) Ho, T. L. *Synthesis* 1979, 1.

(2) (a) Nugent, W. A.; Thorne, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* 1987, *109*, 2788 and references therein. (b) Famili, A.; Farona, M. F.; Thanedar, S. *J. Chem. Soc., Chem. Commun.* 1983, 435.

(3) (a) See ref 2a. (b) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* 1987, *28*, 917. (c) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Ibid.* 1986, *27*, 2829. (d) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* 1985, *107*, 2568.

(4) (a) Allen, A. D.; Naito, S. *Can. J. Chem.* 1976, *54*, 2948. (b) Maas, E. T., Jr.; McCarley, R. E. *Inorg. Chem.* 1973, *12*, 1096.

(5) For examples, see: (a) Cotton, F. A.; Diebold, M. P.; Matusz, M.; Roth, W. J. *Inorg. Chim. Acta* 1986, *112*, 147. (b) Cotton, F. A.; Diebold, M. P.; Llusar, R.; Roth, W. J. *J. Chem. Soc., Chem. Commun.* 1986, 1276. (c) Cotton, F. A.; Diebold, M. P.; Roth, W. J. *Inorg. Chem.* 1985, *24*, 3509. (d) Cotton, F. A.; Duraj, S. A.; Roth, W. J. *J. Am. Chem. Soc.* 1984, *106*, 6987. (e) Cotton, F. A.; Duraj, S. A.; Roth, W. J. *Ibid.* 1984, *106*, 4749. (f) Cotton, F. A.; Duraj, S. A.; Roth, W. J. *Ibid.* 1984, *106*, 3527. (g) Cotton, F. A.; Roth, W. J. *Inorg. Chim. Acta* 1984, *85*, 17. (h) Cotton, F. A.; Hall, W. T.; Cann, K. J.; Karol, F. J. *Macromolecules* 1981, *14*, 233.

(6) For other examples where Bu₃SnH has been used to reduce an inorganic halide, see: (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* 1987, *109*, 3152 (Supplementary Material). (b) Roth, A.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* 1986, *108*, 6823. (c) Fjeldberg, T.; Haaland, A.; Schilling, B. E. R.; Lappert, M. F.; Thorne, A. J. *J. Chem. Soc., Dalton Trans.* 1986, 1551.

(7) Anal. Calcd for NbC₄H₁₀Cl₃O₂: C, 16.60; H, 3.48; Cl, 36.76. Found: C, 16.94; H, 3.71; Cl, 36.65; N, 0.00 (average of six separate analyses on three different samples). See Supplementary Material for further details.

Table I[a] Amino Alcohols After Hydrolysis

amino alcohol	yield[b]	ds[c]	amino alcohol	yield[b]	ds[c]	amino alcohol	yield[b]	ds[c]
1	70[d]		**5**	69	4.5:1	**9**	79	83:1
2	97		**6**	68	3.5:1	**10**	33	6:1
3	90	3:1	**7**	73	6.5:1	**11**	60	3:1
4	82	3:1	**8**	65	3:1	**12**	34	

[a] All compounds were characterized by ¹H, ¹³C, IR, and mass spectral data and C, H, N analysis. [b] All yields (%) are of isolated products. [c] Determined by NMR or GC. For reactions of aldehydes the ratio represents threo/erythro. See Supplementary Material. [d] The imine and NbCl₃(DME) were stirred for 2.5 h before the ketone was added.

We began our investigation of **1** by examining its reactivity with imines since one of our areas of interest is the development of new routes to functionalized amines employing transition-metal reagents.[6a] Reaction of **1** with 1 equiv of *N*-phenyl benzaldehyde imine in tetrahydrofuran (0.5–12 h) followed by hydrolysis with NaOD gave the corresponding deuteriated amine, PhN(D)-CHDPh, indicating that a metal–carbon bond had been formed. A likely intermediate is the metallaaziridine shown in eq 2, a structure for which there is precedent in early transition-metal chemistry.[8] It is important to note that of all the known examples, none are prepared by simply adding an imine to a d² metal center.[9]

$$\text{NbCl}_3(\text{DME}) + \underset{\text{Ph}}{\overset{\text{N}^{\diagup\text{Ph}}}{\|}} \xrightarrow{\text{THF}} (\text{THF})_2\text{Cl}_3\text{Nb} \underset{\text{Ph}}{\overset{\text{N}^{\diagup\text{Ph}}}{\diagdown}} \quad (2)$$

Since the above hydrolysis experiments suggested that the niobium–imine reagent was behaving like an N,C-dianion, we felt that it should react with carbonyl groups (via coordination and insertion into the metal–carbon bond) to give amino alcohols after hydrolysis. As indicated in Table I this does in fact occur (entry 1). We then turned our attention to coupling reactions involving *N*-benzyl and *N*-allyl imines since these groups can be removed by a variety of methods[10] to give the more versatile unsubstituted amines (Table I). The yields for the majority of these reactions are very good, and the reagent is tolerant of some functionalities that are often not compatible with low-valent early transition metal

halides (entries 4 and 8). In the case of entry 12 we believe that rapid isomerization of the imine to an enamine, under the reaction conditions, results in lower yields. All of the reactions with aldehydes are threo selective, and the yields are improved by using an excess of the niobium–imine reagent (1.5 equiv). We have also noticed that the reaction is susceptible to certain steric effects. In particular, we observed no coupling between PhCH₂N= CHCMe₃/NbCl₃(DME) and octanal or between *tert*-butyl methyl ketone and PhCH₂N=CHPh/NbCl₃(DME).

We anticipate that the general reaction described in this communication will prove to be a useful method for the rapid assembly of amino alcohols from readily available starting materials. The synthesis of NbCl₃(DME) as well as a representative procedure for the synthesis of 2-amino alcohols is given below. All reactions were performed under a nitrogen atmosphere.

NbCl₃(DME). A dry, 1-L, 3-necked flask was fitted with an overhead mechanical stirrer and a nitrogen inlet adapter and charged with dimethoxyethane[11] (600 mL) and tributyltin hydride[12] (111 g, 0.38 mol). A 100-mL, round-bottomed flask containing niobium pentachloride[13] (50 g, 0.19 mol) was attached to the setup via a 1-ft piece of rubber tubing fitted with two 24/40 male joints on each end. The reaction was then cooled to –78 °C, and the solution was vigorously stirred[14] while the niobium pentachloride was added over a 35–45-min period, maintaining the bath temperature between –78 and –65 °C. After the addition was complete, the reaction was allowed to warm slowly to between 0 and 20 °C (3–5 h) at which point the apparatus was brought into a drybox.[15] The solid was isolated by filtration and washed

(8) (a) Durfee, L. D.; Fanwick, P. E.; Rothwell, I. P.; Folting, K.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4720. (b) Mayer, J. M.; Curtis, C. J.; Bercaw, J. E. *Ibid.* **1983**, *105*, 2651. (c) Chiu, K. W.; Jones, R. A.; Wilkinson, G.; Galas, A. M. R.; Hursthouse, M. B. *J. Chem. Soc. Dalton* **1981**, 2088. (d) Takahashi, Y.; Onoyama, N.; Ishikawa, Y. *Chem. Lett.* **1978**, 525. (e) Wolczanski, P. T.; Bercaw, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 6450.

(9) For examples of metallaaziridine formation from addition of imines to lower-valent metals, see: (a) Brunner, H.; Wachter, J.; Schmidbauer, J. *Organometallics* **1986**, *5*, 2212 and references therein. (b) Sielisch, T.; Behrens, U. *J. Organomet. Chem.* **1986**, *310*, 179.

(10) *N*-Debenzylation: (a) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515. (b) Adger, B. M.; O'Farrell, C.; Lewis, N. J.; Mitchell, M. B. *Synthesis* **1987**, 53. (c) Mukaiyama, T.; Goto, Y.; Shoda, S. *Chem. Lett.* **1983**, 671. *N*-Deallylation: Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.

(11) Dimethoxyethane and tetrahydrofuran were distilled from sodium–benzophenone.

(12) The Bu₃SnH was prepared from Bu₃SnCl/LiAlH₄ (Kuivila, H. G. *Synthesis* **1970**, 499) or (Bu₃Sn)₂O/polymethylhydrosiloxane (Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81) or purchased from Aldrich Chemical Company.

(13) The niobium pentachloride was purchased from either CERAC or Aldrich Chemical Company. The material from Aldrich was ground to a powder before use.

(14) Vigorous stirring is essential and should be maintained in such a manner that any dark residue formed near the joint where the NbCl₅ is introduced is constantly being washed into the reaction.

with dimethoxyethane (2 × 150 mL) and pentane (150 mL) followed by drying in vacuo (45 min). A brick-red solid (50.6 g, 92%) was obtained.

2-Amino Alcohol Synthesis. A dry 250-mL flask was charged with NbCl₃(DME) (2.0 g, 6.9 mmol) and tetrahydrofuran[11] (ca. 80 mL). A tetrahydrofuran solution (4 mL) of the imine[16] (6.9 mmol) was then added dropwise (via syringe) over 30 s to the stirred mixture. When the solution became a homogeneous dark green (or yellow-green) color (ca. 1 min), the aldehyde or ketone (4.6 mmol) in tetrahydrofuran (ca. 2 mL) was added dropwise over 30 s. After stirring for 30 min the reaction was poured into a separatory funnel and treated with potassium hydroxide (10% w/v, 75 mL) and extracted with ether (2 × 150 mL). The combined ether layers were dried briefly over MgSO₄ and filtered. The ether was removed in vacuo yielding the crude product as an oil which was purified by flash chromatography[17] (silica gel, 230–400 mesh, hexane/ethyl acetate).

Supplementary Material Available: Full NMR, IR, and mass spectral data and C, H, and N analysis information for all amino alcohols (10 pages). Ordering information is given on any current masthead page.

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(15) Alternatively standard Schlenk filtration can be employed.
(16) All imines were prepared by combining the appropriate aldehyde, amine, and excess MgSO₄ in dichloromethane and stirring overnight. The imines were purified either by recrystallization or Kugelrohr distillation.
(17) Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.
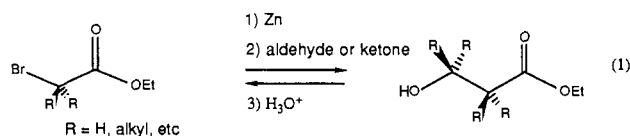
The Reformatsky Reaction

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While the Reformatsky reaction[2] (see eq 1) is celebrating the centennial of its discovery this year, the mechanism is still a matter of controversy. Early mechanistic suggestions[3] have centered

(1)

R = H, alkyl, etc

around the rearrangement of adducts 1 and 2 of the two possible monomeric forms of the Reformatsky reagent (RR) with the majority of the chemical evidence favoring the enolate form 2. However, recent X-ray evidence has shown that the RR is dimeric in THF,[4] throwing doubt on the suggestion that the monomeric forms participate at all. Here we report a detailed theoretical study of the reaction, with use of the MNDO method[5] as implemented by the AMPAC program.[7] MNDO has been recently

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(1) Current address S926, The University of California, San Francisco, San Francisco, CA 94143-0446.
(2) Reformatskii, S. N. Ber. 1887, 20, 1210. For an interesting historical discussion, see: Sementsov, A. J. Chem. Ed. 1957, 34, 530.
(3) This topic is discussed in detail in the following reviews: Gaudemar, M. Organomet. Chem. Rev., Sect. A 1972, 8, 183. Rathke, M. W. Org. React. 1975, 22, 423. Also, see: March, J. Advanced Organic Chemistry; McGraw-Hill Inc.: New York, 1985; p 823.
(4) Dekker, J.; Boersma, J.; van der Kerk, G. J. M. J. Chem. Soc., Chem. Commun. 1983, 553.
(5) Dewar, M. J. S.; Thiel, W. J. Am. Chem. Soc. 1977, 99, 4907.
(6) QCPE, no. 506.

1   2

3   4

5
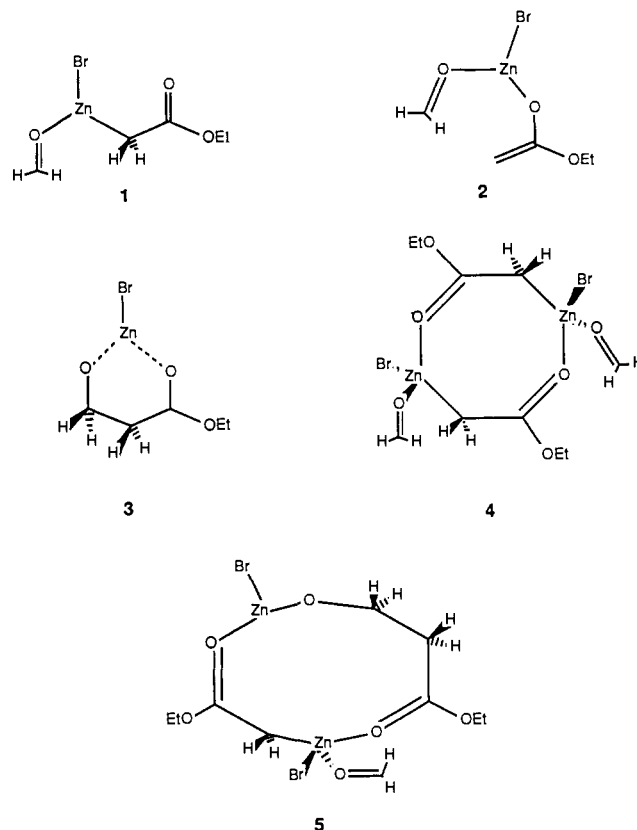
parametrized to handle organozinc compounds.[8] The aldehyde and ether component of the RR was modelled by formaldehyde and dimethyl ether, respectively.

We first needed to know what MNDO predicts for the coordination number around zinc. We find, on the basis of purely energetic considerations, that MNDO favors the coordination around zinc to be three. This seems to be at variance with most of the available experimental evidence, which indicates that the usual coordination number for zinc in solution is four.[8] This discrepancy is not surprising because MNDO tends to overestimate repulsions between neutral atoms.[9] It should be noted here that we have also carried out extensive MNDO calculations on the mechanism of the Reformatsky reaction where the zinc is tetra-coordinated (i.e., with dimethyl ether as well as formaldehyde), and the results do not differ significantly from those we present below.

Chart I gives the reaction profile for the rearrangement of 1 and 2 to 3. Our calculations predict 1 to be more stable than 2 by about 7.8 kcal/mol, 1 and 2 interconverting by a 1,3-shift with an E_a of 26.5 kcal/mol. We next located the transition states (TSs) for the formation of 3 from either 1 or 2. 1 can rearrange to give 3, by a 1,4-shift, with an E_a of 55 kcal/mol, while formation of 3 from 2 only requires 15.45 kcal/mol.

The differences in the E_as are easily understood in terms of the aromaticity or antiaromaticity of the respective TSs.[10] The TS for the 1,4-shift contains four delocalized electrons and is therefore antiaromatic.[10] The TS for conversion of 2 to 3 contains six delocalized electrons and is therefore aromatic. The latter reaction involves a [3,3]-sigmatropic shift, analogous to a Cope or Claisen rearrangement. We therefore would like to classify this rearrangement as a metallo [3,3]-sigmatropic shift (or metalloclaisen). Previous authors[11] have pointed out that the Reformatsky reaction

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(7) Dewar, M. J. S.; Merz, K. M., Jr. Organomet. 1986, 5, 1494.
(8) See: Boersma, J. In Comprehensive Organometallic Chemistry; Wilkinson, Sir G., Ed.; Pergamon Press Ltd.: New York, 1982; p 823.
(9) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. J. Am. Chem. Soc. 1985, 107, 3902.
(10) Dewar, M. J. S. Angew. Chem., Int. Ed. Engl. 1971, 10, 761.
(11) Guetté, M.; Capillon, J.; Guetté, J.-P. Tetrahedron 1973, 29, 3659. Balsamo, A.; Barili, P. L.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. Tetrahedron Lett. 1974, 1005.