

The Role of the Activator for Zinc in the Simmons-Smith Reaction. A Convenient General Procedure¹

Ulf Schuchardt*, João H.S. Nery and Marcelo A. Zuiani

Instituto de Química, Universidade Estadual de Campinas
Caixa Postal 6154, 13081 Campinas, SP, Brasil

Received: April 16, 1991

Uma generalização do procedimento de Rawson e Harrison fornece melhores resultados para a ciclopropanação de olefinas sob condições padrão. Para a reação com cicloexeno (1), o ânion do sal de cobre, que age como ativador, tem um importante papel no rendimento da reação. A espectroscopia de RPE mostra que o sal de cobre não é reduzido, mas atua como catalisador na transferência do carbeno do composto organozinco para a olefina. Ultrassom acelera a reação, principalmente se for usado diiodometano (2a) como reagente, formando o biciclo[4.1.0]heptano (3) com rendimento de 88% após apenas 7 h de reação. O procedimento padrão permite a conversão de álcool alílico (5) a ciclopropilcarbinol (6) com rendimento de 75%, usando 2a como fonte de carbeno. Se 2a for substituído por dibromometano (2b), o rendimento cai para 57%.

A generalization of the procedure of Rawson and Harrison is shown to give better results for the cyclopropanation of olefins under standard conditions. For the reaction with cyclohexene (1), the anion of the activating copper salt plays an important role on the yield of the reaction. ESR spectroscopy shows that the copper salt is not reduced but acts as a catalyst for the carbene transfer from the organozinc compound to the olefin. Ultrasound accelerates the reaction, mostly if diiodomethane (2a) is used as reagent, giving bicyclo[4.1.0]heptane (3) in 88% yield after only 7 h of total reaction time. The general procedure allows conversion of allyl alcohol (5) to cyclopropylcarbinol (6) with a 75% yield if 2a is used as a carbene source and with a 57% yield if 2a is substituted by dibromomethane (2b).

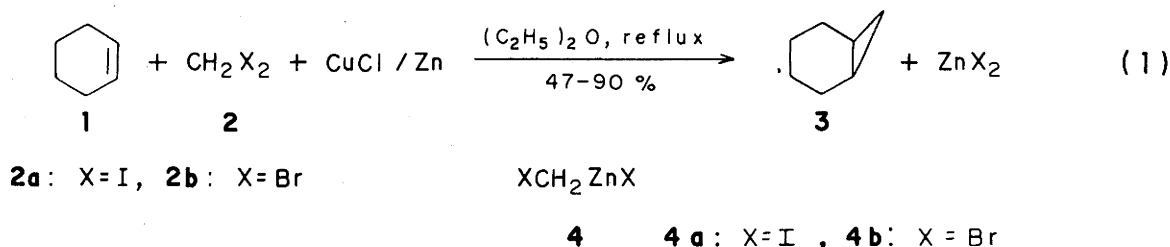
Key words: Simmons-Smith reaction, catalyst, ultrasound.

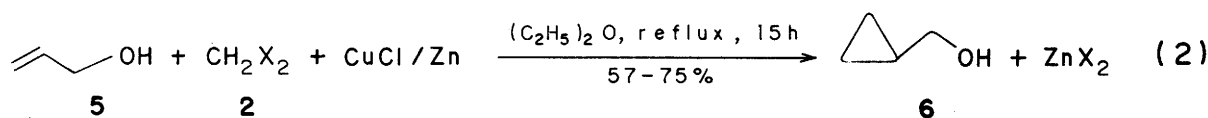
Introduction

On starting a study of the selectivity of the Simmons-Smith reaction² for the cyclopropanation of differently substituted 1,2- and 1,3-dienes³, it was not clear from the literature, which would be the best experimental procedure. Simmons and Smith⁴ reacted a mixture of the olefin and dihalomethane (2) with a previously prepared zinc-copper couple. LeGoff⁵ used a different couple which was activated with some drops of 2 before the addition of a mixture of the reagents. Rawson and Harrison⁶ used a mixture of zinc dust and a cuprous halide and added the olefin before 2, obtaining excellent yields of the cyclopropanation products. Conia *et al.*⁷ prepared a zinc-silver couple, first added

2a, then the olefin, and also reported excellent yields.

In more recent publications it is claimed that the zinc couple can be replaced by metallic copper⁸, that good yields are also obtained with 2b if tetrahydrofuran is used as a solvent⁹ and that ultrasonication promotes the reaction of 2b with the zinc-copper couple, giving good yields at short reaction times¹⁰. Boudjouk and Han¹¹ reported that the cyclopropanation occurs readily even with ordinary zinc if ultrasound is used. Repic and Vogt¹² cyclopropanated methyl oleate with an excess of mossy zinc and 2a in refluxing 1,2-dimethoxyethane, reporting 91% isolated yield, compared to 51% obtained by the normal route.





2a: X=I, 2b: X=Br

We report here a systematic study of the synthesis of bicyclo[4.1.0]heptane (3) (equation 1), in which we varied the order and time of addition of the reagents, the anion of the activating copper or silver salt, the solvent and the reaction time. Furthermore, we present results on experiments with ultrasound, with zinc prepared by the procedure of Rieke¹³ and with zinc supported on graphite¹⁴. Some ESR measurements were undertaken to investigate if the copper salt is reduced by the zinc or acts as a catalyst in the Simmons-Smith reaction. The best reflux conditions were then used for the cyclopropanation of allyl alcohol (5) (equation 2), a reaction which is reported to be difficult¹⁵.

Experimental

Cyclohexene (1) was prepared by dehydration of cyclohexanol (Aldrich, 99%) with conc. sulfuric and phosphoric acids¹⁶. It was first dried with anhydrous calcium chloride, then with metallic sodium wire and distilled onto molecular sieve (4 Å). Diiodomethane (2a) (Fluka, > 98%) and dibromomethane (2b) (Merck, > 99%) were used as purchased as well as the zinc dust (Riedel, > 99%), granular zinc (Aldrich, > 99%) and zinc pieces (Vetec, > 99.5%). The cuprous chloride (Merck), cuprous iodide (Fluka), cuprous cyanide (Aldrich) and silver acetate (Aldrich) were reagent grade (> 99%) and used as purchased. The hydrated cupric sulfate (Fluka, > 99%) and cupric acetate (Riedel, > 99%) were dried *in vacuo* at 110°C for 3 h before use. Silver chloride was precipitated from silver acetate with 2 N aqueous hydrochloric acid and cupric acetylacetonate ($\text{Cu}(\text{acac})_2$) was prepared by the method of Jones¹⁷. Both salts were dried for 3 h at 110°C. Diethyl ether and tetrahydrofuran (both reagent grade) were first dried with calcium chloride, then with metallic sodium wire and distilled before use. The reaction products were analyzed with a Siemens Sichromat I Gas Chromatograph, using a 3 m x 1/8" OV-101 column (for 3) or a 4 m x 1/8" Carbowax 20 M column (for 6) and a flame ionization detector. The products were quantified with a CG Instrumentos Científicos 300 Automatic Integrator with normalization to 100%. The experiments with ultrasound were performed in a Bandelin Sonorex RK 1028H cleaning bath (500 W, 35 kHz). The ¹H-NMR spectra were obtained in CDCl_3 with a Bruker AW-80 using TMS as internal standard. The IR spectra were recorded on a Jasco A-202 as a film between KBr windows. Compounds 3 and 6 were identified by comparison with literature spectra¹⁸. The mass spectra were obtained with a Varian MAT 311A at 70 eV. The ESR spectra were recorded on a Varian E 12 operated at the X band (9.51 GHz).

Cyclopropanation with diiodomethane (2a) under reflux - General Procedure: In a two-necked 100 ml flask,

equipped with a reflux condenser and a dropping funnel, are placed zinc dust (8.5 g, 0.13 g - atom) and cuprous chloride (0.26 g, 0.0026 mol). The system is evacuated (0.1 mmHg) for 30 min and then filled with purified argon. Diethyl ether (25 ml) is added and refluxed with magnetic stirring under argon for 30 min. The olefin (0.05 mol) is added all at once and the reflux continued. 2a (5.25 ml, 0.065 mol) is added dropwise during 4 h. The reaction mixture is refluxed for another 15 h. It is then placed into a centrifuge tube and rotated at 2,500 rpm for 20 min. The liquid phase is removed and the solids washed with two portions of diethyl ether (30 ml each) using centrifugation. The combined liquid phases are washed with three portions of a saturated solution of ammonium chloride (40 ml each), three portions of a saturated solution of sodium bicarbonate (40 ml each) and three portions of distilled water (40 ml each). The ether solution is dried with anhydrous magnesium sulfate, filtered and distilled *in vacuo* for gas chromatographic analysis. The product is isolated, after evaporation of the diethyl ether at normal pressure, by distillation through a 12 cm Vigreux column at reduced pressure (1 mmHg). Yield of 3: 3.6 g (75%); b.p. 114-115°C/700 mmHg (Lit.⁴ b.p. 116-117°C). Yield of 6: 2.2 g (61%); b.p. 121-122°C/690 mmHg (Lit.¹⁹ b.p. 123-124°C/738 mmHg).

Cyclopropanation with dibromomethane (2b) under reflux - General Procedure: The quantity of the reagents is maintained with exception of cuprous chloride, of which 1.29 g (0.013 mol) is added to the zinc to form the couple. The general procedure is analogous to that described above, but it is advantageous to extend the reflux time, after the addition of 2b (4.56 ml, 0.065 mol), to 40 h. The work-up is done as described for the reaction with 2a.

Cyclopropanation with ultrasound - General Procedure: A two-necked 100 ml flask, equipped with a reflux condenser and a dropping funnel, is placed 2 cm above the bottom of the ultrasonic bath. Zinc dust (8.5 g, 0.13 g - atom) and cuprous chloride (1.29 g, 0.013 mol) are placed into the flask, the system is evacuated (0.1 mmHg) for 30 min and then filled with purified argon. Diethyl ether (25 ml) is added, the ultrasonic bath is turned on and the ether refluxed under argon for 30 min. The olefin (0.05 mol) is added all at once and the ultrasonication continued. 2a (5.25 ml, 0.065 mol) or 2b (4.56 ml, 0.065 mol) is added dropwise during 4 h. Ultrasonication and reflux are continued for another 2.5 h (2a) or 5 to 15 h (2b). The work-up of the reaction mixture is done as described for the reflux conditions.

Results and Discussion

First experiments showed that the procedure described by

Table 1. Yield of **3**^a as a function of order of addition of **1** and **2a** (ratio of **1:2a**:CuCl/Zn of 1:1.3:2.6, ratio of Cu:Zn of 1:10, (C₂H₅)₂O under reflux, addition time 4 h, reaction time 36 h).

Product	Order of addition	Yield (%)
3	First all 2a , then 1	47
3	First 20% of 2a , then mixture of 1 and 2a	58
3	Mixture of 1 and 2a	68
3	First all 1 , then 2a	80

^a ¹H-NMR (CDCl₃) and IR (film) spectra identical with lit.¹⁸; MS (70 eV) M/z 96 (M⁺, 10%), 81 (58%), 67 (100%).

Rawson and Harrison⁶ is very convenient as the couple is prepared rapidly, the yields of **3** are high and obtained with a reproducibility within 2%. With the exception of some experiments in Table 4, this procedure was used throughout this study. The yield of **3** as a function of the order of addition of **1** and **2a** is shown in Table 1. In agreement with Rawson and Harrison⁶, the best yields are obtained if first the olefin and then **2a** are added to the reaction mixture. This order of addition avoids a high concentration of the iodomethylzinc iodide (**4a**) which is considered to be the intermediate of the reaction and which reacts slowly with itself or with excess of **2a** to form ethene²⁰. In our opinion this order of addition should also give better yields with the other couples. Tetrahydrofuran is not an appropriate sol-

Table 2. Yield of **3** as a function of addition and reaction time (ratio of **1:2**:CuCl/Zn of 1:1.3:2.6, ratio of Cu:Zn of 1:10, (C₂H₅)₂O under reflux).

Product	2	Addition time (h)	Reaction time	Yield (%)
3	2a	4	36	80
3	2a	4	22	81 ^a
3	2a	4	15	75 ^a
3	2a	4	7	75
3	2a	4	3	58
3	2a	2	15	51
3	2b	4	40	64 ^a
3	2b	4	15	53

^a Average of two determinations.

vent if the Rawson and Harrison couple is used, as it decomposes **4**, giving ethene as the principal product, as already reported by Blanchard and Simmons²⁰. In our experiments using tetrahydrofuran, **3** was obtained from **2a**, as well as from **2b**, in only 8% yield.

As shown in Table 2 the addition and reaction time are important parameters. The addition of **2** should be slow in order to avoid high concentrations of **4**, as the reaction of **4** with **1** is the slowest step²⁰. The time necessary to complete the reaction after the addition of **2** is rather short for **2a** (ca. 7 h) but long for **2b** (ca. 40 h), due to its much lower reactivity. Reduction of the quantity of cuprous chloride added to the zinc increases the yield of **3** if **2a** is used as a carbene source (Table 3). With a molar ratio of 1:50, **3** was reproducibly obtained with a GC yield similar to that reported by Rawson and Harrison⁶. After evaporation of the solvent, pure **3** was isolated by distillation *in vacuo* in 75% yield.

Table 3. Yield of **3** as function of the ration CuCl/Zn (ratio of **1:2**:CuCl/Zn of 1:1.3:2.6, (C₂H₅)₂O under reflux, addition time 4h, reaction time 15h).

Product	2	CuCl:Zn	Yield(%)
3	2a	1:10	75 ^a
3	2a	1:20	82
3	2a	1:50	90 ^a
3	2b	1:10	53
3	2b	1:20	29
3	2b	1:50	3 ^a

^a Average of two determinations.

With **2b** as a carbene source reduction of the amount of cuprous chloride is very prejudicial to the yield. This shows the importance of the activator in the reaction with the less reactive **2b**.

The kind of activator used to form the couple with zinc is very important (Table 4). Cuprous chloride gives the best results but cupric sulfate and cuprous iodide can also be used. With strongly coordinated cupric acetylacetonate and cuprous cyanide the yields of **3** are negligible. This shows clearly that the anion of the copper activator plays an important role in the rate determining step of the reaction. The LeGoff couple gives a moderate yield of only 31% under the same conditions. Silver chloride and acetate give inter-

Table 4. Yield of **3** as function of the activator (ratio of **1:2**:MX_n/Zn of 1:1.3:2.6, (C₂H₅)₂O under reflux, addition time 4h, reaction time 15 h).

Product	2	MX _n	MX _n :Zn	Yield(%)
3	2a	CuCl	1:10	75
3	2a	CuSO ₄	1:10	67
3	2a	CuI	1:10	67
3	2a	Cu(OAc) ₂	1:10	49
3	2a	Cu(acac) ₂	1:10	2
3	2a	CuCN	1:10	0
3	2a	Cu(OAc) ₂ ^a	1:65	31
3	2a	AgCl	1:10	53
3	2a	AgOAc	1:10	54
3	2a	AgOAc ^b	1:10	46
3	2a	AgOAc ^b	1:310	75
3	2b	AgCl	1:10	38

^a LeGoff couple; ^b Conia couple.

mediate results when using the Rawson and Harrison procedure. On the other hand, the Conia couple, with its very reduced silver acetate to zinc ratio⁷, gives the same good results as obtained with the *in situ* prepared cuprous chloride-zinc couple.

The observed anion effect is not in agreement with the statement of Blanchard and Simmons²⁰ that "copper in the zinc couple plays no role in cyclopropane formation but merely serves to activate the zinc metal surface for reaction with methylene iodide". The anion effect can be explained only if it stays coordinated to the copper, i.e. the copper salt is not reduced to copper(0) by the zinc. The copper salt, *per se*, participates in the formation of the cyclopropanation product. As copper(I) is diamagnetic and can not be seen in

Table 5. Yield of **3** under ultrasonic irradiation as a function of addition and reaction time (ratio of 1:2:CuCl/Zn of 1:1.3:2.6, ratio of CuCl: Zn of 1:10, (C₂H₅)₂O under reflux).

Product	2	Addition time (h)	Reaction time (h)	Yield(%)
3	2a	4	2.5	88 ^a
3	2a	2	2.5	70 ^a
3	2b	4	15.0	58
3	2b	4	5.0	47
3	2b	2	5.0	29
3	2b	2	2.5	23

^a Average of two determinations

Table 6. Yield of **6**^a under standard conditions (ratio of 5:2:CuCl/Zn of 1:1.3:2.6, (C₂H₅)₂O under reflux, addition time 4 h, reaction time 15 h).

Product	2	CuCl:Zn	Yield(%)
6	2a	1:50	75
6	2a	1:10	69
6	2b	1:10	57

^a ¹H-NMR (CDCl₃) and IR (film) spectra identical with lit.¹⁸; MS (70 ev) M/z 71 (M⁺ -1,4%); 58 (15%); 43 (100%)

the ESR spectrum, we could only get indirect proof that it is not reduced by the metallic zinc. A freshly prepared Rawson and Harrison couple shows no ESR signal, even after one week, if sealed under argon. If left in open air, the signal of copper(II) appears slowly, showing that cuprous chloride is being oxidized, which would not be possible if it had been reduced to copper(0) in forming the couple. Furthermore, the copper(II) ESR signal of freshly prepared cupric sulfate-zinc couple does not lose any intensity during one week. We, therefore, believe that the copper salt acts as a active catalyst in the carbene transfer from **4** to the olefin²¹. Copper(I) compounds are known to be active in the transfer reaction of carbenes to olefins²⁴, as they can coordinate both species²¹. The same is not as well established for zinc(II) compounds. We, therefore, postulate that **4** transfers the methylene carbene to the copper salt, which also coordinates to the olefin, and that the cyclopropane is formed in its coordination sphere. This would unequivocally explain the influence of the coordinated anions on the yield of **3**. The silver salts probably exhibit a similar effect in this reaction.

Highly activated zinc, obtained by the method of Rieke¹³ or by the reduction of anhydrous zinc chloride with lamellar potassium-graphite¹⁴, produces only small amounts (less than 10%) of **3** from **1** and **2a**. Addition of cuprous chloride to this highly activated zinc improves the yields of **3** only slightly. We believe that the very active zinc reduces the copper salt to copper(0), which has no catalytic effect in the Simmons-Smith reaction. The excellent yield of **3** reported by Rieke *et al.*²⁵ for the reaction of **1** with **2b**, obtained with zinc chloride reduced by lithium is, in our opinion, due to the formation of an intermediate bromomethyl lithium which is known to form **3** in reaction with **1**²⁶. Other reactions, which are reported to give good yields in the absence

of an activator, are apparently catalyzed by impurities in the zinc used²⁷.

Ultrasound strongly enhances the reaction of **1** with **2a** (Table 5). Using an addition time of 4 h, the reaction is already complete 2.5 h later, giving an excellent yield of 88% of **3**. With **2b** ultrasound is less effective; after 15 h of reaction the yield of **3** only increases from 53% (reflux) to 58% (ultrasound). If the addition time of **2a** or **2b** is reduced to 2 h the yield of **3** is significantly smaller. Using ultrasound, zinc dust can be replaced by granular zinc (30 mesh) and zinc pieces (3-5 mm) in the reaction with **2a**, giving only slightly reduced yields of **3**. Interestingly, **2b** does not react with the granular zinc or the zinc pieces under these conditions and can be recovered unchanged after the reaction. If the reaction of **2a** with zinc dust is carried on in the absence of the cuprous chloride activator, no formation of **3** is observed. This shows clearly that, even with ultrasound, the copper(I) compound is needed as a catalyst for the Simmons-Smith reaction.

The most convenient reflux conditions (diethyl ether, 4 h addition time, 15 h reaction time) have been tested for the cyclopropanation of **5** to cyclopropylcarbinol (**6**) (Table 6). Without any modification of the general procedure, **6** is obtained in 75% yield from **2a** and 57% yield from **2b**. These results are much better than the 15-20% of **6** reported by Majerski and Schleyer¹⁵ for the reaction of **5** and **2a** with a commercial zinc-copper couple. Furthermore, we did not observe any formation of dicyclopropylcarbinoxymethane.

Conclusions

We believe that the general procedure herein proposed will also give good results with other olefins, whose cyclopropanation by the Simmons-Smith reaction is considered difficult. The choice of an appropriate copper salt for the activation of the zinc is of major importance for obtained good yields of cyclopropanated products. We find the yields obtained with **2b** more interesting as its price per mol is only around 10% of that for **2a**.

Acknowledgements

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and by the Stiftung Volkswagenwerk. The authors acknowledge fellowships from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The authors thank Prof. Clayton H. Heathcook, University of California, Berkeley, for his interest in our work and Dr. Edson Correa da Silva, Instituto de Física "Gleb Wataghin", Universidade Estadual de Campinas, for the ESR spectra.

References

1. Preliminary communications have been presented at the 3rd Brazilian Meeting on Organic Synthesis, São Carlos, SP, 1989, Abstracts, p. 109 and at the 41st Reunião Anual da Sociedade Brasileira para o Progresso da Ciência, Fortaleza, CE, 1989, Resumos, p. 444.
2. H.E. Simmons, T.L. Cairns, S.A. Vladuchick and C.M. Hoiness, in *Organic Reactions*, vol. 20, W.G. Dauben, (ed) (John Wiley & Sons, New York, 1973), p. 1.
3. Results will be reported in a forthcoming publication.
4. R.D. Smith and H.E. Simmons, *Org. Syntheses Coll. Vol. 5*, 855 (1973).
5. E. LeGoff, *J. Org. Chem.* **29**, 2048 (1964).

6. R.J. Rawson and I.T. Harrison, *J. Org. Chem.* **35**, 2057 (1970).
7. J.M. Denis, C. Girard and J.M. Conia, *Synthesis* **10**, 549 (1972).
8. N. Kawabata, M. Naka and S. Yamashita, *J. Am. Chem. Soc.* **98**, 2676 (1976).
9. B. Fabisch and T.N. Mitchell, *J. Organomet. Chem.* **269**, 219 (1984).
10. E.C. Friedrich, J.M. Domek and R.Y. Pong, *J. Org. Chem.* **50**, 4640 (1985).
11. P. Boudjouk and B.-H. Han, *183rd National Meeting of the American Chemical Society*, Las Vegas, Nevada, 1982, Abstr. No. ORGN 190.
12. O. Repic and S. Vogt, *Tetrahedron Lett.* **23**, 2729 (1982).
13. R.D. Rieke and S.J. Uhm, *Synthesis* **7**, 452 (1975).
14. G.P. Boldrini, D. Savoia, E. Tagliavini, C. Trombini and A. Umami-Ronchi, *J. Org. Chem.* **48**, 4108 (1983).
15. Z. Majerski and P.v.R. Schleyer, *J. Org. Chem.* **34**, 3215 (1969).
16. R.J. Fessenden and J.S. Fessenden, in *Techniques and Experiments for Organic Chemistry*, D.M. Chelton, (ed) (PWS Publishers, Boston, 1983), p. 184.
17. M.M. Jones, *J. Am. Chem. Soc.* **81**, 3188 (1959).
18. (a) *Sadtler Standard Spectra*, n° 2561M, 13244M and 872K (BIORAD Sadtler Division, Philadelphia, PA, 1966);
(b) *The Aldrich Library of Infrared Spectra*, n° 29C, C.J. Pouchert, (ed) (Aldrich Chemical Company, Inc., Milwaukee, 1975).
19. *Beilstein Handbuch der Organischen Chemie*, vol 6 (Springer-Verlag, Berlin, 1923), p.4.
20. E.P. Blanchard and H.E. Simmons, *J. Am. Chem. Soc.* **86**, 1337 (1964).
21. Wittig and Winkler²² reported that bis(halomethyl)zinc, prepared by the reaction of zinc dihalide with diazomethane, transfers the carbene in the absence of an activator rather rapidly to **1**, giving **3** in up to 73% yield after 2 to 5 h of reaction. On the other hand, the organozinc compound formed in the Simmons-Smith reaction is different²² and suffers modifications when the solvent is refluxed²³.
22. G. Wittig and F. Winkler, *Liebigs Ann. Chem.* **656**, 18 (1962); *Chem. Ber.* **97**, 2146 (1964).
23. I.T. Harrison, R.J. Rawson, P. Turnbull and J.H. Fried, *J. Org. Chem.* **36**, 3515 (1971).
24. M.P. Doyle, in *Catalysis of Organic Reactions*, R.L. Augustine, (ed) (Marcel Dekker, Inc., New York, 1986), p. 47.
25. R.D. Rieke, P.T.-J. Li, T.P. Burns and S.T. Uhm, *J. Org. Chem.* **46**, 4323 (1981).
26. W.T. Miller Jr. and C.S.Y. Kim, *J. Am. Chem. Soc.* **81**, 5008 (1959).
27. D.B. Richardson, L.R. Durrett, J.M. Martin Jr., W.E. Putnam, S.C. Slaymaker and I. Dvoretzky, *J. Am. Chem. Soc.* **87**, 2763 (1965).