

Stereoselective Addition of Organocopper Reagents to Cyclic *N*-Acyliminium Ions

Catarina Ludwig and Lars-G. Wistrand* · †

Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Ludwig, C. and Wistrand, L.-G., 1994. Stereoselective Addition of Organocopper Reagents to Cyclic *N*-Acyliminium Ion. – Acta Chem. Scand. 48: 367–371
© Acta Chemica Scandinavica 1994.

Addition of alkylcopper reagents to the chiral *N*-acyliminium ion **2a** occurs with a high degree of *trans* selectivity, in contrast with the addition of π -nucleophiles, where *cis* selectivity has been observed. A mechanism involving the formation of a pre-complex has been proposed in order to account for this selectivity.

N-Acyliminium ions have been shown to be versatile intermediates in the synthesis of naturally occurring alkaloids and amino acids.^{1–6} In particular, intramolecular reactions using chiral *N*-acyliminium ions have been reported to display a high degree of stereoselectivity.^{7,8} Varying degrees of stereoselectivity have been reported using the corresponding intermolecular approach. The problem with the intermolecular reaction is the relative insensitivity of the selectivity to the nucleophile; i.e., the selectivity is determined largely by the structure of the cation. Thus for example, Shono and coworkers have reported that the non-racemic *N*-acyliminium ion **1a** (prepared *in situ* from the corresponding α -methoxy compound **1** by treatment with a Lewis acid) derived from natural (*S*)-proline, reacts with various nucleophiles, e.g., allyltrimethylsilane, vinyl acetate and malonic ester derivatives^{9,10} with essentially identical stereoselectivity (*cis:trans* ~ 7:3, see Scheme 1).¹¹

On the other hand, reaction of the *N*-acyliminium ion **2a** with nucleophiles occurs with a high degree of *cis* selectivity.^{12,13} This has been attributed to stereoelectronically controlled attack on the conformation with an axial ester group, which is the thermodynamically preferred conformation due to A^{1,3} strain.^{14,15} We recently reported that treatment of **1** with alkyl- and alkenyl-copper reagents in the presence of BF₃·Et₂O gives a reversed and increased stereoselectivity.^{16–18} For example, treatment of **1** with two equivalents each of heptylcopper and BF₃·Et₂O gives the corresponding *trans*-5-heptylproline (*cis:trans* = 3:97). A mechanism involving nucleophilic attack on the least hindered face of a sterically biased *N*-acyliminium ion–copper complex was suggested.

Results and discussion

In this report, we present results from the addition of organocopper reagents to the corresponding six-membered ring, i.e., the non-racemic *N*-acyliminium ion **2a**. The precursor to **2a**, the α -methoxylated pipecolic acid derivative **2**, was prepared from L-lysine using a modification of the procedure reported in the literature.^{19,20} Thus, *N*-acylation and esterification of L-lysine gave the protected intermediate **3**, which upon anodic methoxylation (4.5 F mol⁻¹, MeOH–Bu₄NBF₄) furnished the α -methoxy compound **4**. Finally, treatment with *p*-toluenesulfonic acid gave the desired pipecolic acid derivative **2** (Scheme 2). These four steps were carried out without purification of any of the intermediates with an overall yield of 39%.

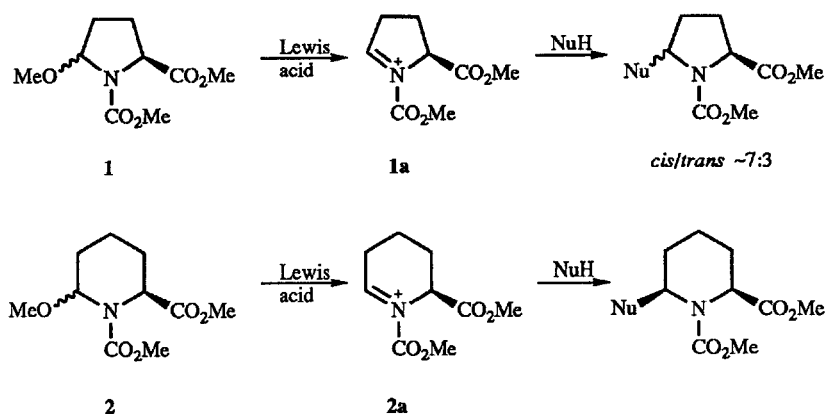
When **2** was reacted with 4 equivalents each of PrCu and BF₃·Et₂O, the formation of two propylated isomers in a 96:4 ratio was observed. In order to identify these isomers, the *cis* compound **6a** was prepared independently by allylation of **2** (allyltrimethylsilane, TiCl₄, CH₂Cl₂, –78°C) followed by hydrogenation (H₂, Pd–C, EtOH). Allylation of **2** has been reported to give exclusive *cis* substitution;^{12,13} in our hands, a *cis:trans* ratio of 95:5 was observed. Gas chromatographic separation of the reaction mixtures established the major isomer in the propylation reaction as the *trans* isomer, **6b** (Scheme 3).

Similar selectivities were observed on butylation and heptylation of **2** using the corresponding alkylcopper reagent in combination with BF₃·Et₂O (Table 1). Thus, alkylation of **2** using alkylcopper reagents gives a reversed selectivity compared with π -nucleophiles, behavior which parallels that of the corresponding proline derivative, **1**.

The identity of **7b** and **8b** was established from their ¹H NMR spectra. In addition to the resemblance to the spectrum of **6b**, the spectra showed the presence of one equatorial proton α to the ester group and one axial proton α

* Author to whom correspondence should be addressed.

† Present address: Nycomed Innovation AB, Ideon Malmö, S-20512 Malmö, Sweden.



Scheme 1.

to the alkyl group as determined by the vicinal coupling constants, consistent with a relative *trans* stereochemistry.²¹ Thus, an intermediate *N*-acyliminium ion–copper(I) complex similar to that suggested for the corresponding proline derivative, shown in Scheme 4, can be invoked in order to rationalize the stereoselectivity of the reaction between **2a** and alkylcopper reagents.

Intermediate copper–alkene π -complexes have been observed²² and isolated²³ in the conjugate addition of organocuprates to α,β -unsaturated esters. Intramolecular coordination of cuprate reagent to oxygen in the conjugate addition of Me_2CuLi to an *ortho*-methoxymethyl cinnamic ester has been suggested.²² One of the resonance forms of *N*-acyliminium ions is actually a cationic aza analogue of an α,β -unsaturated carbonyl compound and thus, an intermediate copper(I)–olefin $d-\pi^*$ complex should be energetically favorable owing to the electron-poor double bond.

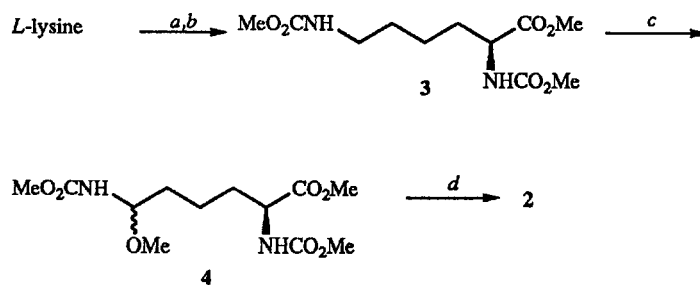
In order to clarify the role of the ester group for coordination in the intermediate complex, we have also investigated the racemic *N*-acyliminium ion precursor **10** which was prepared by a regioselective anodic methoxylation of the corresponding racemic 2-methylpiperidine.²⁴ Reaction of **10** with allyltrimethylsilane in the presence of TiCl_4 gave a 97:3 diastereomeric mixture in favor of the *cis* isomer (in analogy with **2** and as indicated by the ^1H NMR spectrum). Catalytic hydrogenation of **11a** then gave **12a**. Reaction of **10** with PrCu in the presence of

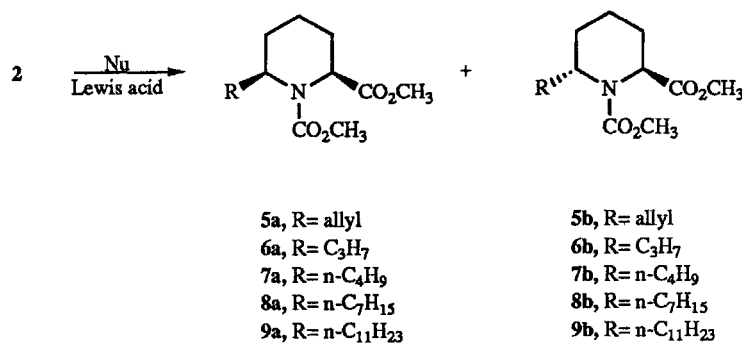
$\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C produced a mixture of **12a** and **12b** in a ratio of 24:76 (Scheme 5). This decrease in selectivity, compared with that observed for **2**, indicates the importance of the ester group for the formation of an intermediate face-selective complex.

In conclusion, we have shown that addition of organocopper reagents to the chiral *N*-acyliminium ion **2a** occurs with a high degree of *trans* selectivity. The possibility of controlling the stereoselectivity by appropriate choice of nucleophile should extend the usefulness of *N*-acyliminium ions in synthetic applications.

Experimental

General. All chemicals used were of highest commercial quality and used without further purification, except as noted. Light petroleum (b.p. $60\text{--}80^\circ\text{C}$) and ethyl acetate, used for chromatography, were distilled before use. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was distilled from CaH_2 before use and stored under an atmosphere of argon. $\text{CuBr} \cdot \text{Me}_2\text{S}$ was prepared according to the method described by House.²⁵ The alkyllithium reagents were prepared from the corresponding alkylbromide and lithium powder in Et_2O at -10°C , and the concentration of the alkyllithium solution (usually around 0.5 M) was determined by titration as described by Watson and Eastham.²⁶ Reaction mixtures were analyzed by capillary GC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a

Scheme 2. a, $\text{ClCO}_2\text{Me}-\text{NaOH}$; b, $\text{HCl}-\text{MeOH}$; c, $-2e$, $\text{MeOH}-\text{Bu}_4\text{NBF}_4$; d, TSOH.



Scheme 3.

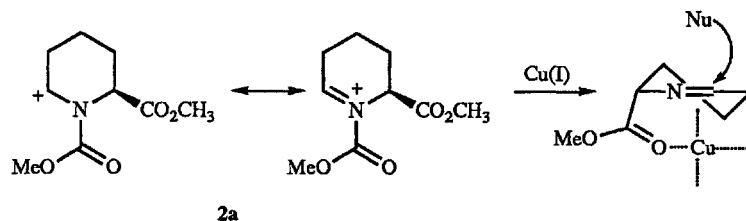
25 m × 0.25 mm OV 1701 column and by TLC on commercially available silica gel/aluminium foil plates. Flash chromatography was performed on TLC grade gel according to Taber.²⁷ ¹H NMR spectra were recorded in CDCl₃ on a Varian XL 300 instrument unless otherwise stated, δ being given in ppm downfield from SiMe₄ and coupling constants in hertz. Optical rotations were determined on a Perkin-Elmer 141 instrument. High resolution mass spectra [MS(hr)] were obtained using a Jeol SX 102 instrument, with direct inlet.

(2S)-Dimethyl 6-methoxypiperidine-1,2-dicarboxylate **2**. The *N*-acyliminium ion precursor **2** was prepared in four steps without purification of the intermediates. To a stirred solution of L-lysine (0.1 mol, 18.2 g) in 2 M aq. NaOH (100 ml) was added simultaneously methyl chloroformate (0.2 mol) in toluene (25 ml) and 100 ml of 2 M aq. NaOH. After being stirred for 1 h, the mixture was cooled to 0°C and acidified with 4 M aq. HCl. The mixture was extracted with EtOAc which was then dried (MgSO₄) and evaporated, giving 23 g of crude product.

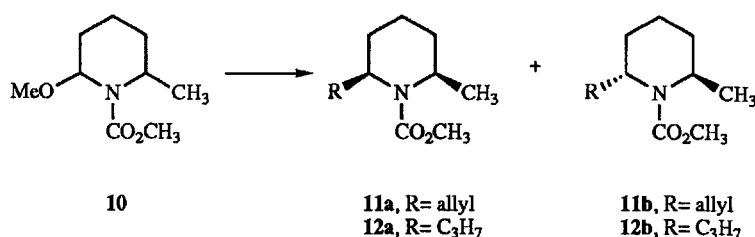
The *N*-protected L-lysine was then dissolved in MeOH (1000 ml), cooled to 0°C and the solution was saturated with HCl (g). The mixture was stirred overnight and then evaporated. The residue was dissolved in CH₂Cl₂ and anhydrous K₂CO₃ was added with stirring. The mixture was filtered and evaporated to give **3** (21.8 g) as a white solid. Anodic oxidation of the crude product (40 mmol, 11.0 g) in MeOH–Bu₄NBF₄ (0.05 M) using an undivided cell and graphite electrodes was then carried out. The reaction was monitored by TLC and was interrupted af-

ter 4.5 F mol⁻¹. The solution was evaporated and triturated with diethyl ether which was filtered and evaporated to give 11.6 g of crude product. The product was dissolved in MeOH and *p*-toluenesulfonic acid (5.9 g, 31 mmol) was added. The reaction was monitored by TLC and, after 35 min, the reaction was complete and CH₂Cl₂ was added. The mixture was extracted with aq. satd. NaHCO₃, H₂O, dried (MgSO₄) and evaporated. Purification by column chromatography (silica gel, light petroleum–ethyl acetate 3:2) gave **2** (4.57 g, 39% from L-lysine) as a colorless liquid. ¹H NMR (300 MHz): δ 5.44 (s, 0.5 H), 5.26 (s, 0.5 H), 4.89 (s, 0.5 H), 4.7 (s, 0.5 H), 3.76, 3.74 (2 s, 3 H), 3.70 (s, 3 H), 3.30, 3.27 (2 s, 3 H), 2.12–2.38 (m, 1 H), 1.68–1.98 (m, 2 H), 1.4–1.68 (m, 3 H).

General procedure for reaction of 2 with alkylcopper reagents. To a stirred solution of CuBr·Me₂S (12 mmol) in anhydrous diethyl ether (40 ml) was added dropwise a solution of the appropriate alkyllithium in diethyl ether (12 mmol) at –25°C. After stirring for 30 min, the mixture was cooled to –70°C and BF₃·Et₂O (12 mmol) was added dropwise. After 5 min, a solution of **2** (3.03 mmol) in anhydrous diethyl ether (5 ml) was added dropwise and after 10 min, the reaction mixture was allowed to reach ambient temperature. The reaction was quenched with a mixture of satd. aq. NH₄Cl and conc. NH₃ (1:1) and stirred for 1 h. The ether layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined phases were washed with satd. aq. NaHCO₃, dried (MgSO₄), filtered and evaporated.



Scheme 4.



Scheme 5.

(2S,6R)-Dimethyl 6-propylpiperidine-1,2-dicarboxylate (6b)

The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 7:3) to give **6b** as a colorless liquid. Yield: 58%. ¹H NMR (300 MHz, 40 °C): δ 4.48 (t, *J* 5.9, 1 H), 4.06 (dddd, *J* 7.7, 5.2, 5.2, 2.6, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 1.84–2.03 (m, 2 H), 1.40–1.84 (m, 6 H), 1.21–1.40 (m, 2 H), 0.93 (t, *J* 7.3, 3 H). MS (hr): 200.0923, calc. for C₁₂H₂₁O₄N–C₃H₇: 200.0923. $[\alpha]_{\text{D}}^{25} = -41.6$ (*c* 0.6, MeOH).

(2S,6R)-Dimethyl 6-butylpiperidine-1,2-dicarboxylate (7b)

The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 3:1) to give **7b** as a colorless liquid. Yield: 82%. ¹H NMR (300 MHz, 50 °C): δ 4.19 (t, *J* 5.8, 1 H), 4.04 (dddd, *J* 8.2, 5.5, 5.5, 2.6, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 1.89–2.01 (m, 2 H), 1.78–1.85 (m, 1 H), 1.40–1.78 (m, 5 H), 1.21–1.40 (m, 4 H), 0.90 (t, *J* 6.9, 3 H). MS (hr): 257.1641, calc. for C₁₃H₂₃O₄N: 257.1627. $[\alpha]_{\text{D}}^{25} = -48.9^{\circ}$ (*c* 1.0, MeOH).

(2S,6R)-Dimethyl 6-heptylpiperidine-1,2-dicarboxylate (8b)

The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 3:1) to give **8b** as a colorless liquid. Yield: 78%. ¹H NMR (300 MHz, 50 °C): δ 4.18 (t, *J* 5.9, 1 H), 4.03 (dddd, *J* 7.8, 5.3, 5.3, 2.8, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 1.82–2.11 (m, 2 H), 1.38–1.82 (m, 6 H), 1.18–1.34 (m, 10 H), 0.86 (t, *J* 6.6, 3 H). MS (hr): 299.2102, calc. for C₁₆H₂₉O₄N: 299.2097. $[\alpha]_{\text{D}}^{25} = -30.0^{\circ}$ (*c* 1.0, MeOH).

(2S,6R)-Dimethyl 6-undecylpiperidine-1,2-dicarboxylate (9b)

The crude product was purified by distillation in a Kugelrohr apparatus followed by column chromatography (silica gel; light petroleum–ethyl acetate 4:1) to give **9b** as a colorless liquid. Yield: 86%. ¹H NMR (300 MHz): δ 4.11–4.21 (m, 1 H), 4.02–4.09 (m, 1 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 1.91–2.02 (m, 2 H), 1.40–1.81 (m, 7 H), 1.22–1.33 (m, 17 H), 0.90 (t, *J* 6.6, 3 H). MS (hr): 355.2723, calc. for C₂₀H₃₇O₄N: 355.2723. $[\alpha]_{\text{D}}^{25} = -31.9^{\circ}$ (*c* 1.0, MeOH).

(2S,6S)-Dimethyl 6-allylpiperidine-1,2-dicarboxylate (5a)

To a stirred solution of **2** (0.70 g, 3.03 mmol) in CH₂Cl₂ (25 ml) at –70 °C was added allyltrimethylsilane (0.96 ml, 6.06 mmol) and TiCl₄ (0.33 ml, 3.03 mmol).

After 40 min, the reaction was complete as monitored by TLC and was allowed to reach ambient temperature. After being stirred with solid Na₂CO₃·10 H₂O, and dried (MgSO₄), the solution was filtered through Celite and evaporated. The product was used without further purification.

(2S,6S)-Dimethyl 6-propylpiperidine-1,2-dicarboxylate (6a)

was prepared by hydrogenation at atmospheric pressure of **5a** in MeOH (25 ml) using palladium-on-carbon (10%, 100 mg) as the catalyst. The reaction mixture was filtered through Celite and the solvent was evaporated off. The product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 4:1) to give a mixture of **6a** and **6b** in a ratio of 95:5 as determined by GLC analysis. Yield: 60% from **2**. ¹H NMR (300 MHz): 4.86 (br s, 1 H), 4.19 (m, 1 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 2.2–2.35 (m, 1 H), 1.42–1.70 (m, 6 H), 1.21–1.40 (m, 3 H), 0.87 (t, *J* 7.1, 3 H). MS (hr): 200.0919, calc. for C₁₂H₂₁O₄N–C₃H₇: 200.0923. $[\alpha]_{\text{D}}^{25} = -69.1^{\circ}$ (*c* 1.0, MeOH).

Methyl 2-methyl-6-propylpiperidine-1-carboxylate (12a) was prepared from **10** using the same method as for **6a**. The crude product was purified by column chromatography using light petroleum–ethyl acetate (7:3) as the eluent. Yield: 84% from **10**. ¹H NMR (300 MHz): δ 4.31 (p, *J* 6.3, 1 H), 4.10 (q, *J* 6.1, 1 H), 3.66 (s, 3 H), 1.21–1.80 (m, 10 H), 1.15 (d *J* 7.0, 3 H), 0.89 (t, *J* 7.2, 3 H). Reaction of **10** with PrCu was performed using the same procedure as described above and gave a mixture of **12a** and **12b** (24:76). Purification by column chromatography (silica gel; light petroleum–ethyl acetate 7:3) gave **12a/12b** in 37% yield. ¹H NMR (**12b**, 300 MHz): δ 3.81–3.97 (m, 2 H), 3.67 (s, 3 H), 1.27–1.93 (m, 10 H), 1.25 (d *J* 6.6, 3 H), 0.91 (t, *J* 7.2, 3 H). MS (hr): 199.1557, calc. for C₁₁H₂₁O₂N: 199.1573.

Acknowledgements. Financial support from the Swedish Natural Science Research Council and the Technical Research Council is gratefully acknowledged.

References

- For a review of *N*-acyliminium ion chemistry, see: Zaugg, H. E. *Synthesis* (1984) 85 and 181.

2. Shono, T. *Top. Curr. Chem.* 148 (1988) 131.
3. Overman, L. E. and Heitz, M. P. *J. Org. Chem.* 54 (1989) 2591.
4. Renaud, P. and Seebach, D. *Helv. Chim. Acta.* 69 (1986) 1704.
5. Thaning, M. and Wistrand, L.-G. *J. Org. Chem.* 55 (1990) 1406.
6. Polniaszek, R. P. and Belmont, S. E. *J. Org. Chem.* 55 (1990) 4688.
7. Speckamp, W. N. and Hiemstra, H. *Tetrahedron* 41 (1985) 4367.
8. Chamberlin, A. R. and Chung, J. Y. L. *J. Org. Chem.* 50 (1985) 4425.
9. Shono, T., Matsumura, Y., Tsubata, K. and Uchida, K. *J. Org. Chem.* 51 (1986) 2590.
10. Asada, S., Kato, M., Asai, K., Ineyama, T., Nishi, S., Izawa, K. and Shono, T. *J. Chem. Soc., Chem. Commun.* (1989) 486.
11. However, Shono *et al.* recently reported that the selectivity of nucleophilic addition to **1a** could be manipulated by changing the alcohol part of the ester function: Shono, T., Fujita, T. and Matsumura, Y. *Chem. Lett.* (1991) 81.
12. Shono, T., Matsumura, Y., Tsubata, K. and Uchida, K. *J. Org. Chem.* 51 (1986) 2590.
13. Shono, T., Matsumura, Y., Onomura, O. and Sato, M. *J. Org. Chem.* 53 (1988) 4118.
14. Brown, J. D., Foley, M. A. and Comins, D. L. *J. Am. Chem. Soc.* 110 (1988) 7445.
15. Comins, D. L. and Foley, M. A. *Tetrahedron Lett.* 29 (1988) 6711.
16. Skrinjar, M. and Wistrand, L.-G. *Tetrahedron Lett.* 31 (1990) 1775.
17. Wistrand, L.-G. and Skrinjar, M. *Tetrahedron* 47 (1991) 573.
18. Thaning, M. and Wistrand, L.-G. *Acta Chem. Scand.* 46 (1992) 194.
19. Shono, T., Matsumura, Y. and Inoue, K. *J. Chem. Soc., Chem. Commun.* (1983) 1169.
20. Irie, K., Aoe, K., Tanaka, T. and Saito, S. *J. Chem. Soc., Chem. Commun.* (1985) 633.
21. For reviews of synthetic approaches to substituted piperidines, see: Baliah, V., Jeyaraman, R. and Chandrasekaran, L. *Chem. Rev.* 83 (1983) 379; Wang, C.-L. J. and Wuonola, M. A. *Org. Prep. Proced.* 24 (1992) 585.
22. Christenson, B., Olsson, T. and Ullenius, C. *Tetrahedron* 45 (1989) 523.
23. Corey, E. J. and Boaz, N. W. *Tetrahedron Lett.* 26 (1985) 6015.
24. Shono, T., Matsumura, Y. and Tsubata, K. *J. Am. Chem. Soc.* 103 (1981) 1172.
25. House, H. O., Chu, C.-Y., Wilkins, J. M. and Ulmen, M. J. *J. Org. Chem.* 40 (1975) 1460.
26. Watson, S. C. and Eastham, J. F. *J. Organomet. Chem.* 9 (1975) 165.
27. Taber, D. F. *J. Org. Chem.* 47 (1982) 1351.

Received November 3, 1993.