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# Highly Regio and Stereoselective Preparation of *Z* Silyl Enol Ethers and *Z* Enol Esters from Ketones via Manganese Enolates[1].

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***Abstract:*** *Mn-enolates are easily and quantitatively obtained under mild conditions (THF, -10°C to rt, 1h) by treatment of ketones with aromatic Mn-amides such as Ph(Me)NMnZ. They allow to prepare Z silyl enol ethers and Z enol esters in high yields and with an excellent regio- and stereoselectivity (kinetic product: ≥ 99%, Z/E: 93/7 to 100/0).*

Silyl enol ethers are very versatile intermediates in organic synthesis,[2] as an example, pure *Z* or *E* enoxysilanes have been used to perform stereoselective aldol addition reactions[3]. Their preparation has been extensively studied and frequently involves the silylation of metal enolates. As a rule, good yields are obtained, the two main problems are the control of the stereoselectivity and, in the case of unsymmetrical ketones, the control of the regioselectivity during the enolization step. Thus, to obtain mainly the *Z* Li-enolates, the ketones must generally be treated with Li-amides at low temperature (-78°C) in the presence of HMPA[4].

In this communication we show that Mn-enolates, a new class of metal enolates which are easily prepared in THF by regio- and stereoselective[5] deprotonation of ketones with Mn-amides under mild conditions[6] (-10°C to rt), readily react with $Me_3SiCl$ to give the *Z* silyl enol ethers with a high selectivity in good yields (Table 1, entries 1, 2, 4 to 6). Moreover, the regioselectivity in favour of the kinetic product is excellent (Entries 3 and 6).

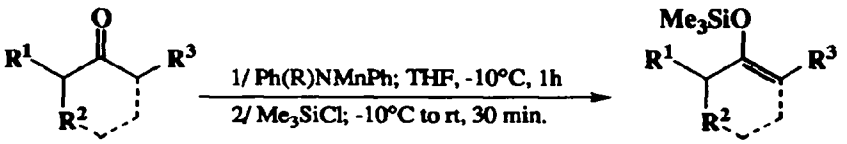


**Table 1.** Regio and Stereoselective Preparation of *Z* Silyl Enol Ethers via Kinetic Mn-Enolates[7].

| Entry | Ketone | Mn-Amide[a] | Yield, %[b] | Z/E[c] | A/B[c,d] |
|---|---|---|---|---|---|
| 1 | EtCOEt | Ph(Me)NMnBu | 74 | 93/7 | - |
| 2 | BuCOBu | Ph(Me)NMnPh | 92 | 97/3 | - |
| 3 | 2-Me-cyclohexanone | Ph(Bu)NMnBr | 90 | - | 99/1[e] |
| 4 | t-BuCOBu | Ph(Me)NMnBu | 87 | 100/0 | - |
| 5 | PhCOPr | Ph(Me)NMnPh | 92 | 98/2 | - |
| 6 | i-PrCOHex | " | 90 | 97/3 | 99/1 |

a/ 1.05 equiv. of Mn-amide are used. For a typical procedure see note 7. b/ Yield of distilled product. c/ Determined by GLC[8] and $^1H$ NMR (400 MHz). d/ Ratio kinetic/thermodynamic products. e/ Reaction performed in ether in the presence of 4 equiv. TMEDA (see Table 6).

To obtain good yields of silyl enol ethers, it is essential to deprotonate the ketones with Mn-amides prepared from aromatic amines ($Ar_2NH$ or ArRNH) since Mn-dialkylamides are clearly less efficient (Table 2 ).

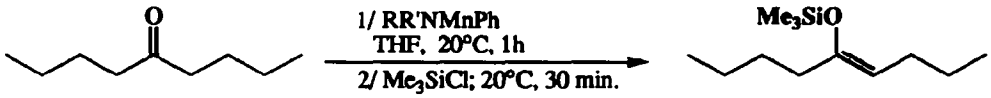


**Table 2.** Deprotonation of 5-Nonanone with N-Aryl and N-Alkyl Mn-Amides.

| Mn-Amide[a] | $Bu_2NMnPh$ | $i\text{-}Pr_2NMnPh$ | Ph(Bu)NMnPh | Napht(Me)NMnPh | $Ph_2NMnPh$ |
|---|---|---|---|---|---|
| Yield, %[b] | 43 | 40 | 93 | 95 | 95 |

a/ 1.05 equiv. of Mn-amide are used b/ Yield of distilled trimethylsilyl enol ether.

In most cases, organomanganese amides RR'NMnR"[9] (Table 3, entry 7) as well as alcoxymanganese amides[9] (Entry 8), halomanganese amides RR'NMnX[9] (Entry 9) and manganese diamides $(RR'N)_2Mn$[9] (0.5 equiv., entry 10) can be used indifferently albeit with these three later the rate of deprotonation is lower[10]. This difference is only important in the case of reactive ketones such as diethyl ketone since the enolization step must be performed with organomanganese amides to suppress the competing aldol addition reaction (Entries 11 and 12). With the very reactive cyclopentanone or methyl ketones the formation of the aldol products cannot be avoided whatever the nature of the Mn-amide (Entry 13).

**Table 3.** Deprotonation of Ketones with Mn-Amides: Influence of the Nature of Ph(Me)NMnZ[a].

| Entry | Ketone | Mn-Amide[a] | Yield, %[b] |
|---|---|---|---|
| 7 | BuCOBu | Ph(Me)NMnPh | 92 |
| 8 | " | Ph(Me)NMnOEt | 92 |
| 9 | " | Ph(Me)NMnCl | 90 |
| 10 | " | 0.5 $[Ph(Me)N]_2Mn$ | 90 |
| 11 | EtCOEt | Ph(Me)NMnPh | 90 |
| 12 | EtCOEt | Ph(Me)NMnCl | 24 |
| 13 | HeptCOMe | Ph(Me)NMnPh | < 5 |

a/ 1.05 equiv. of Mn-amide are used. b/ Yield of distilled trimethylsilyl enol ether.

At room temperature, the deprotonation of ketones with Ph(Me)NMnPh mainly gives the *Z* Mn-enolates (Table 4, entry 14). Interestingly, it is possible to form almost exclusively the *Z* isomer by lowering the temperature of the reaction mixture (Entries 15 and 16).

**Table 4.** Deprotonation of 5-Nonanone with Ph(R)NMnPh[a]: Influence of the Nature of R on the Stereoselectivity of the Reaction.

| Entry | R | Reaction Conditions[b] | Yield, %[c] | Z/E[d] |
|---|---|---|---|---|
| 14 | Me | 20°C, 15 min. | 90 | 77/23[e] |
| 15 | " | 0 to -10°C, 1h | 92 | 97/3 |
| 16 | " | -50°C, 2h | 79 | 99/1 |
| 17 | Bu | 20°C, 1h | 92 | 8119 |
| 18 | " | 0 to -10°C | 91 | 99/1 |
| 19 | Ph | 20°C, 1h | 84 | 95/5 |
| 20 | $Et_2CH$ | 20°C, 1h | 69 | 65/35 |

a/ 1.05 equiv. of Mn-amide are used b/ The silylation was performed at the same temperature c/ Yield of distilled product. d/ Determined by GLC[8] and $^1H$ NMR (400 MHz). e/ 83/17 from Ph(Me)NMnCl.

The stereoselectivity can also be improved by increasing slightly the size of the amino group of PhRNMnZ (for instance, when R= Bu or Ph instead of Me, entries 14, 17 and 19). However, a too bulky R group (R= $Et_2CH$, entry 20) leads to a lower selectivity. From a practical point of view, it is worthy of note that good yields and selectivities (Z ≥ 99%) can be obtained between 0°C and -10°C by using a Mn-amide prepared from the commercially available N-methyl or N-butylaniline (Entries 15 and 18).

The deprotonation of ketones with Mn-amides principally affords the less substituted regioisomer (kinetic regioisomer). The regioselectivity of the reaction depends on two major factors, the size of the amino moiety of the Mn-amide and the nature of the solvent.

The results obtained from various manganese aryl alkyl amides PhRNMnZ (Table 5) show that the regioselectivity clearly depends on the size of the aryl and alkyl groups Ar (see entry 21 and note d) and R (Entries 21 to 28). Nevertheless, when the steric hindrance becomes too important, the regioselectivity and above all the yield decreases (Entry 24). As a rule, the best results are obtained with Mn-amides prepared from N-butyl aniline (Entry 25). In some cases, for example with 2-methyl cyclohexanone, the regioselectivity can be slightly increased by using a N-β-branched alkyl aniline (Entries 26 to 28).

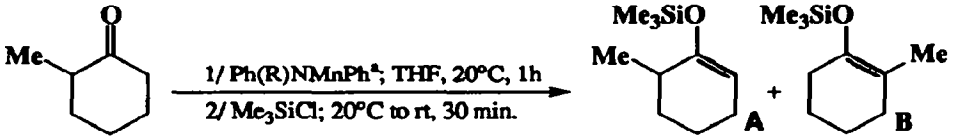


Table 5. Deprotonation of 2-Methylcyclohexanone with Ph(R)NMnPh[a]: Influence of the Nature of R on the Stereoselectivity of the Reaction.

| Entry | R | Yield, %[b] | A/B[c] | Entry | R | Yield, %[b] | A/B[c] |
|---|---|---|---|---|---|---|---|
| 21 | Me[d] | 90 | 84/16[d] | 25 | Bu | 93 | 93/7 |
| 22 | Et | 91 | 92/8 | 26 | $Me_2CHCH_2$ | 81 | 95/5 |
| 23 | i-Pr | 75 | 98/2 | 27 | $Et_2CHCH_2$ | 90 | 96/4 |
| 24 | $Et_2CH$ | 60 | 90/10 | 28 | $PhCH_2$ | 84 | 97/3 |

a/ 1.05 equiv. of Mn-amide are used. b/ Yield of distilled product. c/ Determined by GLC[8] and $^1H$ NMR (400 MHz). d/ When Ar= naphtyl instead of Ph for R=Me; yield: 94%, A/B: 91/9.

All our numerous attempts to replace THF by another solvent have led to a similar or very often to a lower regioselectivity. In addition these experiments frequently gave low yields. The only interesting results have been observed when the deprotonation was performed in a mixture ether/tertiary amine (Table 6). With the appropriate Mn-amide, the kinetic enolates are then formed exclusively (Entry 33). It should be noted that the amine can even be used as ligand (TMEDA, 4 equiv., entries 31 and 33).

Table 6. Deprotonation of 2-Methylcyclohexanone with Ph(R)NMnPh: Influence of the Nature of the Solvent on the Stereoselectivity of the Reaction.

| Entry | Mn-Amide[a] | Solvent | Yield, %[b] | A/B[c] |
|---|---|---|---|---|
| 29 | Ph(Me)NMnCl | THF | 86 | 83/17 |
| 30 | Ph(Me)NMnBr | Ether/$Et_3N$ (3/1) | 74 | 90/10 |
| 31 | Ph(Me)NMnBr | Ether/TMEDA (4 equiv.) | 89 | 92/8 |
| 32 | Ph($Et_2CHCH_2$)NMnCl | THF | 93 | 94/5 |
| 33 | Ph($Et_2CHCH_2$)NMnBr | Ether/TMEDA (4 equiv.) | 90 | > 99/1 |

a/ 1.05 equiv. of Mn-amide are used. b/ Distilled product. c/ Determined by GLC[8] and $^1H$ NMR (400 MHz).

As illustrated above, Mn-enolates are easily silylated. They can also be acylated regio- and stereoselectively by carboxylic acid anhydrides to give the corresponding enol esters in good yields (Table 7).

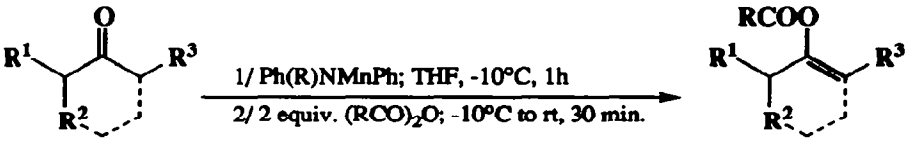


**Table 7.** Regio and Stereoselective Preparation of *Z* Enol Esters via Kinetic Mn-Enolates.

| Entry | Ketone | Mn-Amide[a] | R | Yield, %[b] | Z/E[c] | A/B[c,d] |
|---|---|---|---|---|---|---|
| 34 | EtCOEt | Ph(Me)NMnPh | Pent | 90 | 96/4 | - |
| 35 | i-PrCOHex | Ph(Bu)NMnMe | Et | 95 | 93/7 | 99/1 |
| 36 | 2-Me cyclohexanone | Ph(Bu)NMnCl | Me | 92 | - | 99/1 |

a/ 1.05 equiv. of Mn-amide are used. b/ Yield of distilled product. c/ Determined by GLC[8] and $^1H$ NMR (400 MHz). d/ Ratio kinetic/thermodynamic products.

In conclusion, the regio- and stereoselective preparation of *Z* silyl enol ethers and *Z* enol esters from ketones is easily performed in high yields and under mild conditions via Mn-enolates. From a preparative point of view, it is an interesting new route to these intermediates which have a large field of application in organic synthesis. It should be noted that the obtention of pure *Z* or *E* silyl enol ethers is of great interest in diastereoselective synthesis.[3] Our results on the aldol and Michael addition reactions of Mn-enolates will be published soon.

**Notes and References.**


1. Organomanganese reagents XXVIII, for Part XXVII: Cahiez, G.; Chau, K. and Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3069-3072. The regioselective monoalkylation of ketones via Mn-enolates has been described in part XXVII and in reference 6a. The preparation of Mn-enolates by deprotonation of ketones and by transmetallation from other metal enolates (especially Li-enolates) as well as some of their reactions have been patented.[6b, c]
2. Rasmussen, J. K. *Synthesis* **1977**, 91-110. Brownbridge, P. *Synthesis* **1983**, 1-28 and 85-104.
3. Heathcock, C. H. in *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press, Inc.: Orlando, 1984, vol. 3, 111- 211.
4. Ireland, R. E.; Mueller, R. H. and Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
5. We have mentionned the stereoselectivity of the deprotonation of ketones with Mn-amides in reference 6a, note 6. It should be noted that the reference at the end of this note is 3 instead of 2 as indicated by error.
6. a/ Cahiez, G.; Figadère, B. and Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3065-3068. b/ Cahiez, G.; Figadère, B.; Tozzolino, P.; Cléry, P. *Fr. Pat. Appl.* **1988**, 88/15,806; *Eur. Pat. Appl.* **1990**, EP 373,993; *CA* **1991**, *114*, 61550y. c/ Cahiez, G.; Cléry, P.; Laffitte, J. A. *Fr. Pat. Appl.* **1990**, 90/16413 and **1991**, 91/11814; *PCT Int. Appl.* **1993** WO 93/06071; *CA* **1993**, *118*, P:169340b and *119*, P:116519f.
7. **Typical Procedure:** Preparation of Z-2-Methyl-3-trimethylsilyloxy-3-nonene (Table I, entry 6). A solution of 52.5 mmoles of PhMnN(Me)Ph was prepared by stirring, at room temperature for 30 min., 52.5 mmoles of $MnCl_2$•2LiCl, 52.5 mmoles of Ph(Me)NLi and 52.5 mmoles of PhLi/ether in 80 ml of THF. At -10°C, 50 mmoles of iPrCOHex and, after 30 min., 55mmoles of $Me_3SiCl$ were added. The reaction mixture was stirred for 30 min. then hydrolyzed (2 ml $Et_3N$ then 60 ml $H_2O$). After usual work-up, the product was isolated by distillation (90°C/7 torr) in 90% yield (regioselectivity : 98%, *Z/E*: 97/3).
8. The *Z* and *E* isomers are easily separated on a capillary column OV-1, 25 m x 0,33 mm i.d., 0.5 µm film thickness.
9. For the preparation of Mn-amides see ref. 6a and also patents 6b and 6c.
10. The rate of deprotonation and the yields of Mn-enolates also depend on the presence of LiX in the reaction mixture. Thus, to obtain the best results, at least two equivalents of LiCl are necessary with RR'NMnCl and three equivalents with RR'NMnR". In some cases, it is possible to improve the yield by heating. Thus, the deprotonation of 3-methylcyclohexanone by Ph(Me)NMnPh gave better yields at 60°C (65% of silyl enol ether) than at -10°C (only 15%).


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