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# Highly Regioselective Monoalkylation of Ketones via Manganese Enolates Prepared from Manganese Amides[1].

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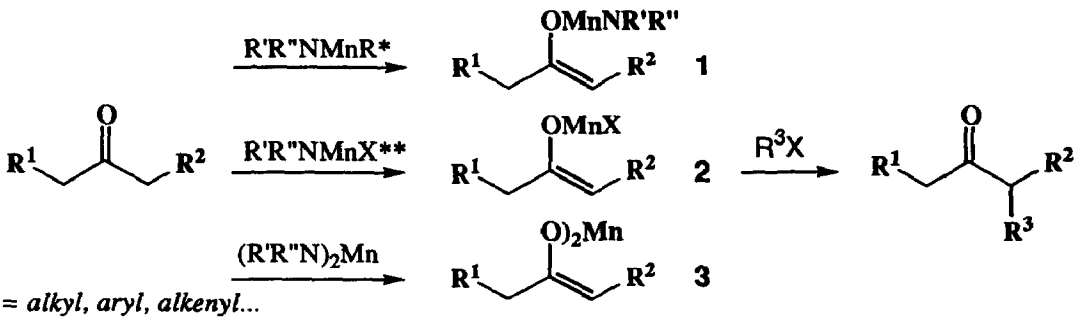
***Abstract:*** *Ketones are regioselectively converted to Mn-enolates by treatment with Mn-amides such as Ph(Me)NMnCl in THF at 20°C. Mn-enolates can then be regioselectively monoalkylated in good yields. The formation of di or polyalkylated products is never observed (< 1%).*

A communication about the alkylation of Mn-enolates recently published in this journal[2] prompts us to claim our clear anteriority in the field since, for some years, we have extensively studied and patented the preparation of Mn-enolates by deprotonation of ketones with Mn-amides or by transmetallation from Li, Na, Mg or K-enolates as well as their use in organic synthesis (including for the monoalkylation of ketones).[3,]

The α-alkylation of ketones via their metal enolates is a very challenging and important reaction in organic synthesis.[4] Li-enolates, generally prepared by deprotonation with LDA, have been used for this purpose extensively. The two major problems generally encountered are the formation of di or polyalkylated side-products in substantial amounts and, with unsymmetrical ketones, a low control of the regioselectivity.[3 , 5]

In this communication, we show that these drawbacks can be almost completely avoided by using Mn-enolates **1**, **2** or **3**, a new class of metal enolates easily prepared regio and stereoselectively[6] by treatment of ketones with Mn-amides (Scheme I).

**Scheme I. Regioselective Preparation and Monoalkylation of Mn-Enolates.**




**R = alkyl, aryl, alkenyl...*
***X = Cl, Br.*

Manganese amides R'R"NMnZ are easily prepared in THF, by reacting an organolithium with a mixture of $MnCl_2$[7]-R'R"NH at 20°C. Depending on the ratio used between the reactants, it is

possible to prepare the chloromanganese amides **4**, the organomanganese amides **5** or the manganese diamides **6** (Scheme II).

**Scheme II. Preparation of Mn-Amides.**

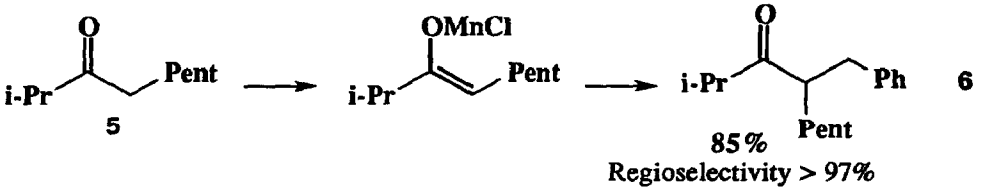
$$x\ RLi + MnCl_2{\cdot}2\ LiCl + R'R''NH \xrightarrow[0°C\ to\ 20°C,\ 15\ min.]{THF} \begin{matrix} R'R''NMnCl{\cdot}3\ LiCl \quad \mathbf{4}\ (x=1) \\ or \\ R'R''NMnR{\cdot}4LiCl \quad \mathbf{5}\ (x=2) \end{matrix}$$

$$2\ RLi + MnCl_2{\cdot}2\ LiCl + 2\ R'R''NH \xrightarrow[0°C\ to\ 20°C,\ 15\ min.]{THF} (R'R''N)_2Mn{\cdot}4\ LiCl \quad \mathbf{6}$$

Contrary to their lithium counterparts, Mn-amides can be stored, under inert atmosphere, at room temperature in THF for several months.[8] The three types of Mn-amides have been used successfully. It is important to note that only the Mn-amides prepared from aromatic amines lead to quantitative yields of Mn-enolates in THF.[9]

The regioselectivity of the enolization closely depends on the nature of the amino group , it can be controlled by varying the size of the R" alkyl group. Thus, an excellent regioselectivity, in favour of the kinetic enolate, can generally be obtained with both cyclic and acyclic ketones (Scheme III and Table II ) by using an N-butyl N-phenyl manganese amide (R"= Bu). In some cases, for instance with the 2-methylcyclohexenone, the regioselectivity can be slightly improved when R" is a β-branching alkyl group such as $Et_2CHCH_2$ (Table II, entry 16). We have observed that in the presence of an excess of the starting ketone, the equilibration of the Mn-enolate occured only very slowly.[10] Therefore, it is much easier to obtain selectively the kinetic Mn-enolates than the kinetic Li-enolates.

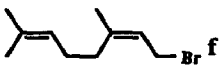
**Scheme III.**




***Typical Procedure:*** The ketone **5** (50 mmol) was added to a solution of ClMnN(Bu)Ph in THF (60 mmol/80 ml) at 20°C. After 1h, DMSO (40 ml) and benzyl bromide (65 mmol) were successively added. The reaction mixture was stirred 1h at 20°C then hydrolyzed (60 ml HCl 1M). After usual work-up, **6** was isolated by distillation (131°C/0.2 torr) in 85% yield (regioselectivity : 97%).

In THF, Mn-enolates can be alkylated (Table I, entries 1 and 5) but the reaction occurs slowly and often gives moderate yields. Numerous polar cosolvents can be added to increase the alkylation rate and to obtain better yields (Table I, entries 6 and 7 and note d). Interestingly, excellent results are obtained with NMP or DMSO, two very cheap and non toxic solvents. Under these conditions, Mn-enolates react with a wide range of alkylating agents to lead to the monoalkylated ketones in excellent yields (Table I). It is interesting to note that the substitution of allylic halides ($S_N2$) occurs stereospecifically (Table I, note f).

**Table I : Monoalkylation of Mn-Enolates Obtained by Treatment of Ketones with Mn-Amides.**

| Entry | Ketone | Mn-Amide[a] | Solvent (Alkylation step) | Temperature | Alkylating Agent[b] | Yield[c] |
|---|---|---|---|---|---|---|
| 1 | BuCOBu | Ph(Me)NMnCl | THF | 20°C | MeI | 57% |
| 2 | | " | THF/DMSO | " | " | 86% |
| 3 | | Ph(Me)NMnMe | " | " | " | 93% |
| 4 | | $[Ph(Me)N]_2Mn$ | " | " | " | 89% |
| 5 | PrCOPr | Ph(Me)NMnCl | THF[d] | 20°C | $PhCH_2Br$ | 43% |
| 6 | " | " | THF/NMP | " | " | 86% |
| 7 | " | " | THF/DMSO | " | " | 91% |
| 8 | " | Ph(Me)NMnZ[e] | THF/DMSO | 50°C | BuI | 67% |
| 9 | " | " | THF/NMP | 20°C | $CH_2=CHCH_2Br$ | 81% |
| 10 | " | " | THF/DMSO | " | $PhCH=CHCH_2Br$ | 86% |
| 11 | " | " | " | " |  [f] | 87% |
| 12 | " | " | THF/NMP | -30°C | $BrCH_2COOEt$ | 88% |
| 13 | " | " | " | -30°C | BrCH(Me)COOEt | 64% |

a/ Enolization step: 1.1 equiv. of Mn-amide, THF, 20°C, 1h. b/ 1.25 equiv., 1h (entries 1 and 8, 3h). c/ Isolated product. d/ THF/DMF: 80%, THF/sulfolane: 83%, THF/DMPU: 85%. e/ Z= Cl or Me f/ The alkylation ($S_N2$) takes place with retention of the configuration of the double bond (>99% Z).

With the Mn-enolates **2** and **3**, the formation of di or polyalkylated ketones has never been observed (< 1%). On the other hand, with the amino enolate **1**, two side reactions occured sometimes; the formation of the alkylated amine and the formation of dialkylated products due to the enolization of the monoalkylated ketone by the amide moiety (OMnNR'R"). Fortunately, the enolate **1** (R'= Ph, R"= Me) generally reacts selectively with one equivalent of allyl bromide in THF to give an allylamine ($R'R"NCH_2CH=CH_2$) and the enolate **2** which is then easily and cleanly monoalkylated. In addition, it is thus possible to use only a stoichiometic amount of alkylating reagent.

**Table II. Regioselective Deprotonation of Unsymmetrical Ketones[a] with Mn-Amides[b] and Regioselective Monoalkylation of the resulting kinetic Mn-Enolates.**

| Entry | Ketone | Alkylating Agent[c] | Monoalkylated Ketone[d] | Regioselectivity[e] |
|---|---|---|---|---|
| 14 | i-PrCOHex | $CH_2=CHCH_2Br$ | 80% | > 99:1 |
| 15 | $PhCH_2(Et)CHCOPr$ | $CH_2=CHCH_2Br$ | 89% | > 99:1 |
| 16 | 2-Me-Cyclohexanone | $PhCH_2Br$ | 90% | 93:7 |

a/ Enolization step: 1.1 equiv. Mn-amide, THF, 20°C, 1h. b/ Mn-amide is Ph(Bu)NMnCl (entries 14 and 15) or $Ph(Et_2CHCH_2)NMnCl$ (entry 16). c/ 1.25 equiv., THF/DMSO, 1h. d/ Isolated product, polyalkylation < 0.5% e/ Ratio αα'/αα-disubstituted ketones.

By comparison with MeI (Table I, entries 2-4), $Me_2SO_4$ gave a low yield (34%). In addition, $BuOSO_2Ph$ does not react (BuI: 67%, Table I, entry 8). This probably indicates that the reaction proceeds via a single electron transfer mechanism.

It is interesting to compare the results obtained from Li and Mn-enolates. Thus, in a well-known report,[11] House has described the benzylation of 2-methylcyclohexanone, via the Li-enolate prepared with LDA, in only 42-45% yield (20% polyalkylated products) with an unsatisfactory regioselectivity (6-benzyl/2-benzyl= 76:24). In this case, the corresponding Mn-enolate allowed to obtain a 91% yield (<1% polyalkylation) and a good regioselectivity (93:7; Table II, entry 16).

In conclusion, we have shown that Mn-enolates, a new class of metal enolates, are regioselectively (kinetic enolates) and quantitatively prepared under mild conditions by deprotonation of ketones with aromatic Mn-amides. These Mn-enolates can be regioselectively monoalkylated in high yields at room temperature. The formation of polyalkylated compounds is avoided (< 1%).

**Notes and References.**


1. Organomanganese reagents XXVI, for Part XXV: Cahiez G., Marquais S. *Synlett* **1993**, *1*, 45-47.
2. Reetz, M.; Haning, H. *Tetrahedron Lett.* **1993**, *34*, 7395-7398.
3. 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. b/ 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. The results described in the above patents have been presented by G.C. in several public conferences in Belgium, France, Germany and the Netherlands. One of these conferences has been held on April 26, 1993 at the Max Planck Institute of Mulheim, Germany, when Prof Reetz informed us that he had recently obtained similar results.
4. a/ Heathcock, C. H. in *Asymmetric Synthesis*, Vol.3, Morrison, J. P. Ed, Academic Press, New York, **1984**, 1-110. b/ House, H. O. in *Modern Synthetic Reactions*, Benjamin W. A., Menlo Park, California, 2nd ed **1972**, 492-570. c/ D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979-2990. d/ Jackman, L.; Lange, B. *Tetrahedron* **1977**, *33*, 2737-2769. e/ House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *16*, 2361-2371.
5. To solve this problem, several procedures have been reported. Generally, to avoid the formation of polyalkylated products, the Li or K-enolate is converted into another metal enolate which is then alkylated. For instances: **Sn and Al-enolates;** Tardella, P. *Tetrahedron Lett.* **1969**, 1117-1120; **B-enolates;** Neghishi, E. I.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *13*, 1341-1344; **Zn-enolates;** Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785-1787. See also the following communication.
6. The stereochemistry of the Mn-enolates has been determined by silylation ($R^1 = R^2 = Pr$, 91% yield, Z > 97%).[2]
7. $MnCl_2$ is often used as its soluble "ate" complexe $MnCl_4Li_2$. See Cahiez, G.; Alami, M. *Tetrahedron*, **1989**, *45*, 4163-4176.
8. Samples freshly prepared or stored for 6 months give the same results.
9. Thus, in the case of dibutylketone (Table I, entry 3), the use of i-$Pr_2$NMnMe or $Bu_2$NMnMe as enolizating agents, only gives 40-50% yield (93% with the aromatic amide Ph(Me)NMnMe).
10. With 2-methylcyclohexanone; the kinetic enolate has been obtained in 93% of regioisomeric purity under kinetic conditions (1.1 equiv. Ph(Me)NMnCl) and in 90% in the presence of a large excess of ketone (200%) after 1h at 20°C (equilibrium conditions).
11. Gall, M.; House, H. O. *Org. Synt. Coll. Vol. VI* **1988**, 121-130.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