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

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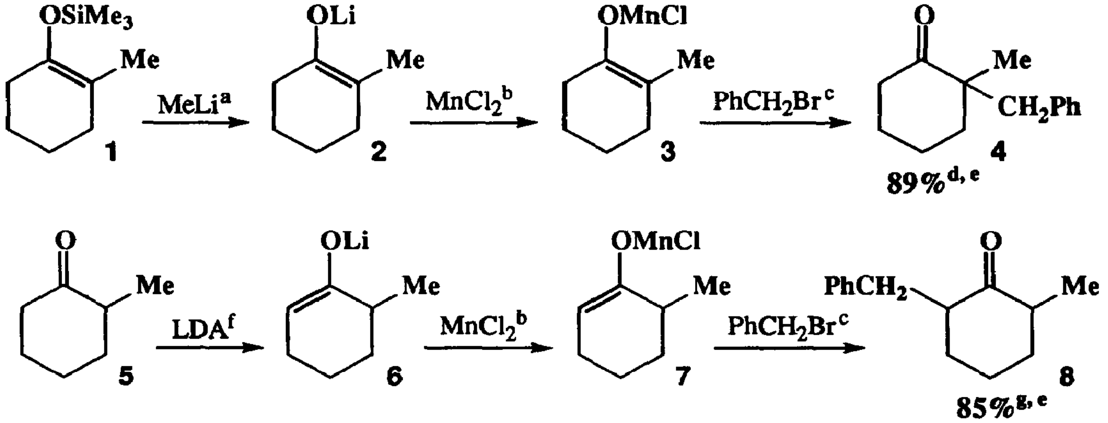
Abstract: *Li-enolates are readily converted to Mn-enolates by treatment with manganese halides. In THF, the reaction is easily and economically performed with manganese chloride at room temperature. Mn-enolates can then be regioselectively monoalkylated in good yields. The formation of di and polyalkylated products is never observed (< 1%).*

In the preceding communication[1], in which we claim our anteriority on a communication recently published in this journal,[2, 3] we have shown that ketones are easily and regioselectively deprotonated by Mn-amides in THF at room temperature to give the kinetic Mn-enolates. In the presence of a polar cosolvent (*e. g.* DMSO or NMP), Mn-enolates are then regioselectively monoalkylated in good yields at room temperature.[1, 3a] However, Mn-amides cannot be used to obtain the thermodynamic Mn-enolates (*i.e.* **3**).[1, 3a] Now, we report that both kinetic and thermodynamic Mn-enolates (*i. e.* **3** and **7**, scheme I) are easily and selectively prepared by transmetallation from the corresponding Li-enolates (*i. e.* **2** and **6**) or from Mg, K and Na-enolates.[3b]

Scheme I. Regioselective Preparation and Monobenzylation of the two Regioisomeric Mn-Enolates of 2-Methyl Cyclohexanone.



a/ 1.05 equ. MeLi, THF, -15°C to rt, 30 min.[4] **b/** $MnCl_4Li_2$,[5] rt, 30 min. **c/** 1.25 equ. $PhCH_2Br$, THF/DMSO, 20°C, 2h. **d/** Distilled product, **4**/**8**= 94:6 (regioisomeric purity of the starting silylenol ether **1** : 95%) **e/** polyalkylation < 1%. **f/** 1.1 equ. LDA, THF, rt, 1h. **g/** Distilled product, **8**/**4** = 94:6. The cis isomer is predominant.

The Regional Editors have been made aware by Dr.G.Cahiez of the near identity of the results described here with those recently published in this Journal [2]. They have nevertheless decided to accept this Letter in view of the anteriority of the patents [3]

The Mn-Li exchange reaction readily occurs quantitatively in ether or in THF with MnI_2 as well as with $MnBr_2$ or better its soluble ate complex $MnBr_4Li_2$[7, 8]. However, it is easier and more economical[9] to perform the transmetallation in THF at room temperature from $MnCl_2$ or its soluble ate complex $MnCl_4Li_2$[5] (scheme I).

As previously reported, Mn-enolates are regioselectively monoalkylated; a polar cosolvent such as DMSO or NMP must generally be added to increase the alkylation rate.[1, 3a] Thus, it is possible to prepare the two regioisomeric ketones **4** and **8** in good yields and with an excellent regioisomeric purity. It is worthy of note that **8** has been obtained by alkylation of the Li-enolate **6** in only 42-45% yield (20% polyalkylated products) with a moderate regioselectivity (**8**/**4**= 76:24).[10] Moreover, the results obtained from Li-enolates clearly depend on the rate of addition of the alkylating agent, an "instantaneous" addition leading to the best results. On the contrary, this parameter is not very important with Mn-enolates, which is especially interesting for large scale applications.

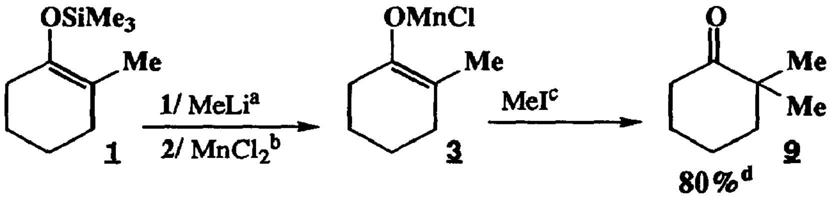
Various ketones have been selectively monoalkylated according to this procedure (Table I and Scheme II). The conversion of Li-enolates to Mn-enolates allows to avoid both regioisomerization and polyalkylation.

Table I. Preparation of Monoalkylated Ketones by Alkylation of Mn-Enolates Prepared from Kinetic Li-Enolates[a] (the results under brakets correspond to the alkylation of Li-enolates)

Starting Ketone	Alkylating Agent[b]	Yield, %[c]	Regioselectivity	Polyalkylation, %
Cyclohexanone	$PhCH_2Br$	88 (55)	-	< 1 (32)
PrCOPr	$PhCH_2Br$	92 (68)	-	<1 (23)
"	$CH_2=CHCH_2Br$	87 (58)	-	<1 (20)
3-Me-Cyclohexanone	$PhCH_2Br$	79 (37)	86/14 (74:26)[d]	<1 (47)
PrCOMe	$PhCH_2Br$	72	82/18[e]	<1

a/ 1.1 equiv. LDA, 0°C, 1h then $MnCl_4Li_2$[5]; rt, 30 min. ((for PrCOMe, the two steps are performed at -78°C for 1h). b/ 1.25 equiv. RX, THF/DMSO, rt, 1h except for PrCOMe: 2 equiv. $PhCH_2Br$, THF/NMP, -78°C, 1h . c/ Distilled product. d/ 6-Benzyl/2-benzyl. e/ Phenyl-3-hexanone/3-benzyl-2-pentanone.

Scheme II. Highly Regioselective Monomethylation of 2-Methylcyclohexanone *via* the Mn-Enolate Prepared from the Thermodynamic Li-Enolate.



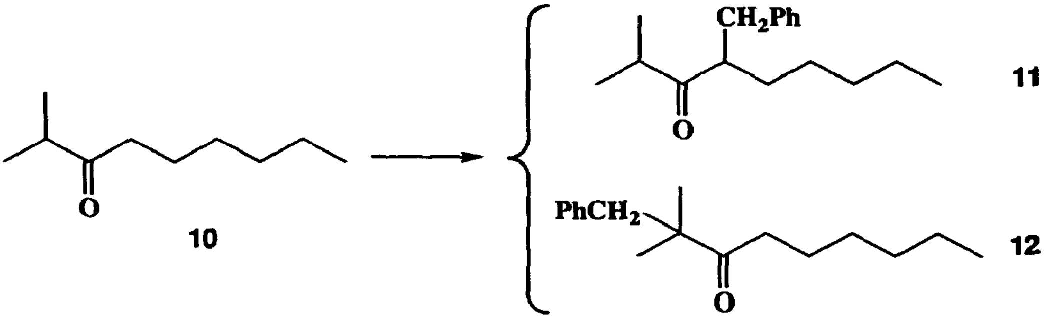
a/ THF, -15°C to rt, 30 min. b/ $MnCl_4Li_2$[5]; rt, 30 min. c/ 1.15 equiv., THF/DMSO, rt, 1h. d/ Regioisomeric purity; 2,2/2,6 dimethyl= 99:1.

Various procedures have been previously reported to perform the monoalkylation of ketones. Thus, Tardella has converted the Li-enolates to Sn- or Al-enolates and Noyori to Zn-enolates whereas Negishi has prepared the K-enolates which are then transformed to B-enolates[11]. Our procedure is clearly simpler and less expensive since the transmetallation is performed with $MnCl_2$ instead of Et_3Al, Bu_3SnCl, Et_3B or Et_2Zn, which are expensive and for some of them toxic or pyrophoric. In addition, no excess of alkylating agent is required (Sn- and Al-enolates) and the hazardous preparation of K-enolates (required for the synthesis of B-enolates) is avoided.

Kinetic Mn-enolates can be obtained either by transmetallation from Li-enolates (see above) or by deprotonation of ketones with Mn-amides.[1] The first procedure may seem easier to carry out since LDA is more usual than aromatic Mn-amides. However, Mn-amides are readily prepared and can be easily stored at room temperature, contrary to LDA.[1, 3]

In fact, the choice of the procedure depends on the nature of the starting ketone. Thus, the Li-Mn transmetallation procedure generally gives better results with the very reactive ketones (*i. e.* methyl ketones and to a less extent cyclohexanone), which easily undergo a 1,2-addition reaction, since the aldol condensation is slightly easier to control with LDA than with Mn-amides. For instance, in the case of the benzylation of cyclohexanone; the transmetallation procedure gives a 88% yield (Table I) and the Mn-amide procedure 65%. On the other hand, the Mn-amide method generally gives a higher regioselectivity and often a better yield with the less reactive ketones such as 2-substituted cyclohexanones or dialkyl ketones (Scheme III).

Scheme III. Regioselective Monobenzylation of 2-Methyl 3-Nonanone

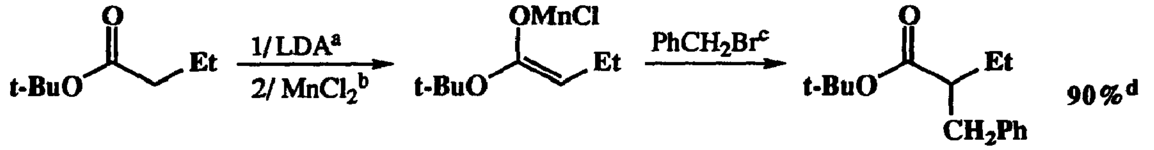


Li-Mn transmetallation procedure[a]: 84%[b] (**11**/**12**= 83:17)
Ph(Me)NMnCl procedure[c]: 85%[b] (**11**/**12**= 97:3)

a/ 1) 1.1 equiv. LDA, rt, THF, 30 min. then $MnCl_4Li_2$[5], rt, 30 min. then 1.5 equiv. $PhCH_2Br$, THF/DMSO, rt, 2h. b/ Yield of distilled product. c/ 1.1 equiv. Ph(Me)NMnCl, THF, rt, 1h then 1.2 eqiv. $PhCH_2Br$, THF/DMSO, rt, 2h.

Of course, the Li-Mn transmetallation reaction can also be performed from the Li-enolates of esters (Scheme IV). The resulting Mn-enolates are easily alkylated under the conditions described above.

Scheme IV.



a/ 1.1 equiv. LDA, THF, -78°C, 1h. b/ $MnCl_4Li_2$[5], -78°C to rt, 30 min. c/ 1.25 equiv. $PhCH_2Br$, THF/DMSO, rt, 2h. d/ Yield of distillated product.

In conclusion, kinetic and thermodynamic Mn-enolates are easily prepared by Li-Mn exchange reaction from the corresponding Li-enolates. The alkylation of Mn-enolates allows to obtain the mono alkylated ketones in excellent yields and with an excellent regioselectivity. The polyalkylation generally observed with Li-enolates is avoided (< 1%). The results are often better than those previously described with other metal enolates (Sn, Al, Zn, B). In addition, the Mn-enolate procedure is clearly superior for large scale applications since it is simpler, cheaper and does not require any toxic or pyrophoric material.

Notes and References.

1. Organomanganese reagents XXVII, for Part XXVI see: Cahiez, G.; Figadère, B.; Cléry, P., preceding communication in this journal..
2. Reetz, M.; Haning, H. *Tetrahedron Lett.* **1993**, *34*, 7395-7398.
3. a/ 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.
4. The Li-enolate **2** was prepared from **1** according to Stork G., Hurdlik P.F. *J. Am. Chem. Soc.* **1968**, *90*, 4464. The silyl enol ether **1** was regiospecifically obtained according to Krafft, M. E.; Holton, R. A. *J. Org. Chem.* **1984**, *49*, 3669 by replacing HMPA by DMPU. On a 150 mmoles scale, yield of distilled product: 40% (unoptimized), regioisomeric purity: 95 %.
5. A solution of $MnCl_4Li_2$ is prepared by mixing $MnCl_2$ + 2LiCl in THF at rt for 1h. See Cahiez, G.; Alami, M. *Tetrahedron*, **1989**, *45*, 4163-4176.
6. We have noted that the cis/trans ratio can vary according to the reaction conditions.
7. An ethereal solution of $MnBr_4Li_2$ is obtained by mixing $MnBr_2$ and 2 LiBr in ether at rt for 2h.[8]
8. For the preparation of RMnBr from $MnBr_4Li_2$ see Cahiez, G., Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 3545-3546.
9. $MnCl_2$ is clearly the cheapest manganese halide. It costs about 3$/Kg (anhydrous material).
10. Gall, M.; House, H. O. *Org. Synt. Coll. Vol. VI* **1988**, 121-130.
11. **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.

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