Tetrahedron Letters, Vol. 33, No. 46, pp. 6963-6966, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Ligand Effects in Selective Carbonyl Addition Reactions of Organomanganese and Cerium Reagents

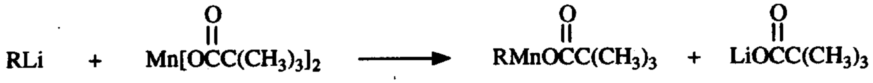
Manfred T. Reetz*, Helmut Haning and Stephan Stanchev#

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 4330 Mülheim/Ruhr, Germany

***Abstract*:** Transmetalation of organolithium reagents RLi (R = CH_3, *n*-Bu) with manganese pivalate produces reagents of the type RMnOC(O)*t*Bu which react stereoselectively with substituted cyclohexanones to afford the axial alcohols preferentially. These reagents as well as cerium ate complexes RCe(O*i*Pr)$_3$MgX react aldehyde-selectively in the presence of ketone functionality.

Carbanions in the form of organolithium reagents constitute the largest and most diverse class of organometallics used in synthetic organic chemistry. Unfortunately, in some cases the reactions with organic substrates show low degrees of chemo- and stereoselectivity. In the 1980's we introduced the concept of controlling "carbanion selectivity" via titanation with $ClTiX_3$ (X = Cl, OR, NR_2, etc.)1). It turned out that the nature of the ligand determines the direction and extent of stereoselectivity in many carbonyl addition reactions. Subsequently, a number of other metals were likewise tested as transmetalating agents, including cerium2), ytterbium3), iron4), cobalt5) and uranium6) salts. However, the possible influence of ligands was generally not studied. Recently, we have shown that ligand effects in classical Grignard reagents RMgL (L = tosylate, carboxylate, etc.) have a pronounced influence on the extent of chemo- and stereoselectivity7). Here we report our initial experience with ligand effects in carbonyl addition reactions of organomanganese8) and cerium2) reagents.

In an in situ reaction mode organolithium reagents were transmetalated with manganese pivalate **2** to produce alkyl- and arylmanganese pivalates **3**. Since we do not currently know the structure, aggregation state or the possible role of the lithium salt **4** which is formed concomitantly, formula **3** is to be regarded as a formal representation.



$$\underset{\mathbf{1}}{\mathrm{RLi}} + \underset{\mathbf{2}}{\mathrm{Mn[O\overset{\overset{O}{\|}}{C}C(CH_3)_3]_2}} \longrightarrow \underset{\mathbf{3}}{\mathrm{RMnO\overset{\overset{O}{\|}}{C}C(CH_3)_3}} + \underset{\mathbf{4}}{\mathrm{LiO\overset{\overset{O}{\|}}{C}C(CH_3)_3}}$$

Upon adding these reagents and the corresponding bromides RMnBr8) to 4-*tert*-butylcyclohexanone **5**, notable ligand effects were observed (Table 1). Significantly, CH_3MnOC(O)*t*Bu9) shows preferred equatorial attack to the extent of 92%, whereas CH_3MnBr results in only 81% diastereoselectivity. The former reaction is comparable to that of $CH_3Ti(OPh)_3$ (93% diastereoselectivity in a very slow reaction)10). Interestingly, the magnesium analog CH_3MgOC(O)*t*Bu leads to a 65 : 35 mixture of **6/7** as do CH_3MgBr and CH_3Li10). Using a different strategy, namely complexation of CH_3MnBr with phosphines, diastereoselectivity can also be influenced (Table 1). For reasons that are currently unclear, the phenyl-reagent PhMnOC(O)*t*Bu reacts stereorandomly, in contrast to the magnesium analog PhMgOC(O)*t*Bu7).

On leave from the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria

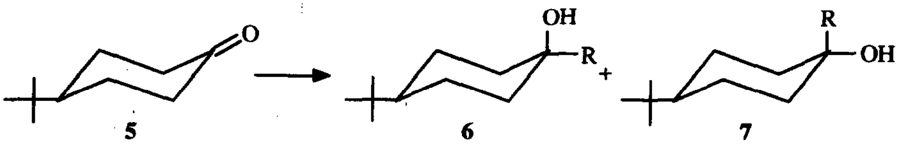
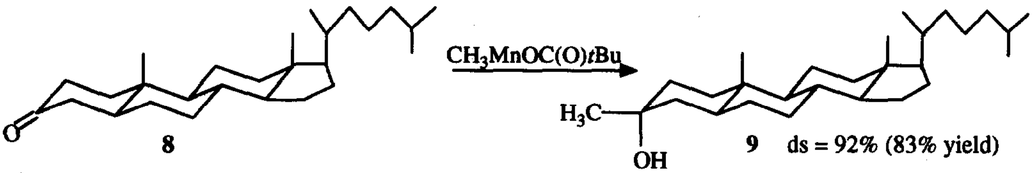


Table 1. Reactions of Organometallics with **5** in THF (-78°C → +22°C)[a].

Reagent	**6**	:	**7**[b]	Conversion (%)
CH_3MnBr[c]	81	:	19	92
$CH_3MnBr \cdot 2\,PEt_3$	82	:	18	64
$CH_3MnBr \cdot 2\,P(iPr)_3$	89	:	11	89
$CH_3MnBr \cdot 2\,P(tBu)_3$	91	:	9	95
$CH_3MnOC(O)tBu$	92	:	8	95 (82)[d]
$CH_3Ce(OiPr)_3Li$	71	:	29	77
$CH_3Ce(OiPr)_3MgCl$[e]	71	:	29	78
n-BuMnBr[c]	87	:	13	92
n-BuMnOC(O)*t*Bu	93	:	7	94 (78)[d]
n-$BuCeCl_2$	79	:	21	80
n-$BuCe(OiPr)_3Li$	84	:	16	72
PhMnBr[c]	53	:	47	83
PhMnOC(O)*t*Bu	50	:	50	91 (72)[d]
$PhMgBr/CeCl_3$	50	:	50	81
$PhCe(OiPr)_3MgCl$	39	:	61	57
$PhCeCl_2$[c]	56	:	44	90
$PhCe(OiPr)_3Li$	58	:	42	89

a) Reactions of manganese reagents (2 eq) at -78°C → +22°C[9], those of cerium reagents (1.3 eq) at -78°C (3 h). b) Determined by GC. c) Prepared by transmetalating RLi with $MnBr_2 \cdot 2LiBr$. d) Isolated yield. e) From $CeCl_3 \cdot 3iPrOH$ and four equivalents of CH_3MgCl.

With respect to ready accessiblility, reactivity, stereoselectivity and ease of performance, no other methylmetal reagent presently known excells $CH_3MnOC(O)tBu$ in equatorial addition reactions to substituted cyclohexanones[11,12]. The reaction with cholestanone **8**[10,13] is another example:



9 ds = 92% (83% yield)

To probe potential ligand effects of organocerium reagents, we first concentrated on ate complexes produced by reacting cerium triisopropoxide[14] with RLi and RMgCl.

$$\mathrm{RLi} + \mathrm{Ce(O}i\mathrm{Pr)_3} \longrightarrow \mathrm{RCe(O}i\mathrm{Pr)_3Li}$$

$$\mathrm{RMgCl} + \mathrm{Ce(O}i\mathrm{Pr)_3} \longrightarrow \mathrm{RCe(O}i\mathrm{Pr)_3MgCl}$$

These reagents appear to be less suited for stereoselective additions to ketone **5** as shown in Table 1. However, the Ce/Mg-ate complexes are highly aldehyde-selective in simple competition reactions involving 1 : 1 mixtures of benzaldehyde and acetophenone (Table 2). It is also significant that PhLi/$CeCl_3$ behaves chemorandomly, in contrast to the >99% aldehyde-selectivity displayed by PhMgBr/$CeCl_3$! Lithiated acetonitrile has been transmetalated previously using titanium[1b,16)], iron[16)], manganese[16)], chromium[16)], nickel[16)], cobalt[16)], copper[16)] and cerium[17)] salts.

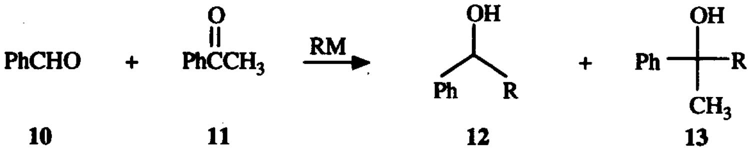


Table 2. Chemoselective Reactions of Organometallics with **10**/**11** in THF.

Reagent	12	:	13	Conversion (%)
CH_3MnBr[a)]	>99	:	<1	95
$CH_3MnOC(O)t$Bu	>99	:	<1	85
$CH_3Ce(OiPr)_2$[b)]	95	:	5	50
3 $CH_3Li/CeCl_3$	50	:	50	99
$CH_3Ce(OiPr)_3Li$[c)]	82	:	18	90
$CH_3Ce(OiPr)_3Li$[d)]	>99	:	<1	91
$CH_3Ce(OiPr)_3MgCl$[e)]	>99	:	<1	80
n-BuLi/$CeCl_3$	58	:	42	95
n-BuMgCl/$CeCl_3$	98	:	2	89
n-BuCe(O*i*Pr)$_3$MgCl	>99	:	<1	72
PhLi/$CeCl_3$	50	:	50	95
PhMgBr/$CeCl_3$	>99	:	<1	81
PhCe(O*i*Pr)$_3$MgBr[f)]	>99	:	<1	80
$NCCH_2MnOC(O)t$Bu[g)]	88	:	12	90
$LiCH_2CN/CeCl_3$	74	:	26	73
$NCCH_2Ce(OiPr)_3MgBr$[h)]	87	:	13	61

a) Prepared by transmetalating CH_3Li with $MnBr_2{\cdot}2LiBr$[8)]. b) Prepared by reacting CH_3Li with $ClCe(OiPr)_2$[15)]. c) From CH_3Li and $Ce(OiPr)_3$. d) Prepared by treating $CeCl_3{\cdot}$ 3 *i*PrOH with three equivalents of *n*-BuMgCl followed by one equivalent of CH_3Li. e) From $CeCl_3{\cdot}$ 3 *i*PrOH and four equivalents of CH_3MgCl. f) From PhMgBr and $Ce(OiPr)_3$. g) This reagent was prepared from lithiated acetonitrile and the equivalent amount of $Mn[OC(O)tBu]_2$. h) Prepared by reacting $NCCH_2MgBr$ with $Ce(OiPr)_3$.

In summary, this communication demonstrates that the exploration of potential ligand effects in such organometallic compounds as organomanganese and cerium reagents can be rewarding. Indeed, new synthetic methodologies evolve, inspite of the fact that structural and mechanistic studies lag behind. More work is necessary with these and other metals, with other organolithium precursors and with different organic reaction partners. The final picture which will evolve is likely to be one of complementarity, i. e., not a single metal or a particular ligand is expected to be optimal in all synthetic situations.

Acknowledgement

This work was supported by the DFG (Leibniz-Program) and the Fonds der Chemischen Industrie. S. Stanchev thanks the Alexander von Humboldt-Stiftung for a fellowship. H. Haning thanks Schering AG for a pre-doctoral stipend.

References and Notes

1. a) Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem.* **1980**, *92*, 1044-1045; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 1011; b) Reetz, M.T.; Steinbach, R.; Wenderoth, B.; Westermann, J. *Chem. Ind. (London)* **1981**, 541-542; c) Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, Berlin, 1986; d) Weidmann, B.; Seebach, D. *Angew. Chem.* **1983**, *95*, 12-26; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31.
2. a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatayima, T.; Kamija, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392-4398; b) Imamoto, T. in *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I., eds., Vol. I, p. 231-250, Pergamon Press, Oxford 1991.
3. Molander, G.; Burkhardt, E.R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990-4991.
4. Kauffmann, T.; Laarmann, B.; Menges, D.; Neiteler, G. *Chem. Ber.* **1992**, *125*, 163-169.
5. Kauffmann, T.; Hopp, G.; Laarmann, B.; Stegemann, D.; Wingbermühle, D. *Tetrahedron Lett.* **1990**, *31*, 511-514.
6. Dormond, A.; Aataliti, A.; Moise, C. *J. Org. Chem.* **1988**, *53*, 1034-1037.
7. Reetz, M.T., Harmat, N.; Mahrwald, R. *Angew. Chem.* **1992**, *104*, 333-334; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 342.
8. a) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 3545-3548; b) RMnI react aldehyde-selectively: Cahiez, G.; Normant, J.F. *Tetrahedron Lett.* **1977**, *18*, 3383-3384; Cahiez, G.; Figadere, B. *Tetrahedron Lett.* **1986**, *27*, 4445-4448.
9. General procedure: $Mn[OC(O)C(CH_3)_3]_2$: $Mn(OAc)_2$ (5.2 g, 30 mmol) and pivalic acid (6.2 g, 61 mmol) were placed in a distillation apparatus and stirred at 150°C for 2 h to remove acetic acid. The product was freed from excess pivalic acid under high vacuum for 2 d. Addition: To a solution of $Mn[OC(O)t\text{Bu}]_2$ (514 mg, 2 mmol) in THF (10 ml) MeLi (1.25 ml, 1.6 M in Et_2O, 2 mmol) was added at -78°C. After stirring for 45 min, ketone **5** (154 mg, 1 mmol) in THF (1 ml) was added. The mixture was stirred for 22 h, during which it was allowed to reach room temperature, hydrolyzed with aq. NH_4Cl (0.7 ml), diluted with ether (50 ml) and extracted with aq. sat. $NaHCO_3$. The aqueous phase was extracted twice with ether, the combined organic layers dried over $MgSO_4$, evaporated to dryness and subjected to chromatography on silica gel using hexane/ether (10 : 1) as eluent. Conversion using only 1.2 eq of $CH_3MnOC(O)t\text{Bu}$ is 70%.
10. Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441-1454.
11. Ashby, E.C; Laemmle, J.T. *Chem. Rev.* **1975**, *75*, 521-546.
12. a) An excess of CH_3Li in the presence of $LiClO_4$ reacts with 4-*tert*-butylcyclohexanone to produce a 92 : 8 mixture of **6**/**7**, but active methyl groups are not utilized: Ashby, E.C.; Noding, S.A. *J. Org. Chem.* **1979**, *44*, 4371-4377; b) An excess of $(CH_3)_2CuLi$ reacts with **5** to afford a 94 : 6 mixture of **6**/**7**, but again active methyl groups are sacrificed: MacDonald, T.L.; Still, W.C. *J. Am. Chem. Soc.* **1975**, *97*, 5280-5281.
13. CH_3MgI reacts with **8** to produce **9** with only 56% diastereoselectivity: Barton, D.H.R.; Campos-Neves, S.; Cookson, R.C. *J. Chem. Soc.*, **1956**, 3500-3506; Beton, J.L.; Halsall, T.G.; Jones, E.R.H.; Phillips, P.C. *J. Chem. Soc.* **1957**, 753-765.
14. $Ce(Oi\text{Pr})_3$ was prepared analogously to $Gd(Oi\text{Pr})_3$ (Mehrotra, R.C.; Batwara, J.M. *Inorg. Chem.* **1970**, *9*, 2505-2510).
15. $ClCe(Oi\text{Pr})_2$ was prepared according to: Sankhla, B.S.; Kapoor, R.N. *Can. J. Chem.* **1966**, *44*, 2131-2137.
16. Kauffmann, T.; Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, *125*, 899-905.
17. Liu, H.-J.; Al-said, N.H. *Tetrahedron Lett.* **1991**, *32*, 5473-5476.

(Received in Germany 20 July 1992)