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REACTION OF ALLYLMANGANESE(II) REAGENTS WITH ALDEHYDES

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Abstract: The reaction of allylmanganese(II) reagents with aldehydes gives alcohols with high regioselectivity. The allylmanganese(II) reagents are prepared by transmetallation between manganese(II) chloride and allyllithium compounds which are generated from allyl phenyl sulfides by reductive lithiation.

The synthetic use of organomanganese compounds is still in its infancy.[1,2,3] The putative allylmanganese intermediates produced when manganese powder or a mixture of manganese(II) chloride and lithium aluminum hydride reacts with allylic bromides have been reported to undergo usefully regiospecific addition to aldehydes and ketones.[4] In particular, the crotyl intermediate adds a carbonyl group only at its internal terminus and only 1,2-addition occurs to conjugated enals and enones. Furthermore, addition to enolizable ketones occurs in good yield.[4b]

Because of the relative unavailability of all but the simplest allyl halides, we considered the possibility of expanding the use of allylmanganese compounds by

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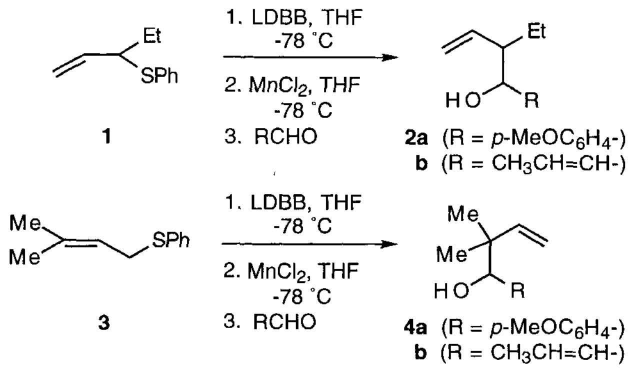
preparing them by transmetallation[2,3] of readily available allyllithiums derived from reductive lithiation of allyl phenyl thioethers.[5] Thus, the reductive lithiation of allyl phenyl sulfides **1** and **3** by lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[6] in THF followed by sequential treatment with anhydrous $MnCl_2$ and an aldehyde yielded homoallylic alcohols with the expected high regioselectivity (Scheme I).

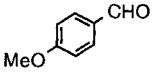
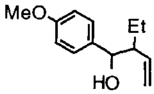
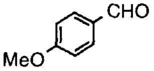
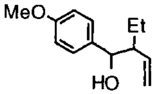
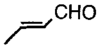
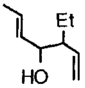
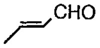
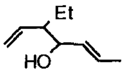
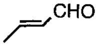
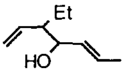
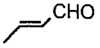
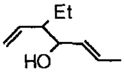
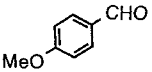
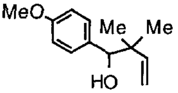
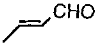
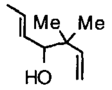
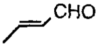
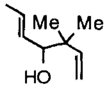
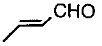
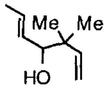


Scheme I

As shown in Table 1, carbonyl addition took place exclusively at the most substituted allyl terminus. The α,β-unsaturated aldehyde showed exclusive 1,2-addition (entries 3-6, 8-10). However, the presence of appreciable diastereoselectivity was not exhibited from the reaction of **1** (entries 1-6). Using commercially available anhydrous manganese(II) chloride (99+% purity) gave higher yields compared to the use of less pure manganese(II) chloride which was generated from the dehydration of manganese(II) chloride tetrahydrate (98% purity) by drying *in vacuo* (compare entries 1,3 with entries 2,5).

Since allyllithiums undergo non-regioselective reactions with carbonyl compounds,[7] this preliminary survey indicates that allylmanganese reagents can

Table 1. Reactions of Aldehydes with Allylmanganese(II) Reagents Derived from Allyl Phenyl Sulfides **1** and **3**

Entry	Sulfide	$MnCl_2$[a] (equiv)	RCHO (equiv)	Reaction conditions	Product	% Yield[b] (diast. ratio)
1	**1**	**A** (1.2)		-78°, 1 h 0°, 15 min		84 (44 : 56)[c]
2	**1**	**B** (2.25)		-78°, 1 h		61 (52 : 48)[c]
3	**1**	**A** (1.2)		-78°, 1 h 0°, 15 min		64 (52 : 48)[d]
4	**1**	**A** (1.2)[e]		-78°, 1 h 0°, 15 min		42 (40 : 60)[d]
5	**1**	**B** (1.2)		-78°, 1 h 0°, 15 min		47 (46 : 54)[d]
6	**1**	**B** (1.1)		-78°, 1 h		47 (46 : 54)[d]
7	**3**	**A** (1.2)		-78°, 1 h 0°, 15 min		83
8	**3**	**A** (1.2)		-78°, 1 h 0°, 15 min		58
9	**3**	**A** (1.5)[f]		-78°, 1 h 0°, 15 min		73
10	**3**	**A** (2.1)		-78°, 1 h 0°, 15 min		70

[a] **A**: Commercially available anhydrous $MnCl_2$ was used after being dried further *in vacuo*. **B**: $MnCl_2 \cdot 4H_2O$ was used after being dried *in vacuo*. [b] Isolated yield. [c] The diastereomeric ratio was determined by GC. [d] The diastereomeric ratio was determined by ^1H NMR. [e] An excess (4 equiv) of TMEDA was added to the allylmanganese compound and the mixture was stirred for 30 min. at -78 °C before the addition of aldehyde. [f] 1.5 equivalents of the allylmanganese compound was used.

indeed be produced by transmetallation and that they show promise of utility in organic synthesis. At the rudimentary stage of development of this field, the yields and stereoselectivity are inferior to those generally attained with the far more thoroughly explored allyltitanium reagents.[7] For example, we have found that treatment of the reductive lithiation product of **1** with titanium isopropoxide followed by crotonaldehyde yielded **2b** in 82% yield with a Diastereoselectivity of 21:79. Nevertheless, future manipulation of the ligands[8] and other parameters could improve the performance of the allylmanganese reagents.

However, even at this early stage, there is one advantage that allylmanganese will have over allyltitanium reagents in certain cases. Whereas the reaction of an allyltitanium(IV) reagent requires rather acidic conditions (5% HCl) for workup, saturated aqueous NH_4Cl can be used in the case of the allylmanganese(II) reagents and thus the latter would appear to be advantageous for reactions the products of which are unstable under acidic conditions

Experimental:

3-(Phenylthio)-1-pentene (1). *s*-Butyllithium (62.2 mL of a 1.30 M solution in cyclohexane, 80.8 mmol) was added to a solution of allyl phenyl sulfide (12.02 g, 80.0 mmol) in THF (200 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 3 h before ethyl iodide (13.73 g, 88.0 mmol) was added at -78 °C. After being stirred for 1 h, the solution was quenched with water (30 mL) at -78 °C, warmed to room temperature, and extracted with ether (3 × 50 mL). The combined ether layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Vacuum distillation, through a 10-cm Vigreux column, afforded 13.0 g (91%) of 3-(phenylthio)-1-pentene as a colorless liquid: bp 75-76 °C (0.1 Torr); ^1H NMR ($CDCl_3$) δ 7.1-7.4 (m, 5 H, Ph), 5.64 (ddd, J = 16.9, 10.1, 8.9 Hz, 1 H, $CH{=}CH_2$), 4.91 (dd, J = 10.1, 1.1 Hz, 1 H, $=CHH$), 4.85 (dd, J = 16.9, 0.8

Hz, 1 H, =CH*H*), 3.47 (m, 1 H, PhSCH), 1.5-1.8 (m, 2 H, CH_2), 0.97 (t, *J* = 7.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.59 (d), 134.83 (s), 132.57 (d), 128.57 (d), 126.88 (d), 115.75 (t), 53.83 (d), 27.29 (t), 11.84 (q).

Preparation of Alcohols. General Procedure: Manganese(II) chloride (453 mg, 3.60 mmol) or manganese(II) chloride tetrahydrate (713 mg, 3.60 mmol) was pulverized in a mortar, dried *in vacuo* while being heated at 120 °C for 3 h and then cooled to room temperature. The vacuum was replaced with an argon atmosphere and THF (40 mL) was added. The resulting slurry was stirred for over 2 h before being cooled to -78 °C and stirred at that temperature for 30 min. In another flask, 3-(phenylthio)-1-pentene (**1**) (535 mg, 3.00 mmol) or 1-(phenylthio)-3-methyl-2-butene (**3**)[9] (535 mg, 3.00 mmol) in THF (10 mL) was added into a preformed solution of LDBB[10] (6.30 mmol) in THF (15 mL) at -78 °C via a syringe pump for 1 h, and the resulting mixture was stirred for an additional 1 h period at -78 °C. The manganese(II) chloride suspension was cannulated to the mixture at -78 °C. After the reaction mixture had been stirred for 3 h at -78 °C, *p*-anisaldehyde (409 mg, 3.00 mmol) or crotonaldehyde (210 mg, 3.00 mmol) was added. The solution was stirred under the reaction condition in Table 1 before addition of saturated aqueous NH_4Cl (30 mL) and water (10mL). The aqueous layer was extracted with ether (4 x 30 mL). The combined ethereal extracts were washed with 5% NaOH (2 x 25 mL) and with brine (30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The product was purified by column chromatography on silica gel (10-15% ethyl acetate / hexanes).

2-Ethyl-1-(4-methoxyphenyl)-3-buten-1-ol (2a) (oil; two diastereomers): IR (neat) 3436, 2961, 2874, 1613, 1512, 1248, 1036, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1-7.3 and 6.8-6.9 (m, 4 H, Ph), 5.65 (ddd, *J* = 17.0, 10.2, 9.4 Hz, 1 H, C*H*=CH_2 from diastereomer A), 5.47 (ddd, *J* = 17.1, 10.3, 9.3 Hz, 1 H, C*H*=CH_2 from diastereomer B), 5.26 (dd, *J* = 15.7, 2.0 Hz, 1 H, CH=C*H*H from diastereomer A), 5.22 (dd, *J* = 22.4, 2.0 Hz, 1 H, CH=CH*H* from diastereomer A), 5.05 (dd, *J* = 18.3, 2.0 Hz, 1 H, CH=C*H*H from diastereomer B), 5.01 (dd, *J* = 25.0, 2.1 Hz, 1 H, CH=CH*H* from diastereomer B), 4.48 (m, 1 H, ArCH from diastereomer B), 4.31 (d, *J* = 7.9 Hz, 1 H, ArCH from diastereomer A), 3.75 (s, 3 H, OCH_3), 2.4-2.6 (br. s, 1 H, OH), 2.1-2.3 (m, 1 H, C*H*CH=), 1.5-1.7 and 1.0-1.3 (m, 2 H, CH_2), 0.84 (t, *J* = 7.4 Hz, 3 H, CH_3 from diastereomer B), 0.76 (t, *J* = 7.4 Hz, 3 H, CH_3 from diastereomer A); ^{13}C NMR ($CDCl_3$) δ 158.87, 158.64, 139.29, 138.32, 134.88, 134.72, 127.97, 127.81, 118.51, 117.09, 113.45, 113.19, 76.22, 76.08, 55.04, 54.53, 53.15, 23.29, 22.71, 11.69; MS *m/z* (EI) (relative intensity) 137 ($M^+ - C_5H_9$, 100), 109 (12); HRMS (EI) calcd for $C_8H_9O_2$ ($M^+ - C_5H_9$) 137.0603, found 137.0603.

3-Ethyl-1,5-heptadien-4-ol (2b) (oil; two diastereomers): IR (neat) 3386, 2963, 2934, 2876, 1640, 1455, 1019, 967, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4-5.8 (m, 3 H, CH=), 5.0-5.1 (m, 2 H, CH_2=), 4.01 (m, 1 H, *H*C(OH) from diastereomer A), 3.81 (dd, *J* = 7.5, 7.5 Hz, 1 H, *H*C(OH) from diastereomer B), 2.10 (m, 1 H, CH_2=CHC*H* from diastereomer A), 1.92 (ddd, *J* = 13.7, 9.7, 3.5 Hz, 1 H, CH_2=CHC*H* from diastereomer B), 1.7 (m, 3 H, C*H*$_3$CH=), 1.6 (br. s, 1 H, OH), 1.1-1.6 (m, 2 H, CH_3C*H*$_2$), 0.87 (t, *J* = 6.7 Hz, 3 H, C*H*$_3$$CH_2$ from diastereomer A), 0.85 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$$CH_2$ from diastereomer B); ^{13}C NMR ($CDCl_3$) δ 139.04 (d), 138.36 (d), 132.15 (d), 131.40 (d), 128.88 (d), 128.24 (d), 127.34 (d), 118.07 (t), 117.48 (t), 75.01 (d), 74.80 (d), 52.77 (d), 52.28 (d), 23.26 (t), 23.19 (t), 17.68 (q), 11.69 (q); MS *m/z* (EI) (relative intensity) 71 ($M^+ - C_5H_9$, 100).

2,2-Dimethyl-1-(4-methoxyphenyl)-3-buten-1-ol (4a): oil; IR (neat) 3478, 2963, 2870, 1613, 1514, 1248, 1036, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ

7.20 (dd, *J* = 6.6, 2.0 Hz, 2 H, Ph), 6.84 (dd, *J* = 6.6, 2.0 Hz, 2 H, Ph), 5.91 (dd, *J* = 17.6, 10.9 Hz, 1 H, C*H*=CH_2), 5.12 (dd, *J* = 10.9, 1.2 Hz, 1 H, =C*H*H), 5.06 (dd, *J* = 17.6, 1.2 Hz, 1 H, =CH*H*), 4.37 (s, 1 H, C*H*(OH)), 3.79 (s, 3 H, OCH_3), 2.00 (s, 1 H, OH), 0.99 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 158.84 (s), 145.22 (d), 133.06 (s), 128.82 (d), 113.55 (t), 112.84 (d), 80.26 (d), 55.16 (q), 42.28 (s), 24.45 (q), 21.12 (q); MS *m/z* (EI) (relative intensity) 137 ($M^+ - C_5H_9$, 100), 109 (13); HRMS (EI) calcd for $C_8H_9O_2$ ($M^+ - C_5H_9$) 137.0603, found 137.0602.

3,3-Dimethyl-1,5-heptadien-4-ol (4b): oil; IR (neat) 3436, 2965, 2872, 1638, 1449, 1377, 1084, 1011, 968, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (dd, *J* = 17.5, 10.9 Hz, 1 H, vinyl), 5.3-5.7 (m, 2 H, vinyl), 5.02 (dd, *J* = 10.9, 1.3 Hz, 1 H, vinyl), 4.98 (dd, *J* = 17.5, 1.3 Hz, 1 H, vinyl), 3.66 (d, *J* = 7.1 Hz, 1 H, *H*C(OH)), 1.84 (br. s, 1 H, OH), 1.65 (d, *J* = 6.2 Hz, 3 H, =CH_2CH_3), 0.94 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 145.09 (d), 130.17 (d), 128.43 (d), 113.14 (t), 79.35 (d), 41.25 (s), 23.74 (q), 21.63 (q), 17.70 (q); MS *m/z* (EI) (relative intensity) 71 ($M^+ - C_5H_9$, 100).

Reaction of crotonaldehyde with allytitanium(IV) reagent generated from 3-(phenylthio)-1-pentene (1) and titanium(IV) isopropoxide. 3-(Phenylthio)-1-pentene (**1**) (535 mg, 3.00 mmol) in THF (10 mL) was added into a preformed solution of LDBB (6.09 mmol) in THF (15 mL) at -78 °C via a syringe pump for 1 h, and the resulting mixture was stirred for an additional 1 h period at -78 °C. Titanium(IV) isopropoxide (1.92 g, 6.75 mmol) was added dropwise to the mixture at -78 °C. After the reaction mixture had been stirred for 30 min at -78 °C, crotonaldehyde (631 mg, 9.00 mmol) was added. The solution was stirred for 30 min at -78 °C before addition of 5% HCl (30mL) at -78 °C. The remainder of the workup procedure was identical to those above. Column chromatography on silica gel (50 % methylene chloride / hexanes) afforded the alcohol **2b** (345 mg, 82%). The diastereomeric ratio of **2b** (21 : 79) was determined by ^{1}H NMR analysis.

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