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Reagent Control of Stereochemistry in Allylic Additions to Chiral Aldehydes with CpMo(NO)(X)(2-methallyl) Complexes of High Enantiomeric Purity

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Reactions of (*R*)- and (*S*)-CpMo(NO)(η^3-methallyl)X(X = camphorsulfonate, Cl, Br, I) with chiral α-substituted aldehydes yield homoallylic alcohols with high diastereoselectivity. Reactions of (*R*)- and (*S*)-CpMo(NO)(η^3-methallyl)L^s[L^s = (1*S*)-(+)-10-camphorsulfonate] with D-glyceraldehyde acetonide yield the corresponding homoallylic alcohols in >98% diastereomeric excess. Reactions with racemic 2-phenylpropionaldehyde and nonracemic 3-benzyloxy-2-methylpropanol are also considered and show that there is very high reagent control of stereochemistry in additions to the carbonyl group.

Keywords: chiral synthesis; asymmetric reactions; homoallylic alcohols; chiral aldehydes; camphorsulfonate

INTRODUCTION

The reaction of chiral aldehydes with allyl metal compounds to yield chiral homoallylic alcohols has been of great interest owing to their application in asymmetric synthesis.[1] We have been interested in examining the full potential of chiral Mo(II) allyl compounds as reagents for this reaction. Previously, we have shown that homoallylic alcohols can be obtained in high enantiomeric excess (ee) by nucleophilic addition of prochiral aldehydes to enantiomerically pure allylmolybdenum complexes.[2,3] The reaction of benzaldehyde with (−)-NMCpMo(NO)(η^3-methallyl)Cl(NMCp = neomenthylcyclopenta-dienyl) proceeds with 97% stereoselectivity. This result encouraged us to study the reactions of the neomenthylcyclopentadienyl complexes with chiral α-substituted aldehydes. However, owing to the slow rates of these reactions we have developed an alternative and more reactive allylmolybdenum system. Recently we have prepared (*R*)- and (*S*)-CpMo(NO)(η^3-methallyl)L^s, **1** (L^s = (1*S*)-(+)-10-camphorsulfonate), and separated the diastereomers.[3] This provides a convenient method for the preparation of enantiomerically pure CpMo(NO)(η^3-methallyl)X (X = Cl, Br, I). Reactions of these enantiomerically pure CpMo(NO)(η^3-methallyl)Cl complexes with benzaldehyde yield the homoallylic alcohols in >98% ee.[3] Herein we report the results of the reactions of the enantiomers of CpMo(NO)(η^3-methallyl)X (X = L^s) with D-glyceraldehyde acetonide that yielded the corresponding homoallylic alcohol in >98% diastereomeric excess (de). Reactions with nonracemic 3-benzyloxy-2-methylpropanol indicate that similar selectivities would be observed with the enantiomerically pure aldehyde.

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RESULTS AND DISCUSSION

(*R*)- and (*S*)-camphorsulfonate complexes, **1**, were prepared in 95% de as previously reported[3] and used without further purification. The halide compounds, **2–4**, were prepared by adding the sodium salts of the required halide to the camphorsulfonate complexes in $CHCl_3$ or acetone solution.[3] The stereochemistry at the metal center is retained in the conversion.[4] It is more efficient to achieve very high enantiomeric purity in the halides via recrystallizations starting with 95% ee halide than attempting further purification of **1** via fractional crystallization.

The reaction of an achiral organometallic with a chiral aldehyde would be expected to show some diastereoselectivity owing to differences in the ease of approach of the reagent to the two faces of the aldehyde. Following Cram's analysis,[5]

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(-)-(S)

(+)-(R)

1, X=L^S
2, X=Cl
3, X=Br
4, X=I

one diastereomer should be preferred on the basis steric arguments and this is known as the Cram product, whereas the other is known as the anti-Cram product. For example, addition to (*R*)-2-phenylpropionaldehyde (Eqn [1]) would yield two products, which are now often designated as *syn* and *anti* isomers, depending upon the relative orientation of the methyl and hydroxyl substituents in the products, (**6**, for R = methallyl).

Reactions with enantiomerically pure aldehydes

Reaction of (±)-**2** with D-glyceraldehyde acetonide, **7**, yielded the homoallylic alcohol in a ratio of *syn* (**8a**)/*anti* (**8b**) of 54:46 (Eqn [2]; Table 1, entry 4). Roush *et al.*[6] reported a yield of 29:71 (*syn*/*anti*) for reaction of pinacol allylboronate with **7**. Thus, the inherent diastereofacial selectivity of **7** is moderate. (One might note that the selectivity in this case is opposite to that predicted by the Cram rule.) The high enantiomeric purities found in the reactions of NMCpMo(NO)(η^3-methallyl)Cl with other aldehydes[2] encouraged us to determine whether we could achieve *reagent control* with the CpMo(NO)(η^3-methallyl)X system and could overcome the inherent directing power of the chirality of **7** in asymmetric synthesis. Reactions of nearly diastereomerically pure **1** and nearly enantiomerically pure **2** and **3** with enantiomerically pure **7** were performed and the results are shown in Table 1. In entry 3, (−)-**1** (96% de) yielded the homoallylic alcohol, **8a**, in 96% de, which demonstrates that the overall stereochemistry of the reaction is >98% de. This shows that the diastereomerically pure allylmolybdenum complexes proceed in >98% diastereofacial selectivity and that the reagent control of stereochemistry can overcome the inherent selectivity of the chiral aldehyde.

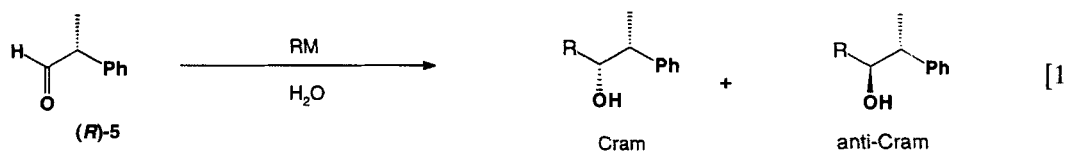
The chloride complex, (−)-**2**, gave higher stereoselectivity (entry 6) than the bromide complex, (−)-**3** (entry 7). Previous results have shown a correlation between the rate of the reaction and the ee of the product for the halides, i.e. the faster the rate the better the ee.[3] The rates for the reactions of the halides decrease in the order **2**>**3**>**4** and the ee of the products follow the same trend. The camphorsulfonate complex gives the highest de and it also has the fastest reaction.

Reactions with racemic aldehydes

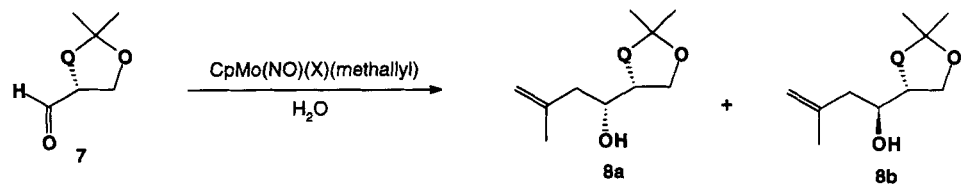
It is relatively difficult to obtain some chiral aldehydes in high enantiomeric purity, but complications can result in the interpretation of the results owing to different rates of reaction for *matched* and *mismatched* pairs of reagents and substrates. These effects can be seen by considering reactions with racemic **5**.

For (±)-**5**, Yamamoto *et al.*[7] reported isolating products with ratios of 2:1 to 5.1:1 (*syn*/*anti*) depending upon the reagent. Heathcock *et al.*[8] also reported yields from 1.3:1 to 7:1 (*syn*/*anti*), this being the highest reported de for this type of reaction. These reactions were generally carried out with achiral allyl reagents. With a racemic organometallic, there is an additional factor of differing rates for the enantiomeric organometallics on a given face of the aldehyde. In some cases this can lead to a *mutual kinetic resolution*, where one enantiomer of the reagent reacts, for all intents and purposes, with one enantiomer of the aldehyde. The reaction of (±)-2-phenylpropionaldehyde, **5**, with (±)-CpMo(NO)(η^3-methallyl)Cl, **2**, to give the diastereomeric 5-methyl-2-phenylhex-5-en-3-ols, **6**, was found to be very slow and to proceed with very low diastereoselectivity (Table 2, entries 1–5). This indicates that there is not a large rate difference between the different enantiomers of the aldehyde with a particular enantiomer of **2**; however, there is some tendency toward forming the *syn* isomer (**6a** and **6c**), as expected from Cram's rule (Eqns [3a], [3b]).

Using the camphorsulfonate reagent, **1**, decreased the reaction time but did not increase the de of the products, suggesting that the intrinsic



(*R*)-5 Cram anti-Cram [1]



[2]

diastereofacial selectivity shown by **5** is low for any of these organomolybdenum reagents. Reaction of (−)-NMCpMo(NO)(η^3-methallyl)Cl with excess **5** did not show a significant kinetic selectivity as indicated by the ratio of diastereomers, but did proceed to give each diastereomer in 96% ee. Thus, it follows that the pure (*S*)-Mo complex should yield nearly exclusively **6a** and **6d** upon reaction with (*R*)-**5** and (*S*)-**5**, respectively. Furthermore, it follows that for the racemic molybdenum reagent, reaction of (*R*)-**5** produces predominantly **6a** whereas (*S*)-**5** produces predominantly **6c** owing to the modest rate preference for forming *syn* products.

Reactions with nonracemic aldehydes

Reaction of (±)-**2** with (*R*)-(−)-3-benzyloxy-2-methylpropanal, (*R*)-**9**, yielded 1-benzyloxy-2,5-dimethyl-5-hexen-2-ol, **10**, in a *syn*/*anti* ratio of 51:49 (Eqn [4a]). A *syn*/*anti* ratio of 1:5 for the addition of isopropyl MgBr to **9** has been previously reported.[9] Although the de was low for the racemic molybdenum chloride compound, as one might have anticipated, it was greatly increased when diastereomerically and enantiomerically pure allylmolybdenum complexes were used (Table 3). The preparation of **9** involves a Swern oxidation, a step that often yields a product of only modest enantiomeric purity (~70%) when carried out on a scale of several grams. In multistep syntheses, products in lower ee are sometimes acceptable because diastereomers are formed in reactions with enantiomerically pure reagents later in the synthesis which allow separation. The results in Table 3 do not reflect the overall stereochemistry of the reaction because the enantiomeric purity of **9** was only 72% ee. Thus the minor product is really the other diastereomer, i.e. in entry 1 the major product is **10a** and the minor product is **10d**, which is the enantiomer of **10b** (this can be shown with a chiral shift reagent experiment with the product alcohols). Therefore, reactions performed with 100% de molybdenum complex could have only yielded products with a maximum of 72% de in these experiments with 72% ee aldehyde. The highest de achieved with these molybdenum complexes is 68% (Table 3, entries 1, 3 and 6). Thus the overall stereochemistry for this reaction is very high, although the observed de is not.

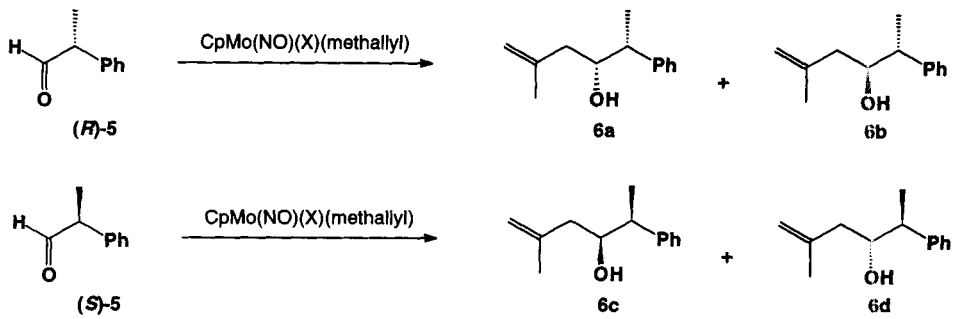
Reaction of (+)-**1** (90% de) with >95% de (*S*)-(+)-3-benzyloxy-2-methylpropanol, (*S*)-**9**, yielded 1-benzyloxy-2,5-dimethyl-5-hexen-2-ol, **10c**, in 90% de (Eqn [4b]; Table 4). Thus if one had 100% ee in both reagents, one would expect >99% de and ee in the product.

In conclusion, our allylmolybdenum complexes are very effective for chiral α-substituted aldehydes as well as aryl, alkyl and unsaturated aldehydes.[2] These complexes can overcome the inherent selectivity of the chiral aldehydes and

Table 1 Reaction of CpMo(NO)(η^3-methallyl)X and D-glyceraldehyde acetonide, **7**

Entry	Mo complex (−/+)	Mol equiv. of **7**	Conc. of Mo complex (mol l^{-1})	Time (h)	Conversion (%)	**8a**/**8b**,[a] *syn*/*anti*
1	**1** (94:6)	4	0.61	1	100	92:8
2	**1** (6:94)	4	0.76	1	100	8:92
3	**1** (98:2)	2	0.55	1	100	98:2
4	**2** (50:50)	4	1.44	1	100	48:52
5	**2** (98:2)	2	0.50	23	100	95:5
6	**3** (98:2)	2	0.55	23	94	93:7

[a] The ratios of products were determined by 490 MHz ^{1}H NMR in C_6D_6. The resonances selected for analysis were the olefin protons at δ 4.97–4.87 and the methyl protons at δ 1.81 and 1.74.



[3]

can yield either the Cram or the anti-Cram products with high stereoselectivity. The camphorsulfonate complexes can be made on a gram scale and the separation of the diastereomers is facile, as is the conversion to the halide. These allylmolybdenum complexes are air-stable and can be stored indefinitely.

EXPERIMENTAL

All manipulations were performed using standard Schlenk conditions. Deuterated solvents were purchased from CID Isotopes and were dried with 4 Å molecular sieves. Triethylamine, dichloromethane (CH_2Cl_2) and acetonitrile were purified by distillation from calcium hydride (CaH_2) under nitrogen before use. The tetrahydrofuran (THF) was purified by distillation from potassium benzophenone under nitrogen before use. All other solvents were of analytical grade and were used without further purification. Adsorption alumina (80–200 mesh) and silica gel (100–200 mesh) were purchased from Fisher. Preparative TLC was performed using silica gel plates (60 F_{254}) purchased from EM Science. All NMR spectra were acquired on Bruker 250 MHz, QE 300 MHz and Yale 490 MHz spectrometers. Chemical shifts are reported in ppm downfield from TMS. IR data were obtained using a Nicolet 5-SX FT-IR spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter using a thermostated cell. GC separations were performed on a chiral liquid-phase Cyclodex-B column (30 m × 0.25 mm) purchased from J & W Scientific.

D-Glyceraldehyde acetonide, **7**, was prepared from D-mannitol diacetonide and was used after vacuum distillation.[10] The nonracemic 3-benzyloxy-2-methylpropanols, **9**, were synthesized from the appropriate methyl 3-hydroxy-2-methylpropionate.[11] There is an inversion of configuration in the synthesis; hence, (*S*)-(+)-3-benzyloxy-2-methylpropanal is obtained from the (*R*)-(−)-3-hydroxy-2-methylpropionate.[11]

Reaction of CpMo(NO)(X)(η^3-methallyl) and aldehydes

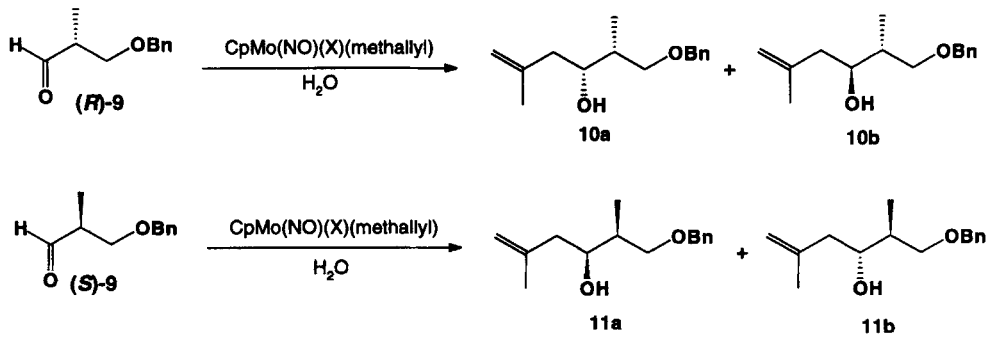
All experiments were performed using a general method. In a typical reaction, 1 equiv. of CpMo(NO)(η^3-methallyl)X and 2 equiv. of the

Table 2 Reaction of CpMo(NO)(η^3-methallyl)X and 2-phenylpropionaldehyde, **5**

Entry	Mo complex	Mol equiv. of **5**	Concn. of Mo complex (equiv. Mo ml^{-1})	Time[a] (h)	(**6a**+**6c**)/(**6b**+**6d**),[b] *syn*/*anti*
1	**2**	4	0.10	24	61:39
2	**2**	1	0.20	36	60:40
3	**2**	2	0.10	7	63:37
4	**1**	2	0.15	18	56:44
5	**1**	2	0.25	3	57:43

[a] The reaction times indicate the time required for >95% conversion of the molybdenum complexes.

[b] The ratio of the *syn* and *anti* products were determined by 250 or 490 MHz ^{1}H NMR using the signals at δ 1.70 and 1.76, respectively.



aldehyde were allowed to react in the presence of 1 equiv. of dichloroethane (δ 3.70), as an internal integration standard, in an NMR tube with CD_2Cl_2. The reaction was monitored by ^1H NMR spectroscopy (300 MHz) and was considered complete upon the disappearance of the Cp^- resonance of the starting material. The product was purified after isolation by preparative TLC with CH_2Cl_2 as an eluent.

NMR spectra

NMR spectroscopy provided the most useful method of identifying and measuring relative percentages of products. The chiral gas-chromatography (GC) column allowed determination of ratios of diastereomers of **10**, but did not separate the enantiomers. The enantiomers of **10** were best distinguished with chiral shift reagent experiments (see below).

NMR data for 6a and 6b

^1H and ^{13}C NMR spectra were the same as those previously reported.[5]

NMR data for 8a

^1H NMR (C_6D_6, 490 MHz): δ 4.97 (s, 1H), 4.94 (s, 1H), 3.94–3.98)m, 1H) 3.80–3.87 (m, 2H), 3.66–3.70 (m, 1H), 2.45 (dd, 1H, J = 8.6, 14 Hz), 2.15 (dd, 1H, J = 4.5, 1 Hz), 1.81 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.55, 25.37, 26.66, 29.77, 42.14, 66.07, 69.89, 78.69, 113.65, 141.78.

NMR data for 8b

^1H NMR (C_6D_6, 490 Mhz): δ 4.92 (s, 1H), 4.87 (s, 1H), 4.05–4.15 (m, 2H), 3.97 (q, 1H), 3.87 (m, 1H), 2.42 (dd, 1H, ZJ = 3.6, 14 Hz), 2.15 (dd, 1 H, J = 9.2, 14 Hz), 1.74 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.37, 25.33, 26.65, 29.77, 41.75, 65.41, 69.81, 78.41, 113.76, 141.92.

Table 3 Reaction of CpMo(NO)(η^3-methallyl)X and (*R*)-(−)-3-benzyloxy-2-methylpropanal, (*R*)-**9**

Entry	Mo reagent (−/+)	Mol equiv. of **9**[a] (72% ee)	Conc. of Mo complex (mol l^{-1})	Time (h)	Conversion (%)	(**10a** + **10c**)/(**10b** + **10d**),[b] *syn*/*anti*
1	**1** (97:3)	2	0.37	2	100	84:16[c]
2	**1** (3:97)	2	0.32	2	100	17:83[d]
3	**1** (98:2)	2	0.32	3	100	84:16[c]
4	**2** (50:50)	2	0.35	17	100	51:49
5	**21** (98:2)	2	0.45	17	100	83:17
6	**3** (2:98)	2	0.41	17	95	16:84
7	**4** (2:98)	2	0.34	42	80[e]	18:82

[a] The ratio of (*R*)-**9**:(*S*)-**9** was 86:14; therefore values for *syn*/*anti* products could only range from 86:14 to 14:86, even if the reaction were 100% stereoselective.

[b] The ratios of products were determined by GC at 140 °C. The retention time for *anti* product, **10b** and **10d**, was 88.2 min and for the *syn* product, **10a** and **10c**, it was 90.5 min.

[c] Shift reagent experiments indicate that the product is 82% **10a** and 16% **10d**.

[d] Shift reagent experiments indicate that the product is 16% **10b** and 81% **10c**.

[e] The aldehyde proton resonance at δ 9.75 had disappeared although the Cp proton was still present, suggesting that a side reaction was also consuming the aldehyde.

Table 4 Reaction of CpMo(NO)(η^3-methallyl)L[a], **1**, and (*S*)-(+)-3-benzyloxy-2-methylpropanal, (*S*)-**9**[a]

Entry	Mo reagent (−/+)	**10c/10d** *syn/anti*[b]
1	93:7	7:93
2	5:95	95:5

[a] The enantiomeric purity of (*S*)-**9** was >95%.
[b] *Syn/anti* ratios were determined by NMR and GC.

NMR data for 10a and 10c

^{1}H NMR ($CDCl_3$, 490 MHz): δ 7.24–7.33 (m, 5H), 4.83 (s, 1H), 4.77 (s, 1H), 4.50 (s, 2H), 3.93 (m, 1H), 3.48–3.54 (m, 2H), 2.10–2.20 (m, 2H), 1.87 (m, 1H), 1.74 (s, 3H), 0.95 (d, 3H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$, 123 MHz): δ 10.81, 22.38, 29.69, 37.76, 42.84, 70.71, 73.38, 74.45, 112.92, 127.59, 128.41, 143.09. (These data correlate well with those previously reported).[6]

NMR data for 10b and 10d

^{1}H NMR ($CDCl_3$, 490 MHz): δ 7.23–7.34 (m, 5H), 4.84 (s, 1H), 4.77 (s, 1H), 4.50 (s, 2H), 3.68 (m, 1H), 3.49–3.58 (m, 2H), 2.08–2.27 (m, 2H), 1.86 (m, 1H), 1.75 (s, 3H), 0.95 (d, 3H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$, 123 MHz): δ 13.98, 22.37, 38.51, 43.42, 72.39, 73.37, 73.99, 113.04, 127.59, 127.64, 128.39, 138.04, 143.16. (These data correlate well with those previously reported).[7]

Shift reagent data for 10

The 5-methyl singlets of **10a**, **10c**, **10b** and **10d** are superimposed at δ 1.75. Upon the addition of [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]$_3$Eu the apparent singlet splits into four singlets. In a typical experiment (490 Mhz), observed shifts are: δ 2.049 (**10a**); δ 2.139 (**10b**); δ 2.307 (**10c**); and δ 2.480 (**10d**). These experiments allow determination of the enatiomeric composition of the diastereomeric ratios determined by conventional NMR experiments. With the relatively high enantiomeric purities observed, however, the accuracy of the enantiomer ratios can be poor owing to overlap of peaks; therefore the tables generally report diastereomeric ratios **(10a + 10c)/(10b + 10d)**.

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