

Observations on Selectivity Reversal during Chiral Auxiliary-directed Asymmetric Nucleophile Additions to Arene–Manganese Tricarbonyl Complexes

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A study of hydride nucleophile reactions with η^6 -(2R, 5R)-dimethylpyrrolidinybenzene–manganese tricarbonyl hexafluorophosphate **1** reveals an unexpected reversal of selectivity during addition of hydride to the diastereotopic *meta* carbons, which is explained on the basis of changes in transition state location as the reactivity of the nucleophile is varied.

Addition of nucleophiles to arene–transition metal complexes leads to important methodology for the conversion of aromatic molecules to substituted cyclohexadienes or cyclohexenones,¹ but few successful approaches have been documented for obtaining asymmetric induction during the key nucleophile addition reactions.² We recently reported³ on nucleophile additions to arene–manganese complex **1**, which gave products of structures **2** and **3**, with the former in excess. We rationalized our observations on the basis of steric approach control, whereby nucleophilic attack is preferred at the sterically more accessible *meta* position (C6 in structure **1**; this numbering is consistent with that used in our earlier X-ray structure).

We now report an unexpected reversal of selectivity which occurs when less reactive nucleophiles are added to complex **1**. This phenomenon was first observed when **1** was allowed to react with NaBH₄ or LiBH₄, whereupon a 1:4 mixture was obtained in favour of **3** (R = H).[†] The assignment was confirmed by an X-ray crystal structure determination on the major product.[‡] The results of a series of hydride additions are collected in Table 1, which includes the reactions of **1** with PhMgBr and MeLi, the latter also giving reversed selectivity compared with PhMgBr.[§] Clearly, our earlier analysis of this stereoselectivity is inadequate.

There are a number of possible explanations for such a reversal of selectivity. First, a change in mechanism was ruled out by deuterium labelling studies, wherein it was observed that

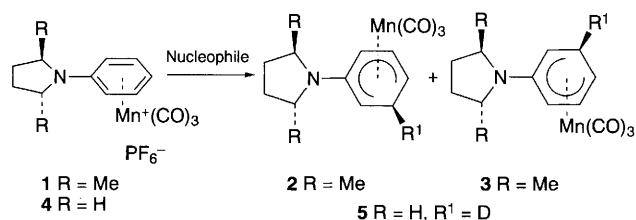


Table 1 Diastereoselectivities observed during hydride additions to complex **1** (all at -78°C in THF). Results of PhMgBr and MeLi additions are included for comparison

Nucleophile	Yield (%)	2:3
Li(C ₅ H ₁₁) ₃ BH	84	11.5:1 ^a
Na(C ₄ H ₉) ₃ BH	82	5.7:1
Li(C ₄ H ₉) ₃ BH	77	5.1:1
LiEt ₃ BH	75	2.8:1
LiAlH ₄	81	2.1:1
Li(Bu ^t O) ₃ AlH	70	1.4:1
LiBH ₄	85	1:3.8
NaBH ₄	80	1:4.3
PhMgBr	60	95:5
MeLi	57	1:3 ^b

^a The ratio was 13:1 at -100°C in THF, while in CH₂Cl₂ at -95°C a 24:1 ratio of diastereoisomers was obtained using this reagent. ^b This reaction was run in CH₂Cl₂ at -90°C ; a complex mixture of products was obtained from reactions run in THF. In contrast PhMgBr–CH₂Cl₂ gave a 14:1 mixture in favour of isomer **2**, but in low yield.

complex **4** gave the same product **5** on reaction with either LiAlD₄ or NaBD₄. Thus, LiAlH₄ and NaBH₄ both react by direct delivery of hydride to the arene ring *anti* to the manganese, rather than one taking an indirect pathway *via* attack at CO ligand or metal, which would result in *syn* addition.⁴ A second possible explanation would require that certain nucleophiles add to **1** under steric approach control, to favour product **2**, while others might react under orbital and/or charge control. Differentiation between the electronic effects at the two *meta* positions might result from distortion of the arene–Mn(CO)₃ structure, which has in fact been shown to occur. Thus, molecular modelling (PCModel[®]) and X-ray crystal structure determination³ both show a rotation of the Mn(CO)₃ group away from perfect alignment with the C–N bond and *meta* carbons (Fig. 1), although no difference in C–Mn bond lengths was observed for the two *meta* positions. That any accompanying electronic effects, such as changes in FMO coefficients and/or charge distribution, act in *opposition* to steric approach control was ruled out by the following observations.

The ¹³C NMR spectrum of **1** shows C6 at slightly lower field (δ 106.4) than C8 (δ 105.8). This observation suggests that C6 is slightly more electrophilic than C8, but the charge difference is insufficient to account for the 95:5 diastereoselectivities that are observed during reactions with PhMgBr and Li(C₅H₁₁)₃BH. *Ab initio* calculations (GAUSSIAN 92) on complex **1** were run with a minimal basis set (STO-3G),⁵ using atom coordinates from the X-ray crystal structure. These calculations are in good agreement with the ¹³C NMR data, gross orbital populations at C6 and C8 being 1.00164 and 1.02675, respectively. The arene carbon coefficients for the frontier MOs are shown in Fig. 2. The HOMO and LUMO show only slight differences in coefficients at C6 and C8, but both of these orbitals would favour addition at C6. As with many transition metal π -complexes, a cluster of orbitals is obtained in the energy range of the LUMO.⁶ In the present case, the SLUMO shown in Fig. 2 is 0.02686 a.u. higher in energy than the LUMO. This orbital has a significantly greater coefficient at C6 and C8, and might well become involved in bond formation with energetic nucleophiles. Overall, the present work indicates that steric approach control, charge control and FMO control all favour nucleophile addition at *meta* carbon C6. Consequently, an alternative explanation must be sought for the observed nucleophile-dependent selectivity reversal.

The above results led to a consideration of possible changes in the position of the transition state (TS) as the nucleophile is

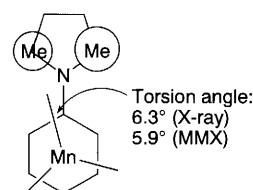


Fig. 1 Structure of complex **1** showing rotation of Mn(CO)₃ group away from axial methyl

varied. Intuitively, one might anticipate that very reactive nucleophiles would add to **1** via an early TS, while a late TS would be favoured for less reactive nucleophiles. It is known⁷ that primary kinetic isotope effects are maximum (k_H/k_D ca. 9–10 for C–H bond breaking) for reactions that involve a symmetrical TS, while k_H/k_D is smaller for both early and late TSs. In order to determine k_H/k_D , we carried out competition studies on complexes **1** and **4**, using the commercially available hydride/deuteride systems $\text{LiEt}_3\text{BH}(\text{D})$, $\text{LiAlH}_4(\text{D}_4)$, and $\text{NaBH}_4(\text{D}_4)$, and the results are summarized in Table 2. Complex **4** was employed as a cross-check using a system in which NMR estimates are not compromised by the presence of varying proportions of diastereoisomers; in the present case, H/D ratios were determined by both ^1H NMR and mass spectrometry, which gave excellent agreement. The results of kinetic isotope effects are consistent with the postulate that a later TS is involved when less reactive nucleophiles are employed,⁸ but at the present time the precise location of transition states for each nucleophile cannot be determined.

We propose that reactions of **1** involving early transition states proceed under a combination of steric approach and orbital control, both of which favour addition at *meta* carbon C6. Such a postulate is consistent with there being very little C–Nu bond formation at the energy maximum, and with the possibility that very reactive nucleophiles might experience a strong interaction with the SLUMO of the complex. Less reactive nucleophiles experience a late TS, and in these cases there should be a correlation between product ratios and relative stability, the latter being reflected in the energies of the diastereoisomeric transition states. The reaction of **1** with $\text{Li}(\text{Bu}^t\text{O})_3\text{AlH}$ is noteworthy in this regard (Table 1), since it is a sterically demanding nucleophile of diminished reactivity compared with LiAlH_4 .[¶]

In summary, we believe the data reported herein indicate that the asymmetric reaction of nucleophiles with complexes of

general structure **1** can be tuned to favour either mode of *meta* addition by judicious choice of nucleophile. We propose that the position of the transition state is of the utmost importance in determining the outcome of these reactions, suggesting that design of reaction parameters can be accomplished to maximize stereocontrol in either direction.

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Footnotes

† Consistent patterns are observed in the ^1H NMR spectra of these complexes, corresponding to the diastereoisomers **2** and **3**. In the case of hydride addition products, the H(3) resonance is observed as a doublet of doublets (J 5.9, 2.3 Hz), at δ 4.79 for **2** and δ 4.69 for **3**. Integration of these peaks provided an estimate of diastereoselectivity.

‡ The X-ray crystal structure determination of complex **3** ($\text{R}^1 = \text{H}$) was performed by Professor John Protasiewicz and Ms Rebecca Zaniewski, Department of Chemistry, Case Western Reserve University. Details will be published elsewhere.

§ In our earlier publication³ we assigned the incorrect stereochemistry (**2**) to the major product from reaction of **1** with MeLi , based on the assumption that all nucleophiles would be under steric approach control. With the acquisition of a more extensive NMR data set, it is clear from the consistent trends observed for all sets of diastereoisomers that structure **3** ($\text{R}^1 = \text{Me}$) must be assigned to this product. (The reversal observed for PhMgBr compared with MeLi is not due to a change in the counterion, since PhLi gives diastereoselectivity analogous to PhMgBr .³)

¶ It should be noted that LiAlH_4 and NaBH_4 are both essentially insoluble in THF at the reaction temperature, and so these reactions are not homogeneous, therefore not amenable to absolute rate measurements. All the other reactions in Table 1 are essentially solution phase, although complex **1** is only partially soluble. Since NaBH_4 and LiBH_4 give very similar diastereoselectivities, it does not appear that reversal of selectivity is a function of reaction homogeneity.

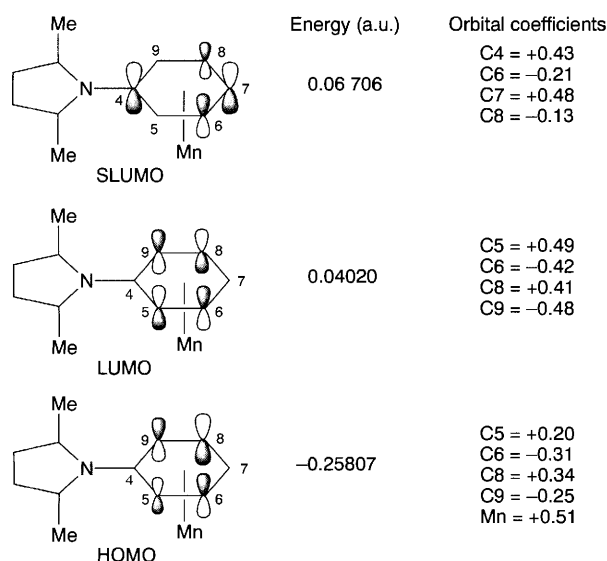


Fig. 2 FMO coefficients and energy levels for complex **1**

Table 2 Primary kinetic isotope effects for hydride additions to complexes **1** and **4**

Complex	Hydride source	k_H/k_D
4	$\text{LiEt}_3\text{H}(\text{D})$	1.3
4	$\text{LiAlH}_4(\text{D}_4)$	2.2
4	$\text{NaBH}_4(\text{D}_4)$	5.5
1	$\text{LiEt}_3\text{H}(\text{D})$	1.2
1	$\text{NaBH}_4(\text{D}_4)$	5.3

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