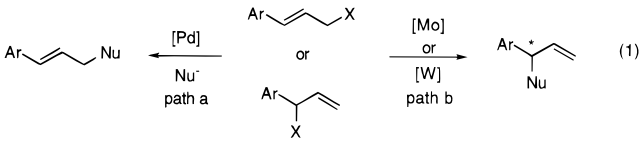
Asymmetric Molybdenum-Catalyzed Alkylations

Barry M. Trost* and Iwao Hachiya

Department of Chemistry, Stanford University
Stanford, California 94305-5080

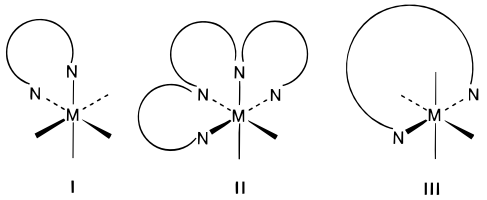
Received September 19, 1997

Interest in molybdenum-[1,2] and tungsten-catalyzed[3] reactions of allyl substrates with nucleophiles stemmed from the issue of regioselectivity. Most notably, with aryl-substituted allyl systems, palladium-catalyzed reactions normally provide products from attack at the less substituted terminus, even with chiral ligands (eq 1, path a).[4] On the other hand, molybdenum and tungsten



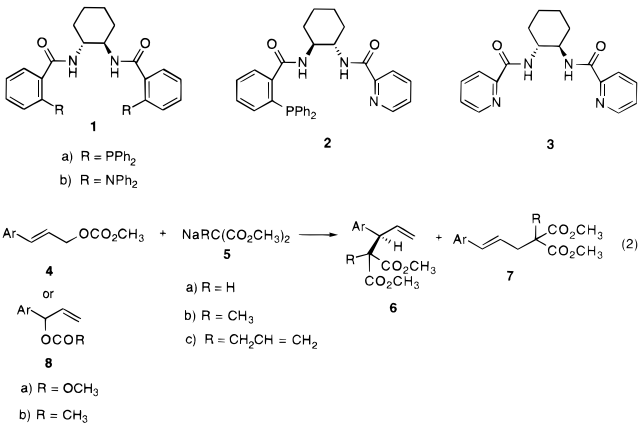
(1)

catalysts favor attack at the more substituted terminus (eq 1, path b). The value of products of the latter type as building blocks makes a highly regio- and enantioselective method desirable. A recent report utilizing tungsten with phosphinooxazoline ligands with only dimethyl malonate as the pronucleophile proved promising, whereas the isostructural molybdenum complex was described as "not useful as a catalyst".[5] Early studies in our laboratories utilizing a variety of chiral nitrogen-based ligands for molybdenum failed to give any appreciable asymmetric induction.[6,7] In both cases, ligation of the octahedral complexes involves structures such as **I**. Creating helical-like chiral



complexes represented by **II** may create a more effective chiral environment. An alternative might be to bridge in a trans fashion as in **III**. We report our recent preliminary observations designed toward complexes of these latter types that have led to reactions according to path b of eq 1 with high regioselectivity as well as enantioselectivity.

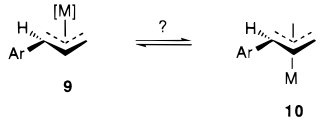
Initial experiments focused on the use of tungsten with chiral ligands **1**,[8] **2**,[9] and **3**.[10] The catalyst was generated by stirring a



1:1.5 mixture of $(C_2H_5CN)_3W(CO)_3$:ligand in THF at 60 °C. The test reaction employed the cinnamate **4** (Ar = Ph) with dimethyl sodiomalonate (**5a**) in THF at reflux. With ligands **1a**, **1b**, and **2**, the reaction either failed or generated only trace amounts of products. These results mirror our earlier results which suggested that phosphines deactivated the tungsten catalyst compared to pyridines.[3] On the other hand, the Pfaltz[5] ligand system involves both a phosphine and an imine. The first sign of some success came in the use of the nitrogen ligand **3** whereby, with 5 mol % of catalyst, a low yield of a 19:1 ratio of **6**:**7** (Ar = Ph, R = H), where **6** had an enantiomeric excess (ee) of 98% was observed. Increasing the catalyst to 15 mol % increased the yield to 55% and the **6**:**7** ratio to 49:1 with **6** still having 98% ee.

In contrast to the results of Pfaltz, switching to the molybdenum system proved better. As summarized in Table 1 (entry 1), repeating the above but replacing the tungsten complex by $(C_2H_5CN)_3Mo(CO)_3$ gave an 88% yield of a 97:3 ratio of **6**:**7** (Ar = Ph, R = H) with **6** having an ee of 99%. Lowering the temperature to room temperature (entry 2) still provided a good yield and somewhat improved regioselectivity while maintaining a high ee.

A key question relates to the mechanism of the asymmetric induction. Since **4** is achiral, the catalyst may differentiate the enantiotopic faces leading preferentially to π-allylmolybdenum complex **9** or **10** and then onto product. Alternatively, the two diastereomeric π-allylmolybdenum complexes **9** and **10** may be in dynamic equilibrium (eq 3) in which the enantiodifferentiation



(3)

occurs by preferential nucleophilic attack on **9** or **10**. Starting from the chiral substrate **8** (Ar = Ph) differentiates these two possibilities. If the first scheme operates, either a kinetic resolution or racemic product would be observed. In the latter instance, we should see results similar to those obtained with the achiral allylic substrate **4**. As shown in entries **3** and **4**, the results starting with **8** (Ar = Ph) mostly mirror those starting from **4** (Ar = Ph) (entries 1 and 2). While the observed small differences

(1) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543; **1987**, *109*, 1469. Trost, B. M.; Lautens, M. *Tetrahedron* **1987**, *43*, 4817 and references therein. Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9590.

(2) For early work on stoichiometric π-allylmolybdenum alkylations, see: Adams, R. D.; Chodosh, D. F.; Faller, J. W.; Rosan, A. M. *J. Am. Chem. Soc.* **1979**, *101*, 2570. McCleverty, J. A.; Murray, A. J. *J. Organomet. Chem.* **1978**, *149*, C29. For more recent work, see: Rubio, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 891.

(3) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757. Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176.

(4) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 585−662. (b) However, for a recent interesting exception with Pd catalysis, see: Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561.

(5) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.

(6) Merlic, C. A. Ph.D. Thesis, University of Wisconsin, 1988.

(7) For asymmetric alkylations with enantiomerically pure stoichiometric complexes, see: Faller, J. W.; Chao, K.-H. *J. Am. Chem. Soc.* **1983**, *105*, 3893. Faller, J. W.; Chao, K.-H. *Organometallics* **1984**, *3*, 927. For an overview, see: Faller, J. W.; Mazzieri, M. R.; Nguyen, J. T.; Parr, J.; Tokunaga, M. *Pure Appl. Chem.* **1994**, *66*, 1463.

(8) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(9) Richter, W. Unpublished work in these laboratories.

(10) Chapman, R. L.; Vagg, R. S.; Watton, E. C.; Barnes, D. J. *J. Chem. Eng. Data* **1978**, *23*, 349. Also see: Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023.

S0002-7863(97)03298-8 CCC: $15.00
Published on Web 01/23/1998

Table 1. Mo-Catalyzed Asymmetric Allylic Alkylations[a]

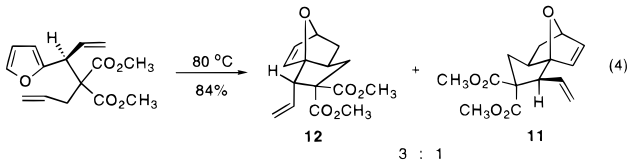
entry	**4** or **8**, Ar	**5** R	*T*, °C	time, h	% yield[b]	**6**:**7**	% ee[c,d] of **6**
1	**4**, Ph	H	reflux	3	88	32:1	99
2	**4**, Ph	H	rt	3	70 (90)	49:1	99
3	**8a**, Ph	H	reflux	3	70	13:1	92
4	**8a**, Ph	H	rt	3	61 (68)	32:1	97
5	**8a**, 2-thienyl	H	reflux	2	78	19:1	88
6	**8a,** 2-pyridyl	H	reflux	2	69 (82)	8:1	96
7	**8a**, 1-naphthyl	H	reflux	2	82	99:1	87
8	**4**, Ph	CH_3	reflux	4	67	24:1	98[d]
9	**4**, 2-furyl	CH_3	reflux	2	71	32:1	97
10	**8b**, 2-furyl	CH_3	reflux	2	65	32:1	87
11	**8b**, 2-furyl	CH_3	rt	18	54	99:1	95
12	**8a**, 2-pyridyl	CH_3	reflux	2	71	5:1	94
13	**8a**, 2-thienyl	CH_3	reflux	2	71	13:1	75
14	**8b**, 2-furyl	$CH_2CH{=}CH_2$	rt	12	50	99:1	98[e]

[a] All reactions were performed with 10 mol % $(C_2H_5CN)_3Mo(CO)_3$ and 15 mol % **3** in THF at 0.1 M. [b] Isolated yields. Yields in parentheses are based upon recovered starting material. [c] Determined by chiral HPLC using Daicel Chiralcel OD and Chiralpak AD eluting with heptane-2-propanol. The major isomer assigned as *S* by comparison to the literature for **6** (Ar = Ph, R = H) and **6** (Ar = 1-naphthyl, R = H) and the rest by analogy. [d] Because of priorities, the same absolute configuration of the product derived from the substituted malonate with Ar = Ph corresponds to the *R* configuration. [e] The ee was determined on the subsequent transformation product.

suggest that both paths may be occurring to some extent, the major path involves nucleophilic attack on equilibrating π-allylmolybdenum complexes. Thus, either allylic regioisomeric starting material can be used with a preference for the achiral isomer.

Having established the ability to generate **6** (Ar = Ph) with excellent regio- and enantioselectivity, we examined variation of the aromatic ring. An electron-rich thiophene ring (entry 5)[11a] and an electron-deficient pyridine ring (entry 6)[11a] gave good selectivities. A bulkier naphthalene substrate (entry 7)[11b] still gave good results.

Increasing the steric bulk of the nucleophile by using **5b** still gave excellent results with both carbocyclic and heterocyclic substrates (entries 8,[11a] 9,[11a] 10,[11a] 11,[11a] and 12[12]). Only in the case of the thiophene substrate did we see a deterioration of the ee to 75% for the product[12] (entry 13), although no attempt has been made to optimize this reaction. The regioselectivity was still good. Increasing the steric bulk further by using the allylmalonate nucleophile **5c** did slow the reaction (entry 14),[13] but the regio- and enantioselectivities were still excellent. In this case, heating the alkylation product at 80 °C in 5:2 water:ethanol gave the diastereomeric Diels−Alder adducts **11** and **12** in a 3:1 ratio, each of which had an ee of 98% (eq 4) as determined by chiral HPLC. For the furan substrate bearing the leaving group at the secondary carbon, the acetate **8b** rather than carbonate **8a** ester was employed.



(4)

This asymmetric alkylation provides the first example of a practical catalytic system for molybdenum.[14] The remarkable insensitivity of the high selectivity over the temperature range 20−65 °C may suggest a fairly rigid chiral active site. While we have focused on reactions that cannot be achieved efficiently with palladium,[4b] this new catalytic system may be more generally useful. The regioselectivity observed here for attack at the more substituted terminus is generally significantly higher than with our earlier achiral molybdenum catalysts. For example, previous reactions with dimethyl methylmalonate and cinnamyl substrates normally led to attack at the less substituted allyl terminus even when catalyzed with molybdenum complexes.[1] With chiral ligand **3**, equally good selectivity for attack at the more substituted terminus occurs for both dimethyl malonate and its substituted analogues **5b**,**c**. The reactivity should be noted compared to other molybdenum catalysts bearing nitrogen ligands according to structure **I**. These reactions typically require heating at reflux for 24 h or more.[1,6] In contrast, the reactions reported herein typically proceed in 2−3 h at reflux and even room temperature suffices. We suggest that these results are more in accord with complexes of type **III** than of type **II**. Furthermore, molecular modeling indicates that complexes such as **III** are strongly preferred over **I** and **II** for ligand **3**.[15] In the case of type **III** complexes, the bridging ligand would promote ligand dissociation and would be coordinatively unsaturated. As a result, rates of ligand exchange (i.e., rates of substrates and products going on and off molybdenum) should be faster. In addition, a coordinatively unsaturated π-allylmetal complex should exhibit higher reactivity toward nucleophiles. Clearly, any further discussion should await structural characterization of the active complex. Trying to understand the sense of the stereochemical induction becomes very difficult here since it is not clear that this molybdenum reaction proceeds by a double-inversion or double-retention mechanism. With achiral molybdenum complexes, some evidence supports the notion that it proceeds via a double-retention pathway rather than the more common double-inversion pathway.[14,16] At this stage, this catalytic system represents an excellent approach for regio- and enantioselective alkylations at the more substituted terminus of cinnamyl-like systems. It also suggests that molybdenum-catalyzed processes at least complement palladium-catalyzed processes. Considering the lower cost of molybdenum compared to palladium, the prospects that it may be more generally useful will also be an important direction to pursue.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs and JSPS for a postdoctoral fellowship for I.H. Mass spectra were obtained from the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: General experimental procedures and characterization data for **6** (Ar = Ph, 2-furyl, 2-thienyl, 2-pyridyl, and 1-naphthyl, R = H, CH_3, or $CH_2CH{=}CH_2$) (6 pages). See any current masthead page for ordering and Web access instructions.

JA973298A

(11) (a) For the products of these reactions, see ref 3. (b) For the products of these reactions, see ref 5.

(12) All new products have been fully characterized spectroscopically and the elemental compositions established by combustion analysis.

(13) Trost, B. M.; Lautens, M.; Hung, M.-H.; Carmichael, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 7641.

(14) In a footnote, asymmetric induction in a catalytic process involving a *meso*-π-allylmolybdenum fragment is noted. See: Dvorák, D.; Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1995**, *117*, 6130.

(15) A CaChe molecular modeling system was employed for these calculations.

(16) Faller, J. W.; Linebarrier, D. *Organometallics* **1988**, *7*, 1670.