Stereochemistry of Molybdenum(0)-Catalyzed Allylic Substitution: The First Observation of a Syn−Syn Mechanism†

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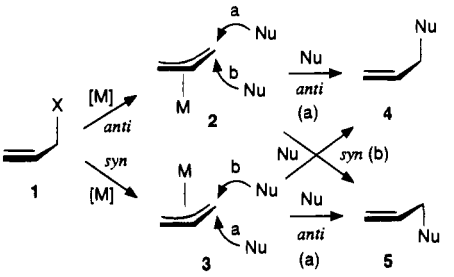
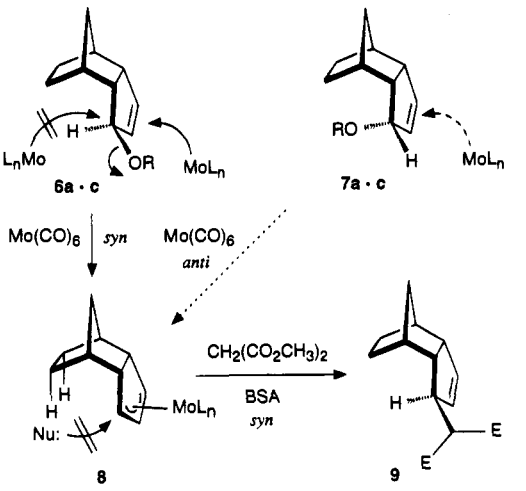
Palladium(0)-catalyzed allylic substitution occurs via η^3-complexes, which arise from allylic substrates almost invariably in an anti fashion (**1** → **2**; M = Pd).[1−4] The subsequent reaction and stabilized C-nucleophiles (e.g., malonates) again proceeds with an anti mechanism (Scheme 1), giving **4** (overall retention of configuration).[1] On the other hand, nonstabilized nucleophiles (e.g., PhZnCl) react with these complexes in a syn fashion to give **5** (overall inversion).[5,6] Trost has found that, like palladium, the molybdenum(0)-catalyzed substitution of allylic esters with malonates also gives predominantly or exclusively products of overall retention (**1** → **4**; M = Mo).[7] Although this outcome strongly implies an analogous mechanism (i.e., anti−anti) for Mo, it has never been rigorously proven.[7] The stoichiometric reaction has been found by Faller[8] and Liebeskind[9] to produce Mo−η^3-complexes via a syn pathway (**1** → **3**), which suggests that the actual mechanism for Trost's catalytic reaction might be syn−syn rather than anti−anti. However, the subsequent (stoichiometric) reaction with stabilized nucleophiles occurs with inversion (**3** → **5**).[8,9] Herein, we provide evidence for the *unprecedented syn−syn mechanism* (**1** → **3** → **4**) operating in the catalytic process, as obtained from the reactivity of allylic derivatives **6** and **7**.

Scheme 1



Scheme 2[a]



[a] **a**, R = CH_3CO; **b**, R = CF_3CO; **c**, R = $(CH_3)_2NCO$; E = CO_2CH_3.

The allylic acetate **6a** is known to be inert to Pd(0)-catalyzed allylic substitution,[3,6,10] whereas its epimer **7a** reacts readily with PhZnCl/Pd(0); however, **7a** in inert toward $LiCH(CO_2Me)_2$/Pd-(0).[6] This behavior has been rationalized as follows:[6] the *endo* face of **6a** is sterically hindered so that formation of the required η^3-complex in the anti fashion is precluded (Scheme 2). On the other hand, **7a** can readily produce the η^3-Pd-complex (analogous to **8**), which can react only with nucleophiles capable of a syn mechanism (i.e., **2** → **5**).[3,6] We reasoned that, should the syn−syn mechanism operate in the Trost Mo(0)-catalyzed reactions, **6a** ought to react with malonate/Mo(0), while **7a** should be inert.

We first explored the reaction of **6a** with the silyl enol ether, generated from dimethyl malonate and *N,O*-bis(trimethylsilyl)-acetamide (BSA),[11] in the presence of $Mo(CO)_6$ in toluene (method A) under conditions similar to those used by Trost.[7] Monitoring by GC showed that **6a**, indeed, reacted and that >90% conversion to **9** was reached in 6 h (Table 1; entry 1).[12] The reaction with $NaCH(CO_2Me)_2$ (method B) proceeded at a similar rate (entry 2). In sharp contrast, **7a** was inert toward the BSA conditions (entry 7) and a very slow reaction was detected with $NaCH(CO_2Me)_2$ (only 9% conversion at 110 °C/6 h; entry 8).

These experiments strongly support the syn−syn mechanism (**6a** → **8** → **9**).[13] We reasoned that the rate of the syn reaction may be boosted by an initial coordination of the Mo catalyst to

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(2) The syn mechanism has been observed in two instances as a result of precoordination of Pd(0) to the leaving group ($Ph_2PCH_2CO_2$ or Cl).[3,4]

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(10) In fact, **6a** reacts with PhZnCl/Pd(0) extremely slowly (in 2 days),[3b] which was not noticed in the original investigation.[6]

(11) Trost reported that dimethyl malonate/BSA exhibited better stereoselectivity in the Mo-catalyzed substitution than the lithium or sodium enolate.[7]

(12) Diagnostic for the proof of the *exo* configuration of **9** is the coupling pattern of 3-H (i.e., of the allylic hydrogen adjacent to the carbon carrying the substituent) in the ^1H NMR spectrum: whereas for the *exo* derivatives (e.g., **6a**, **6c**, their parent alcohol, and **9**) this proton has a vicinal coupling $J \leq 2$ Hz, the *endo* epimers **7** are characterized by $J \geq 9$ Hz.

(13) Control experiments showed that no **6a** ⇌ **7a** interconversion occurs.

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Table 1. Molybdenum-Catalyzed Allylic Substitution of **6** and **7** with Dimethyl Malonate[a]

					conversion (%)[c,d]			
entry	substrate	R	meth[b]	temp (°C)	1 h	2 h	4 h	6 h
1	**6a**	CH_3CO	A	100	18	41	84	92
2	**6a**	CH_3CO	B	100	19	46	96[e]	
3	**6b**	CF_3CO	A	100	8	12	25	34
4	**6c**	Me_2NCO	A	100	78	98	100	
5	**6c**	Me_2NCO	B	100	11	26	69[e]	
6	**6c**	Me_2NCO	C	110	41	71	100	
7	**7a**	CH_3CO	A	110	0	0	0	0
8	**7a**	CH_3CO	B	110	≤2	3	6	9
9	**7b**	CF_3CO	A	110	27	51	71	87
10	**7b**	CF_3CO	B	110	100			
11	**7b**	CF_3CO	B[f]	110	84	97	100	
12	**7c**	Me_2NCO	A	110	0	0	0	≤1
13	**7c**	Me_2NCO	B	110	1	2	4	6

[a] With 15 mol % $Mo(CO)_6$ in toluene. [b] A: with BSA. B: with NaH. C: no additive. [c] Determined by capillary GC as a disappearance of the starting material (with Ph_2O as an internal standard). [d] Isolated yields: 91% (entry 1); 90% (entry 2); 96% (entry 4); 73% (entry 11). [e] Rate determined by ^1H NMR for a one-flask competing experiment (**6a** vs **6c**). [f] No catalyst added.

the carbonyl oxygen of the acetoxy group.[14] Hence, increasing the electron density on this oxygen by electron donation should result in acceleration of the formation of the intermediate complex **8**, whereas electron withdrawal should slow down the syn reaction. Simultaneously, the electron-withdrawing effect should enhance the leaving capability of the group, thus favoring the anti mechanism. Trifluoroacetate is known to be a good leaving group in allylic substitution[15] and to have a non-nucleophilic carbonyl oxygen.[16] On the other hand, the carbonyl of carbamates is much more Lewis basic,[17] whereas the leaving capability of this group is modest.[3]

The epimeric trifluoroacetates **6b** and **7b** and carbamates **6c** and **7c** were therefore synthesized and submitted to reaction conditions identical to those applied to acetates **6a** and **7a**. Whereas **6b** has been found to react ca. 3 times slower (entry 3) than **6a**, substantial acceleration (ca. 2.5-fold) has been observed for carbamate **6c** (entry 4).[18] As expected by analogy with Pd(0),[19] **6c** reacted even in the absence of BSA or NaH (entry 6). The *endo* series exhibited an entirely opposite behavior: trifluoroacetate **7b** (entries 9 and 10) turned out to react much faster than acetate **7a** (entries 7 and 8), and the reaction was observed even in the absence of the catalyst (entry 11), which can be attributed to the enhanced leaving capability of the CF_3CO_2 group. Finally, carbamate **7c** was practically inert (entries 12 and 13).[20-22] All this behavior is in excellent agreement with the above hypothesis.

In conclusion, using the sterically biased allylic substrates **6a-c** and **7a-c**, we have demonstrated, for the first time, that Mo(0)-catalyzed allylic substitution can, indeed, occur as a syn-syn sequence, **6** → **8** → **9**.[23] Precoordination of the Mo catalyst to the leaving group appears to accelerate the formation of the intermediate η^3-complex via the syn mechanism, as demonstrated by the reaction rates for acetate, trifluoroacetate, and carbamate derivatives (compare entries 1, 3, and 4).[22] These findings show that Mo(0) can be used in those cases where Pd(0) fails, which considerably broadens the applicability of the transition-metal-catalyzed substitution. Moreover, in view of the syn delivery of the nucleophile, asymmetric induction (by chiral ligands) in the Mo-catalyzed substitution may become more promising than that in the Pd version.[24]

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Note Added in Proof. The complexes prepared from $(MeCN)_3W(CO)_6$ and chiral phosphanodihydrooxazoles have now been reported to exhibit high enantioselectivity (61-96% ee) for the reaction of allylic phosphates with $NaCH(CO_2Me)_2$: Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462.

Supplementary Material Available: Experimental procedures and spectral data for the new compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(18) Interestingly, method B gave the opposite result: **6a** reacts ca. twice as fast as **6c**.

(19) Carbonates do not require added base in the Pd(0)-catalyzed substitution since RO^- (a base) is formed from the $ROCO_2$ group in situ along with the η^3-complex (and CO_2): (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757. (c) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921. (d) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugihara, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. Carbamates exhibit the same behavior: (e) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449. (f) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1987**, *28*, 4837. (g) Minami, I.; Yuhara, M.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 2737.

(20) Note that, in the Pd(0)-catalyzed substitution, carbamates react in the same fashion as acetates and other leaving groups (i.e., anti).[3b]

(21) Dimethyl methylmalonate exhibits analogous reactivity under the same reaction conditions (A and B). Thus, 82% and 84% conversion, respectively, of **6a** into the methyl analogue of **9** was observed after 4 h at 110 °C. By contrast, **7a** was inert.

(22) The $Mo(CO)_6$-catalyzed reaction of (*R*)-(+)-PhCH=CHCH(OR)-CH_3 (**i**, R = Ac; **ii**, R = $CONMe_2$; ≥99% ee[3]) with $CH_2(CO_2Me)_2$/BSA in toluene or diglyme follows the same trend: **ii** reacts 2.5 times faster than **i**, producing a 2:1 mixture of the regioisomers $PhCH(CHE_2)CH{=}CHCH_3$ (**iii**) and $PhCH{=}CHCH(CHE_2)CH_3$ (**iv**). The latter isomer is formed with ≥90% overall retention of configuration (from both **i** and **ii**), as revealed by the analysis[3] of the ^1H NMR spectrum of the crude mixture in the presence of (+)-Eu(tfc)$_3$. The same level of retention has also been observed with $MeCH(CO_2Me)_2$/BSA in toluene. These results parallel those for **6** and **7** (implying the syn-syn mechanism) and demonstrate that sterically unbiased substrates can react with high stereoselectivity. By contrast, when BSA was replaced with NaH (in toluene), almost totally racemic product was obtained, which indicates competing mechanisms.

(23) The acetate **6a** failed to react with a stoichiometric amount of $Mo(CO)_6$ [in the absence of $CH_2(CO_2Me)_2$ and BSA or NaH], which supports the notion[7] that $(CO)_{6-n}Mo[CH(CO_2Me)_2]_n$, generated in the reaction mixture, is the actual catalyst.

(24) For the first attempts at asymmetric induction in the Mo-catalyzed allylic substitution (2-12% ee), see: Merlic, C. A.; Ph.D. Thesis, University of Wisconsin, Madison 1988, pp 184-222. Our preliminary experiments with a complex prepared from $Mo(CO)_6$ and 2,2'-bis[(4*S*)-4-benzyl-2-oxazoline] showed >80% ee for the conversion of **6a** into **9**.