Selective Reduction of Carbonyl Groups with Systems composed of $(\eta^5\text{-}C_5H_5)_2MoH_2$ and Protonic Acids: New highly Regio- and Diastereo-selective Reduction of Ketones

Takashi Ito,* Miho Koga, Susumu Kurishima, Makoto Natori, Norihiro Sekizuka, and Ken-ichiro Yoshioka

Department of Materials Chemistry, Faculty of Engineering, Yokohama National University, 156 Tokiwadai, Hodogaya-ku, Yokohama 240, Japan

The system consisting of $(\eta^5\text{-}C_5H_5)_2MoH_2$ and protonic acids such as RCO_2H, HCl, and $p\text{-}MeC_6H_4SO_3H$ reduced aldehydes and ketones under mild conditions chemoselectively; an extremely high diastereoselectivity was achieved by using the reaction intermediate $(\eta^5\text{-}C_5H_5)_2Mo(H)OSO_2C_6H_4Me\text{-}p$ in the reduction of 4-t-butylcyclohexanone.

It has long been known that the molybdenum(IV) dihydride $(cp)_2MoH_2$ (**1**) (cp = $\eta^5\text{-}C_5H_5$) has basic character and is easily protonated to give $[(cp)_2MoH_3]^+$ (**2**).[1] During the course of our detailed studies on the chemistry of this molybdenum trihydride with the formal oxidation number of 6,[2–4] we found that the system consisting of (**1**) and protonic acids (HA) such as carboxylic acids, HCl, and TsOH (Ts = $p\text{-}MeC_6H_4SO_2$) reduces aldehydes and ketones to yield the corresponding alcohols under mild conditions [equation (1)]. The system also reduced allylic alcohols† although it was unreactive to unsubstituted alkenes. It is interesting that (**1**) alone, which is inert to the carbonyl group, can be used in the catalytic hydrogenation of some alkenes.[5]

$$(cp)_2MoH_2 + 2\,HA + 2R^1(R^2)C{=}O \rightarrow \underset{(1)}{} \quad 2R^1(R^2)CHOH + \underset{(3)}{(cp)_2MoA_2} \qquad (1)$$

Some of the results are shown in Table 1. Acetaldehyde and acetone are reduced by this system easily at room temperature, while ethyl acetate was not reduced at all. α,β-Unsaturated ketones were reduced to yield saturated ketones and alcohols indicating that 1,4-reduction takes place. An important feature of this reducing system is that the diacetate (**3**) (A = AcO) produced can be converted quantitatively to the starting (**1**) by treatment with $NaBH_4$ in propan-2-ol. Thus the complex can be recycled.

The stereochemistry of the carbonyl reduction was examined by using substituted cyclohexanones as the substrate. The reduction of 4-t-butylcyclohexanone afforded *cis*-4-t-butylcyclohexanol as the main product when >2 equiv. of acid, *e.g.* RCO_2H (R = CF_3, Me, Et, or Bu^t), HCl, or TsOH were used. The diastereoselectivity was found to decrease with increasing bulk of the alkyl group in carboxylic acids and by reducing the amount of acid. In particular, use of 1 equiv. of TsOH resulted in inversion of the diastereoselectivity from excess of the *cis*-isomer to excess of the *trans*-isomer as shown in Figure 1.

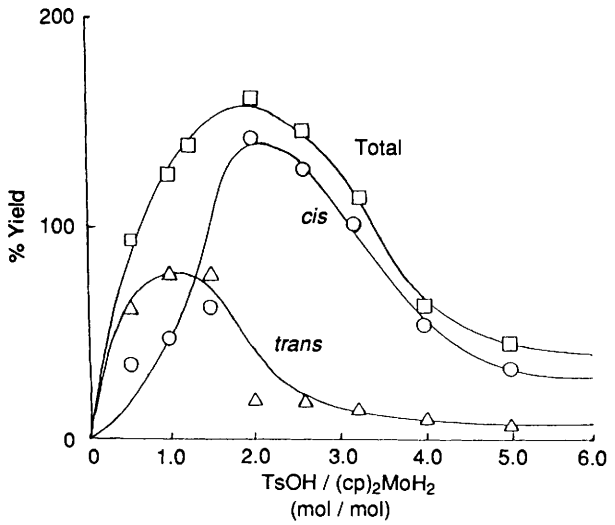

Figure 1. Dependence of diastereoselectivity on the relative proportion of acid in the reduction of 4-t-butylcyclohexanone to 4-t-butylcyclohexanol using $(cp)_2MoH_2$ and TsOH in tetrahydrofuran at room temperature.

$$(cp)_2MoH_2 \underset{(1)}{} \xrightarrow[(i)]{HA,\ R^1R^2C{=}O} \underset{(4)}{(cp)_2Mo(H)A} + R^1R^2CHOH$$

$$\underset{(4)}{(cp)_2Mo(H)A} \xrightarrow[(ii)]{HA,\ R^1R^2C{=}O} \underset{(3)}{(cp)_2MoA_2} + R^1R^2CHOH$$

Scheme 1. Possible reaction pathway.

† Since the mechanism of the reduction of allylic alcohols is quite different from that for reduction of carbonyl groups, a detailed description of the former is not given in the present report and will be reported elsewhere.

Table 1. Reduction of organic carbonyl compounds with cp_2MoH_2 (**1**)/acetic acid (HOAc).[a]

Substrate	$(cp)_2MoH_2$ /mmol	AcOH, mol/mol (**1**)	Time /h	Product	(mmol[b])
MeCHO	0.470	71	0.5	$MeCH_2OH$	(0.785)
Me_2CO	0.520	50	24	Me_2CHOH	(0.931)
$CH_2[CH_2]_4CO$	0.501	70	24	$CH_2[CH_2]_4CHOH$	(0.787)
$MeCOCH{=}CH_2$	0.501	88	20	$MeCOCH_2Me$	(0.281)
				$MeCH_2CH(Me)OH$	(0.200)
$CH_2{=}CHCO_2Me$	0.292	60	24	$MeCH_2CO_2Me$	(0.304)
$CH_2{=}C(Me)CO_2Me$	0.406	43	72	Me_2CHCO_2Me	(0.053)
$MeCO_2Et$	0.369	62	62	No reaction	

[a] Room temperature. Large excess of substrate was used. [b] Yields are determined by GLC.

Similar results were obtained when 4-t-butylcyclohexanone was reduced with $(cp)_2MoH_2$ and acetic acid in methanol at 50 °C.‡

These stereochemical studies suggest that the reaction proceeds *via* two successive pathways, in which $(cp)_2Mo(H)A$ (**4**) is a key intermediate. Thus, in step (i) in Scheme 1, the starting dihydride (**1**) interacts with the substrate to give one mole each of alcohol and the monohydride (**4**). In the next step (ii), another mole of the substrate interacts with (**4**) to give a second mole of product together with the disubstituted molybdenum complex (**3**). The existence of two successive pathways (steps i and ii in Scheme 1) was further substantiated by following by ^1H NMR spectroscopy the reduction of 4-t-butylcyclohexanone with (**1**) and acetic acid in $[^2H_6]$benzene. Thus, the signal assignable to the cp protons of the monohydrido intermediate (**4**) (A = AcO) was observed at δ 4.77 during the reaction; the intensity of the signal increased during the first stage and decreased as (**3**) was formed. The diastereoselectivity may be rationalised by assuming that there is no stereoselectivity in step (i) whereas step (ii) proceeds highly selectively. In accord with this assumption, 100% selectivity (*cis*-isomer) was achieved when 4-t-butylcyclohexanone was reduced using independently prepared $(cp)_2MoH(OTs)$. The isolated yield of pure *cis*-4-t-butylcyclohexanol was 68% based on the ketone.

Two pathways are possible for both steps (i) and (ii), involving nucleophilic attack of the metal on the carbonyl carbon, the electrophilicity of which is enhanced by protonation at its oxygen atom, and involving initial protonation of (**1**) to give trihydride cation (**2**),[2] into the Mo–H bond of which the carbonyl group inserts giving an alkoxo intermediate. The former pathway, which is similar to those proposed for ketone and aldehyde reduction with $[Mo(CO)_5]^-$,[6] seems to be more plausible than the latter on the basis of detailed kinetic studies which will be reported elsewhere.

We thank the Ministry of Education, Science and Culture, Japan for support by a Grant-in Aid for Scientific Research (No. 63550640) and for Special Project Research (Nos. 62215013 and 63106004). T. I. thanks Shinsei-shigen-kyokai for financial support.

Received, 9th February 1990; Com. 0/00610F

‡ When 1 equiv. of acetic acid was used, reaction without a solvent was too slow at room temperature to give reasonable yields of the alcohol. However, the use of methanol as solvent resulted in a surprising enhancement of the rate so that high yields of the alcohol resulted from reactions at 50 °C.

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