On the Sense of the Enantioselection in Hydrogen Transfer Reactions from 2-Propanol to Ketones

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Abstract: An explanation for the reversal in the sense of the enantioselectivity observed in hydrogen transfer reactions from 2-propanol to ketones catalyzed by the ruthenium or osmium amino acidates $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)M(Aa)Cl]$ and $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)M(Aa)]_3[BF_4]_3$ [Aa = piperidine-2-carboxylate (pip), *N*-methyl-L-phenylalaninate (MePhe)] is given; the molecular structures of $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)Cl]$ (**1**), $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)]_3[BF_4]_3$ (**2**), $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)M(MePhe)Cl]$ [M = Ru (**3**), Os (**4**)] are also reported.

Keywords: amino acids; enantioselectivity; hydrogen transfer; osmium; ruthenium

Asymmetric reduction of prochiral ketones to give chiral secondary alcohols of high enantiomeric purity is a major application of homogeneous catalysis by chiral transition metal complexes.[1] Very recently, Noyori and coworkers have proposed a concerted mechanism for metal-catalyzed transfer hydrogenation of ketones. The mechanism operates for catalysts containing primary or secondary amines and implies the simultaneous transfer of a proton and a hydride through a six-membered metallacycle intermediate.[2]

Amino acids are inexpensive chiral compounds that have been used as ligands to build up new organometallic compounds which have proved to be excellent enantioselective catalysts for the hydrogen transfer reaction from 2-propanol to acetophenone.[3] When *N*-substituted α-amino acidates coordinate to a metal through the nitrogen this atom becomes a chiral center. This is the case for the piperidine-2-carboxylate (Pip), prolinate (Pro) or azetidine-2-carboxylate (Aze) (Figure **1 a**, n = 2, 1, or 0, respectively) or for the *N*-methylphenylalaninate (MePhe) (Figure **1 b**) metal complexes.

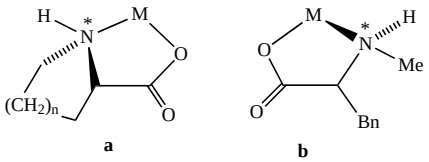

Figure 1. Chiral amino acidate nitrogen atoms.

Several molecular structures of prolinate complexes determined by X-ray diffractometric methods have been reported and, interestingly, the nitrogen always adopts the same configuration as the asymmetric amino acidate carbon.[4] Similarly, only diastereomers with equal configurations at both carbon and nitrogen have been detected in the crystal structures for azetidine-2-carboxylate complexes.[5]

In sharp contrast, we present here the molecular structures[6] of two L-piperidine-2-carboxylate containing osmium compounds, $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)Cl]$ (**1**) and $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)]_3[BF_4]_3$ (**2**), as well as two *N*-methyl-L-phenylalaninates, $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)M(MePhe)Cl]$ [M = Ru (**3**), Os (**4**)],[7] in which the most intriguing feature is that the nitrogen and the asymmetric carbon of the amino acidate present opposite configurations: S_C,R_N (Figure 2).[8] It seems worthy to comment that epimerization at nitrogen (or at carbon) has not been reported so far for half-sandwich transition metal amino acidate compounds.[9]

Previous studies from our group have shown that, in the hydrogen transfer reaction from 2-propanol to acetophenone, while the L-prolinate and L-azetidine-2-carboxylate ruthenium trimers $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Aa)]_3[BF_4]_3$ (Aa = L-Pro, L-Aze) gave an enantiomeric excess (ee) in *R*-2-phenylethanol, the related L-piperidine-2-carboxylate $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(L\text{-}Pip)]_3[BF_4]_3$ preferentially induces the formation of the *S* alcohol.[3b] Further experiments using as catalysts the new osmium analogues $\{(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Aa)]_3[BF_4]_3$, [Aa = L-Aze (**5**), L-Pro (**6**), L-Pip (**2**)]}, that we report here for the first time, reveal a similar behavior. Thus, the L-prolinate and L-azetidine-2-carboxylate complexes give the *R* alcohol and the L-piperidine-2-

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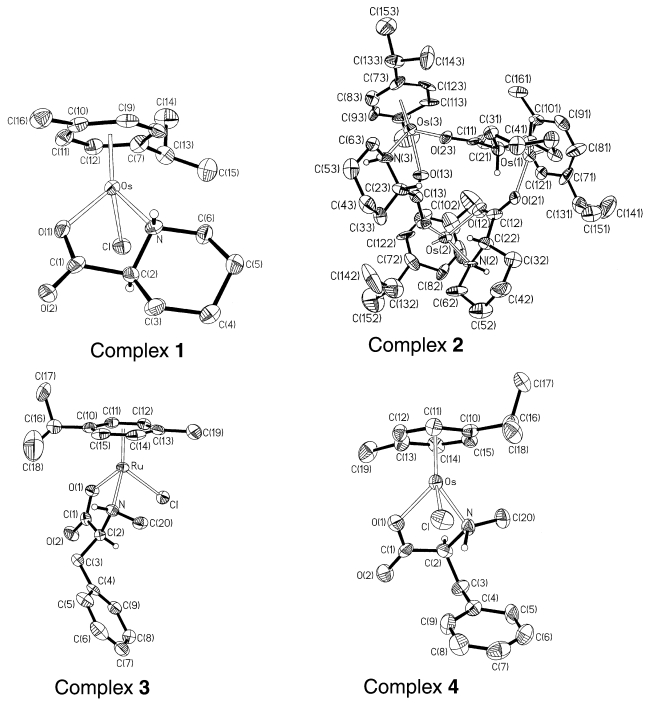

Figure 2. ORTEP plot of compounds $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)Cl]$ (**1**), $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)]_3[BF_4]_3$ (**2**), $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(MePhe)Cl]$ (**3**), and $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(MePhe)Cl]$ (**4**). Selected bond lengths (Å) and angles (°): Compound **1**: Os – N 2.135(4), Os – O(1) 2.098(4), Os – Cl 2.4036(13); O(1) – Os – N 76.24(16), O(1) – Os – Cl 86.93(11), N – Os – Cl 86.16(12). Compound **2**: Os(1) – N(1) 2.148(11), Os(1) – O(11) 2.111(11), Os(1) – O(21) 2.105(11), Os(2) – N(2) 2.129(13), Os(2) – O(12) 2.090(12), Os(2) – O(22) 2.057(11), Os(3) – N(3) 2.087(13), Os(3) – O(13) 2.143(9), Os(3) – O(23) 2.088(11); O(11) – Os(1) – O(21) 83.9(4), O(11) – Os(1) – N(1) 75.9(4), O(21) – Os(1)-N(1) 82.4(4) O(12) – Os(2) – O(22) 83.8(4), O(22) – Os(2) – N(2) 81.5(4), O(12) – Os(2) – N(2) 76.3(5) O(23) – Os(3) – O(13) 82.7(4), O(13) – Os(3) – N(3) 75.9(5), O(23) – Os(3) – N(3) 80.5(5). Compound **3**: Ru – N 2.139(4), Ru – O(1) 2.072(3), Ru – Cl 2.4113(11); O(1) – Ru – N 77.98(13), O(1) – Ru – Cl 86.82(10), N – Ru – Cl 85.86(11). Compound **4**: Os – N 2.117(8), Os – O(1) 2.086(6), Os – Cl 2.401(2); O(1) – Os – N 76.8(3), O(1) – Os – Cl 82.66(19), N – Os – Cl 80.4(2).

carboxylate preferentially affords the *S* alcohol. Furthermore, both the ruthenium and the osmium *N*-methyl-L-phenylalaninates **3** and **4** catalyze the formation of 2-phenylethanol with ee in the *S* isomer (Table 1).

At this point, we suspect that the different sense of the enantioselection would be related to the different configuration adopted by the nitrogen atom when coordinated. In fact, we can explain the observed ee by assuming that a concerted mechanism is operating.[2] Figure 3 shows the proposed six-membered metallacycle intermediate. L-Prolinates (type A) and *N*-methyl-L-phenylalaninates (type B) have been selected as representative examples of the two types of enantioselection. The metallacycle only can be built up when the metal and the nitrogen present the same configuration, i.e., for S_M epimers of the A type (S_C,S_N) or for R_M epimers of the B type (S_C,R_N).[10] To account for the obtained results, *R*-alcohol for the former and *S*-alcohol for the latter, the acetophenone phenyl group has to be eclipsing the p-MeC_6H_4-*i*-Pr ring. In this disposition the carbonyl group interacts with catalysts of the type A through its *Si* face but *via* its *Re* face to type B catalysts, in good agreement with the stereochemical outcome. Most probably, the recognition of carbonyl enantiofaces is made by attractive CH/π interactions between the arene ligand and the aromatic acetophenone group, as Noyori et al. have recently proposed based on theoretical calculations for related (arene)ruthenium systems.[11]

To obtain further evidence in support of this proposal we have attempted the reduction of the dialkyl ketone 4-phenyl-2-butanone. By using this substrate, we try to disrupt the CH/π interactions and then, on the basis of steric grounds, to reverse the sense of the enantioselection for both types of catalysts. The results collected in Table 1 strongly support this hypothesis. The L-prolinates $[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)M(Pro)Cl]$ [M = Ru, Os (**7**)][7] afforded (*S*)-4-phenyl-2-butanol whereas *N*-methyl-L-phenylalaninates produced (*R*)-4-phenyl-2-butanol, preferentially.

In summary, assumption of Noyori's mechanism for the hydrogen transfer reaction from 2-propanol to acetophenone or 4-phenyl-2-butanone, catalyzed by α-amino acidate complexes, explains the ee obtained. The enantioselection originates from the CH/π interactions between the p-MeC_6H_4-*i*-Pr ligand and the acetophenone phenyl group.[11] Interestingly, the explanation includes reverse induction on the nitrogen configuration

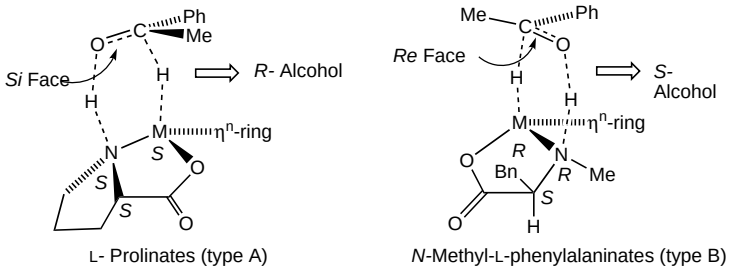

Figure 3. Proposed transition states for the hydrogen transfer reactions.

Table 1. Reduction of ketones by hydrogen transfer from 2-propanol.

No.	Substrate	Catalyst	t [h]	TOF	ee [%]
1	Acetophenone	$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Pro)]_3[BF_4]_3$	1	97	75 (*R*)[a]
2		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Aze)]_3[BF_4]_3$	1	70	55 (*R*)[a]
3		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Pip)]_3[BF_4]_3$	0.5	48	60 (*S*)[a]
4		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Aze)]_3[BF_4]_3$	1.25	24	50 (*R*)
5		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pro)]_3[BF_4]_3$	1.25	47	72 (*R*)
6		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pip)]_3[BF_4]_3$	1.75	47	52 (*S*)
7		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(MePhe)Cl]$	1	60	37 (*S*)
8		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(MePhe)Cl]$	2	24	32 (*S*)
9		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pro)Cl]$	1	57	66 (*R*)
10		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Pro)Cl]$	1	92	70 (*R*)[b]
11	4-Phenyl-2-butanone	$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(Pro)Cl]$	1.5	42	32 (*S*)
12		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Ru(MePhe)Cl]$	1	56	14 (*R*)
13		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(Pro)Cl]$	3	45	30 (*S*)
14		$[(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}i\text{-}Pr)Os(MePhe)Cl]$	6	36	5 (*R*)

[a] Ref.[3b]
[b] Ref.[3a]

for two related types of α-amino acidates. Furthermore, the proposed mechanism implies discrimination on the catalytic activity of metal epimers. Only the *S* forms at metal diastereomers are active in L-prolinate catalysts (type A) while the opposite is true for *N*-methyl-L-phenyl alaninates (type B).

Experimental Section

Hydrogen Transfer Procedure

Catalyst (0.04 mmol), HCOONa (0.053 – 0.08 mmol, as ca. 1 M aqueous solution), and 2-propanol (5.6 mL) were mixed under nitrogen at room temperature in a flask which was then equipped with a reflux condenser and immersed to an oil bath at 83 °C. To the boiling solution, the ketone (2.66 mmol) was added in 1 mL of 2-propanol. The reactions were monitored by gas-liquid chromatography using a CP-Cyclodex-B 236M, 25 m × 0.25 mm × 0.25 μm film, column.

Acknowledgements

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[6] X-ray data for **1 – 4** measured at 173 K, Bruker SMART APEX CCD diffractometer, Mo Kα ($\lambda = 0.71073$ Å) radiation. Crystal data for **1**: $C_{16}H_{24}ClNO_2Os$, $M = 488.01$; orthorhombic, $P2_12_12_1$; yellow prismatic block; $a = 6.1960(5)$, $b = 14.6441(11)$, $c = 17.7441(14)$ Å; $U = 1610.0(2)$ Å^3; $Z = 4$; $\mu = 8.090$ mm^{-1}; 10641 reflections measured, 3812 unique ($R_{int} = 0.051$). Final $R_1 = 0.0297$ (3607 obs. reflect.), $wR2 = 0.0565$, GoF = 0.998 (all reflect.); Flack par. = −0.003(10). Complex **2**: $C_{48}H_{72}B_3F_{12}N_3O_6Os_3 \cdot C_4H_{10}O$, $M = 1692.24$; tetragonal, $P4_32_12$; yellow lamina; $a = b = 15.431(2)$, $c = 58.650(12)$ Å; $U = 13965(4)$ Å^3; $Z = 8$; $\mu = 5.521$ mm^{-1}; 76838 reflections measured, 12304 unique ($R_{int} = 0.142$). Final $R_1 = 0.0590$ (7192 obs. reflect.), $wR2 = 0.1186$, GoF = 0.926 (all reflect.); Flack par. = 0.002(15). Complex **3**: $C_{20}H_{26}ClNO_2Ru \cdot 0.25(CHCl_3)$, $M = 478.78$; orthorhombic, $P2_12_12_1$; orange prismatic block; $a = 5.7930(4)$, $b = 18.7768(12)$,

$c = 19.8553(12)$ Å; $U = 2159.7(2)$ Å^3; $Z = 4$; $\mu = 0.956$ mm^{-1}; 26858 reflections measured, 5308 unique ($R_{int} = 0.0515$). Final $R_1 = 0.0430$ (4730 obs. reflect.), $wR2 = 0.1292$, GoF = 1.025 (all reflect.); Flack par. = 0.04(5). Complex **4**: $C_{20}H_{26}ClNO_2Os$, $M = 538.07$; monoclinic, $P2_1$; yellow needle; $a = 10.3670(12)$, $b = 6.6771(7)$, $c = 13.6406(15)$ Å, $\beta = 93.131(2)^\circ$; $U = 942.81(18)$; $Z = 2$; $\mu = 6.917$ mm^{-1}; 6258 reflections measured, 3983 unique ($R_{int} = 0.044$). Final $R_1 = 0.0391$ (3488 obs. reflect.), $wR2 = 0.0812$, GoF = 0.990 (all reflect.); Flack par. = $-0.041(14)$.

[7] Complexes **1** – **7** have been prepared starting from the corresponding dimers [{(η^6-*p*-MeC_6H_4-*i*-Pr)MCl}$_2$(μ-Cl)$_2$] following previously reported experimental procedures.[3,5a] See also: D. Carmona, A. Mendoza, F. J. Lahoz, L. A. Oro, M. P. Lamata, E. San José, *J. Organomet. Chem*. **1990**, *396*, C17.

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