Chiral Ru/PNNP complexes in catalytic and stoichiometric electrophilic O- and F-atom transfer to 1,3-dicarbonyl compounds*

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Abstract: The asymmetric hydroxylation and fluorination catalyst [Ru(OEt₂)₂(PNNP)]²⁺ (PNNP = chiral tetradentate ligand with a P₂N₂ donor set) reacts with 1,3-dicarbonyl compounds to give dicationic adducts and, upon deprotonation, the corresponding enolato complexes. The relevance of these species to catalytic O- and F-transfer is investigated.

Keywords: asymmetric catalysis; 1,3-dicarbonyl compounds; hydroxylation; fluorination; ruthenium.

INTRODUCTION

Recently, our research group has been developing Ti(TADDOLato) complexes for asymmetric electrophilic F-, O-, and S-atom-transfer reactions [1]. After the fluorination of β-ketoesters with Selectfluor™ (F-TEDA) as fluorinating agent [1a], we have reported the asymmetric hydroxylation of 1,3-dicarbonyl compounds by electrophilic oxygen transfer from N-sulfonyl oxaziridine (Scheme 1) [1b].

Scheme 1
In a complementary approach, we have developed ruthenium catalysts containing chiral tetradentate ligands with a P₂N₂ donor set (PNNP). The most selective catalyst [Ru(OEt₂)₂(PNNP)]²⁺ (5) is produced by double chloride abstraction from [RuCl₂(PNNP)] (2) with (Et₃O)PF₆ (2 equiv) in CH₂Cl₂ as noncoordinating solvent (not 1 equiv (Et₃O)PF₆ as erroneously stated in ref. [1b]). The resulting complex catalyzes the electrophilic F- or O-transfer with up to 92 and 47 % ee, respectively (Scheme 2) [1b].

![Scheme 2](image)

The advantage of the ruthenium catalytic system with respect to the titanium complex 1 is that the former uses less reactive F- and O-transfer reagents and can therefore be used with highly enolized substrates whose enol form would react with Selectfluor or with the sulfonyl oxaziridine in a noncatalyzed (and hence nonenantioselective) fashion. [Ru(OEt₂)₂(PNNP)]²⁺ (5) is more efficient than 1 in the hydroxylation of α-acetyl-N-benzyl-δ-valerolactame, 4, (66 % enol, 47 vs. 19 % ee) [1b] and in the fluorination of ethyl 2-benzyl-3-oxo-butanoate (18 % enol, 73 vs. 6 % ee) [2].

**CATALYTIC HYDROXYLATION: THE EFFECT OF THE OXIDANT**

An interesting feature of [Ru(OEt₂)₂(PNNP)]²⁺ (5) is that hydrogen peroxide as oxidant gives similar enantioselectivity (38 % ee) as compared to cumyl hydroperoxide (47 % ee). We find now that the enantioselectivity strongly depends on the oxidant used, as PhIO gives 18 % ee with opposite sense of induction. This makes the involvement of an oxo complex in the oxidation unlikely. Thus, to gain mechanistic insight of the F- and O-transfer reactions, we studied the ruthenium adducts containing 3 and 4, the best performing substrates in asymmetric fluorination and hydroxylation.

**DICATIONIC RUTHENIUM COMPLEXES WITH 1,3-DICARBONYL COMPOUNDS**

The highly reactive dication 5, formed in situ from 2 and (Et₃O)PF₆, reacts instantly and quantitatively with 3 or 4 (1 equiv) in CH₂Cl₂ solution (Scheme 3).

![Scheme 3](image)
The dicationic adducts 6a and 6b are formed as a single diastereoisomer and contain the dicarbonyl forms of the substrates (Chart 1).

**MONOCATIONIC ENOLATO COMPLEXES**

The deprotonation of 6a and 6b with NEt₃ (1 equiv) produces a single diastereoisomer of the monocationic enolato complexes 7a and 7b, respectively (Chart 1). These complexes have been studied by ¹H and ¹³C NMR spectroscopy and by X-ray diffraction (Figs. 1 and 2).

Fig. 1 X-Ray structure of 7a.

Fig. 2 X-Ray structure of 7b.

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Complexes \( \textbf{6b} \) or \( \textbf{7b} \) react with \( \text{H}_2\text{O}_2 \) to give the \( \alpha \)-hydroxy derivative of \( \textbf{4} \). In Scheme 4, the outcome of these stoichiometric reactions is compared with the results of the catalytic hydroxylation of \( \textbf{4} \) promoted by the same complexes. The sense of induction is the same in the four reactions.

![Scheme 4](image)

For the upper right reaction, we assume that complex \( \textbf{6b} \) is the actual catalyst, as it is instantaneously formed by reaction of the bis(ether) adduct \( \textbf{5} \) with \( \textbf{4} \). Thus, complex \( \textbf{6b} \) gives similar enantioselectivity in the stoichiometric and in the catalytic oxidation, whereas this is not the case for the enolato analog \( \textbf{7b} \). Additionally, the yield of the stoichiometric hydroxylation of the enolato complex \( \textbf{7b} \) is surprisingly low.

The present results suggest that the dicarbonyl adduct \( \textbf{6b} \) is involved in the catalytic cycle, rather than enolato complex \( \textbf{7b} \). This is in contradiction with the mechanism proposed by Adam for the (nonenantioselective) nickel-catalyzed hydroxylation of \( \beta \)-ketoesters, in which an enolato complex is attacked electrophilically by the oxidant (in that case, dimethyldioxirane) [3].

As oxene and \( \text{F}^+ \) are isoelectronic, electrophilic fluorination is analogous to the oxidation reaction described above. To assess the relevance of \( \textbf{6a} \) and \( \textbf{7a} \) to the catalytic fluorination described in Scheme 2, these complexes were treated with \( \text{N-fluorobenzenesulfonylimide (NFSI)} \) (1 equiv) (Scheme 5). Both \( \textbf{6a} \) and the enolato complex \( \textbf{7a} \) gave the fluorinated product with lower enantioselectivity (albeit with the same sense of induction) than obtained in the catalytic reaction with \( \textbf{5} \) as catalyst (92 % ee). This is surprising, as \( \textbf{5} \) forms \( \textbf{6a} \) in the presence of the substrate \( \textbf{3} \).

Thus, we investigated the possibility that a Ru(III) species is involved in the catalytic cycle. Complex \( \textbf{5} \) was oxidized (with \( \text{AgPF}_6 \), 3 equiv) and then treated with \( \textbf{3} \) (9 equiv) to give the paramagnetic Ru(III) complex \[\text{Ru(enolato)(PNNP))}(\text{PF}_6)_2 \textbf{(8a)}\], which was isolated and characterized by mass spectrometry and elemental analysis. Complex \( \textbf{8a} \) reacts with NFSI to give 2-\textit{tert}-butoxycarbonyl-2-fluorocyclopentanone with 90 % ee, which is very close to the values obtained in the catalytic reaction (92 % ee, Scheme 2) [2]. Furthermore, isolated \( \textbf{8a} \) gives the same enantioselectivity as \( \textbf{5} \) (both 92 % ee) when used as catalyst in the above reaction.
The involvement of a Ru(III) complex, possibly 8a, in catalysis is also supported by the observation that the enantioselectivity increases during the reaction with 5 as catalyst (Fig. 3).

The formation of 8a during the catalytic reaction is a concrete possibility, as NFSI is a good oxidant. For the same reason, the involvement of a Ru(III) species in the hydroxylation reaction cannot be excluded. However, we have no evidence thereof at this point. It is possibly relevant to this issue that the catalytic hydroxylation is orders of magnitude faster than fluorination (few minutes vs. several hours).

Finally, to assess the stereochemical aspects of these reactions, we are determining the absolute configurations of 6a, 6b, and 8a, and of the hydroxylated and fluorinated products.
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REFERENCES