Expanding the scope of asymmetric electrophilic atom-transfer reactions: Titanium- and ruthenium-catalyzed hydroxylation of β-ketoesters

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The enantioselective formation of a quaternary stereogenic center coinciding with a hydroxylation process is a very rare reaction from a homogeneous catalysis point of view. Indeed, to our knowledge, no asymmetric transition-metal-catalyzed direct hydroxylation has been reported before. We describe here our initial study concerning the enantioselective α-hydroxylation of various β-ketoesters catalyzed by Lewis-acidic complexes. Specifically, it was found that the Ti complex [TiCl2((R,R)-1-Np-TADDOLato)(MeCN)2] affords the hydroxylated products in high yield and enantioselectivities up to 94% enantiomeric excess when using 2-(phenylsulphonyl)-3-(4-nitrophenyl)oxaziridine as the oxidizing agent. Chiral enantiopure compounds of the latter type have been used previously in stoichiometric asymmetric hydroxylation reactions. We also show that, in a complementary approach with H2O2 as the oxidant, the Ru(II) complex [RuCl(OE2)(CS,S)-PNNP)]PF6 catalyzes the same type of transformation in a case of substrates showing a very substantial extent of enolization under reaction conditions; being, however, unreactive toward only weakly enolized β-ketoesters.

Reactions involving both the formation of new carbon--heteroatom bonds and the concomitant generation of a new stereogenic center are prototypical transformations in asymmetric catalysis. Thus, for example, hydroboration, hydrosilylation, epoxidation, and aziridination of olefins, as well as allylic substitutions with heteroatom nucleophiles, have been extensively studied (1). However, catalytic halogenations, in particular fluorinations, and direct hydroxylations have received much less attention in the asymmetric catalysis community.

Recently, we developed an enantioselective catalytic process in which β-ketoesters are fluorinated at the 2-position with an electrophilic fluoride donor such as Selectfluor [also called F-TEDA (TEDA, triethylendiamine), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis{tetrafluoroborate} (2–5)]. Our work inspired further developments involving chiral Pd catalysts (6) and chiral phase transfer catalysts for the same type of fluorination (7).

The α-hydroxycarbonyl functional unit is ubiquitous in natural products and bioactive compounds, such as, e.g., carbohydrates, antibiotics, and antitumor agents; therefore, it is also present in synthetic intermediates and in chiral auxiliaries in view of the stereoregulating ability of the hydroxy group (8). The α-function-alization of carbonyl compounds most often relies on the reaction of enolate anions, or enol derivatives with electrophiles. The direct activation of the enol form of keto derivatives has recently been introduced as a new synthetic methodology to achieve α-amination (9) or, as already mentioned, α-haloxygenation (2–5). So far, the only straightforward enantioselective α-hydroxylation is the reaction of enolate salts with enantiopure N-sulfonyloxaziridines, acting as electrophilic oxygen sources, as developed by Davis (10, 11). However, despite considerable efforts in the area of synthetic methods toward α-hydroxycarbonyl derivatives (refs. 12, 13 and references therein, and 14), to the best of our knowledge there are only two reports in the literature dealing with asymmetric catalysis. Thus, aromatic cyclic ketones have been α-hydroxylated by oxygen under basic conditions and in the presence of chiral phase-transfer catalysts thereby reaching enantioselectivities up to 77% enantiomeric excess (ee) (15, 16). No enantioselective catalytic method relying on transition-metal complexes has been reported before. A recent report by Yamamoto (17) describes the enantioselective Ag-catalyzed addition of nitrosobenzene to stannyl enol ethers leading indirectly to α-hydroxyketones.

The starting point of our investigation is the observation that Lewis acidic Ni(II) complexes catalyze the hydroxylation of 1,3-dicarbonyl compounds by dimethyldioxirane (18). We report herein a catalytic, enantioselective α-hydroxylation of β-ketoesters by using chiral transition-metal Lewis acids and electrophilic oxygen sources (such as dimethyldioxirane and oxaziridines). By using the same Ti catalyst successfully exploited in fluorination chemistry, α-hydroxy-β-ketoesters are obtained in excellent yield and enantioselectivities up to 94% ee. This concept can be extended from “hard” (Ti) to “soft” Lewis acids, in particular Ru(II)-based ones. Thus, in a complementary approach, we also report the hydroxylation of highly enolized 1,3-dicarbonyl compounds with hydrogen peroxide in the presence of the chiral ruthenium catalyst 2 (Fig. 1) that we...

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Abbreviations: ee, enantiomeric excess; Selectfluor [also called F-TEDA; TEDA, triethylendiamine], 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis{tetrafluoroborate}; (S,S)-PNN, N,N-bis(o-diphenylphosphino)benzylidene-(15,2,5)-diaminocylo-hexane.

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†Complex 2 is depicted as the trans isomer for simplicity. However, 31P NMR evidence suggests that it is present as the cis–β isomer with O trans to P (21).

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previously applied in the asymmetric epoxidation and cis-selective cyclopropanation of olefins (19–21).

Materials and Methods

General. Reactions with air- or moisture-sensitive materials were carried out under an argon atmosphere by using Schlenk techniques. Complexes [TiCl3(R,R)-1-Np-TADDOLato(MeCN)2] (1, bis(acetonitrile)dichloro[{4R,5R}-2,2-dimethyl-α,α,α′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2-)]κO,O′)[titanium] (22) and [RuCl(OEt2)(S,S)-PNNP]PF6 (2, (S,S)-PNNP is N,N′-bis(o-diphenylphosphino)benzylidene) -1(4,2,3)-diaminocyclohexane) (21), 2-(phenylsulfonyl)-3-(1-nitrophenyl)oxaziridine (11), and dimethyl(dichloromethylene) (23) were prepared according to published procedures. Enantiomeric excesses were determined by HPLC with Agilent (Palo Alto, CA) HPLC 1100 or HPLC 1050 Series systems and/or by GC with a ThermoQuest Instruments TRACE GC-2000 Series apparatus equipped with a Supelco beta-DEX 120 column. Details of the analytic procedures are described in Supporting Text, which is published as supporting information on the PNAS web site. Ti-catalyzed fluorination reactions were carried out as reported (2).

Titanium-Catalyzed Hydroxylation. The β-ketoester 3 (0.2 mmol), complex 1 (8 mg, 0.01 mmol), and 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine (67 mg, 0.22 mmol) were successively added to freshly distilled dichloromethane (2 ml) in a Schlenk tube, and the reaction was stirred at room temperature for 2–24 h. The course of the reaction was monitored either by TLC or by 1H NMR spectroscopy [by integration of the signals of the oxaziridine proton at δ 5.62 vs. that of the N-(benzenesulfonyl)-(4-nitrophenyl)imine proton at δ 9.15 (approximate reaction times for full consumption of the starting material were as follows: 3b, 2 h; 3c, 4 h; 3f, 5 h; 3g, 1 h; 3h, 2 h; 3i, 6 h; and 3j, 30 min)]. Dichloromethane was evaporated under reduced pressure, and the beige residue was extracted with hexane (2 × 2 ml). The reactions with 3a, 3d, and 3e were stopped after 12, 20, and 24 h, respectively, without monitoring. After evaporation of the hexane, the residue was subjected to flash chromatography on silica gel to give pure 2-hydroxy-derivative 4, which was analyzed by 1H NMR and chiral HPLC (see Supporting Text). The absolute configuration of kjellmanianone (4i) was determined to be S from the (+)-sign of the optical rotation (by comparison with a literature value) (24). The absolute configurations of the other products were not determined.

Ruthenium-Catalyzed Hydroxylation. The catalyst was prepared by adding (Et3O)PF6 (2.5 mg, 0.01 mmol, 1 eq) to a CH2Cl2 (2 ml) solution of complex 2 (8.3 mg, 0.01 mmol) and stirring the resulting solution for 2 h. A color change during the reaction time indicated the formation of the ether adduct [RuCl(OEt2)(PNNP)]+. Subsequently, the substrate (0.2 mmol) was added to the catalyst solution (0.01 mmol, 5 mol % vs. substrate). Finally, aqueous (30%, 9.8 M) hydrogen peroxide (0.15 ml, 1.5 mmol, 7.35 eq) or cumyl hydroperoxide (0.074 ml, 0.4 mmol, 2 eq) was added in one portion under vigorous stirring (Table 1). The reaction was monitored by TLC analysis during 14 h of reaction time. Product isolation and purification was carried out as described above.

Results and Discussion

Titanium-Catalyzed Hydroxylation. In preliminary experiments, we investigated the reactivity of racemic β-ketoesters with dimethylsulfoxide. Thus, treatment of ethyl 2-methylbutyrate (3a) with the dioxirane (2.4 eq) in acetone solution in the presence of a substoichiometric amount (5 mol %) of the Ti complex 1 as chiral Lewis acid gave ethyl 2-methyl-2-hydroxy-butyr ate (4a) in 50% yield and 45% ee after 30 min of reaction time (Scheme 2). A general problem of this procedure is the presence of traces of water contaminating the acetone solution of the oxidant, thus causing progressive decomposition of the catalyst during the reaction and decreasing the product yield. The problem was circumvented by using 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine (5) as oxidant. This reagent is a stable, nonhygroscopic, and easy-to-handle solid. Compounds of this type are known to smoothly react with alkenes to give epoxides, and the transposition of this protocol to silyl enol ethers allows the isolation, after hydrolysis, of the corresponding α-hydroxyketones (11). Using oxaziridine 5, the reaction of 3a (Table 1) gave a similar ee (56%) but a much higher yield (94%) than with dimethylsulfoxide (45% ee and 50% yield, respectively). Thus, all further reactions were carried with 5 as oxidant. The results of the catalytic experiments that were carried out in this study are summarized in Table 1.

The enantioselectivity of the hydroxylation reaction increases with increasing steric bulk of the ester residue, as suggested by the reactions of the benzyl and phenyl esters 3b and 3c, and as already observed in the analogous fluorination reaction (2). Thus, phenyl 2-methylpentanoate (3e) gave a high ee in both reactions (84% and 88% ee for hydroxylation and fluorination, respectively). In contrast, lower enantioselectivity is obtained when bulky groups occupy the 2-position (3d, 9% ee) or the 4-position (3e, 41% ee). The cyclic substrates 3f and 3g are also hydroxylated with low enantioselectivity (4% and 27% ee, respectively). Somewhat surprisingly, changing from the ethyl ester (3g) to i-butyl ester (3h) boosted the enantioselectivity dramatically, and the corresponding hydroxylation product 4h was isolated in 97% yield and 94% ee.

Beside affording efficient enantiocontrol with some substrates, this new catalytic approach also affords high chemo- and regioselectivities. Thus, ethyl 2-benzyl-3-oxo-butanate (3d) gives ethyl 2-hydroxy-2-benzyl-3-oxo-butanate 4d with excellent yield (albeit only 9% ee), whereas the noncatalytic hydroxylation of metal enolates of 3d by (camphorylsulfonyl)oxaziridines gives low yields, partly because of a competing Baeyer–Villiger side-reaction (25). Such a selectivity could indicate the absence of an anionic enolate intermediate, thus supporting the proposed mechanism (vide infra). In contrast, the Ni-catalyzed oxidation of alkene-substituted β-ketoesters with the more reactive dioxirane occurs with opposite chemoselectivity, i.e., affording the olefin epoxidation product preferentially (18).

The antibiotic kjellmanianone (4i), which has been isolated from the marine algae Sargassum kjellmanianum (26), is prepared in two steps from commercially available 3-methoxy-2-cyclopenten-1-one (Scheme 3). The Ti-catalyzed hydroxylation of 3i to give 4i is an alternative to the previously reported stoichiometric oxidation by a chiral N-sulfonyloxaziridine (27), although the enantioselectivity is

Scheme 2. Ti-catalyzed enantioselective hydroxylation of β-ketoesters.
only 30% ee. Again, 3i is selectively hydroxylated to the natural product 4i, and no detectable epoxidation of the C=C double bond occurs, although oxaziridine 5 is known to be an efficient epoxidation agent (28).

As enols react with 2-(phenylsulfonyl)-3-(p-nitrophenyl)oxaziridine, the Ti-catalyzed reaction is only amenable for 1,3-dicarbonyl compounds that are only marginally enolized under neutral conditions and must coordinate to Ti to react (this appears to be a necessary, although not sufficient, condition). This is the case for 3a, 3b, 3c, and 3e in Table 1. In contrast, substrates for which the enol form is present at equilibrium in substantial amounts undergo the uncatalyzed reaction with 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine: Hydroxylation with 5 in the absence of catalyst, for the respective time of the catalyzed reactions, leads to full conversion for substrates 3e and 3k and 12% conversion for substrate 3a but to conversions below 5% for substrates 3b, 3d, 3g, 3h, and 3i. The background reaction lowers the enantioselectivity, as it is very much likely the case for 3d and 3f. The structurally related acyl lactames 3j and 3k drastically differ in their extent of enolization, the enol form not being detectable for 3j but being the major component in the case of 3k. In fact, the former substrate is hydroxylated at a moderate level of enantioselectivity, whereas its congener 3k affords only a marginal ee. This observation opens the possibility to improve the system by modulating the free enol content by changing the solvent, because the enol content is solvent-dependent. Preliminary experiments using substrate 3b shows comparable yields and lower ee in tetrahydrofuran and acetonitrile (70% and 67% ee, respectively).

### Table 1: Titanium- and ruthenium-catalyzed asymmetric hydroxylations

<table>
<thead>
<tr>
<th>Substrate (3)</th>
<th>Product (4)</th>
<th>% Enol*</th>
<th>Ti complex 1†</th>
<th>Yield, %</th>
<th>ee, %</th>
<th>Ru complex 2</th>
<th>Yield, %</th>
<th>ee, %</th>
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<td>a‡</td>
<td></td>
<td>3</td>
<td>94</td>
<td>56 (45)§</td>
<td></td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>4</td>
<td>90</td>
<td>73 (71)¶</td>
<td></td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>3</td>
<td>89</td>
<td>84 (88)§</td>
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<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>18</td>
<td>93</td>
<td>9 (6)§</td>
<td>42</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>2</td>
<td>90</td>
<td>41 (62)¶</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>50</td>
<td>&gt;99</td>
<td>4 (20)§</td>
<td>53</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td></td>
<td>3</td>
<td>84</td>
<td>27 (66)§</td>
<td>11</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h</td>
<td></td>
<td>4</td>
<td>97</td>
<td>94 (86)¶</td>
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<td>—</td>
<td></td>
</tr>
<tr>
<td>i</td>
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<td>0</td>
<td>85</td>
<td>30 (15)**</td>
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<td>—</td>
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</tr>
<tr>
<td>j</td>
<td></td>
<td>0</td>
<td>84</td>
<td>60 (5)**</td>
<td>0</td>
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<td>—</td>
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</tr>
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<td></td>
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<td>97</td>
<td>19</td>
<td>60††</td>
<td>47</td>
<td></td>
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</tbody>
</table>

*Measured in CDCl₃.
†Enantiomeric excess of the fluorination reactions in parentheses.
‡With dimethylidioxirane as oxidant, yield and ee were 50% and 45%, respectively.
§Unpublished results.
¶See ref. 2.
||With NFSI as fluorinating agent.
**This work.
††Cumyl hydroperoxide (1 eq) as oxidant in CH₂Cl₂ at 0°C. With H₂O₂ as oxidant, 80% yield and 38% ee were obtained (CH₂Cl₂, 25°C).
A possible mechanism for this transformation is the epoxidation of the Ti-bound enolate form of the β-ketoester and subsequent ring-opening to the 2-hydroxylated 1,3-dicarboxyl compound, as proposed for the nonenantioselective Ni-catalyzed reaction (18). Moreover, the fact that, at least for the substrates in Table 1, the enantioselectivity of the hydroxylation reaction roughly parallels that of the corresponding asymmetric fluorination suggests a mechanistic similarity between the two reactions, at least in one aspect. The transfer of the electrophilic fragment (formally F⁺ or oxene O₂) from the reagent to the Ti-bound enolate is the common enantioselectivity-determining step. However, as we have reported for the Ti-catalyzed fluorination, the catalyst may form up to eight diastereoisomeric 1:1 adducts with the substrate in its enolate form (4). A detailed computational analysis of these intermediates indicated that, for catalysts containing (R,R)-TADDOLs, the major product enantiomer is formed via Si-side attack of the electrophilic agent onto the coordinated enolate in the preferred diastereoisomeric form. This is illustrated in Scheme 4 for the case of kjellmanianone, 4i, for which the absolute configuration is known. However, for both halogenation and hydroxylation, the control of enantioselectivity is a complex issue depending on the diastereoisomeric composition of the catalyst/substrate adducts and their relative kinetics of the electrophile transfer step.

To validate the hypothesis of the parallel mechanistic nature of the hydroxylation and fluorination reactions, we completed the investigation of the best hydroxylation substrate discovered in this study, namely 3h, by testing it in the (previously unattempted) titanium-catalyzed fluorination. Surprisingly, the standard protocol with Selectfluor as the fluoride source afforded only 20% ee (Scheme 5), a value much lower than the enantioselectivity obtained in hydroxylation (94% ee, Table 1). Interestingly, when N-fluorobenzenesulfonimide (NFSI) was used as fluorinating agent instead of Selectfluor, the enantioselectivity increased dramatically (86% ee) and approached the value observed in hydroxylation. The change in the selectivity is accompanied by a diminished reactivity of the N–F fluorinating agent, as expressed by, e.g., its redox potential. In fact, NFSI (E° = −1.441 V vs. Ag/Ag⁺ electrode) is a milder electrophilic F-transfer agent than Selectfluor (E° = −0.296 V vs. Ag/Ag⁺ electrode) (29). Accordingly, the yield of the fluorinated product 6h drops from 90% after 2 h of reaction time (Selectfluor) to 35%, at reaction completion after 24 h (NFSI). Evidently, the modestly enolized substrate 3h undergoes the uncatalyzed reaction with the more potent fluorinating agent to a larger extent than other substrates displaying a similarly low enol content.

**Ruthenium-Catalyzed Hydroxylation.** The mechanistic hypothesis described above suggests an alternative approach to the hydroxylation of highly enolized 1,3-dicarbonyl compounds, that is, the enantioselective epoxidation of a free enol by oxene transfer from an oxo complex. Thus, we tested the previously developed Ru-based catalysts for the asymmetric epoxidation of olefins with H₂O₂ as oxidant, [RuCl₂((S,S)-PNNP)]⁺ and [RuCl₂(OET₂)((S,S)-PNNP)]⁺ (Fig. 1) (19–21). Substrate 3f, which is 50% in the enol form, is converted to 4f with 53% yield and 36% ee in the presence of [RuCl₂(OET₂)((S,S)-PNNP)]PF₆ (2) as catalyst (5 mol %) and aqueous H₂O₂ (7 eq) (Scheme 6). A control reaction showed that no hydroxylation occurs when no metal catalyst is added. Better results are obtained with 3k (80% yield and 38% ee), a substrate displaying an even higher degree of enolization. With cumyl hydroperoxide as oxidant (in CH₂Cl₂ at 0°C), the enantioselectivity increased to 47% ee (Table 1).

In agreement with our mechanistic hypothesis, the yield of the reaction parallels the enol content of the substrate. Thus, 3b (4% enol form) gives only 10% yield, whereas 3c and 3e (3 and 2% enol form, respectively) are completely unreactive (Table 1). In contrast, 3d, whose enol form is 18% of total, gives 4d with 42% yield and 20% ee. Albeit low, this enantioselectivity is better than that obtained with the titanium/oxaziridine (1/5) system (9% ee), as the enol form of 3d reacts with the oxidant 5 in a noncatalyzed manner. Finally, as expected based on their low enol content (0–4%), the cyclic substrates 3h–j are completely unreactive, whereas 3g (3% enol) gives 4g in 11% yield and 15% ee. To check this hypothesis, we used tetrahydrofuran as solvent for the hydroxylation of 3k, which is enolized to 72% in this solvent (vs. 66% in CDCl₃). However, both yield and enantioselectivity were lower in tetrahydrofuran (60% yield, 23% ee) than in CH₂Cl₂ (80% yield, 38% ee), suggesting that the previously observed detrimental effect of the coordinating ligands on the reactivity and activity (20) outweighs the expected activity increase related to the higher enol form content.  

Scheme 4. Proposed catalytic cycle for the Ti-catalyzed hydroxylation reaction, accounting for the observed absolute configuration of the major enantiomeric form of kjellmanianone (4i).
As already observed for catalyst I, the enantioselectivity of the reaction reflects that of a related transformation. In fact, the ee observed with 3f (36%) is similar to that obtained with the related complex [RuCl(PNNP)]PF₆ in the epoxidation of 1,2-dihydropyrene (41%) (19). This analogy is suggestive of the involvement of the enol form of 1,2-dihydronaphthalene (41%) (19). This analogy is suggestive of the related complex [RuCl(PNNP)]PF₆ in the epoxidation of 1,2-dihydronaphthalene (41%) (19). This analogy is suggestive of the related complex [RuCl(PNNP)]PF₆ in the epoxidation of 1,2-dihydronaphthalene (41%) (19).

Concluding Remarks

In conclusion, we disclosed here a direct enantioselective hydroxylation of β-ketoesters. The methodology used allows the displacement of the keto-enol tautomerism by addition of a catalytic amount of a chiral transition-metal Lewis acid and the reaction of the resulting enolato complex with electrophilic oxygen sources, such as dimethyldioxirane and substituted oxaziridines. Highly enolized substrates that spontaneously react with the latter oxidants can be hydroxylated by using “softer” Lewis acids based on a late transition metal, such as [RuCl(L)(PNNP)]⁺, in combination with H₂O₂, a cheap and environmentally benign oxidant. The enantioselectivities reached for the β-ketoesters reported in Table 1 are widely scattered and reach only in a few cases levels of practical utility (up to 94% ee) and show a pronounced dependence on substrate structural properties, with the catalyst used in this study. Future work in our laboratory shall therefore address the issue of catalyst optimization in view of expanding the scope of this potentially very useful reaction that has been so far largely neglected in the asymmetric catalysis community.

We thank Dr. M. Massaccesi for preparing compounds 3j and 3k. This work was supported by the Swiss National Science Foundation.