Q1 Palladium-catalysed enantioselective α -hydroxylation of β -ketoesters

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Highly enantioselective α -hydroxylation of cyclic and acyclic 1,3-ketoesters can be achieved with up to 98% ee using a dicationic palladium(II) catalyst and dimethyldioxirane as oxidant.

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Palladium-catalysed enantioselective α -hydroxylation of β -ketoesters†

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Received (in Cambridge, UK) 8th April 2009, Accepted 1st May 2009

First published as an Advance Article on the web

DOI: 10.1039/b907151b

Highly enantioselective α -hydroxylation of cyclic and acyclic 1,3-ketoesters can be achieved with up to 98% ee using a dicationic palladium(II) catalyst and dimethyldioxirane as oxidant.

Direct α -hydroxylation of β -ketoesters produces valuable synthetic intermediates containing three contiguous carbons in different oxidation states.¹ Achieved by the addition of an electrophilic oxygen to a stabilised enol(ate), good enantioselectivity can be obtained using stoichiometric amounts of base and an optically pure oxidant, such as camphorylsulfonyl-oxaziridine (also known as Davis' reagent).²

Asymmetric catalytic reactions were first accomplished by Mezzetti *et al.*, who set an important benchmark of 94% ee by using a TADDOL-Ti(IV) catalyst and *N*-arylsulfonyloxaziridine as oxidant.³ To date, this was matched only by Shibata *et al.*, who attained up to 97% ee in the reactions of cyclic substrates, by employing a catalyst generated from DPFox/Ni(ClO₄)₂ and a saccharin-derived oxaziridine (Fig. 1).^{4,5}

Previously, we reported the use of dicationic (diphosphine) palladium(II) catalysts for highly enantioselective addition of aromatic amines to Michael acceptors containing 1,3-dicarbonyl chelating substrates.⁶ Herein, we will demonstrate that these catalysts can also be used to effect enantioselective hydroxylation of several cyclic and acyclic β -ketoesters (Fig. 2).⁷

Using [(*R*-BINAP)Pd(OH)₂]²⁺[TfO][−]₂ (**1**)⁸ as the catalyst, dimethyldioxirane (DMD) was chosen as the source of electrophilic oxygen in this work:⁹ the volatility of this oxidant and its side product (acetone) eliminates the need for column chromatography, expediting reaction workup and analysis.

Two cyclic β -ketoesters 2-alkylcarboxylate indanone (**i**) and 2-alkyl carboxylate cyclopentanone (**ii**) were initially selected as substrates. At 5 mol% catalyst loading, reactions were completed uniformly in 0.5 h at −20 °C, affording hydroxylated products with encouragingly high levels of selectivity (Table 1, entries 1–7).[†] As noted in earlier studies, the size of the ester substituent proved critical for the attainment of high ee values—for the hydroxylation of 2-alkylcarboxylate indanone (**i**), a steady rise from 26 to 85% ee was observed with increasing steric bulk (**2a–2d**, entries 1–4). In comparison, a

greater level of stereoselectivity was obtained in the absence of the fused aromatic ring: for the hydroxylation of 2-alkyl carboxylate cyclopentanones (**ii**), 87% ee was obtained for the ethyl ester **3a**, increasing to 98% for the *tert*-butyl ester **3c** (entries 5–7)—the highest stereoselectivity reported for this substrate.

Given that hydroxylated pyrrolidines and pyrrolidinones are prevalent core structures in biologically active molecules and natural products,¹⁰ the effect of incorporating nitrogen heteroatom into the cyclic ring was examined. Retaining the *tert*-butyl ester for maximum stereodifferentiation, three pyrrolidin-4-one-3-carboxylates (**iii**), containing different *N*-protecting groups, were prepared and subjected to the hydroxylation reaction (entries 8–10). The results showed that a nitrogen heteroatom can be accommodated at this position without any detrimental effect, and ee's in excess of 90% can be obtained. However, the choice of the *N*-substituent is important for the product stability—the Moc-protected product **4a** decomposes within an hour at room temperature.

Next, two *tert*-butyl pyrrolidin-2-one carboxylates (**iv**) were prepared and subjected to the hydroxylation reaction. Compared to other substrates, the acidity of the enolisable proton is significantly lower in these systems. This resulted in a notable attenuation in reactivity, which was overcome by raising the temperature to 0 °C. Under these conditions, the reaction provided 77% ee for the substrate **5a** (entry 11). Furthermore, by substituting the benzyl protecting group with a carbamate (Boc), the formation of **5b** can be accelerated, to afford an excellent yield and 96% ee (entry 12).

Acyclic β -ketoesters are challenging substrates for electrophilic hydroxylation reactions. Due to their inherent low reactivity, processes such as the Baeyer–Villiger rearrangement often become competitive during the oxidation process.^{2,11} With this in mind, preliminary experiments were conducted

Fig. 1 Reported catalysts for enantioselective α -hydroxylation of β -ketoesters.

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† Electronic supplementary information (ESI) available: Detailed experimental procedure, characterisation data and selected NMR spectra. See DOI: 10.1039/b907151b

Fig. 2 β -Ketoester substrates examined in this work.

Table 1 α -Hydroxylation of cyclic β -ketoesters^a

Entry	Product	Temp/°C	Time/h	Yield% ^b	ee ^c (%)
1	2a (R = Me)	−20	0.5	95	26
2	2b (R = Et)	−20	0.5	88	48
3	2c (R = <i>i</i> -Pr)	−20	0.5	86	48
4	2d (R = <i>t</i> -Bu)	−20	0.5	95	85
5	3a (R = Et)	−20	0.5	89	87
6	3b (R = Bn)	−20	0.5	78	66
7	3c (R = <i>t</i> -Bu)	−20	0.5	88	98 ^d
8	4a (Z = CO ₂ Me)	−20	0.5	38 ^e	95
9	4b (Z = CO ₂ Bn)	−20	0.5	97	90
10	4c (Z = CO ₂ <i>t</i> -Bu)	−20	0.5	93	93
11 ^f	5a (Z = Bn)	0	48	91	77
12	5b (Z = Boc)	0	18	99	96
13 ^f	6a (R = Me)	0	48	62	65
14 ^f	6b (R = Et)	0	48	65	62
15 ^f	6c (R = <i>t</i> -Bu)	0	48	55	88

^a Unless otherwise stated, general reaction conditions: ketoester substrate (0.123 mmol), catalyst **1** (0.0123 mmol, 5 mol%), DMD (0.05–0.09 M in acetone, 1.2 equiv.), CH₂Cl₂ (0.5 mL). ^b Isolated yield of the purified product, replicated to $\pm 5\%$. ^c Determined by chiral HPLC. ^d Determined by chiral GC. ^e Low yield due to product decomposition at room temperature. ^f Reactions performed with 20 mol% catalyst and 2 equivalents of oxidant.

dation in yield or selectivity.¹⁶ Furthermore, formation of side product is not an issue, even when reactions are slow. Preliminary mechanistic studies revealed that reaction is likely to occur *via* cooperative Brønsted and Lewis acid catalysis. Further studies are underway, including the reaction

Scheme 1 Coordination behaviour of a 1,3-ketoester to dicationic palladium catalysts **1** and **7**.

Fig. 3 $^{31}\text{P}\{-^1\text{H}\}$ spectra recorded with solutions in CD_2Cl_2 : complex **7** (top), and with **1a** added (bottom).

Fig. 4 Predicted stereochemical pathways in the transition state.

optimisation of acyclic ketoester substrates, and their application to asymmetric synthesis.

Part of this work was performed by AMRS at Pfizer's Sandwich laboratories (January–March 2008). We are grateful to Dr Richard Webster for his assistance and useful discus-

sions during this period. The authors thank EPSRC (DTA) and Pfizer for financial support, and Johnson Matthey Plc for the loan of Pd salts.

Notes and references

† Typical reaction procedure: a mixture of ketoester (0.123 mmol) and catalyst **1** (6.15 μmol) in CH_2Cl_2 (0.5 mL) was cooled to -20°C , whereupon a solution of DMD (0.05–0.09 M in acetone, 0.148 mmol) was added slowly. Upon completion of the reaction (monitored by TLC), the mixture was filtered through a short plug of silica and concentrated. If necessary, the crude product was further purified by column chromatography.

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- Trace of moisture present in DMD caused decomposition of the Ti-TADDOL catalyst (ref. 3), while the presence of molecular sieves is necessary for nickel catalysis (ref. 4).