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Asymmetric enamide hydrogenation in the synthesis of *N*-acetylcolchinol: a key intermediate for ZD6126

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Abstract—A synthesis of *N*-acetylcolchinol, a key intermediate in the synthesis of ZD6126, was developed. The enantiodifferentiating step required the catalytic asymmetric hydrogenation of an enamide. After screening a range of metal and ligand combinations it was found that (*S*,*S*)-^{i}Pr–FerroTANE Ru(methallyl)$_2$ and [(*S*,*S*)-^{t}BuFerroTANE Rh(COD)]BF_4 gave both high enantioselectivity (>90% ee) and high catalyst utility (molar $S/C = 1000$).
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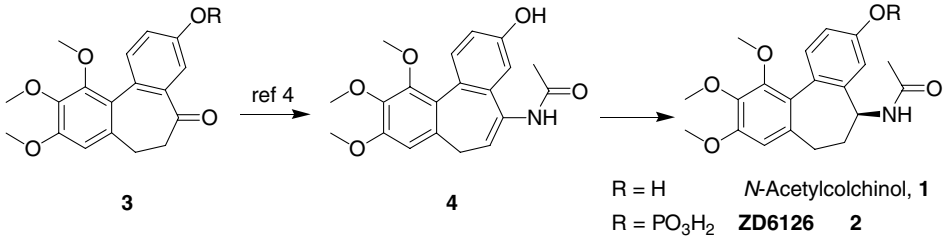
ZD6126 is a water soluble phosphate prodrug of *N*-acetylcolchinol.[1] It has been shown to be a tubulin-binding agent which causes the selective destruction of tumour vasculature leading to extensive tumour necrosis.

Catalytic asymmetric hydrogenation has been successfully applied to the enantioselective reduction of enamides over a number of years using a wide range of catalysts. The hydrogenation of enamines to furnish isoquinoline alkaloids represents one of the earliest applications of BINAP ruthenium catalysts.[5] These early efforts were very successful with a high degree of enantioselectivity being demonstrated. The substrates examined were mostly *exo*cyclic enamides. Initial studies on *endo*cyclic enamides concentrated on the readily accessible 2-aminotetraline derivatives. Hydrogenation of these was concentrated exclusively on the use of ruthenium catalysts.[6,7] The development of the reductive acetylation of oximes allowed access to a much wider range of enamides.[8,9] As broader ranges of substrates became readily accessible it was found that rhodium based catalysts could be successfully applied to the hydrogenation of enamides. The phospholane ligands such as DuPhos, BPE[8,10] and PennPhos[9] have proved to be particularly



Early syntheses of *N*-acetylcolchinol relied on semi-synthetic routes from naturally occurring colchicine derived from the genus *Colchicum* such as Autumn Crocus.[1b,2] In order to furnish ZD6126 on a commercial scale an alternative, fully synthetic synthesis of *N*-acetylcolchinol was sought.[3] The synthetic strategy chosen focused on the use of ketone **3**. The ketone was converted to enamide **4** via an iron mediated acetylation of the corresponding oxime.[4] The asymmetric hydrogenation of this enamide **4** would furnish the desired *N*-acetylcolchinol.

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effective. More recently, monodentate phosphite[11] and phosphoramidite[12] based rhodium catalysts have been applied to enamide hydrogenation, however, only acyclic enamides were examined.

The level of enantioselectivity achievable in the asymmetric hydrogenation of *endo*cyclic enamides is greatly influenced by ring size. Five-membered indanyl substrates have been successfully hydrogenated by several catalyst systems, however, only a limited number of catalysts have been successfully applied to the asymmetric hydrogenation of the six-membered 1-tetralone derivatives.[8,9,13] There are very few asymmetric hydrogenations of enamides within seven-membered rings recorded, those that are known have significantly lower selectivity than the five- and six-membered rings (80–82% ee).[14]

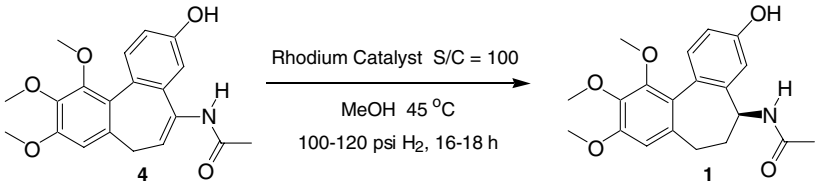
With very few concrete examples available in the literature a wide screen was undertaken of a range of rhodium and ruthenium catalysts[15] in order to discover a suitable catalyst for the asymmetric hydrogenation of **4**.[4] A wide range of rhodium catalysts were initially examined (Table 1).[15] At room temperature the reaction was sluggish with only low conversions achieved with all catalysts. Warming to 45 °C allowed essentially complete conversion under similar conditions.

Several classes of ligands were effective in furnishing the product in moderately high enantioselectivity. The benefit of a modular ligand design is once again exemplified, the two most effective ligands (entries 4 and 8) are both members of ligand classes for which a wide range of variants are readily available enabling the selection of the optimal catalyst for this particular class of substrate.

Ruthenium based catalysts were examined under similar conditions to those used for rhodium catalysts. At 45 °C, conversion was low, increasing the temperature to 65 °C gave suitably high conversion (Table 2).

Although a wide range of ligand types were examined in this screen of ruthenium catalysts including biarylphosphines, the best results were achieved with phospholane

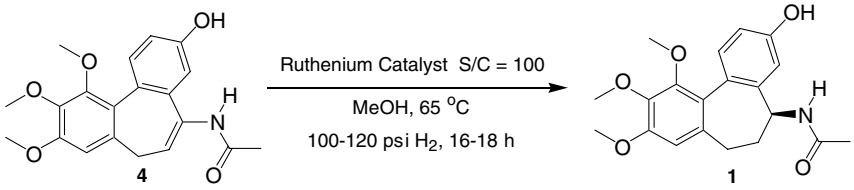
Table 1. Selected rhodium catalysed hydrogenations of **4**



Entry	Catalyst	Conversion[a] (%)	ee[a] (%)
1	[(*R*,*R*)-^{i}Pr–DuPhos Rh(COD)]BF_4	97	53 (*S*)
2	[(*S*,*S*)-Me–BPE Rh(COD)]OTf	100	69 (*S*)
3	[(*S*,*S*)-^{i}Pr–FerroTANE Rh(COD)]BF_4	98	60 (*R*)
4	[(*S*,*S*)-^{t}Bu–FerroTANE Rh(COD)]BF_4	96	86 (*R*)
5	[(*S*)-Xyl–PhanePhos Rh(COD)]BF_4	100	58 (*S*)
6	[(*R*)-(*S*)-JOSIPHOS Rh(COD)]BF_4	96	56 (*R*)
7	(*R*)-(*S*)-$FcPCy_2CHCH_3PCy_2$[$Rh(COD)_2$]BF_4	>95	66 (*R*)
8	(*R*)-(*S*)-$FcPPh_2CHCH_3P$-$^{t}Bu_2$[$Rh(COD)_2$]BF_4	>95	81 (*R*)
9	[(*S*)-Me–PhenylNANE Rh(COD)]BF_4	64	56 (*R*)
10	[(*R*)-OxazolinePPh_2 Rh(COD)]BF_4	96	65 (*S*)
11	[(*S*,*S*)-CHIRAPHOS Rh(COD)]BF_4	25	63 (*R*)

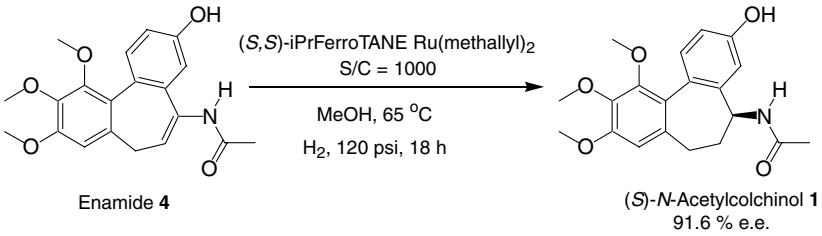
[a] Conversion and selectivity were measured by HPLC.

Table 2. Selected ruthenium catalysed hydrogenations of **4**



Entry	Catalyst	Conversion (%)	ee (%)
1	(*R*,*R*)-Me-DuPhos $Ru(O_2CCF_3)_2$[a]	16	76 (*R*)
2	[(*R*,*R*)-Me–DuPhos $Ru(C_6H_6)Cl$]BF_4	100	73 (*R*)
3	[(*R*,*R*)-Me–DuPhos $Ru(C_6H_6)Cl$]Cl	100	70 (*R*)
4	(*S*,*S*)-Et–FerroTANE $Ru(O_2CCF_3)_2$	100	71 (*R*)
5	(*S*,*S*)-^{i}Pr–FerroTANE Ru(methallyl)$_2$	100	85 (*S*)

[a] Reaction temperature 45 °C.



Scheme 1. Hydrogenation of ZD6126 enamide.

and phosphetane ligands.[15] There have been previous attempts to utilise phospholane ligands in ruthenium catalysed hydrogenation of enamides but the selectivities achieved have generally been significantly lower than those obtained in this study.[7] A selection of iridium catalysts were also examined and proved to be disappointing, in most cases, conversion was modest and in all cases, selectivity was very low or negligible.[15]

The reaction conditions chosen for the preliminary catalyst screen were designed to reveal which catalytic systems gave high enantioselectivity for the asymmetric hydrogenation of enamide **4**. A series of experiments were undertaken in order to investigate the effect of some process variables on the hydrogenation reaction. Previous studies in our laboratories have shown solvent to have significant effects on hydrogenation reactions. A range of solvents were thus examined, THF and a toluene/methanol mixture gave slight improvements in the selectivity for the rhodium catalysed hydrogenation.[15] Conversely, these solvent systems gave very poor results for the ruthenium based catalyst. This is an indication of the markedly different mechanisms for the ruthenium and rhodium catalysed reaction. This is further emphasised by the fact that the two ligands examined, (*S*,*S*)-^{t}Bu–FerroTANE and (*S*,*S*)-^{i}Pr–FerroTANE while having the same absolute stereochemistry, gave rise to equal and opposite stereoselectivity of the product (Table 1, entry 4 and Table 2, entry 5).

The most significant test of these catalysts' practicality was their utilisation at low catalyst loading. Both (*S*,*S*)-^{i}Pr–FerroTANE Ru(methallyl)$_2$ and [(*S*,*S*)-^{t}Bu–FerroTANE Rh(COD)]BF_4 were shown to be effective at molar substrate to catalyst ratios of 500 and 1000, giving the desired product in 94 and 90% ee, respectively.[15] We decided to investigate the use of (*S*,*S*)-^{i}Pr–FerroTANE Ru(methallyl)$_2$ for the asymmetric hydrogenation of **4** on a slightly larger scale (Scheme 1). At a molar *S*/*C* of 1000 the reaction proceeded smoothly at 65 °C to provide (*S*)-*N*-acetylcolchinol **1** in 91.6% ee.[16] The higher selectivities observed in the larger scale reactions compared to the screening reactions are attributed to better mixing leading to a more efficient hydrogen gas transfer into the reaction mixture. It has long been recognised that hydrogen mass transfer and solution hydrogen concentration are intimately linked to rate and selectivity.[17]

A wide range of enantioselective rhodium, ruthenium and iridium catalysts were screened in order to find a suitable catalyst for the asymmetric hydrogenation of enamide **4** to provide (*S*)-*N*-acetylcolchinol **1**, the final intermediate in the synthesis of ZD6126 **2**. Several catalysts were identified, which gave reasonably high enantioselectivity. Of these a ruthenium catalyst (*S*,*S*)-^{i}Pr–FerroTANE Ru(methallyl)$_2$ and a rhodium catalyst [(*S*,*S*)-^{t}Bu–FerroTANE Rh(COD)]BF_4 both based on FerroTANE ligands gave the best results in terms of both selectivity and reactivity. For most enamide substrates, either a rhodium based catalyst or a ruthenium based catalyst is normally found to be superior. We believe that this is the first time that a rhodium and ruthenium based system has provided similar results for the same enamide substrate.

While further work is required to fully optimise the application of these catalysts for the hydrogenation of **4**, it is clear from these preliminary results that the catalysts identified provide access to *N*-acetylcolchinol with a high level of enantiomeric purity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.090.

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15. For full details of the catalytic asymmetric hydrogenation screening, see Supplementary data.
16. Enamide **4** (0.701 g, 1.97 mmol) and (*S*,*S*)-^{i}Pr–Ferro-TANE Ru(methallyl)$_2$ (1.4 mg, 2 μmol) were weighed into a glass liner. The liner was assembled into a PARR pressure vessel with a magnetic stir bar. A nitrogen atmosphere was established and methanol (20 ml) was added. The vessel was pressurised with hydrogen to 110 psi, heated to 65 °C and the reaction stirred overnight. A small sample was analysed by ^{1}H NMR spectroscopy and chiral HPLC [Chiralcel OD-RH, water 80% acetonitrile 20%, (*R*)-*N*-acetylcolchinol B 16.6 min, (*S*)-*N*-acetylcolchinol B 20.2 min], which showed 100% conversion and 91.6% ee. The solvent was removed and the residue was triturated with ethyl acetate and heptane to give **1** as an off white powder 0.695 g. ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (1H, d, $J = 8$ Hz), 7.23 (1H, d, $J = 8$ Hz), 6.76–7.79 (1H, m), 6.90–6.74 (2H, m), 4.87 (1H, s), 4.56–4.66 (1H, m), 3.87 (3H, s), 3.85 (3H, s), 3.48 (3H, s), 2.44–2.55 (1H, m), 2.19–2.32 (2H, m), 2.00 (3H, s), 1.87–1.96 (1H, m). ^{13}C NMR (101 MHz, CD_3OD) δ 23.0, 31.9, 40.3, 50.9, 57.0, 61.7, 62.0, 109.4, 111.2, 114.6, 126.9, 127.1, 132.5, 137.1, 142.7, 142.8, 152.5, 154.1, 158.3, 172.8.
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