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Amidation of silyl enol ethers and cholesteryl acetates with chiral ruthenium(II) Schiff-base catalysts: catalytic and enantioselective studies†

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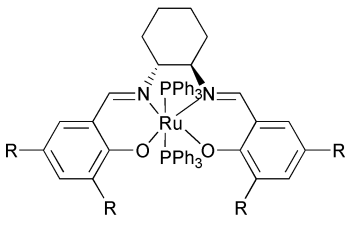
Chiral ruthenium(II)–salen complexes [Ru^{II}(salen)(PPh_3)$_2$] catalyse asymmetric aziridination of alkenes with up to 83% ees, asymmetric amidation of silyl enol ethers with up to 97% ees, and allylic amidation of cholesteryl acetates with good regioselectivity.

Metal-catalysed aziridination and amidation of hydrocarbons offer useful means for the synthesis of aziridines, amides, and amines.[1] In contrast to the numerous studies on asymmetric organic oxidations, asymmetric C–N bond formations, particularly those involving amidation of C–H bonds, are less developed. Recent studies by us[1] and others[2] demonstrated the usefulness of chiral metalloporphyrin catalysts for asymmetric nitrene transfer reactions. However, the reported ee values are moderate. Because synthesis of chiral porphyrin ligands requires tedious steps, improvement of ee through structural modification of chiral metalloporphyrin catalysts would be a difficult task. In this context, we turn our attention to salen ligands, which are easily synthesised and modified. Jacobsen[3] and Katsuki[4] have reported chiral Cu(I) and Mn(III) salen complexes for asymmetric alkene aziridination and amidation of saturated hydrocarbons. Because high valent ruthenium–tosylimido complexes are reactive,[5] we envision that chiral ruthenium–salen complexes should hold promising prospects in developing new catalysts for enantioselective C–N bond formation. We describe here the aziridination of alkenes and amidation of silyl enol ethers and cholesteryl acetates catalysed by chiral ruthenium(II)–salen complexes.

The catalysts **1**–**3** were obtained in high yields (~80%) by reacting the H_2 salen ligands with [$Ru^{II}(PPh_3)_3Cl_2$] in ethanol.§

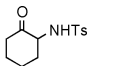
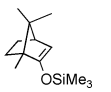
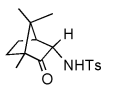
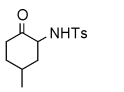
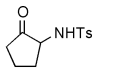
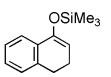
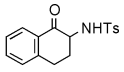
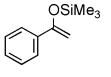
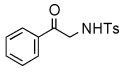
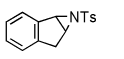
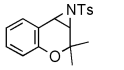


1 R = NO_2; **2** R = I; **3** R = Br

They are effective catalysts for asymmetric amidation of silyl enol ethers and aziridination of alkenes using PhI=NTs as nitrogen source. The results obtained for a series of substrates are summarised in Table 1. Using (1-cyclohexenyloxy)trimethylsilane as substrate and 12.5 mol% of complex **1** (based on substrate) as catalyst, all the conversion, yield and ee values were improved when dichloromethane was the solvent (entries 1, 2 and 3). When only 5 mol% catalyst was used, the ee value decreased from 74% (entry 1) to 16 % (entry 4), and when catalyst loading was 20 mol%, the ee value slightly increased (79%, entry 5). In absence of catalyst, the reaction of (1-cyclohexenyloxy)trimethylsilane with PhI=NTs was slow. After 12 h reaction, all the PhI=NTs was consumed, but about 10% 2-[*N*-(*p*-tolylsulfonyl)amino]cyclohexanone (based on starting substrate) was obtained.

Amino ketones are of importance in natural products, drugs, and are useful building blocks for organic synthesis. To our knowledge, there are two reports[6,7] on asymmetric catalytic amidation of silyl enol ethers to give α-amino ketones. In this work, silyl enol ethers were chosen as substrates, and target products were α-amino ketones. As shown in Table 1, the conversions range from 23 to 92% when different substrates are used. The best conversion was 92% with yield 73% for amidation of (1-styrenyloxy)trimethylsilane catalysed by **2**

Table 1 Asymmetric amidation of silyl enol ethers and aziridination of alkenes catalysed by Ru^{II}–salen complexes[a]

Entry	Sub-strates	Products	Catalyst	Con-version	Yield[b]	Ee[c]
1			**1**	28	78	74
2[d]			**1**	15	71	24
3[e]			**1**	22	75	50
4[f]			**1**	23	75	16
5[g]			**1**	40	75	79
6			**2**	25	74	71
7			**3**	23	75	97
8			**1**	41	72	—
9			**2**	43	73	—
10		*(endo)*	**3**	27	73	—
11			**1**	23	76	59
12			**2**	25	72	29
13			**3**	37	85	66
14			**1**	53	75	33
15			**2**	60	74	58
16			**3**	47	73	74
17			**1**	52	76	14[h]
18			**2**	56	83	10[h]
19			**3**	40	73	58[h]
20			**1**	74	73	—
21			**2**	92	73	—
22			**1**	34	68	83
23			**2**	30	74	42
24			**3**	31	74	19
25			**1**	46	84	45
26			**2**	31	74	51
27			**3**	31	75	19

[a] Reaction conditions: catalyst : substrate : PhI=NTs = 1 : 8 : 12 (molar ratio), rt, 2 h, CH_2Cl_2. [b] Yield (%) based on substrate consumed. [c] Ee (%) determined by HPLC using chiral whelk-ol column. [d] Acetonitrile as solvent. [e] Benzene as solvent. [f] 5% catalyst was added. [g] 20% catalyst was added. [h] Determiend by HPLC using chiral OJ column.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b109272c/

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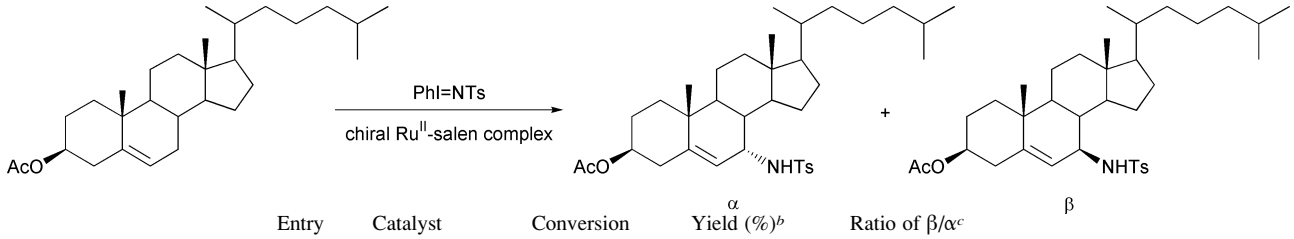
Table 2 Allylic amidation of cholesteryl acetate catalysed by Ru^{II}–salen complexes[a]



α β

Entry	Catalyst	Conversion	Yield (%)[b]	Ratio of β/α[c]
1	**1**	24	73	1.6 : 1
2	**2**	26	74	2.3 : 1
3	**3**	28	71	1.1 : 1

[a] Reaction conditions: catalyst : substrate : PhI=NTs = 1 : 8 : 12 (molar ratio), rt, 2 h, CH_2Cl_2. [b] Yield based on substrate consumed. [c] Ratio was determined by ^1H NMR.

(entry 21). For [1-(4′-methyl)cyclohexenyloxy]trimethylsilane, (1-naphthalenyloxy)trimethylsilane, and (1-cyclopentenyloxy-)trimethylsilane, the ee values are moderate to good with **3** as catalyst. Notably, the amidation of (1-cyclohexenyloxy)trimethylsilane catalysed by **3** afforded 97% ee, which represents the highest ee value reported for such a reaction.[6,7] The amidation of D(+)-camphor trimethylsilyl enol ether gave only *endo*-amino ketone, and the *exo* product was undetectable.

The aziridination of indene and chromene has also been investigated. The conversion is moderate (30–46%), and yield is good (68–84%). The ee values range from 19 to 83%. The highest ee of 83% was found with **1**. Unlike the amidation of silyl enol ethers, **3** gave low ee values in aziridination of indene and chromene. When *cis*-ß-methylstyrene was used as substrate with **2** as catalyst, the *cis* aziridine was the main product (conversion 24%, yield 73%) with the molar ratio of *cis* to *trans* aziridines being 84 : 16, showing that a stepwise pathway analogous to that proposed by Mansuy and co-workers[8] should be operative for the aziridination. The reaction is almost non-enantioselective (ee ~ 2%), in sharp contrast to related rhodium-catalysed aziridination reported by Muller (73%).[9]

Amino steroids have been shown to have noteworthy pharmacological activity, for instance, as anesthetics and enzyme inhibitors on the central nervous system.[10] Dodd and Dauban[11] demonstrated the copper-catalysed aziridination of 11-pregnene-3,20-dione in 53% yield with PhI = NSes (Ses = 2-(trimethylsilyl)ethanesulfonyl). Breslow[12] reported the amidation of equilenin acetate with PhI = NTs catalysed by [Mn(TPFPP)Cl] (TPFPP = *meso*-tetrakis(pentafluorophenyl-)porphyrinato dianion) in 47% yield. In this work, we reported the first amidation of steroids such as cholesteryl acetate by PhI = NTs with metal salen catalysts. As shown in Table 2, the catalysts exhibited good regioselectivity as the amidation only occurred at the 7-substituted position of the cholesteryl ring, and there was no 4-site amidation or 5,6-site aziridination product. The amidation products have two isomers with α and β configurations (the spectral data of the α isomer are identical with those reported in the literature[13]), respectively. Catalyst **2** showed the best β selectivity with a β : α ratio of 2.3 : 1 (Table 2, entry 2).

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Notes and references

§ **General procedure for ruthenium-catalysed asymmetric aziridination and amidation with PhI = NTs.** A solution of substrate (0.16 mmol) in dry dichloromethane (4 mL) was added through syringe to a Schlenk flask containing ruthenium catalyst (0.02 mmol) and molecular sieves (4 Å, 150 mg). The mixture was stirred at rt for 10 min, then treated with PhI = NTs (0.24 mmol) for 2 h. The molecular sieves were filtered and washed with DCM. The filtrate and washings were evaporated to dryness and the solid was purified by column chromatography (silica gel, 230–400 mesh; *n*-hexane : EtOAc = 4 : 1 as eluent).**1** FAB-MS: *m/z* 1126 $[M]^+$, 864 $[M - PPh_3]^+$; Calcd. for $C_{56}H_{46}N_6O_{10}P_2Ru{\cdot}4H_2O$ C 56.14, H 4.54, N 7.01; found: C 56.08, H 4.25, N 6.74%. ^1H NMR ($CDCl_3$) δ 8.31 (d, 2H, *J* = 3 Hz, CH = N), 7.10–7.40 (m, 34H, Ar-H), 3.15 (2H, m, CH-N), 1.2–2.6 (6H, m, CH_2); ^{31}P NMR ($CDCl_3$) δ 31.06.**2** FAB-MS: *m/z* 1450 $[M]^+$, 1188 $[M - PPh_3]^+$, 926 $[M - 2PPh_3]^+$; Calcd. for $C_{56}H_{46}I_4N_2O_2P_2Ru{\cdot}0.5C_6H_{14}$: C 47.47, H 3.58, N 1.88; found: C 47.02, H 3.55, N 1.45%; ^1H NMR ($CDCl_3$) δ 8.02 (d, 2H, *J* = 2.2 Hz, CH = N), 6.80–7.60 (m, 34H, Ar-H), 3.77 (2H, m, CH-N), 1.2–2.6 (6H, m, CH_2); ^{31}P NMR ($CDCl_3$) δ 29.57.**3** FAB-MS: *m/z* 1262 $[M]^+$, 1000 $[M - PPh_3]^+$, 738 $[M - 2PPh_3]^+$; ^1H NMR ($CDCl_3$) δ 7.86 (d, 2H, *J* = 2.1 Hz, CH = N), 6.80–7.51 (m, 34H, Ar-H), 3.68 (2H, m, CH-N), 1.2–2.6 (6H, m, CH_2); ^{31}P NMR ($CDCl_3$) δ 29.56.

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