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TETRAHEDRON: *ASYMMETRY*

Ruthenium catalyzed asymmetric transfer hydrogenation of β-ketoesters

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Abstract

Chemoselective transfer hydrogenation of β-ketoesters to the corresponding alcohols is achieved in the presence of catalytic combinations of $[RuCl_2(\eta^6\text{-arene})]_2$ and ephedrine or diamino type chiral ligands with activities up to 190 h^{-1} at 20°C and moderate to good enantiomeric excesses ranging from 36 to 94%.

Asymmetric catalytic transfer hydrogenation using 2-propanol as a hydrogen source has proved in recent years to be a valuable selective method for reducing simple aryl alkyl ketones[1–6] and α,β-acetylenic ketones.[7] Efficient catalytic systems developed by Lemaire, Noyori, Helmchen and others combine a Rh, an Ir, or better, a Ru[1] precursor with a simple chiral bidentate ligand having an NH moiety such as a diamine or an aminoalcohol. Very few results have been reported on the performance of these systems for the reduction of β-ketoesters,[8,9] although this route to optically active β-hydroxy esters, a valuable class of chiral intermediates, would afford, if feasible, obvious advantages over the corresponding asymmetric hydrogenation. Knochel et al. reported recently that the transfer hydrogenation of ethyl acetoacetate **1a**, (Scheme 1) catalyzed by a Ru complex bearing a chiral ferrocenic secondary diamine proceeds much slower than that of simple ketones (TOF_{50}=ca. 30 h^{-1} at 80°C)[10] and gives the corresponding β-hydroxy ester **2a** in only 20% *ee*[11] This statement prompted us to present our first results in this field, which show that high catalytic activity together with total chemoselectivity, but still modest enantioselectivity are attainable.

The chiral Ru complexes were prepared in situ by heating a mixture of $[RuCl_2(\eta^6\text{-arene})]_2$ and a chiral ligand (2 equiv. vs. Ru) in 2-propanol. Screening experiments conducted under typical reaction conditions[11] using *i*PrOK (6 equiv. vs. Ru) as a co-catalyst and ethyl acetoacetate **1a** as a model substrate indicated that only a limited number of bidentate ligands give significantly active catalysts, of which (1*S*,2*R*)-ephedrine and some derivatives of (1*S*,2*S*)-diphenylethylenediamine are notable (Fig. 1).

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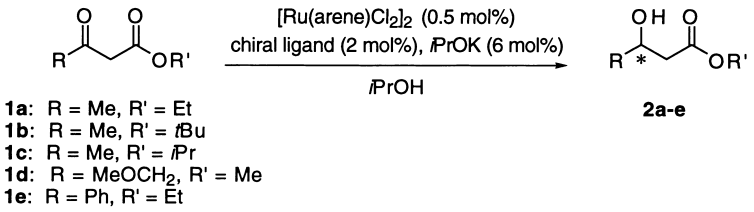

Scheme 1.

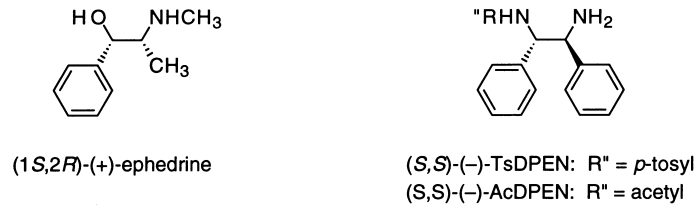

Fig. 1.

Quantitative GLC monitoring and NMR spectroscopy revealed that the reaction always proceeds with total chemoselectivity for β-hydroxyesters, thus showing that reduction of active methylene ketones under moderately basic conditions does not compete with aldolisation side-processes.

As shown in Table 1, the catalytic performance for the reduction of **1a** is also strongly affected by the nature of the arene ligand in the Ru precursor (entries 1–8). The combination $[RuCl_2(C_6H_6)]_2$/ephedrine affords the most active system (TOF_{50}=300 h^{-1} at 50°C, 14 h^{-1} at 20°C), but **2a** is recovered in only 36–39% *ee*[12] On the other hand, the $[RuCl_2(C_6Me_6)]_2$/TsDPEN system affords the best *ee* so far (56%), but the activity drops dramatically. A reversal in the configuration of **2a** is observed going from the Ru(benzene) to the Ru(*p*-cymene) precursor with both chiral ligands (compare entries 2/3 and 5/6).

Most interestingly, the transfer hydrogenation of *t*Bu ester **1b** proceeds much faster than for **1a**, the reaction being completed within 1 h at 20°C (TOF_{50}=190 h^{-1}; entry 9), and yields the reduction product, **2b**, in a slightly higher *ee* than **2a**. The reaction of *i*Pr ester **1c** leads to intermediary results (TOF_{50}=30 h^{-1}; entry 10). We assume that the dramatic increase in the reduction rate going from R′=Et to R′=*t*Bu in these acetoacetic esters is related to the bulkiness of the R′ group, which possibly prevents the formation of less reactive chelated species.

The influence of the substituent R α to the keto function was also examined (entries 11–15). For β-ketoester **1d**, the optimal activity is obtained with the $[RuCl_2(C_6H_6)]_2$/ephedrine system, while the $[RuCl_2$(*p*-cymene)$]_2$/ephedrine combination affords a slightly better *ee* but proved to be extremely sluggish. Similar trends in the catalytic performance are observed for aromatic β-ketoester **1e**, the $[RuCl_2$(*p*-cymene)$]_2$/TsDPEN system offering the best compromise activity/enantioselectivity.

If alcohols **2a**–**d** can be recovered in only 36–56% *ee* so far, *ee*s as high as 94% are observed for **2e**; this observation is in direct line with previous studies which have shown the beneficial influence of an unsaturated α-substituent in the enantiodifferentiation of simple ketones.[1–7] However, **1e** is reduced in only 40% ee with the $[RuCl_2(C_6H_6)]_2$/ephedrine catalyst (entry 13). Indeed, the results of this study clearly demonstrate the dramatic influence of the arene ligand both on the enantioselectivity and the activity of the catalyst. Efforts in this direction are under progress.

Table 1
Asymmetric transfer hydrogenation of β-ketoesters **1a–e**[a]

Entry	Subst.	Catalytic system arene / chiral ligand	T (°C)	Time[b] (h)	Conv. (mol %)	$t_{1/2}$ [c] (min)	*e.e.* (%)	Conf.[d]
1	**1a**	benzene / ephedrine	20	10	100	210	39	*S* (+)
2	**1a**	benzene / ephedrine	50	0.5	100	10	36	*S* (+)
3	**1a**	*p*-cymene / ephedrine	50	2	100	50	15	*R* (–)
4	**1a**	hexamethylbenzene / ephedrine	50	46	34	-	6	*R* (–)
5	**1a**	benzene / TsDPEN	50	3	100	70	15	*R* (–)
6	**1a**	*p*-cymene / TsDPEN	50	2	100	16	15	*S* (+)
7	**1a**	hexamethylbenzene / TsDPEN	50	20	63	840	56	*R* (–)
8	**1a**	*p*-cymene / AcDPEN	50	2	100	50	23	*S* (+)
9	**1b**	benzene / ephedrine	20	1	98	16	44	*S* (+)
10	**1c**	benzene / ephedrine	20	4	100	100	40	*S* (+)
11	**1d**	benzene / ephedrine	50	2	100	35	15	*S* (–)
12	**1d**	*p*-cymene / ephedrine	50	46	38	-	36	*S* (–)
13	**1e**	benzene / ephedrine	50	2.5	99	22	40	*S* (–)
14	**1e**	*p*-cymene / ephedrine	50	15	85	300	94	*S* (–)
15	**1e**	*p*-cymene / TsDPEN	50	3	95	60	93	*S* (–)

[a][**1**] / [*i*PrOK] / [chiral ligand] / [Ru] = 100 : 6 : 2 : 1, [**1**] = 0.1 mol.l^{-1}, *i*PrOH = 20 mL. Conversion of **1** into **2** (the sole product observed) and *e.e.*'s of **2** were determined by quantitative GLC analysis (BPX5 and chiral permethylated-β-Cyclodex columns). [b]Reaction time was not necessarily optimized. [c]Half-reaction time. [d]Determined by polarimetry comparisons and/or GLC comparisons with authentic samples.

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8. Transfer hydrogenation of β-ketoester **1d** using HCO_2H as the hydrogen source and the catalytic combination $[RuCl_2(C_6H_6)]_2$/TsDPEN affords **2d** in 93% *ee*; see Ref. 1.

9. Note also that the transfer hydrogenation of α-ketoester $PhCOCO_2Me$ in *i*PrOH using Rh/C_2-diamine catalysts affords methyl mandelate in up to 99% *ee*; Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett*. **1993**, *34*, 6897–6898.
10. TOF_{50}=turnover frequency expressed in mol of produced alcohol/mol of Ru.h and calculated at 50% conversion.
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12. In every case, *ee* values were constant (±4%) throughout the whole reaction course, thus indicating that no significant racemization occurred with the present catalytic systems.