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TETRAHEDRON: *ASYMMETRY*

Steric effects in the enantioselective transfer hydrogenation of 2-aroylacetates

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Abstract

Benzoylacetate esters and aryl-substituted derivatives are efficiently reduced in 2-propanol using the readily available catalytic combination (1*S*,2*R*)-ephedrine/$[RuCl_2(\eta^6$-*p*-cymene$)]_2$ to give the corresponding alcohols in high yields and enantioselectivities (up to 94% ee).

Despite significant advances in recent years, the catalytic enantioselective transfer hydrogenation of ketones remains essentially limited to simple aryl alkyl ketones and α,β-acetylenic ketones.[1] Studies by us and others have shown that the reduction of functionalized ketones, such as the important β-ketoesters, with Ru- and Rh-based catalysts leads in general to sluggish activity and/or poor enantioselectivities.[2–4] The few notable exceptions to this trend are: (a) the reduction of $PhCOCO_2Me$ in *i*PrOH using Rh/C_2-diamine catalysts which affords methyl mandelate in up to 99% ee;[5] (b) the reduction of $PhCOCH_2CO_2Et$ **1a** using the HCO_2H/NEt_3 system and the catalytic combination (*S*,*S*)-TsDPEN/$[RuCl_2(C_6H_6)]_2$ which affords the corresponding alcohol **2a** in 93% ee;[6] (c) the recently reported transfer hydrogenation of $PhCO(CH_2)_nX$ derivatives (n=1–3, X=OR, OCOR, $NRCO_2R'$) with a Ru–[*cis*-1-aminoindan-2-ol] system in 38–97% yields and 79–88% ees.[7] We here report that effective enantioselective transfer hydrogenation of various 2-aroylacetates can be achieved using 2-propanol as the hydrogen source in the presence of simple catalytic combinations of (1*S*,2*R*)-ephedrine with an adequate $[RuCl_2(\eta^6$-arene$)]_2$ precursor (Scheme 1).

In order to assess the effect of phenyl substituents on catalytic performance, aroylacetate ethyl esters **1c**–**f** and **1h**–**i** were prepared by condensation of the corresponding deprotonated acetophenone derivative on diethylcarbonate.[8] In addition, to probe the influence of the alkoxycarbonyl moiety, *tert*-butyl esters **1b**,**g** were synthesized by transesterification of the corresponding ethyl ester. The chiral catalyst precursors were prepared ex situ by heating a mixture of $[RuCl_2(\eta^6$-arene$)]_2$ and (1*S*,2*R*)-(+)-ephedrine (2 equiv. vs. Ru) in 2-propanol, and transfer hydrogenation was carried out at 50°C under usual reaction conditions.[9] Representative results are reported in Table 1.

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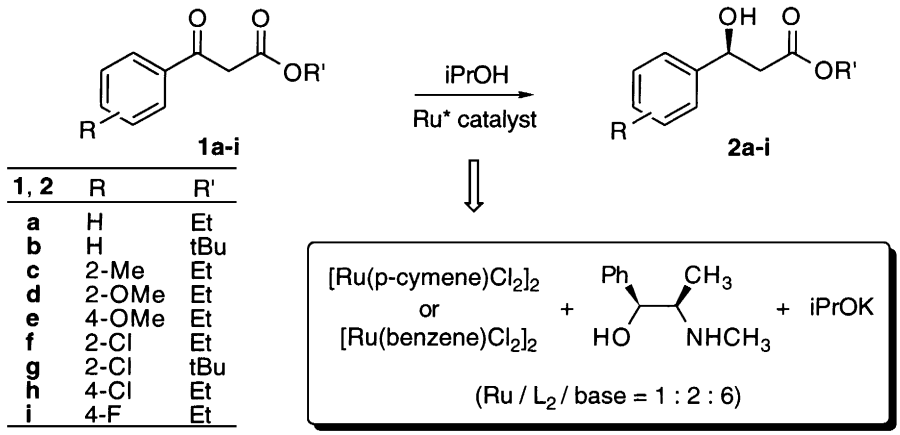


1, 2	R	R'
a	H	Et
b	H	tBu
c	2-Me	Et
d	2-OMe	Et
e	4-OMe	Et
f	2-Cl	Et
g	2-Cl	tBu
h	4-Cl	Et
i	4-F	Et

Scheme 1.

Table 1
Asymmetric transfer hydrogenation of 2-aroylacetates **1a–i**[a]

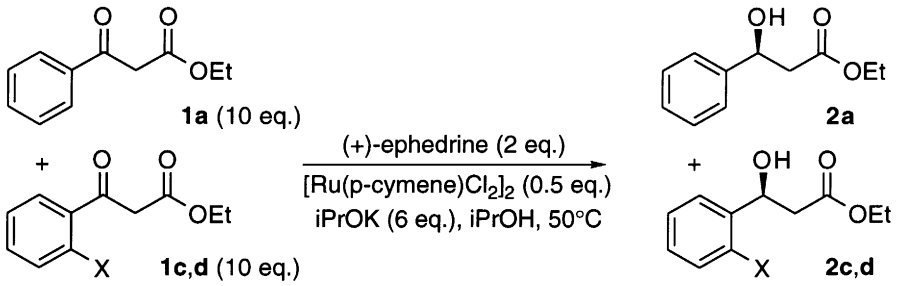
Entry	Subst.	Catalytic system (arene)	**1** / Ru	Time[b] (h)	Yield[c] (mol %)	TOF_{50}[d] (h^{-1})	*ee*[e] (%)	Conf.
1	**1a**	benzene	100	2.5	99	136	40	*S* (–)
2	**1a**	*p*-cymene	100	15	>99	10	94	*S* (–)
3	**1b**	*p*-cymene	100	1	>99	120	89	*S* (–)
4	**1c**	*p*-cymene	20	2	95	10	75	(–)
5	**1d**	benzene	100	0.5	99	>200	8	(–)
6	**1d**	*p*-cymene	100	1	>99	>100	82	(–)
7[f]	**1d**	*p*-cymene	100	16[f]	27	–	83	(–)
8	**1e**	benzene	100	0.16	>99	>200	22	*S* (–)
9	**1e**	*p*-cymene	100	16	>99	nd	82	*S* (–)
10	**1f**	*p*-cymene	20	14	>99	nd	72	(–)
11	**1g**	*p*-cymene	20	14	>99	nd	64	(–)
12	**1h**	*p*-cymene	20	1	>99	25	81	(–)
13	**1i**	*p*-cymene	20	1	>99	30	84	(–)

[a] [**1**] = 0.1 M, iPrOH = 20 mL, T = 50°C unless otherwise stated. [b] Reaction time was not necessarily optimized. [c] Yield of **2a-i** (the sole product observed) as determined by quantitative GLC analysis on a BPX5 column and/or ^{1}H NMR. [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mole of **2**/(mole of Ru.h). [e] *Ee* of **2a-i** as determined by chiral GLC analysis using a Chirasil-DEX-CB column and H_2 as a carrier gas. [f] T = 20°C.

In nearly all cases, virtually quantitative yields of **2** were obtained in reasonable times. A screening of different $[RuCl_2(\eta^6\text{-arene})]_2$ precursors revealed that catalytic performances are strongly affected by this parameter; i.e., the benzene complex induces significantly higher rates than its *p*-cymene equivalent (as judged from the catalyst turnover frequency at half-reaction, TOF_{50}) but the latter complex generates much more enantioselective[10] catalytic species (compare entries 1/2, 5/6 and 8/9). The present results follow the same trend as that observed for the reduction of other types of functionalized ketones with similar systems,[2,4] and suggest that the bulkier the arene, the lower the catalytic activity, the higher

the enantioselectivity. The reduction of *tert*-butyl esters **1b**,**g** proceeds faster than that of their ethyl equivalents **1a**,**f** but is less enantioselective (compare entries 2/3 and 10/11). This increase in the apparent rate going from ethyl to *tert*-butyl esters is most likely related to the bulkiness of the *tert*-butoxy group, which possibly prevents the formation of less or non-reactive species; the decrease in enantioselectivity, an opposite and more marked trend compared to the reduction of simple alkyl β-ketoesters,[2,4] indicates the relatively high sensitivity of this process to steric factors. In fact, when *ortho* substituents are introduced on the phenyl ring, ees remain of synthetic interest but they are systematically lower than for the reduction of **1a**. It seems indeed that this drop in enantioselectivity reflects more steric than electronic factors (and possible coordinating abilities) as the bulkier the substituent, the lower the ee (Cl, **1f**<Me, **1c**<OMe, **1d**<H, **1a**) (compare entries 2/4/6/10 and 1/5). Despite there being no obvious correlation of ees with Hammett parameters, electronic factors cannot be definitively ruled out in view of the comparable decrease of ees upon the introduction of *para* substituents (entries 2/9/12/13 and 1/8).

In the course of this ongoing study, we also observed a relevant phenomenon. When transfer hydrogenation of a 1:1 mixture of **1a** and **1c** was conducted under the usual reaction conditions (see Scheme 2), it turned out that the reduction of **1c** barely proceeded before that of **1a** was completed (Fig. 1). So, in contrast with the nearly identical reactivities of these two aroylacetates in individual experiments (see TOF_{50} values in Table 1), a catalytic kinetic resolution occurs on the mixture. The same parallel experiment was repeated on a 1:1 mixture of **1a** and **1d**, knowing that **1d** is reduced more than one order of magnitude faster than **1a** in separate experiments using the *p*-cymene–Ru precursor; in this case, the transformation of both aroylacetates proceeded at a comparable apparent rate (yields of **2a** and **2d**=37 and 46% after 5 min, 72 and 90% after 10 min, under the conditions of Scheme 2), evidencing less spectacularly the same phenomenon. In both parallel experiments, β-hydroxyesters **2** were formed with the same ees as in individual experiments (Table 1). This kinetic resolution brings up some interesting mechanistic features and reflects, in our opinion, the relative affinities of aroylacetates for the active Ru species. Considering Noyori's mechanism,[6] we assume that this affinity corresponds to the easiness of approach of the aroylacetate (one preferred enantioface) toward the 18 electron hydrido complex [HRu(η^1,η^1-ONHMe)(η^6-arene)] for hydrogen transfer. The fact that, in the mixtures of aroylacetates so far investigated, the less hindered one, i.e. **1a**, reacts faster is consistent with this hypothesis.



Scheme 2.

Efforts are currently under way to enlarge this study in order to confirm the latter hypothesis and to rationalize steric effects on catalytic performance in transfer hydrogenation of β-ketoesters.

Acknowledgements

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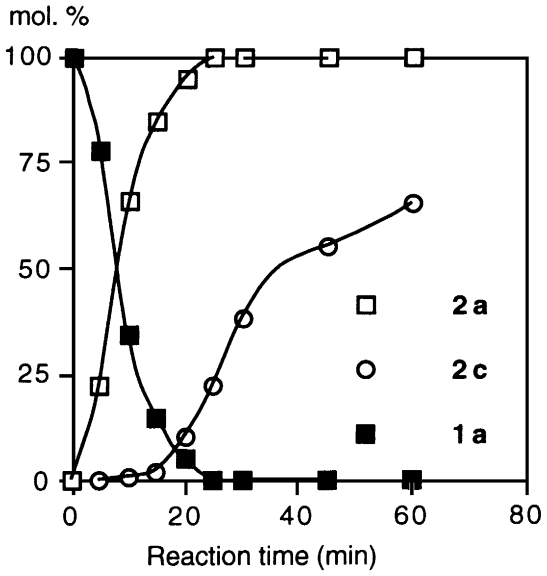

Fig. 1.

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4. We have found recently that significantly improved (with respect to well-established systems such as Ru–TsDPEN) catalytic activities (up to 600 h^{-1} at 20°C) and enantioselectivities (56–89% ee) can be achieved for the reduction of simple alkyl β-ketoesters, methoxyacetone and 2-acetylpyridine in 2-propanol by using catalytic combinations of an adequate $[RuCl_2(\eta^6\text{-arene})]_2$ precursor and *N*-substituted derivatives of (1*S*,2*R*)-norephedrine such as (1*S*,2*R*)-*N*-benzyl-norephedrine. Everaere, K.; Carpentier, J.-F.; Mortreux, A.; Bulliard, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4083–4086.
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9. A typical procedure is as follows (entry 2): In a 100 mL Schlenk tube placed under nitrogen, $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol) was added to a solution of (1*S*,2*R*)-ephedrine (6.6 mg, 0.04 mmol) in *i*PrOH (5 mL). The mixture was stirred at 80°C for 20 min leading to an orange homogeneous solution. After cooling to room temperature, *i*PrOH (14 mL), ethyl benzoylacetate (**1a**, previously distilled, 384 mg, 2.0 mmol) and *i*PrOK (0.12 m in *i*PrOH, 1.0 mL, 0.12 mmol) were added. The reaction vessel was stirred at 50°C and the reaction was monitored by GLC analysis of aliquots (BPX5 and Chirasil CB columns). After completion, the solution was concentrated under vacuum and the crude product was chromatographed on silica to give **2a** as a colourless oil (0.35 g, 92%). The identity of products **2a**–**i** was established by MS, ^1H and $^{13}C\{^1H\}$ NMR, in agreement with literature data.
10. 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.