

Enantioselective Monoreduction of 2-Alkyl-1,3-diketones Mediated by Chiral Ruthenium Catalysts. Dynamic Kinetic Resolution

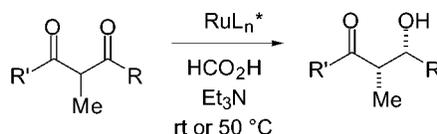
Florence Eustache, Peter I. Dalko, and Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin,
75231 Paris Cedex 05, France

janine.cossy@espci.fr

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ABSTRACT



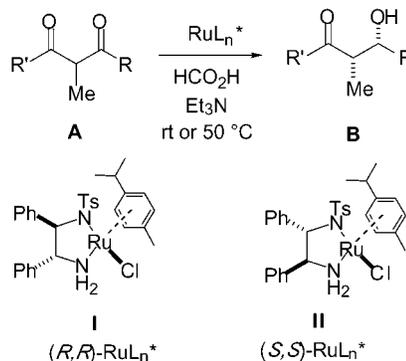
The reduction of 2-alkyl-1,3-diketones using (*R,R*)- or (*S,S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) in the presence of formic acid and triethylamine affords *syn*-2-alkyl-3-hydroxy ketones as the major products with high enantioselectivity.

Asymmetric transformation of compounds containing configurationally labile groups is an elegant way to create simultaneously two or more stereogenic centers in a single chemical operation.¹ Despite the interest in such transformations, only a few enantioselective methods have been developed in the past few years.^{1–3} One of them, pioneered by Noyori et al., allows the formation of optically active 2-alkyl-3-hydroxy esters through the use of ruthenium-mediated asymmetric reduction of β -keto esters.³ As an extension of our studies on the enantioselective reduction of β -dicarbonyl compounds,⁴ 2-alkyl-1,3-diketones of type **A** were investigated.

We wish to report that the dynamic kinetic resolution of such compounds using (*R,R*)- or (*S,S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) in the presence of

formic acid and triethylamine affords selectively 2-methyl-3-hydroxy ketones of type **B** in high diastereo- and enantioselectivity (Scheme 1).

Scheme 1. Dynamic Kinetic Resolution of 1,3-Diketones



The reduction of 2-methyl-1,3-diketone **1** in the presence of (*R,R*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) [(*R,R*)-RuL_n*] **I** (1%), triethylamine (2 equiv), and formic acid (5 equiv) in dichloromethane at room temperature

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Scheme 2. Reduction of 2-Methyl-1,3-diketone **1**

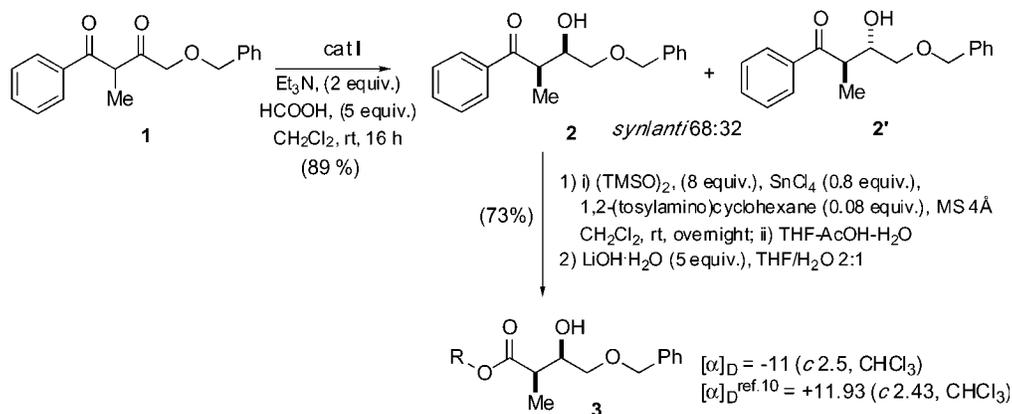
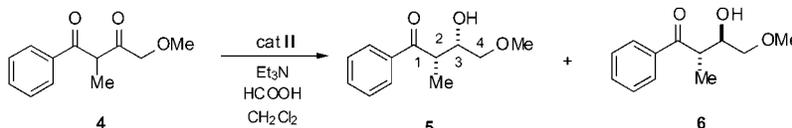


Table 1. Influence of the Catalyst/Substrate Ratio and Temperature on the Dynamic Kinetic Resolution of **4**



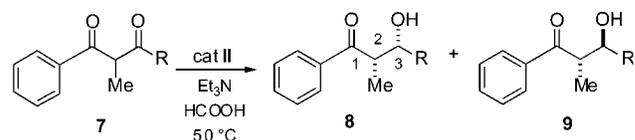
entry	T ($^{\circ}\text{C}$)	cat. (%)	time	yield (%)	convn (%)	5/6 ^{5a,b}	5 ee ^{6a} (%)	5 conf	6 ee ^{6a} (%)	6 conf
1	50	5.0	0 h 45 min	96	100	72/28	88	2 <i>S</i> ,3 <i>S</i>	37	
2	20	5.0	3 h 0 min	95	100	77/23	92	2 <i>S</i> ,3 <i>S</i>	48	
3	50	0.5	1 h 15 min	89	100	78/22	93	2 <i>S</i> ,3 <i>S</i>	48	
4	20	0.5	30 h 0 min	53	54	72/28	92	2 <i>S</i> ,3 <i>S</i>	48	

afforded β -hydroxy ketones **2** and **2'** in a ratio of 68/32^{5a} (yield 89%) (Scheme 2). The two isomers were separated, and the major *syn* compound **2** was obtained with an enantiomeric excess of 93%.^{6a} The relative stereochemistry of **2** was determined by ^1H NMR coupling constants,⁷ and the absolute configuration of the newly formed stereogenic centers was assigned by using Trost's mandelic ester method.⁸ According to this analysis, the reduction of **1**, using (*R,R*)- RuL_n * **I**, afforded **2** as the major product. Furthermore, the absolute configuration of **2** was ascertained by chemical correlation. Accordingly, the hydroxy ketone **2** was transformed to the corresponding acid **3** by a Baeyer–Villiger oxidation⁹ followed by saponification. The optical rotation of the obtained acid **3** was compared to the $[\alpha]_{\text{D}}$ of the enantiomer described in the literature.¹⁰

The influence of the catalyst/substrate ratio and the influence of the temperature on the stereoselectivity of the dynamic kinetic resolution were studied on compound **4** (Table 1). The reduction of **4** by using the (*S,S*)- RuL_n * catalyst **II** led to an inseparable mixture of two diastereoisomers, **5** and **6**,^{5a,b} favoring the (2*S*,3*S*)-isomer **5**.⁸ Considerable rate acceleration was observed in the formation **5** and **6** by performing the reaction at 50 $^{\circ}\text{C}$ compared to room temperature (Table 1, entries 1, 2 and 3, 4). The diastereo- and enantioselectivity of the transformation was only marginally influenced by the temperature and by the catalyst/substrate ratio. However, the reaction time was increased at lower catalyst/substrate loading (entry 4).

Additional examples of this dynamic kinetic resolution are reported in Table 2. The monoreduction of the 2-methylbenzoyl ketones **7a** ($\text{R} = \text{Me}$) and **7b** ($\text{R} = \text{homoallyl}$) proceeded chemo- and stereoselectively (Table 2, entries 1–2, *syn/anti* $\geq 91/9$,^{5b} $\text{ee}_{\text{syn}} \geq 96\%$). The relative stereo-

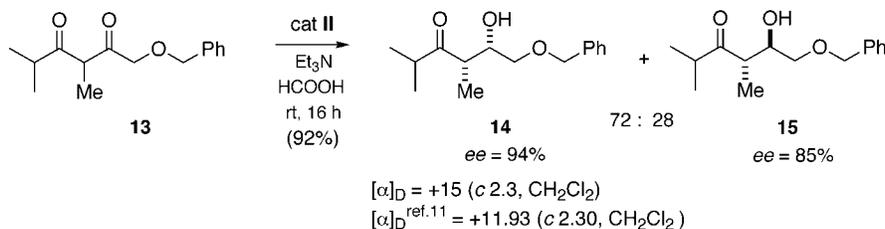
Table 2. Influence of R Groups on the Reduction of 2-Methyl-1,3-diketones



entry	7	R	yield (%) 8 + 9	convn (%)	8/9	8 ee (%)	8 conf	9 ee (%)	9 conf
1	a	$-\text{CH}_3$	84	96	92/8 ^{5b}	96 ^{6b}	2 <i>S</i> ,3 <i>R</i>		
2	b	$-(\text{CH}_2)_2\text{CH}=\text{CH}_2$	87	89	91/9 ^{5b}	98 ^{6d}	2 <i>S</i> ,3 <i>R</i>		
3	c	$-\text{CH}_2\text{NHCBz}$	81	100	83/17 ^{5b}	89 ^{6c}	2 <i>S</i> ,3 <i>S</i>	84 ^{6c}	
4	d	$-(\text{CH}_2)_2\text{NHBoc}$	88	100	97/3 ^{5b}	97 ^{6c}	2 <i>S</i> ,3 <i>R</i>	80 ^{6c}	

chemistry of the hydroxy and methyl groups was determined by ^1H NMR analysis, and the absolute configurations of the newly formed stereogenic centers were determined by the mandelic ester method.⁸ Likewise, the reduction of compounds having heteroatom-containing side chains such as

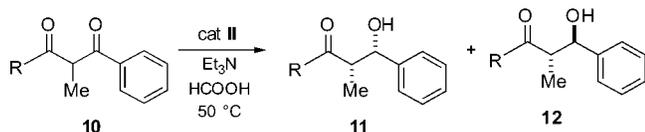
Scheme 3. Reduction of an Aliphatic 1,3-Diketone



7c–7d (entries 3–4) afforded the *syn* isomers as the major product with an enantiomeric excess greater than 89%.

When bulky groups (phenyl or isopropyl) were present such as in compounds **10a** (R = phenyl) and **10b** (R = isopropyl), the reaction proceeded at a lower rate than that for compounds **1**, **4**, and **7a–d** (Table 3). The increase of

Table 3. Influence of Sterically Hindered R Groups on the Reduction of 2-Alkyl-1,3-diketones



entry	10	R	reaction time	yield (%)	convn (%)	11/12	11 ee (%)	11 conf	12 ee (%)	12 conf
1	a	Ph	24 h	38	57	67/33 ^{5a,b}	25 ^{6d}	2 <i>S</i> ,3 <i>S</i>	25 ^{6d}	
2	b	<i>i</i> -Pr	3 days	36	39	66/34 ^{5a}	91 ^{6e}	2 <i>S</i> ,3 <i>S</i>	18 ^{6e}	

steric hindrance around the ketone decreased both the diastereo- and enantioselectivity of the reduction. For the reduction of compound **10a** (R = Ph) (Table 3, entry 1), the dynamic kinetic resolution afforded a 67/33^{5a,b} mixture of an inseparable mixture of *syn/anti* diastereomers **11a** and **12a** in 38% combined yield with 25% ee^{6d} for each diastereomer (57% conversion). The absolute configurations of the newly formed stereocenters were deduced from X-ray crystal structure analysis of the fully reduced product issued from **10a**.⁴ Likewise, in the case of diketone **10b** having an isopropyl group, a mixture of two inseparable diastereomers in a ratio 66/34 was obtained^{5a} and the major *syn* isomer **11b** was formed with 91% ee.^{6e}

An aryl activating group was not necessary for the reaction. The reduction of diketone **13** afforded a 72/28^{5a} mixture of β -keto alcohols **14** and **15** in 92% yield and with 94% ee for

the *syn* isomer **14** (Scheme 3). While the relative stereochemistry was established by ¹H NMR analysis,⁷ the (*S,S*) absolute configuration of **14** was ascertained by comparing the optical rotation of the product with the literature value.¹¹ Also, the absolute configurations of the newly formed stereogenic centers were ascertained by using Trost's mandelic ester method.⁸

In summary, a short entry to 2-alkyl 3-hydroxy ketones by using configurationally labile α -substituted dicarbonyl compounds was developed. The dynamic kinetic resolution of these compounds, by using a RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene)-mediated reduction in the presence of formic acid and triethylamine, afforded the major *syn* compounds for a variety of linear substrates with high enantioselectivity (ee in the range of 88–98%). This method complements the recently developed β -ketoiminato cobalt complex mediated enantioselective reduction of Yamada et al. which produces the *anti* isomer as the major product.¹² These reactions offer an alternative for the preparation of aldol type intermediates by a non aldol pathway under easily scalable conditions.¹³ The application of this reaction to the synthesis of natural products is currently underway.

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Supporting Information Available: Experimental procedures for the transfer hydrogenation reaction and characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) The absolute configurations of the alcohols were determined via the (*R*)- and (*S*)-*O*-methylmandelic esters, according to Trost B. M.; Bellelire, J. L.; Godolski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370–2374.

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(5) The diastereoselectivity was determined (a) by ¹H NMR analysis. (b) By HPLC analysis.

(6) The enantiomeric purity was determined by chiral HPLC. Conditions: (a) Daicel Chiracel OD-H column; eluent hexane/2-propanol: 98/2. (b) Daicel Chiracel OD-H column; eluent hexane/2-propanol: 99/1. (c) Daicel Chiracel OJ-H column; eluent hexane/2-propanol: 95/5. (d) Daicel Chiracel OJ-H column; eluent cyclohexane/2-propanol: 95/5. (e) Daicel Chiracel OJ-H column; eluent hexane/2-propanol: 98/2.

(7) For discussion of the stereostructural assignment of aldol-type products by using ¹H NMR, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1984; Vol. 3, pp 111–212.