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

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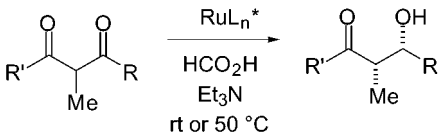
ABSTRACT

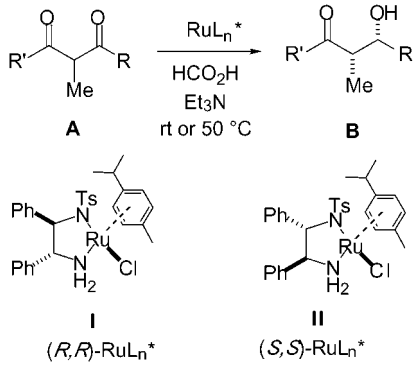


The reduction of 2-alkyl-1,3-diketones using (*R*,*R*)- or (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylenediamine](*p*-cymene) in the presence of formic acid and triethylamine affords *syn*-2-alkyl-3-hydroxy ketones as the major products with high enantioselectivity.

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 enantiocatalytic 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 enantiocatalytic 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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(2) For enzymatic dynamic kinetic resolution, see: Pesti, J. A.; Yin, J.; Zhang, L−h.; Anzalone, L. *J. Am. Chem. Soc.* **2001**, *123*, 11075−11076.

(3) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144−152. For a recent review, see: Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.

(4) Cossy, J.; Eustache, F.; Dalko, P. I. *Tetrahedron Lett.* **2001**, *42*, 5005−5007.

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

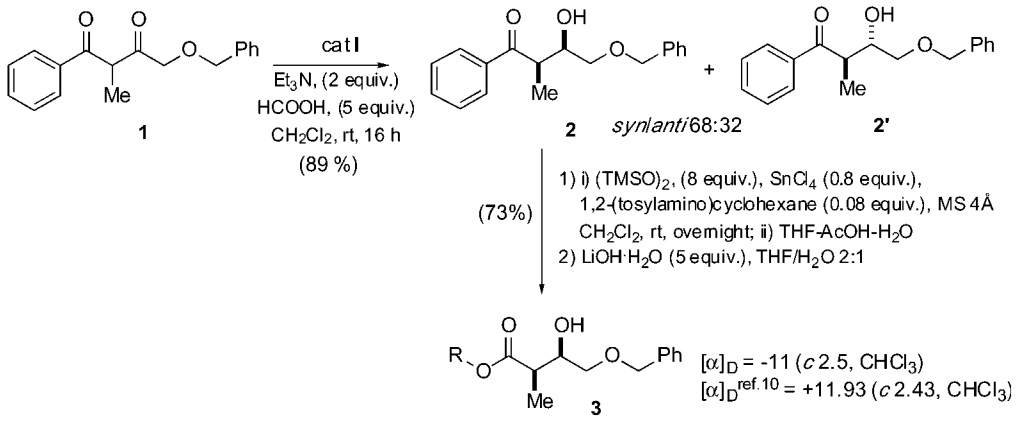
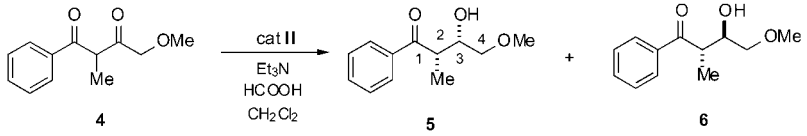


Table 1. Influence of the Catalyst/Substrate Ratio and Temperature on the Dynamic Kinetic Resolution of **4**



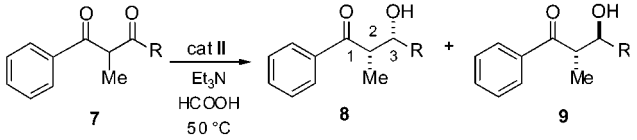
entry	*T* (°C)	cat. (%)	time	yield (%)	convn (%)	**5**/**6**[5a,b]	**5** ee[6a] (%)	**5** conf	**6** ee[6a] (%)	**6** conf
1	50	5.0	0 h 45 min	96	100	72/28	88	2*S*,3*S*	37	
2	20	5.0	3 h 0 min	95	100	77/23	92	2*S*,3*S*	48	
3	50	0.5	1 h 15 min	89	100	78/22	93	2*S*,3*S*	48	
4	20	0.5	30 h 0 min	53	54	72/28	92	2*S*,3*S*	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 ^{1}H 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 oxidation[9] followed by saponification. The optical rotation of the obtained acid **3** was compared to the $[\alpha]_D$ 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 °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).

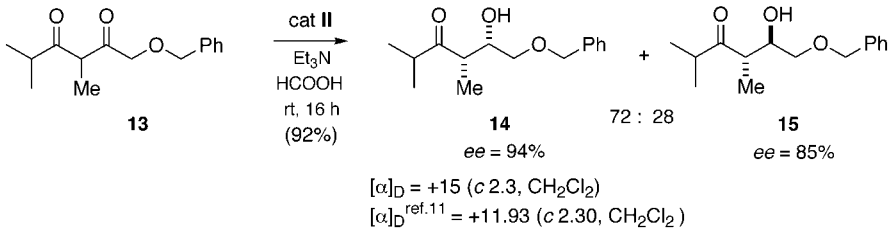
Additional examples of this dynamic kinetic resolution are reported in Table 2. The monoreduction of the 2-methylbenzoyl ketones **7a** (R = Me) and **7b** (R = homoallyl) proceeded chemo- and stereoselectively (Table 2, entries 1−2, *syn*/*anti* ≥ 91/9,[5b] ee$_{syn}$ ≥ 96%). The relative stereochemistry of the hydroxy and methyl groups was determined by ^{1}H 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

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**	-CH$_3$	84	96	92/8[5b]	96[6b]	2*S*,3*R*		
2	**b**	-(CH$_2$)$_2$CH=CH$_2$	87	89	91/9[5b]	98[6d]	2*S*,3*R*		
3	**c**	-CH$_2$NHCBz	81	100	83/17[5b]	89[6c]	2*S*,3*S*	84[6c]	
4	**d**	-(CH$_2$)$_2$NHBoc	88	100	97/3[5b]	97[6c]	2*S*,3*R*	80[6c]	

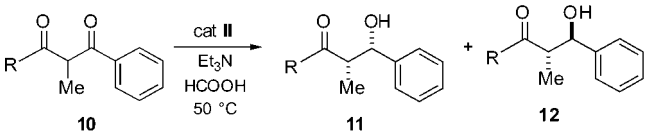
Scheme 3. Reduction of an Aliphatic 1,3-Diketone



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 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]

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*S*,3*S*	25[6d]	
2	**b**	*i*-Pr	3 days	36	39	66/34[5a]	91[6e]	2*S*,3*S*	18[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 alcools **14** and **15** in 92% yield and with 94% ee for the *syn* isomer **14** (Scheme 3). While the relative stereochemistry was established by ^{1}H 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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(5) The diastereoselectivity was determined (a) by ^{1}H 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 OD-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 ^{1}H NMR, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1984; Vol. 3, pp 111−212.

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

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(13) For a comprehensive review of catalytic enantioselective aldol reaction, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. For related reactions affording *β*-hydroxy ketones by non aldol pathway, see: (a) Krauss, I. J.; Wang, C. C.-Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514-11515. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052 and references cited.