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Ruthenium-catalyzed asymmetric reduction of 1,3-diketones using transfer hydrogenation

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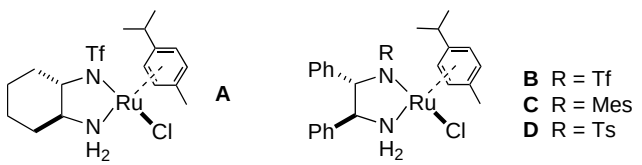
Abstract—1,3-Diketones were reduced to 1,3-diols by using RuCl[*N*-(tosyl)-1,2-(diphenylethylenediamine) (η^6-arene)] in the presence of formic acid and triethylamine. 1,3-Diols were obtained in good chemical yields and with high ee when symmetrical diketones were reduced.

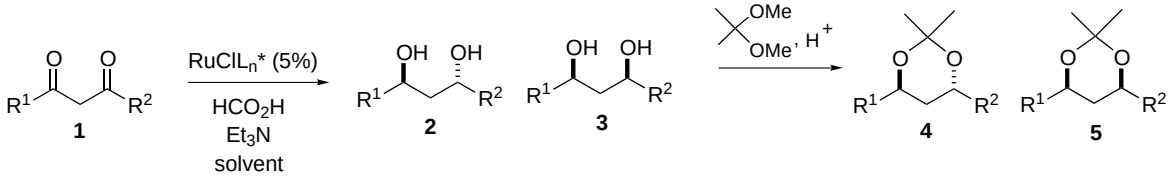
Catalytic asymmetric hydrogenation using chiral ruthenium complexes is a powerful method of producing chiral alcohols and amines with excellent enantioselectivity.[1] Highly efficient chiral diamine-based Ru(II) catalysts such as RuCl[*N*-(arylsulfonyl) cyclohexyl-1,2-diamine) (η^6-arene)] or RuCl[*N*-(arylsulfonyl)-1,2-(diphenylethylenediamine) (η^6-arene)] complexes have been developed either for catalytic hydrogenation under H_2 pressure or transfer hydrogenation using 2-propanol or formic acid.[2] Here, we report a practical asymmetric reduction of 1,3-diketones to the corresponding 1,3-diols with good diastereo- and enantioselectivities, using a catalytic amount of RuCl[(*N*-arylsulfonyl)-1,2-diamine (*p*-cymene)] complexes **A**–**D** in the presence of Et_3N and formic acid (Schemes 1 and 2).



Scheme 1.

The reduction of 1,3-diphenyl-1,3-propanedione **1a** (R^1 and R^2 = Ph) with catalyst **A** (0.05 equiv.) in the presence of Et_3N (2.0 equiv.) and formic acid (5.0 equiv.) in CH_2Cl_2, DMF or under solvent free conditions afforded an inseparable mixture of *anti*- and *syn*-1,3-diols **2a** and **3a**. The products were transformed to the corresponding ketals **4a** and **5a** that were separated. The enantiomeric purity of ketal **4a**, and consequently of diol **2a**, was established by chiral HPLC.[3] The absolute configurations of the newly formed stereocenters were determined by X-ray diffraction of the corresponding Mosher's esters.[4] According to these results the (*S*,*S*)-**A** complex gives rise to the (*S*,*S*)-diol **2a**. The results are summarized in Table 1.

The influence of solvent and temperature on the selectivity of the reaction was examined using catalyst **A** (Table 1). Best results were obtained in CH_2Cl_2 at 25°C (entry 2) and 50°C (entry 3). When the reaction was performed either in DMF (entry 4) or without solvent (entry 5), diols **2a** and **3a** were obtained in poor to modest yields. Although the rate of the reaction increased with the temperature (entries 1–3), the com-



Scheme 2.

Keywords: 1,3-diketones; 1,3-diols; reduction; ruthenium; catalyst.

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Table 1. Reduction of 1,3-diketone **1a** in the presence of catalyst **A**

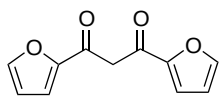
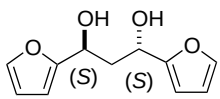
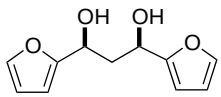
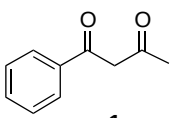
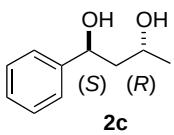
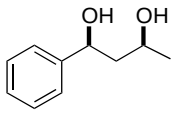
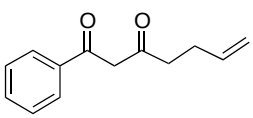
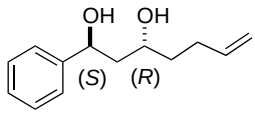
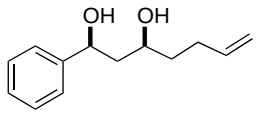
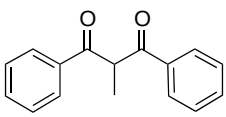
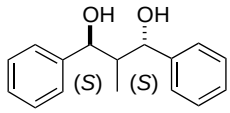
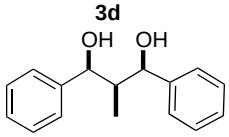
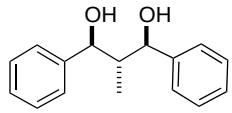
Entry	Solvent	*T* (°C)	Time	Yield (%)[5] (**2a**+**3a**)	dr (**2a**:**3a**)	ee (%) (**4a**)
1	CH_2Cl_2	0	4 days	0	—	—
2	CH_2Cl_2	25	5 days	79	83:17	96
3	CH_2Cl_2	50	6 h	80	76:24	95
4	DMF	40	3 days	12	73:27	95
5	None	25	3 days	63	71:29	96

Table 2. Reduction of 1,3-diketone **1a** using catalysts (*S*,*S*)-**B**, **C** or **D**

Entry	Catalyst	*T* (°C)	Time (h)	Yield (%)[5] (**2a**+**3a**)	dr (**2a**:**3a**)	ee (%) (**4a**)	Config. (**4a**)
1	**B**	25	48	96	97:3	99.0	(*S*,*S*)
2	**B**	50	3.5	91	86:14	99.0	(*S*,*S*)
3	**C**	25	72	48	98:2	99.7	(*S*,*S*)
4	**D**	25	48	95	95:5	99.7	(*S*,*S*)
5	**D**	50	4	83	98.5:1.5	99.8	(*S*,*S*)

bined yields of **2a**/**3a** as well as the diastereo- and enantioselectivity of the reaction were not affected considerably. According to these results, optimum conditions for the reduction of ketone **1a** (dr = 76/24; ee for the (*d*,*l*) compound **2a** = 95%) are the use of CH_2Cl_2 at a temperature of 50°C. Hoping to improve the

Table 3. Reduction of ketones **1b**–**e** using catalyst (*S*,*S*)-**D**. Reaction conditions: CH_2Cl_2 at 50°C for 6 h

Entry	Starting material	Products (*ee*)	*Anti/Syn*	Yield (%)
1	 **1b**	 **2b** *	 **3b**	95/5	85
2	 **1c**	 **2c** (*ee* = 83%)	 **3c**	58/42	79
3	 **1d**	 **2d** *	 **3d**	57/43	91
4	 **1e**	 **2e** (*ee* = 94.5%)	 **3e**  **3e'**	**2e/3e/3e'** 70 /15/15	55

* ee not determined.

diastereomeric ratio, we examined catalysts **B**, **C** and **D** in CH_2Cl_2 at 25 and 50°C. The results are reported in Table 2.

As observed previously, the chemical yield as well as the diastero- and the enantioselectivity of the reduction of **1a** were not affected considerably by the temperature. The best dr and ee values were obtained using catalyst **D** in CH_2Cl_2 at 50°C (entry 5) (dr = 98.5/1.5, ee (**2a**) = 99.8%). Consequently the enantioselective reduction of 1,3-diketones was generalized to substrates **1b**–**1e** under these conditions. The results are summarized in Table 3.

When the reduction of **1b** was effected with catalyst **D**, diols **2b** and **3b** were obtained in a ratio of 95/5 and with a yield of 85% (entry 1). Unfortunately, the ee of **2b** could not be determined at the diol stage or by transforming them to their corresponding ketals as they polymerized under acidic conditions. In the case of compound **1c**, diols **2c** and **3c** were isolated as a 58/42 mixture in 79% yield. The enantioselectivity of **2c** was measured from the corresponding ketals[3] (83%) and the absolute configuration (*S*,*R*) of the newly created centers were assigned by comparing the optical rotation with the literature data.[6]

When dione **1d** was transformed to diols **2d** and **3d** using catalyst **D**, the products were obtained in high yield (91%) but the diastereoselectivity was low (dr = 57/43). When **1e** was reduced using catalyst **D** under standard conditions three products, **2e**, **3e** and **3e′**, were isolated in 55% combined yield, in a ratio of 70/15/15. The enantiomeric excess of **2e** was measured from the corresponding ketal **4e** (ee = 94.5%) using chiral HPLC.[3] The absolute configuration of the newly created stereogenic centers were determined by X-ray diffraction of the corresponding Mosher's ester.[4]

It is worth noting that the reduction of symmetrically substituted 1,3-diaryl-1,3-diketones afforded diols of reasonably high dr and ee (up to 90%) compared to unsymmetrically substituted 1,3-diketones (i.e. when alkyl and aromatic group were present in the α-positions). The diastereomeric ratios of diols from these reductions were considerably lower (57/43 and 58/42). As chiral 1,3-diols are useful building blocks, their transformation to biologically active compounds is under investigation and the results will be reported in due course.

Acknowledgements

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