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Highly Diastereo- and Enantioselective Synthesis of Monodifferentiated *syn*-1,2-Diol Derivatives through Asymmetric Transfer Hydrogenation via Dynamic Kinetic Resolution

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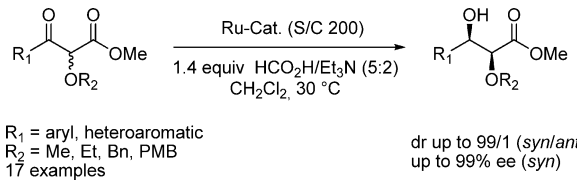
ABSTRACT



The first enantio- and diastereoselective approach to α-alkoxy-substituted *syn*-β-hydroxyesters through highly efficient catalytic asymmetric transfer hydrogenation via dynamic kinetic resolution reactions from the corresponding racemic β-ketoesters is described. In this atom-economical process, two contiguous stereogenic centers are generated simultaneously with an excellent diastereoselectivity (up to 99/1) and enantioselectivity (up to 99%), allowing a rapid access to a wide variety of aromatic and heteroaromatic monodifferentiated *syn*-1,2-diols.

Chiral 1,2-diols are important structural motifs present in many natural products, such as carbohydrates, polyketides, or alkaloids,[1] and have found wide applications in organic synthesis either as chiral ligands or auxiliaries.[2] Several efficient synthetic approaches to chiral 1,2-diols have already been reported;[3] however, most of them suffer from the fact that the resulting two hydroxyl groups were not differentiated. Thus, the synthesis of monodifferentiated diols remains a challenge. In 2008, a catalytic glycolate aldol route to the preparation of stereodefined differentiated 1,2-diols have been reported by Denmark et al.[4] Remarkably, both *syn*- and *anti*-1,2-diols can be obtained under the same catalytic system. However, conversion of the ester moiety to a more reactive silyl ketene acetal as well as the need of a stoichiometric amount of $SiCl_4$ are an unavoidable necessity, which significantly decreases the overall reaction efficiency. Myers et al.[5] have recently reported the synthesis of optically pure

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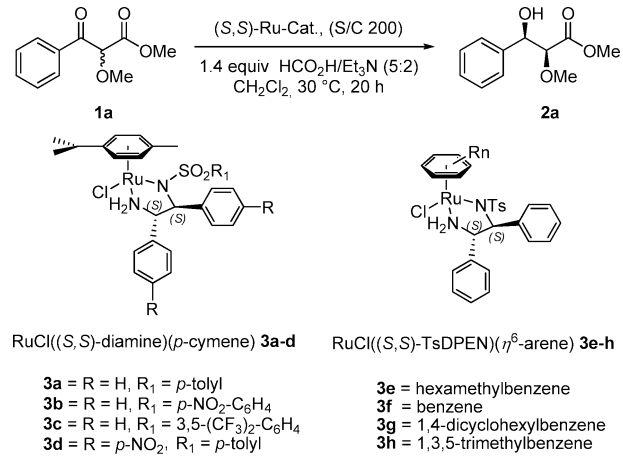
cyclic *anti*-1,2-diol monosilyl ether derivatives in high isolated yields and good to excellent selectivities using an epoxidation−reduction sequence. However, this route has some disadvantages that limits its practicality such as the use of a high catalyst loading (30 mol %) combined with an excess of reagents. In addition, this method remains essentially restricted to cyclic silyl enol derivatives. Therefore, the development of new catalytic highly enantio- and diastereoselective transformations to access optically pure monodifferentiated 1,2-diols with a high level of selectivity and a high atom efficiency is still in great demand. We[6] and others[7] have previously demonstrated that dynamic kinetic resolution (DKR)[8] in association with ruthenium-catalyzed asymmetric hydrogenation turned out to be an elegant and powerful synthetic tool to control two adjacent stereogenic centers in one single chemical operation and with high atom efficiency. We envisaged that the combination of DKR techniques with the asymmetric transfer hydrogenation[9] of readily available racemic α-alkoxy-substituted *β*-ketoesters could provide a conceptually new and straightforward route to the preparation of stereodefined monodifferentiated 1,2-diols units. To the best of our knowledge, such an approach has never been reported in the literature.[10]

Our initial investigations concentrated on the evaluation of various diamine-based Ru(II) catalysts **3a**−**h**, in order to identify the most suitable catalyst system for the asymmetric transfer hydrogenation of racemic α-methoxy *β*-ketoester **1a** (Table 1). These preliminary experiments were carried out in dichloromethane at 30 °C for 20 h with a substrate to catalyst molar ratio (S/C) of 200:1 using a 5:2 formic acid and triethylamine azeotropic mixture as hydrogen source. The results depicted in Table 1 clearly showed that the stereochemical outcome of the reaction is strongly affected by the structure of both the chiral diamine and the η^6-arene ligands. Indeed, transfer hydrogenation of **1a** using Noyori's Ru(II)-TsDPEN[11] catalyst **3a** bearing *p*-cymene as η^6-arene provides the syn[12] product **2a** in 93% conversion with an encouraging diastereoselectivity of 90/10 and an enantiomeric excess up to 99% (Table 1, entry 1). Changing the arylsulfonyl group of the diamine ligand from *p*-toluenesulfonyl to

Table 1. Screening of Diamine-Based Ru (II) Catalysts[a]



entry	Ru catalyst	conv[b] (%)	dr syn/anti[b]	ee syn[c] (%)
1	**3a**	93	90/10	>99
2	**3b**	>99	85/15	>99
3	**3c**	>99	82/18	>99
4	**3d**	>99	88/12	>99
5	**3e**	7	91/9	nd
6	**3f**	>99	55/45	91
7	**3g**	77	93/7	>99
8	**3h**	>99	95/5	>99

[a] Reactions were conducted using a 1 M solution of substrate (1 mmol). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC).

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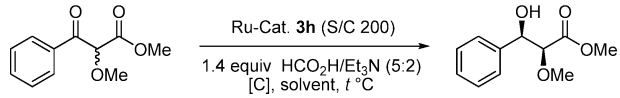
Table 2. Optimization of the Reaction Conditions Using TsDPEN Ruthenium Catalyst[a]



1a 2a

entry	solvent	C^b (mol L^{-1})	temp (°C)	conv[b] (%)	dr syn/anti[b]	ee syn[c] (%)
1	CH_2Cl_2	1	30	>99	95/5	>99
2	CH_2Cl_2	0.5	30	>99	95/5	>99
3	CH_2Cl_2	0.2	30	>99	97/3	>99
4	CH_2Cl_2	0.1	30	>99	97/3	>99
5	CH_2Cl_2	0.2	50	>99	97/3	>99
6	CH_2Cl_2	0.2	10	4	nd	nd
7	THF	0.2	30	>99	97/3	>99
8	Dioxane	0.2	30	>99	96/4	>99
9	Et_2O	0.2	30	>99	91/9	>99
10	Toluene	0.2	30	>99	95/5	>99
11	MeOH	0.2	30	78	87/13	>99
12	*i*-PrOH	0.2	30	99	92/8	>99
13	CH_3CN	0.2	30	>99	96/4	>99
14	DMF	0.2	30	>99	95/5	>99
15[d]	CH_2Cl_2	0.2	30	>99	97/3	>99

[a] Reactions were conducted using a 1 mmol of substrate. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). [d] S/C = 500.

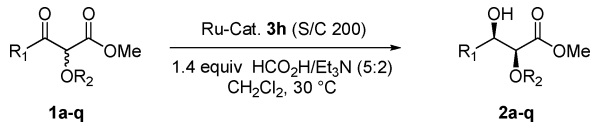
a more electron-withdrawing group such as *p*-nitrobenzenesulfonyl (catalyst **3b**) or 3,5-bis(trifluoromethyl)benzenesulfonyl (catalyst **3c**) slightly increased the catalytic activity in terms of conversion, giving **2a** in 99% conversion with up to 99% enantiomeric excess, but lower diastereoselectivity (Table 1, entries 2 and 3). Similar results were obtained when catalyst **3d**, bearing a *p*-nitro group on the phenyl ring of the *N*-tosyldiamine moiety, was employed (Table 1, entry 4). Modification of the η^6-arene in the reference Ru(II)-TsDPEN catalyst also significantly affected the stereochemical outcome of the reaction (Table 1, entries 5−8). For example, transfer hydrogenation of **1a** using catalyst **3e** possessing η^6-arene = hexamethylbenzene afforded the differentiated *syn*-1,2-diol **2a** with an encouraging diastereoselectivity of 91/9 but in only 7% conversion (Table 1, entry 5). When the reaction was performed with catalyst **3f** (η^6-arene = benzene), full conversion into the desired product **2a** was obtained. However, although the enantioselectivity still remained high, the diastereoselectivity of the reaction was very low (Table 1, entry 6). Changing the η^6-arene ligand from *p*-cymene to 1,4-dicyclohexylbenzene (catalyst **3b**) slightly increased the stereoselectivity, while conversion dropped significantly (Table 1, entry 7). Finally, from this survey, the Ts-DPEN ruthenium catalyst **3h** possessing the η^6-arene = mesitylene emerged as the best catalyst, yielding the reduced product **2a** in more than 99% conversion with a diastereomeric ratio of 95/5 and perfect enantioselectivity (Table 1, entry 8, ee >99%).

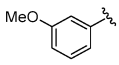
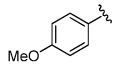
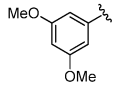
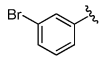
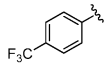
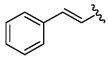
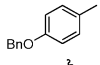
Encouraged by these results, we then investigated the effect of the following sequence: concentration, temperature and solvent aiming at improving the diastereoselectivity. The results are summarized in Table 2. We found that the diasteromeric ratio could be increased from 95/5 to 97/3 when the reaction was run under more diluted conditions with no erosion of conversion and enantioselectivity (Table 2, entries 1−4). Increasing the temperature from 30 to 50 °C did not affect the stereochemical outcome of the reaction, whereas a decrease in the reaction temperature from 30 to 10 °C resulted in almost no conversion (Table 2, entries 5 and 6). Further optimization focused on the solvent employed. With the exception of MeOH, conversions and ee values greater than 99% with good to excellent diasteromeric ratio ranging from 87/13 to 97/3 were achieved in all tested solvents (Table 2, entries 7−14). From this survey, CH_2Cl_2 and THF proved to be the most suitable solvents with regard to both selectivity and reactivity, providing the reduced product **2a** in a highly enantio- and diastereoselective manner with, respectively, 99% ee and a dr ratio of 97/3 (Table 2, entries 3, 5, and 7). Reducing the catalyst loading from S/C 200 to S/C 500 did not affect the catalytic efficiency, thus giving the product **2a** with similar high levels of stereoselectivity (Table 2, entry 15).

To assess the substrate scope, a full set of α-alkoxy-substituted β-ketoester derivatives **1a**−**q** were hydrogenated under the optimized conditions using the TsDPEN ruthenium complex **3h** as catalyst. Examination of the results listed in Table 3 shows that the reaction proceeded well in most cases, giving aryl- and heteroaromatic-substituted products **2a**−**q** in full conversion with excellent diastereo- and enantioselectivities, irrespective of the electronic nature of the substitution pattern. For example, compounds **1** possessing either electron-withdrawing or electron-donating groups at

(12) The absolute stereochemistry was confirmed by the X-ray single-crystal structure (see the Supporting Information).

Table 3. Asymmetric Transfer Hydrogenation Catalyzed by TsDPEN Ruthenium Catalyst **3h**[a]



entry	substrate			convn.	dr	*ee syn*
	1	R_1	R_2	[%][b]	*syn/anti*[b]	[%][c]
1	**1a**		Me	> 99	97/3	> 99
2	**1b**		Me	> 99	97/3	> 99
3	**1c**		Me	80	90/10	> 99
4	**1d**		Me	> 99	97/3	> 99
5	**1e**		Me	> 99	97/3	> 99
6	**1f**		Me	> 99	97/3	> 99
7	**1g**		Me	80	70/30	> 99
8	**1h**		Me	> 99	97/3	> 99
9	**1i**		Me	> 99	97/3	> 99
10	**1j**		Me	> 99	96/4	98
11	**1k**		Me	> 99	96/4	> 99
12	**1l**		Me	> 99	> 99/1	> 99
13[d]	**1m**		Me	> 99	> 99/1	> 99
14	**1n**		Me	> 99	> 99/1	> 99
15[e]	**1o**		Et	> 99	> 98/2	99
16	**1p**		Bn	> 99	97/3	> 99
17	**1q**		PMB	> 99	97/3	> 99

[a] Reactions were conducted using a 0.2 M solution of substrate **1** (1 mmol). [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SFC). [d] Reaction performed with S/C = 100. [e] Substrate **1o** bearing ethyl ester group instead of methyl ester.

the para position on the phenyl rings gave uniformly high enantioselectivities (98−99% ee) and diastereoselectivities (96/4 to 97/3 dr) (Table 2, entries 2, 5, and 9−11).

Similar good results in terms of both reactivity and selectivity were obtained when the reaction was performed with α-methoxy β-ketoester derivatives **1** containing electron-rich as well as electron-poor substituents at the meta position of the aromatic moiety (Table 3, entries 4, 6, and 8). Although ortho substitution led to a decrease in the catalytic efficiency, thus giving the product in moderate conversions and diastereoselectivities, high enantioselectivities up to 99% were still attained (Table 3, entries 3 and 7). This result could be attributed to the unfavored steric hindrance between the ortho-substituted group of the substrate and the catalyst during the reaction. Heteroaromatic compounds can also be used as partners, as demonstrated by the excellent results obtained with thiophene (**1l**) and furan (**1m**) derivatives (Table 2, entries 12 and 13). Similar impressive results were obtained with the cinnamyl derivative **1n**, providing the expected product **2m** in almost full conversion and perfect selectivity (Table 3, entry 14). As showed in Table 3, α-substituted β-ketoester derivatives **1o**, **1p**, and **1q** bearing, respectively, an ethoxy, a benzyloxy (Bn), and a *p*-methoxybenzyloxy group (PMB) at the α position also proved to be suitable substrates for this new process. Indeed, the corresponding adducts **2o**, **2p**, and **2q** were obtained in more than 99% conversion with excellent diastereo- and enantioselectivities (Table 3, entries 15−17). It should be noted that Me, Bn, and PMB protecting groups could be removed to provide the corresponding *syn*-1,2-diols.[13,14]

In conclusion, we have successfully achieved the first example of a Ru-catalyzed asymmetric transfer hydrogenation of readily available racemic α-alkoxy-substituted β-ketoesters via dynamic kinetic resolution. In this atom-economical process, two contiguous stereogenic centers are controlled simultaneously with excellent diastereoselectivity (up to 99/1) and enantioselectivity (up to 99%), allowing rapid access to a wide variety of aromatic as well as heteroaromatic monodifferentiated *syn*-1,2-diols that are otherwise difficult to prepare by asymmetric catalysis. The scope of this reaction is currently under investigation, and its application to the synthesis of natural products is underway in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization of new compounds and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See the Supporting Information for details.