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Asymmetric Synthesis

Efficient Synthesis of Differentiated *syn*-1,2-Diol Derivatives by Asymmetric Transfer Hydrogenation–Dynamic Kinetic Resolution of α-Alkoxy-Substituted β-Ketoesters

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Abstract: Asymmetric transfer hydrogenation was applied to a wide range of racemic aryl α-alkoxy-β-ketoesters in the presence of well-defined, commercially available, chiral catalyst Ru^{II}–(*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine) and a 5:2 mixture of formic acid and triethylamine as the hydrogen source. Under these conditions, dynamic kinetic resolution was efficiently promoted to provide the corresponding *syn* α-alkoxy-β-hydroxyesters derived from substituted aromatic and heteroaromatic aldehydes with a high level of diastereoselectivity (diastereomeric ratio (d.r.) > 99:1) and an almost perfect enantioselectivity (enantiomeric excess (*ee*) > 99%). Additionally, after extensive screening of the reaction conditions, the use of Ru^{II}- and Rh^{III}-tethered precatalysts extended this process to more-challenging substrates that bore alkenyl-, alkynyl-, and alkyl substituents to provide the corresponding *syn* α-alkoxy-β-hydroxyesters with excellent enantiocontrol (up to 99% *ee*) and good to perfect diastereocontrol (d.r. > 99:1). Lastly, the synthetic utility of the present protocol was demonstrated by application to the asymmetric synthesis of chiral ester ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate, which is an important pharmacophore in a number of peroxisome proliferator-activated receptor α/γ dual agonist advanced drug candidates used for the treatment of type-II diabetes.

Introduction

Many processes that control the generation of stereogenic centers in an elegant manner typically rely on the development of enantioselective syntheses by asymmetric catalysis. This research area has rapidly attracted the interest of the scientific community with regards to the high-value compounds generated, which can be crucial intermediates for the preparation of pharmaceutical agents and advanced materials. One of the most significant examples of asymmetric catalysis appeared in 1995 when Noyori and co-workers discovered that a chiral catalyst, namely Ru^{II}–TsDPEN (TsDPEN = *N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine), was able to drive the transfer hydrogenation of aryl-, alkyl-, and related ketones[1] and imines[2] to provide the corresponding alcohols and amines with high levels of selectivity. Since this pioneering work, catalytic asymmetric transfer hydrogenation (ATH)[3] with propan-2-ol or HCO_2H as the hydrogen source has become a powerful tool for asymmetric reduction of ketones, comparable to classical asymmetric hydrogenation[4] with molecular hydrogen and a chiral Ru^{II}–biphosphane catalyst. Indeed, thanks to its simple execution, the use of readily available and less-sensitive catalysts and the availability of hydrogen sources, ATH has established itself as an essential and elegant tool for enantioselective synthesis. In particular, successful ATH applications that involve dynamic kinetic resolution (DKR),[5] which combines a kinetic resolution step with in situ racemization of a configurationally labile center, have been extensively described[6] and provide an additional attractive and powerful tool to control two contiguous stereogenic centers with high levels of selectivity and high atom economy in a single operation starting from racemic mixtures.

Continuing our ongoing research toward the synthesis of relevant biologically active compounds by transition-metal-catalyzed asymmetric reduction,[7] in a preliminary communication,[8] we described a highly efficient procedure for ATH of prochiral α-alkoxy-β-ketoesters coupled with a DKR process under mild reaction conditions with HCO_2H/NEt_3 as the hydrogen source and well-defined, commercially available chiral catalyst Ru^{II}–TsDPEN. In this earlier effort, we demonstrated that easily accessible racemic aryl α-alkoxy-β-ketoesters could be efficiently transformed to the corresponding monodifferentiated 1,2-diols with almost perfect enantioselectivity (enantiomeric excess (*ee*) up to 99%) and excellent diastereoselectivity (dia-

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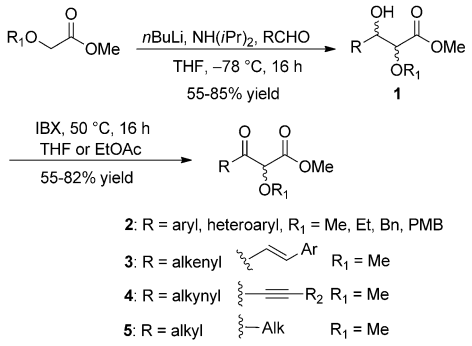
stereomeric ratio (d.r.) up to 99:1) in favour of the *syn* product for a wide variety of substrates bearing diverse functionalized aromatic and heteroaromatic moieties. However, although highly efficient, the method reported in our preliminary study suffered from the drawback of a narrow substrate scope limiting its practicality: the reaction was restricted to aryl and heteroaryl α-alkoxy-substituted β-ketoesters. Pursuing our efforts, we decided to study ATH–DKR processes further with the aim of extending their scope to more-demanding substrates such as alkenyl-, alkynyl- and alkyl derivatives. After extensive screening of the reaction conditions, we found that tethered Rh^{III}–TsDPEN and Ru^{II}–TsDPEN complexes, instead of the classical Noyori Ru^{II}–TsDPEN catalyst, proved essential to reduce the more challenging classes of substrates with both high reactivity and selectivity. In this contribution, we report the full details of our investigation, as well as application of the present protocol to the formal enantioselective synthesis of AZ-242 (Tesaglitazar), a drug candidate in development at AstraZeneca for the treatment of type-II diabetes.[9]

Results and Discussion

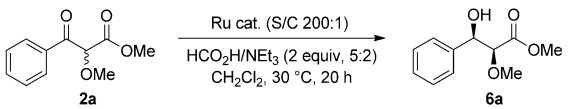
Compounds **2**–**5**, required for our study, were readily prepared on a gram scale from commercially available or easily accessible aldehydes by a two-step sequence: aldol reaction followed by oxidation of the resulting alcohol in the presence of 2-iodoxybenzoic acid (IBX) in THF or EtOAc (Scheme 1). By this procedure, a wide range of aryl, heteroaryl, and alkenyl α-alkoxy-substituted β-ketoester derivatives with both electron-donating and electron-withdrawing substituents on the aromatic moiety were obtained in moderate to good overall yields (50–70%). The above-mentioned protocol was also successfully used to synthesize diversely functionalized alkynyl- and alkyl α-methoxy-substituted β-ketoester substrates with a slightly lower global average yield of 50%.

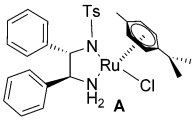
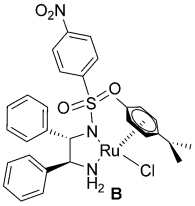
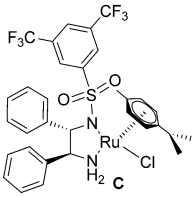
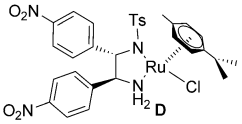
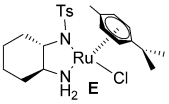
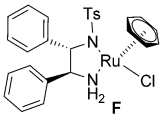
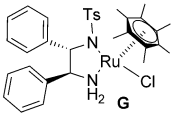
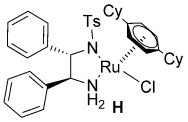
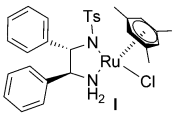


Scheme 1. General synthesis of racemic α-alkoxy-β-ketoesters.

With substrates **2**–**5** in hand, we started our investigation by identifying the most suitable catalytic system for ATH–DKR of racemic phenyl-substituted α-methoxy-β-ketoester **2a** (Table 1). To this end, various tosylated diamine-based Ru^{II} catalysts with structural alterations to either the chiral diamine backbone (**A**–**E**) or the η^6-arene ligand coordinated to the ruthenium atom (**F**–**I**) were screened. The test reactions were performed in CH_2Cl_2 at 30 °C for 20 h with a substrate/catalyst ratio (S/C) of 200:1 in the presence of a 5:2 HCO_2H/NEt_3 azeo-

Table 1. Screening of Ru^{II} precatalysts for ATH of **2a**.[a]



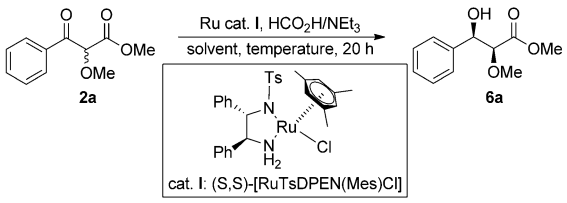
Entry	Ru catalyst	Conv. [%][b]	d.r. (*syn*/*anti*)[c]	*ee* (*syn*) [%][d]
1	 **A**	93	90:10	>99
2	 **B**	>99	85:15	>99
3	 **C**	>99	82:18	>99
4	 **D**	>99	88:12	>99
5	 **E**	74	83:17	50
6	 **F**	>99	55:45	91
7	 **G**	7	91:9	nd[e]
8	 **H**	77	93:7	>99
9	 **I**	>99	95:5	>99

[a] Reaction concentration = 1 M solution of substrate (1 mmol). [b] Conversion was determined by analysis of the ^{1}H NMR spectrum of the crude product. [c] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [d] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SCF). [e] nd = not determined.

tropic mixture as the hydrogen source. The results presented in Table 1 show that highly disparate catalytic activities were observed depending on the diamine ligand used. More specifically, when the ATH reaction of **2a** was performed in the presence of the Noyori's Ru^{II}–TsDPEN catalyst (**A**), which bears *p*-cymene as the η^6-arene, the *syn* product[10] **6a** was obtained in 93% conversion with an encouraging 90:10 d.r. and almost perfect enantioselectivity (>99% *ee*) (Table 1, entry 1). Additionally, replacement of the toluene-*p*-sulfonyl group on the chiral diamine ligand with the more-electron-withdrawing *p*-nitrobenzene (**B**) or 3,5-bis(trifluoromethyl)-benzene group (**C**) gave **6a** in full conversion with similarly high *ee* values of 99%, but with a significant drop in the d.r. values from 90:10 to 85:15 and 82:18, respectively (Table 1, entry 1 versus entries 2 and 3). Also, modification of the ethylene bridge of the TsDPEN ligand with a *p*-nitrobenzene substituent (**D**) instead of a phenyl group had little effect on the stereochemical outcome of the catalytic process (Table 1, entry 1 versus entry 4). In sharp contrast, the reaction conducted with catalyst **E**, which bore a 1,2-diaminocyclohexane diamine ligand afforded the expected product **6a** with a comparable level of diastereoselectivity, but with greatly reduced conversion and enantioselectivity (Table 1, entry 5). The data presented in Table 1 also clearly demonstrates that the nature of the η^6-arene ligand coordinated to the ruthenium center strongly influences the reactivity and selectivity of the reaction, illustrated by the results obtained with Ru^{II}–TsDPEN based catalysts **F**–**I**. In the presence of catalyst **F**, which has a benzene ligand, full conversion occurred but with almost no diastereoselectivity. (Table 1, entry 6). Replacement of the η^6-arene *p*-cymene ligand with sterically hindered hexamethylbenzene (**G**) or 1,4-dicyclohexylbenzene (**H**) afforded product **6a** with good to excellent selectivity. However, use of the above catalysts also resulted in dramatically decreased conversions of 7 and 77%, respectively (Table 1, entries 7 and 8). Finally, from this catalyst survey, the Ru^{II}–TsDPEN precatalyst **I**, which bears a mesitylene ligand, was identified as the best candidate for this reaction and yielded **6a** quantitatively with an excellent d.r. (95:5) and superior enantioselectivity (>99% *ee*, Table 1, entry 9).

Encouraged by these results and to improve the catalytic activity of this process further, the effects of several key parameters, such as the amount and ratio of HCO_2H/NEt_3, the reaction concentration, the nature of the solvent, the catalyst loading, and the temperature were also studied. The results of these experiments are shown in Table 2. The catalytic system did not operate properly (no conversion was observed) if the relative concentration of NEt_3 was too low (Table 2, entry 1). The use of a 5:2 mixture of HCO_2H/NEt_3 led to completion of the reaction. Also, diminishing the amount of HCO_2H from 4 to 2 equivalents gave better results, providing **6a** with a 95:5 d.r. and >99% *ee* (Table 2, entries 2 and 3). Furthermore, by decreasing the reaction concentration from 0.5 to 0.2 or 0.1 mol L^{-1}, the d.r. was improved to 97:3 and the enantioselectivity remained high (99% *ee*) (Table 2, entries 4–6). With the exception of methanol, which led to a conversion of only 78%, the ATH–DKR process was tolerant of a wide range of solvents in terms of conversion, diastereoselectivity, and enantioselectivity of the reaction (Table 2, entries 7–16). To our delight, decreasing the catalyst loading from S/C = 200:1 to S/C = 500:1 resulted in the formation of **6a** with a similarly high reaction rate and selectivity (Table 1, entry 8). Finally, the temperature of the reaction was postliminarily considered. Raising the reaction temperature from 30 °C to 50 °C did not have any repercussion on the catalytic efficiency, but a decrease to 10 °C brought the conversion to only 10% (Table 2, entries 17 and 18). Based on this initial screening, the optimized reaction conditions were: CH_2Cl_2 (0.2 mol substrate/L, precatalyst **I** (0.5 mol%), 5:2 HCO_2H/NEt_3 (2 equiv), 30 °C).

Table 2. Screening of reaction conditions for ATH of **2a** catalyzed by Ru^{II} catalyst **I**.[a]

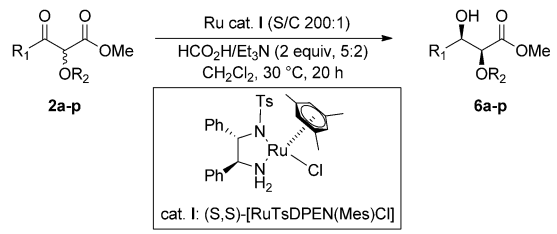


Entry	HCO_2H/NEt_3 ([equiv])	Conc. [mol L^{-1}]	Solvent	*T* [°C]	Conv. [%][b]	d.r. (*syn*/*anti*)[b]	*ee* (*syn*) [%][c]
1	8:1 (4)	1	CH_2Cl_2	30	0	nd[d]	nd
2	5:2 (4)	1	CH_2Cl_2	30	>99	87:13	nd
3	5:2 (2)	1	CH_2Cl_2	30	>99	95:5	nd
4	5:2 (2)	0.5	CH_2Cl_2	30	>99	95:5	>99
5	5:2 (2)	0.2	CH_2Cl_2	30	>99	97:3	>99
6	5:2 (2)	0.1	CH_2Cl_2	30	>99	97:3	>99
7	5:2 (2)	0.2	CH_2Cl_2	30	>99	97:3	>99
8[e]	5:2 (2)	0.2	CH_2Cl_2	30	>99	97: 3	>99
9	5:2 (2)	0.2	MeOH	30	78	87:13	>99
10	5:2 (2)	0.2	*i*PrOH	30	99	92:8	>99
11	5:2 (2)	0.2	CH_3CN	30	>99	96:4	>99
12	5:2 (2)	0.2	DMF	30	>99	95:5	>99
13	5:2 (2)	0.2	toluene	30	>99	95:5	>99
14	5:2 (2)	0.2	Et_2O	30	>99	91:9	>99
15	5:2 (2)	0.2	THF	30	>99	97:3	>99
16	5:2 (2)	0.2	dioxane	30	>99	96:4	>99
17	5:2 (2)	0.2	CH_2Cl_2	10	10	nd	nd
18	5:2 (2)	0.2		50	>99	97:3	>99

[a] Substrate (1 mmol), 20 h. [b] Determined by analysis of the ^1H NMR spectrum of the crude product. [c] Determined by CSP-SCF. [d] nd = not determined. [e] S/C = 500:1, 20 h.

A library of aryl and heteroaryl α-alkoxy-substituted β-ketoesters (**2a**–**p**) was subjected to the ATH–DKR process under the optimized conditions. As shown in Table 3, the electronic nature of the aromatic substituent in the substrate only slightly influenced the stereochemical outcome of the catalytic transformation. More specifically, electron-donating substituents, such as methyl and methoxy groups, were tolerated just as well as electron-withdrawing substituents, such as bromine, fluorine, and trifluoromethyl groups, leading to the desired products **6a**–**k** (Table 3, entries 1–11) in excellent conversions with almost perfect enantioselectivity (≥99% *ee*) and excellent d.r. values (up to 97:3). It should be mentioned that sterically hindered substrates, such as *ortho*-substituted α-methoxy-β-ketoesters **2c** and **2g**, exhibited lower conversions (80%) and de-

Table 3. ATH–DKR of aryl and heteroaryl α-alkoxy-substituted β-ketoesters.[a]



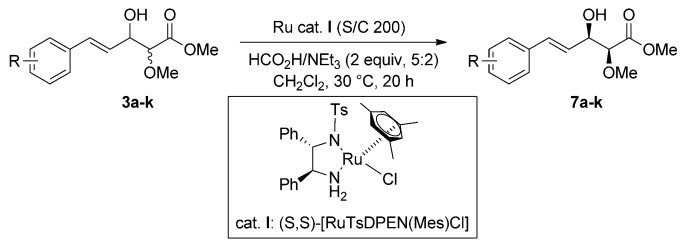
Entry	Product	Conv. [%][b]	d.r. (*syn*/*anti*)[b]	*ee* (*syn*) [%][c]
1	**6a**	>99	97:3	>99
2	**6b**	>99	97:3	>99
3	**6c**	80	90:10	>99
4	**6d**	>99	97:3	>99
5	**6e**	>99	97:3	>99
6	**6f**	>99	97:3	>99
7	**6g**	80	70:30	>99
8	**6h**	>99	97:3	>99
9	**6i**	>99	97:3	>99
10	**6j**	>99	97:3	>99
11	**6k**	>99	96:4	98
12	**6l**	>99	96:4	>99
13	**6m**[d]	>99	>99:1	>99
14	**6n**	>99	>99:1	>99
15	**6o**	>99	>98:2	99
16	**6p**	>99	>97:3	>99

[a] Reaction concentration = 0.2 M; substrate (1 mmol). [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Determined by CSP-SCF. [d] S/C = 100:1.

creased diastereoselectivity whatever the electronic nature of the substituent. However, the enantioselectivity remained >99% *ee* (Table 3, entries 3 and 7). This lower reactivity is presumably caused by increased steric hindrance between the catalyst and *ortho*-substituent of the substrate during the course of the reaction. Interestingly, substrates with heteroaromatic rings, such as 2-thienyl (**2l**) and 2-furanyl (**2m**), were also quantitatively converted to the corresponding diols (**6l** and **6m**; Table 3, entries 12 and 13) with similarly impressive levels of diastereo- (d.r. ≥ 96:4) and enantiocontrol (>99% *ee*). The data reported in Table 3 also illustrates that α-substituted β-ketoester derivatives **2n**–**p**, which have ethyl, benzyl (Bn), and *p*-methoxybenzyl (PMB) substituents, respectively, on the α-oxygen atom were also suitable partners for this process. Indeed, under the optimized reaction conditions, the expected products **6n**–**p** were obtained (Table 3, entries 14–16) with full conversion and high diastereoselectivity (d.r. = 97:3 to >99:1) and excellent enantioselectivity (≥99% *ee*). Notably, the Bn and PMB protecting groups could be easily removed to provide the valuable corresponding diols by using standard reported conditions.[11] For example, hydrogenolysis of the benzyl ether group of **2p** with H_2 over Pd/C resulted in the formation of the corresponding diol (not shown) in excellent isolated yield without loss of stereoselectivity (92% yield, 97:3 d.r., >99% *ee*).[12] This first insight clearly demonstrated the ability of Ru^{II}–TsDPEN catalysts to create two contiguous stereogenic centers with excellent control of both the diastereo- (up to 99:1 d.r.) and enantioselectivity (up to 99% *ee*).

To assess the substrate scope of this ATH–DKR process, a wide range of more challenging alkenyl-, alkynyl- and alkyl-derived substrates were prepared and tested. We first studied the reactivity of various cinnamaldehyde derivatives **3a**–**k** under the optimized conditions with Ru^{II}–TsDPEN catalyst **I**. The results of these experiments are reported in Table 4. The reaction worked well in most cases and gave the desired alcohols **7a**–**k** with full conversion and very high selectivity (Table 4, entries 1–3 and 5–11). For example, the α-methoxy-

Table 4. ATH–DKR of alkenyl α-methoxy-substituted β-ketoesters.[a]



Entry	Product	Conv. [%][b]	d.r. (*syn*/*anti*)[b]	*ee* (*syn*) [%][c]
1	**7a**	>99	99:1	99
2	**7b**	>99	99:1	99
3	**7c**	>99	98:2	99
4	**7d**	0	–[d]	–[d]
5	**7e**	>99	97:3	98
6	**7f**	>99	97:3	99
7	**7g**	>99	96:4	97
8	**7h**	>99	94:6	97
9	**7i**	>99	93:7	94
10	**7j**	>99	97:3	98
11	**7k**	>99	>99:1	98

[a] Reaction concentration = 0.2 M; substrate (1 mmol). [b] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [c] Determined CSP-SCF. [d] No reaction.

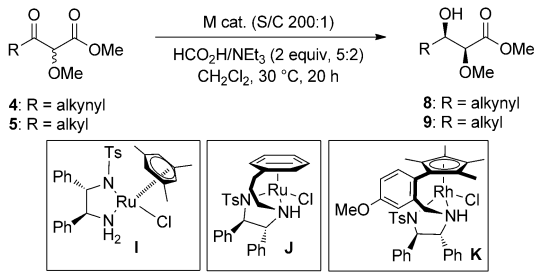
substituted β-ketoester **3a** bearing an unsubstituted cinnamaldehyde moiety was quantitatively transformed to the corresponding reduced adduct **7a** (Table 4, entry 1) with almost perfect diastereo- (99:1 d.r.) and enantiocontrol (99% *ee*).

The electronic nature of the phenyl-ring substituent also clearly influenced the stereochemical outcome of the reaction. For instance, substrates bearing electron-donating groups, such as methyl (**3b–c**) and methoxy (**3e–f**) substituents, were efficiently converted with excellent diastereo- and enantioselectivity (Table 4, entries 2, 3, 5, and 6; 97:3 to 99:1 d.r., up to 99% *ee*). In contrast, a significant decrease in catalytic performance in terms of selectivity was observed with substrates that had electron-withdrawing substituents (Table 4, entries 7–9) such as fluoro- (**3g–h**) and nitro groups (**3i**). The data presented in Table 4 also demonstrates that catalytic activity was influenced by a steric effect, illustrated by the results obtained for the family of α-methoxy-substituted β-ketoesters **3b–d** bearing a tolyl substituent. No reaction occurred with *ortho*-tolyl substrate **3d** (Table 4, entry 4), whereas *para*- and *meta*-substituted substrates **3b** and **3c** gave full conversion, ≥98:2 d.r., and 99% *ee* (Table 4, entries 2 and 3). This observation may be attributed to a mismatched interaction in the transition state, which probably prevents the approach of the catalyst to the *ortho*-substituted substrate, despite the presence of the alkenyl spacer. Interestingly, naphthyl-containing substrate **3j**, with greater steric demand, is well tolerated in this process and gives the desired diol **7j** with full conversion, a high d.r. of 97:3, and up to 98% *ee* (Table 4, entry 10). Lastly, the presence of a 2-thienyl heteroaromatic moiety did not impact the catalytic efficiency and the reduced product **7k** was provided with excellent diastereo- and enantioselectivity (Table 4, entry 11; >99:1 d.r., 98% *ee*).

Based on these findings, we extended the substrate scope of the ATH–DKR process to increasingly challenging alkynyl- (**4**) and alkyl- (**5**) α-methoxy-substituted β-ketoester derivatives, which, to the best of our knowledge, have never been used in such a process. The data compiled in Table 5 shows that the stereochemical course of the reaction was highly catalyst dependent. Indeed, alkynyl substrates with a phenyl (**4a**) or pentyl chain (**4b**) attached to the alkyne function were completely inert under the previously optimized reaction conditions with Ru^{II}–TsDPEN catalyst **I**. A possible explanation that may account for these results is the existence of unfavorable steric hindrance imposed by the rigid linear alkynyl unit, which prevents interactions between catalyst **I** and substrate **4** (Table 5, entries 1 and 4). To circumvent this reactivity problem, inspired by the work of Wills and co-workers, we turned our attention to the use of tethered Ru^{II}–TsDPEN catalyst **J**,[13] known to be a highly active precatalyst for ATH of hindered ketones,[13f,14] imines,[14] and acetylenic ketones,[15] and Rh^{III}–TsDPEN precatalyst **K**, a complex developed in our group.[16] Unfortunately, neither **J** nor **K** reduced substrate **4a**, presumably due to incompatibility in the spatial arrangement of the substrate with the tethered catalyst (Table 5, entries 2–3).

Pleasingly, both **J** and **K** led to full conversion of heptynyl-substituted substrate **4b** (Table 5, entries 5 and 6) with good

Table 5. ATH–DKR of alkynyl and alkyl α-methoxy-substituted β-ketoesters catalyzed by **I** or tethered Ru^{II} and Rh^{III} precatalysts **J** and **K**.[a]

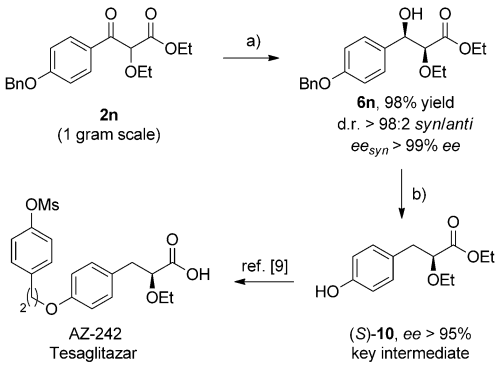


Entry	Product	Cat.	Conv. [%][b]	d.r. (*syn*/*anti*)[b]	*ee* (*syn*) [%][c]
1		**I**	0	–	–
2		**J**	0	–	–
3	**8a**	**K**	0	–	–
4		**I**	0	–	–
5	**8b**	**J**	>99	85:15	96[d]
6		**K**	>99	98:2	>99[d]
7		**I**	50	70:30	97[e]
8	**9a**	**J**	>99	50:50	97[e]
9		**K**	>99	81:19	93[e]
10		**I**	30	65:35	nd[f]
11	**9b**	**J**	>99	86:14	93[e]
12		**K**	35	–	nd
13		**I**	0	–	–
14	**9c**	**J**	>99	90:10	97[e]
15		**K**	0	–	–
16		**I**	>99	50:50	21
17	**9d**	**J**	>99	67:33	74
18		**K**	>99	77:23	86

[a] Reaction concentration = 0.2 M; substrate (1 mmol). [b] Determined by analysis of the ^{1}H NMR spectrum of the crude product. [c] Determined by CSP-SCF. [d] Determined from the corresponding fully reduced benzoylated product by CSP-SCF. [e] Determined from the corresponding benzoylated product by HPLC. [f] nd = not determined.

to high d.r. values (85:15 and 98:2, respectively) and excellent *ee* values (96 and >99%, respectively). This success greatly encouraged us to extend this ATH–DKR process to more-challenging alkyl α-methoxy-β-ketoester substrates incorporating, for instance, pentyl (**5a**), isopropyl (**5b**), cyclohexyl (**5c**), and phenylethyl (**5d**) side chains. As can be seen from the data in Table 5, the stereochemical outcome of the reaction is highly substrate- and catalyst dependent. For example, when the reaction was conducted in the presence of Ru^{II}–TsDPEN catalyst **I**, although high enantiocontrol (97% *ee*) was induced for substrate **9a** (Table 5, entry 7), only poor to moderate conversion and selectivity was obtained for almost all the alkyl substrates tested (Table 5, entries 7, 10, and 13). Prolonging the reaction time to 48 h did not improve the observed conversion. Pleasingly, alkyl α-methoxy-β-ketoester derivatives **5a–c** were efficiently transformed into their reduced analogues **9a–c** in the presence of the commercially available tethered Ru^{II}–TsDPEN precatalyst **J** with excellent enantioselectivity (97, 93, and 97% *ee*, respectively), but with disparate *syn* diastereomeric control ranging from 50:50 to 90:10 d.r. (Table 5, entries 8, 11, and 14). When the tethered metal ion in the TsDPEN-based precatalyst was changed from Ru^{II} to Rh^{III}, contrasting results were obtained. Indeed, the use of catalyst **K** led to the best outcome: starting from flexible pentyl substrate **9a** full conversion, 81:19 d.r., and 93% *ee* were obtained, whereas only little, or no, catalytic efficiency was obtained for the more sterically demanding substrates **9b** and **9c**, which contained an isopropyl or cyclohexyl moiety, respectively (Table 5, entries 9, 12, and 15). These results clearly suggest that our tethered Rh^{III}–TsDPEN precatalyst **K** is much more sensitive to steric effects than the tethered Ru^{II}–TsDPEN precatalyst **J**, probably due to the presence of its *meta*-methoxyphenyl-substituted arm. In the case of substrate **5d** possessing a phenylethyl moiety, full conversion was reached under all the catalytic conditions employed, but the selectivity of the reaction was strongly catalyst dependent. Indeed, no diastereoselectivity and poor enantioselectivity (21% *ee*) was obtained when the reaction was performed in the presence of Ru^{II} catalyst **I** (Table 5, entry 16), whereas use of tethered Ru^{II}–TsDPEN precatalyst **J** and our Rh^{III}–TsDPEN precatalyst **K** led to significantly better selectivity, with 67:33 and 77:23 d.r. and 74 and 86% *ee*, respectively (Table 5, entries 17 and 18).

Finally, the ATH–DKR protocol was also applied to the asymmetric synthesis of chiral ester ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)-propanoate **10**,[17] which is an important intermediate in a number of peroxisome proliferator-activated receptor α/γ dual agonist advanced drug candidates used for the treatment of type-II diabetes,[18] such as AZ-242 (Tesaglitazar)[9] and DRF-2725 (Ragaglitazar; not shown).[19] As shown in Scheme 2, the hydrogenation reaction of α-ethoxy-β-ketoester **2n** was carried out on a gram scale to provide **6n** in high isolated yield with excellent asymmetric induction (d.r. >98:2, >99% *ee*). Subsequent deoxygenation by using Et_3SiH and trifluoroacetic acid (TFA), followed by removal of the benzyl group provided the anticipated key intermediate ethyl ester (*S*)-**10** with >95% *ee* (Scheme 2).



Scheme 2. Formal asymmetric synthesis of Tesaglitazar, a) **I** (S/C = 200:1), 5:2 HCO_2H/Et_3N (2 equiv), CH_2Cl_2, 30 °C, 20 h, quantitative; b) i) Et_3SiH (1.2 equiv), TFA (5.0 equiv), CH_2Cl_2, rt, 12 h; ii) H_2 (50 bar), $Pd(OH)_2$ (10% *w*/*w*), THF, 15 h, 98% over two steps.

Conclusion

The Ru^{II}-catalyzed ATH–DKR reaction was successfully applied to a wide variety of racemic α-alkoxy-β-ketoesters derived from substituted aromatic and heteroaromatic benzaldehydes and cinnamaldehydes. In this reaction, two contiguous stereogenic centers were simultaneously controlled with excellent diastereo- (up to 99:1 d.r.) and enantioselectivity (up to 99% *ee*). The use of tethered Ru^{II} and Rh^{III} precatalysts allowed us to extend this process to more challenging substrates bearing alkynyl- and alkyl substituents, which, to the best of our knowledge, have never been used in such a process, to provide the corresponding *syn* α-alkoxy-β-hydroxyesters with excellent enantiocontrol (up to 99% *ee*) and good to perfect diastereoselectivity (up to 99:1 d.r.). Attractive features of this transformation include the mild reaction conditions, operational simplicity and practicability, broad substrate scope, and high selectivity. Lastly, this strategy was efficiently applied to the synthesis of an important intermediate en route to AZ-242 (Tesaglitazar), which exhibits antidiabetic properties.

Experimental Section

All reactions were run under an argon atmosphere. Reaction vessels were dried under vacuum and cooled under a stream of argon. CH_2Cl_2 and THF were distilled prior to use from calcium hydride and sodium/benzophenone, respectively. Solvents, reagents, and chemicals were purchased from Sigma–Aldrich, Alfa Aesar, TCI, or Acros Organics and were used as purchased, unless stated otherwise. Substituted cinnamaldehydes and alkynyl derivatives were obtained according to literature procedures.[20] ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 300 spectrometer (300 and 75 MHz, respectively). Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), relative to $\delta_H = 7.26$ ppm (s; $CHCl_3$) or $\delta_C = 77.0$ ppm (t; $CDCl_3$). Coupling constants (*J*) are reported in Hertz [Hz]. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were routinely run with broadband decoupling. *Ee* values were determined by SFC, performed with a BERGER instrument equipped with a UV detector or by HPLC performed with a Waters e2695 instrument equipped with a UV detector. Chiral analyses were performed with Chiralcel columns, eluting with the solvent mixture indicated. $[Ga]_D$ values [$deg\,cm^2\,g^{-1}$] were recorded with a PerkinElmer 241 polarimeter at $\lambda = 589$ nm (sodium lamp).

General procedure for the Ru^{II}- or Rh^{III}-catalyzed ATH of α-alkoxy-β-ketoxyesters 2–5

α-Alkoxy-β-ketoester (1.0 mmol, 1.0 equiv) and chiral Ru^{II} or Rh^{III} catalyst (0.005 mmol, 0.005 equiv) were dissolved in anhydrous CH_2Cl_2 (5 mL) and 5:2 HCO_2H/NEt_3 (170 μL, 2 mmol, 2 equiv) was added dropwise. The mixture was stirred under argon for 20 h. The reaction was neutralized by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The solution was decantated and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a pad of silica gel (pentane/CH_2Cl_2 50:50) to afford the desired chiral *syn* α-alkoxy-β-hydroxyester as the major product.

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Keywords: alpha-alkoxy-beta-ketoesters · asymmetric catalysis · asymmetric transfer hydrogenation · dynamic kinetic resolution · ruthenium

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