Article

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Multiple Absolute Stereocontrol in Cascade Lactone Formation *via* Dynamic Kinetic Resolution Driven by the Asymmetric Transfer Hydrogenation of Keto Acids with Oxo-Tethered Ruthenium Catalysts

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ABSTRACT: A straightforward asymmetric construction of chiral fused γ- and δ-lactones containing multiple contiguous stereocenters was successfully developed by either (1) the dynamic kinetic resolution-asymmetric transfer hydrogenation (DKR-ATH) reaction using oxo-tethered Ru(II) complexes followed by *syn*-selective lactonization or (2) the tandem DKR-ATH/lactonization in combination with asymmetric hydrogenation catalyzed by Ru-chiral diphosphine complexes. The expedient protocol is applicable to the enantioselective synthesis of natural wine lactone and a biologically active benzo-fused lactone with an unprecedented level of diastereo- and enantioselectivity.

INTRODUCTION

The development of straightforward and selective access to complex molecules from relatively simple starting compounds is an ideal goal of modern target-oriented synthesis. In accordance with this trend, the control of multiple stereogenic centers synchronized with the construction of polycyclic frameworks is a viable approach to simplify stepwise synthetic procedures with minimal consumption of reagents. The conversion of readily available and configurationally labile racemic molecules via dynamic kinetic resolution (DKR) has advanced, allowing the achievement of simultaneous asymmetric induction methods for substantially diverse enantioenriched compounds in a diastereoselective manner.[1] In particular, DKR premised on the reduction of enolizable carbonyl compounds has been recognized as a potent strategy to deliver optically active alcohols with vicinal chiral centers, encouraged by Noyori's trailblazing work on the asymmetric hydrogenation of β-keto esters using BINAP-Ru catalysts thirty years ago.[2] The utility of reductive DKR processes has been further accentuated by taking advantage of asymmetric transfer hydrogenation (ATH) reactions with bifunctional Ru catalysts (**1** and **2**) containing chiral *N*-sulfonyl-1,2-diamine scaffolds.[3,4] With a growing understanding of the DKR-ATH methodology, single enantiomers possessing three or more stereocenters have been furnished directly via the double reduction of 1,3-diketones[5] and 2,3-disubstituted 1-indanones.[6] In the seminal reports by Johnson's group,[7] a third stereogenic center was concomitantly built by diastereoselective lactonization subsequent to DKR-ATH of β-aryl α-keto esters having a prochiral geminal diester functionality at the γ-position.

In the course of systematic studies on structural tuning of the bifunctional catalysts derived from sulfonylated 1,2-diphenylethylenediamine (DPEN), we designed a new family of oxo-tethered Ru complexes (DENEB)[8] that exhibit outstanding catalytic performance for the ATH of simple ketones (Figure 1). Given the prominent stereodiscrimination ability and robustness stemming from the covalent linkage between the arene and chiral diamine ligands,[9,10] we conceived that the bifunctional oxo-tethered Ru catalysts can make farther multiple stereoinductions feasible and allow for the forward successive transformation of the generated alcohols. The ATH of γ-keto esters or acids, for instance, in conjunction with the intramolecular esterification of the interim alcohols appears to be conducive to a straightforward and stereoselective lactone synthesis by controlling the stereochemical configuration at the α-carbon by DKR through the cyclization, as well as at the β- and γ-carbons by the DKR-ATH.

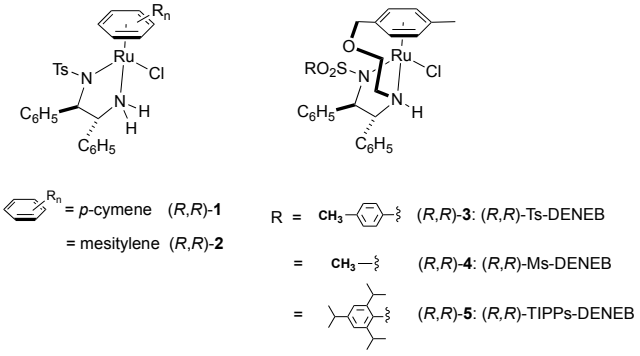


Figure 1. Structure of nontethered and tethered Ru-DPEN catalysts.

The γ-lactone structure is likely to be observed in many natural products and biologically active compounds, as typified by the polycyclic molecules containing contiguous chiral centers shown in Figure 2. Wine lactone (**6**),[11] which is implicated as a contributor to the wine aroma, has been identified among the volatile constituents of white wine[12] and other products.[13] A benzo-fused lactone (**7**), 1,4,5,9b-tetrahydronaphtho[2,1-*b*]furan-2-one, has aroused interest due to its potential biological activities, such as its antitumor and anti-inflammatory properties.[14] As a stepping stone to the direct and stereoselective synthesis of fused rings featuring

multiple stereogenic centers, the development of concise routes to these lactones is a great challenge.[15] We present here an advantageous lactonization process via DKR-ATH that enables multiple stereocontrolled ring formations from racemic substituted ketones.

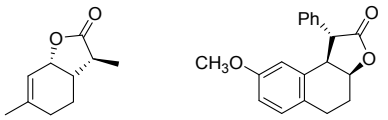
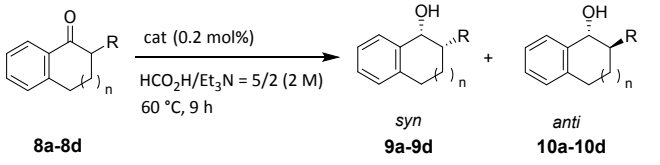


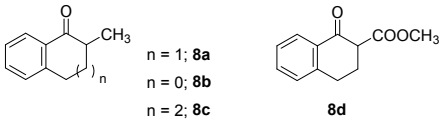
Figure 2. Natural or biologically active fused γ-lactones.

RESULTS AND DISCUSSION

DKR-ATH of α-Substituted Benzo-fused Ketones. To assess the catalytic compatibility of oxo-tethered complexes with DKR, we initially examined the ATH of a racemic α-tetralone derivative (**8a**) using DPEN-derived Ru complexes at a loading of 0.2 mol% in an azeotropic mixture of formic acid and triethylamine with a molar ratio of 5:2 at 60 °C for 9 h. As shown in Table 1, the oxo-tethered Ts-substituted Ru(II) complex (*R*,*R*)-**3** ((*R*,*R*)-Ts-DENEB) displayed fascinating catalytic activity and diastereo- and enantioselectivity (entry 3), while the prototype catalysts, (*R*,*R*)-**1** and (*R*,*R*)-**2**, resulted in little conversion of **8a** (entries 1 and 2). The reaction proceeded in a *syn*-selective manner, rendering (1*R*,2*R*)-alcohol **9a** with 97% ee, which accommodates the reduction of the configurationally interconvertible ketone via DKR.

Table 1. Asymmetric Transfer Hydrogenation of *α*-Substituted Cyclic Ketones





entry	substrate	catalyst	time, h	% yield[a] (*syn*/*anti*)[b]	% ee[c] (*syn*)
1	**8a**	(*R*,*R*)-**1**	9	<5	—
2	**8a**	(*R*,*R*)-**2**	9	<5	—
3	**8a**	(*R*,*R*)-**3**	9	90 (92/8)	97[d]
4	**8b**	(*R*,*R*)-**3**	5	98 (98/2)	98
5[e]	**8c**	(*R*,*R*)-**4**	5	85 (94/6)	98
6	**8d**	(*R*,*R*)-**3**	7	99 (>99/1)	>99.9

[a] Isolated yield. [b] Determined by ^{1}H-NMR analysis of the crude products. [c] Determined by HPLC analysis. [d] Enantioselectivity of the *anti* isomer was 98% ee. [e] 1 mol% of the catalyst.

Performing the reduction of 2-methylindanone (**8b**) under the identical conditions, (*R*,*R*)-**3** afforded the *syn*-product in 98% yield with a high level of diastereoselectivity (96% de) and enantioselectivity (98% ee) (entry 4). Although the DKR-ATH of a 7-membered benzsuberone derivative (**8c**) with (*R*,*R*)-**3** was very sluggish, the use of 1.0 mol% of the Ms-substituted analog (*R*,*R*)-**4** gave the expected *syn*-(*R*,*R*)-product (**9c**) in 85% yield with a high diastereomeric ratio of 94:6 and an excellent enantiomeric excess of 98% (entry 5). Notably, the reduction of the α-tetralone derivative (**8d**) with a methoxycarbonyl group at the β-position revealed that (*R*,*R*)-**3** tolerated an ester group, leading to the virtually stereopure *syn*-(*R*,*R*)- β-hydroxy ester (>99% de and >99.9% ee) (entry 6).

The possible transition states for DKR-ATH with 2-substituted α-tetralone derivatives catalyzed by (*R*,*R*)-**3** are shown in Figure 3. An established favorable edge-to-face interaction between the η^6-arene ligand and the aryl group of the substrate serves to stabilize the transition state.[16] The transition state affording the *anti* product is energetically less favored because of steric hindrance due to the substituent R, whereas eq. (1) will operate proactively to produce the alcohol with *syn*-selectivity.

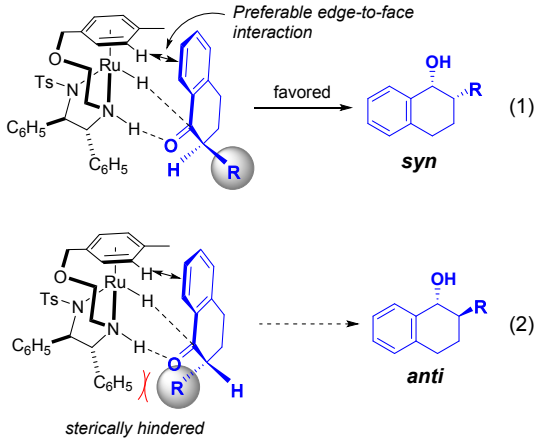
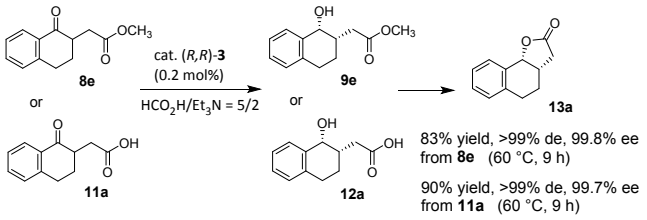


Figure 3. Proposed transition state for the DKR-ATH.

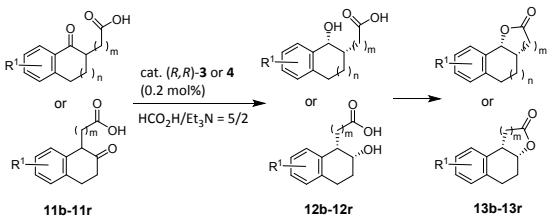
Spontaneous Lactonization via DKR-ATH. By getting a boost from the positive effects of the oxo-tethered Ru(II) complexes on the marked enhancement of the catalytic activity and stereoselectivity, we explored the successive lactonization via DKR of an ester-functionalized α-tetralone (Scheme 1). When the ATH of a cyclic ketone (**8e**) substituted with a CH_2COOCH_3 moiety was performed with 0.2 mol% of (*R*,*R*)-**3** in an azeotropic mixture of formic acid and triethylamine (5:2), the fused γ-lactone (**13a**) was successfully obtained in 83% yield with exceptional *syn*-selectivity (>99% de) and enantioselectivity (99.8% ee). The identical configuration of the (*S*,*S*)-lactone product with the α-substituted alcohols **9a-9d** was in accordance with the combined DKR mechanism involving lactonization. Moreover, the oxo-tethered catalyst was operative with an unprotected γ-keto acid (**11a**) without deterioration under identical ATH conditions. A specific diastereomer of transient γ-hydroxy acid (**12a**) was spontaneously esterified, affording a better isolated yield of **13a** than that from the γ-keto ester (**8e**) (90% yield vs 83% yield).

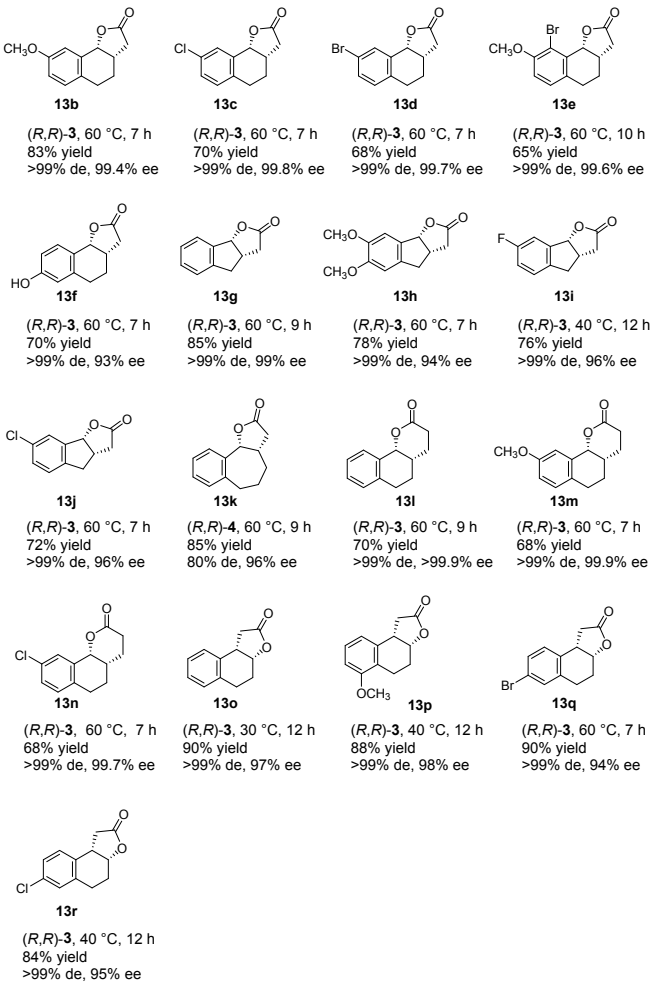
Scheme 1. Successive DKR-ATH/Lactonization of α-Tetralone-based γ-Keto Ester and γ-Keto Acid



With the oxo-tethered Ru(II) complexes (*R*,*R*)-**3** and **4**, the asymmetric tandem lactone synthesis proved to be a versatile approach, and the results of the ATH of racemic γ- or δ-keto carboxylic acids are summarized in Table 2. Under the optimized conditions of a substrate/catalyst ratio of 500 at 60 °C for 7 h, 7-methoxy or 7-halogenated α-tetralones (**11b**-**11d**) were smoothly converted to give the corresponding γ-butyrolactones in 68–83% yield with desirable diastereo- and enantiomeric excesses (**13b**-**13d**). X-ray crystallographic analysis on **13c** and **13d** determined the absolute configuration to be (3a*S*,9b*R*), which is consistent with the abovementioned ATH products of **9a-d**. In the ATH of **11b** using (*R*,*R*)-**3**, alcoholic intermediates (**12b-*syn*** and **12b-*anti***) were obtained in 2% and 7% yield, respectively, along with the target lactone (**13b**) in 83% yield (>99% de, *syn*) (Scheme 2). These results suggest that the *syn*-alcohol (**12b-*syn***) was preferentially lactonized after the ATH of α-tetralone, leading exclusively to *syn*-lactone **13b**.

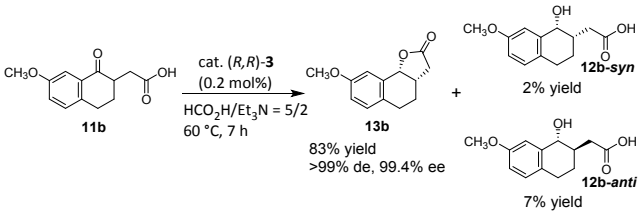
Table 2. Substrate Scopes of DKR-ATH/Lactonization of α- and β-Tetralone Derivatives[a]





[a] Isolated yield.

Scheme 2. Stereochemical Outcome of the DKR-ATH of γ-Hydroxy Acid 11b



Although a slight decrease in the catalytic rate was observed for a more sterically congested substrate (**11e**) substituted at the 7- and 8-positions, the corresponding lactone (**13e**) was produced with remarkable diastereo- and enantioselectivities of >99% de and 99.6% ee. A substrate bearing a phenolic hydroxy group at the 6-position was tolerated in the ATH with (*R*,*R*)-**3** to give **13f** in 70% yield with 93% ee. A functionalized 1-indanone derivative having a carboxylic acid (**11g**) was also transformed into the corresponding lactone (**13g**) with an incomparable de and an ee exceeding 99%. Other methoxy- or halogen-substituted analogs (**11h**-**11j**) proceeded in the sequential reaction for 7–12 h to give γ-lactones in nearly the same yields with 94–96% ee. For a γ-keto acid pertaining to a 7-membered cyclic ketone (**11k**), (*R*,*R*)-**4** afforded **13k** with the better results of 85% yield and 96% ee than (*R*,*R*)-**3** (65% yield and 92% ee), albeit with the formation of a

slight amount of the *anti*-diastereomer (*syn*/*anti* = 90:10). Notably, δ-keto acids on the platform of α-tetralone having a propanoic acid side chain provided easy access to fused δ-lactones (**13l-13n**) in 68-70% isolated yield with almost perfect de and ee values (>99% de, 99.7–>99.9% ee).

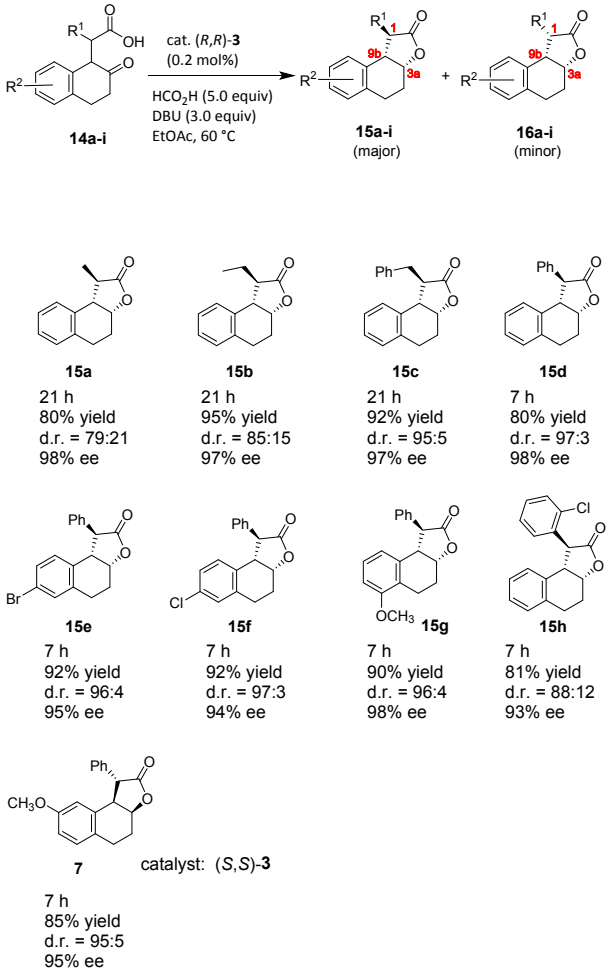
In addition to the aromatic ketone substrates represented by the α-tetralone derivatives, β-tetralones were found to be feasible in the ATH-lactonization protocol, leading to the corresponding γ-lactones (**13o-13r**) in 84–90% yield with excellent de and ee values (>99% de, 94–98% ee) even at a lower reaction temperature. The absolute configuration of **13o**, which was determined as (3a*R*, 9b*S*) after its transformation into **15a** (*vide infra*, see the Supporting Information), assures analogous enantiotopic face selection for the ketonic group. The oxo-tethered Ru catalyst can reduce efficiently with outstanding levels of 1,2-stereoinduction, whereas the diastereo- and enantioselectivities in the previous studies on DKR of α-substituted β-tetralone derivatives have remained moderate.[17]

Construction of Three Contiguous Stereocenters via DKR-ATH/Lactonization. Encouraged by the significant results from the ATH/lactonization sequence with the oxo-tethered Ru(II) complexes in terms of the stereocontrol at the ring junction, we further tested β-tetralone derivatives (**14a-i**) bearing a chiral carboxymethyl moiety to construct three contiguous stereocenters on fused γ-butyrolactones at a stretch. Following the optimal reaction conditions complemented with the screening of base and solvent (Table S1), the ATH catalyzed by (*R*,*R*)-**3** with a catalyst loading of 0.2 mol% was conducted using 5 equiv of formic acid and 3 equiv of DBU in EtOAc at 60 °C, and the results are summarized in Table 3. When the stereochemically unbiased γ-keto acid (**14a**) with a methyl substituent was subjected to the ATH, a diastereomeric mixture of tetrahydronaphthalene-fused γ-lactones (**15a** and **16a**) was obtained with good diastereoselectivity (dr = 79:21). The major isomer **15a** was successfully isolated after chromatography with 80% yield and excellent enantioselectivity (98% ee). The (1*R*,3a*R*,9b*S*) configuration of **15a**, which was established from the X-ray crystallographic analysis (Figure 4), corroborated the extensional stereoinduction that evolved from the *syn*-selective DKR-ATH. Presumably, during the ATH/lactonization, the methyl substituent at the α-position of the carboxyl group flipped to converge with a structurally favored isomer, avoiding a repulsive interaction with the arene ring.

The substituent adjacent to the carboxylic acid influenced the diastereoselectivity. An ethyl-substituted substrate afforded the lactonization product (**15b**) in 95% yield and 97% ee with a slightly increased diastereomeric ratio of 85:15. Changing the substituent to a more sterically demanding benzyl (**14c**) or phenyl (**14d**) group remarkably improved the diastereoselectivity (dr = 95:5 and 97:3, respectively) while maintaining excellent enantioselectivity (97–98% ee). The introduction of electron-deficient halogens (**14e** and **14f**) and an electron-donating methoxy group (**14g**) into the β-tetralone skeleton did not deteriorate the yield (90–92%) or the stereoselectivity (dr = 96:4 to 97:3; 94–98% ee), whereas α-(2-chlorophenyl)-γ-keto acid (**14h**) resulted in a slight loss of diastereoselectivity (dr = 88:12). These absolute configurations can be settled during the lactone formation. In fact, the diastereoselectivity was not mostly changed with maintaining the notable enantiomeric excess during the progress of the reaction of **14f** (Table S8 in the Supporting Information), implying that epimerization of the product hardly proceeded under the DKR-ATH conditions.

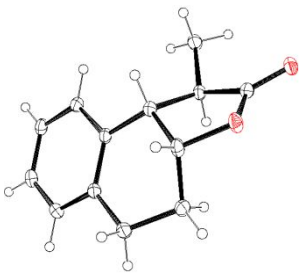
To highlight the synthetic utility of this approach, a concise synthesis of the targeted bioactive lactone (**7**) was achieved by utilizing the (*S*,*S*) form of catalyst **3** for the sequential asymmetric reduction-cyclization of the stereochemically unspecified 7-methoxy-2-tetralone with a phenylacetic acid substructure (**14i**). The enantiomerically opposite configuration of the product **7** relative to the structures of **15e**, **15f**, and **15g** was also confirmed by X-ray crystallography (see the Supporting information).

Table 3. Synthesis of Chiral γ-Lactones Containing Three Contiguous Stereocenters by the DKR-ATH/Lactonization of β-Tetralone Derivatives[a,b,c,d]



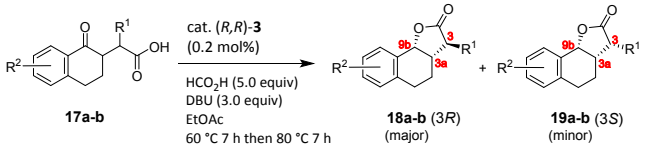
[a] Isolated yield. [b] Stereochemistry of all products at the 3a- and 9b-positions was completely the *cis* isomer (>99% de). [c] d.r. values are the ratios of **15** and **16**. [d] ee values are the ratios of the 9b*R* and 9b*S* enantiomers.

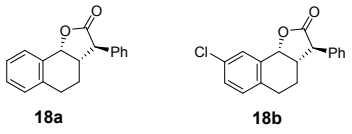
Figure 4. X-ray crystal structure of **15a**.



Meanwhile, α-tetralone analogs (**17a** and **17b**) were also found to be efficiently lactonized with an extremely high level of enantioselectivity (98.3% ee and 99.7% ee, respectively) and a reasonable diastereoselectivity (dr = 5:1 and 4:1) (~~Scheme 3~~Table 4). An X-ray crystallographic analysis of the major product **18b** verified the absolute configurations as (3*R*,3a*S*,9b*R*) (see the Supporting information). The (3a*S*,9b*R*) stereochemistry was completely identical to that of all other lactones synthesized by (*R*,*R*)-**3**, which supported the reliable stereodiscriminatory ability of the oxo-tethered catalysts. The 3*R*-product was preferentially created upon cyclization to avoid the steric repulsion between the α-tetralone skeleton and the phenyl substituent at the stereochemically variable α-position of the carboxyl group, thus, the formation of the saucer-shaped structure of the 3*S*-epimer **19** was less favored. Compared to β-tetralone derivatives in which the substituent on the side chain is situated more closely to the fused arene, diastereocontrol in the lactonization of α-tetralones was found to be rather degraded. It is noteworthy that the diastereoselectivity was inverted by replacement of the aryl substituent with a sterically less congested methyl group (**17c**), leading to a 1:2 mixture of the corresponding 3*S*- and 3*R*-lactones (**18c** and **19c**), both with almost perfect enantioselectivity (Scheme 43). The (3*R*,3a*S*,9b*R*)-configuration of the major product **19c** was established by single-crystal X-ray analysis, and the crystalline sponge method[18] was carried out to assign the 3*S*-epimeric structure of **18c** (see the Supporting information). The *syn*,*syn*-selective reductive cyclization did not appear to be directed to wine lactone synthesis.

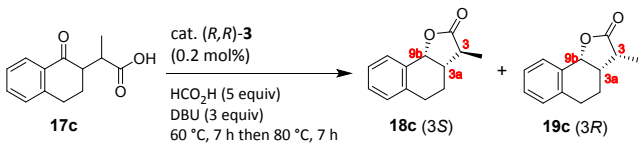
Table 4~~Scheme 3~~. Synthesis of Chiral γ-Lactones Containing Three Contiguous Stereocenters by the DKR-ATH/Lactonization of α-Tetralone Derivatives[a,b,c,d]





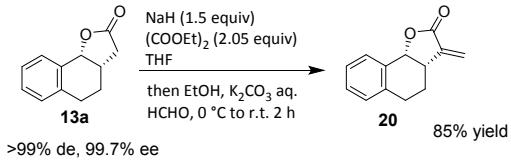
[a] Isolated yield. [b] Stereochemistry of all products at the 3a- and 9b-positions was completely the *cis* isomer (>99% de). [c] d.r. values are the ratios of **18** and **19**. [d] ee values are the ratio of the 9b*R* and 9b*S* isomers.

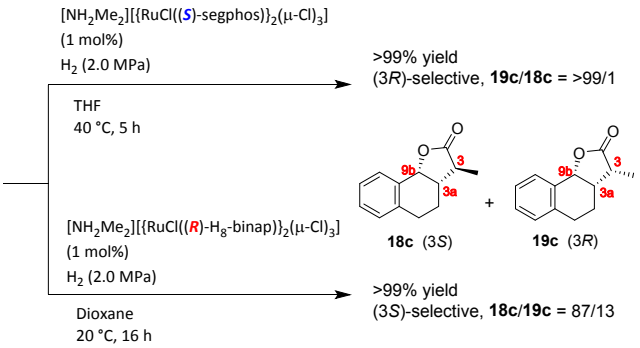
Scheme 43. Asymmetric Synthesis of 3-Methyl-3a,4,5,9b-tetrahydronaphtho[1,2-b]furan-2(3*H*)-one via DKR-ATH/Lactonization

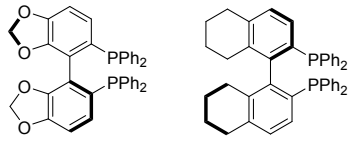


Alternative Route to Fused Lactones via Asymmetric Hydrogenation of α-Methylene-γ-butyrolactone. To showcase convenient approaches to both diastereomers of **18c** and **19c** in a complementary fashion, we next tried the diastereoselective hydrogenation of a fused α-methylene-γ-butyrolactone (**20**) derived from α-tetralone (Scheme ~~54~~). The *exo*-olefinic substrate (**20**) was easily prepared by treatment of the stereochemically defined lactone (**13a**, >99% de and 99.7% ee) with diethyl oxalate and formaldehyde reagents without the loss of optical purity.[19] We embarked on test experiments using an (*S*)-SEGPHOS-ligated[20] ruthenium dimer complex (i.e., $[NH_2Me_2][\{RuCl((S)\text{-segphos})\}_2(\mu\text{-}Cl)_3]$), which has been utilized as a powerful hydrogenation catalyst (Table S2).[21] To our delight, 3*R*-lactone (**19c**) was obtained quantitatively as a single diastereomer after hydrogenation with 2.0 MPa of hydrogen gas using 1 mol% of the catalyst in THF at 40 °C for 5 h. In view of the chiral and bent structure of **20** as confirmed by X-ray crystallography, the favorable addition of hydrogen to the convex face of the substrate led to the 3*R* product of **19c**.

Scheme ~~54~~. Asymmetric Synthesis of 3-Methyl-3a,4,5,9b-tetrahydronaphtho[1,2-b]furan-2(3*H*)-one via the Diastereoselective Hydrogenation of the Fused α-Methylene-γ-butyrolactone (20)





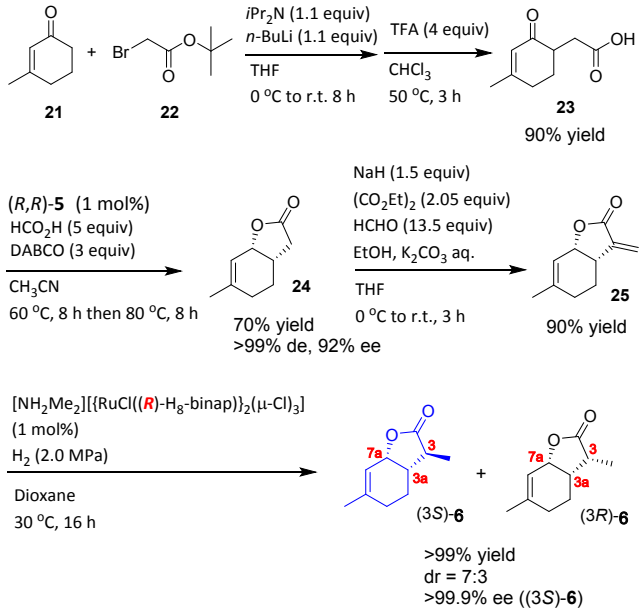


Although the use of the (*R*)-enantiomer catalyst, $[NH_2Me_2][\{RuCl((R)\text{-segphos})\}_2(\mu\text{-}Cl)_3]$, resulted in a disappointing selectivity for the 3*S*-epimer (**18c**/**19c** = 34/66), the related (*R*)-H$_8$-BINAP[22] complex, $[NH_2Me_2][\{RuCl((R)\text{-}H_8\text{-binap})\}_2(\mu\text{-}Cl)_3]$, was found to be effective for diastereoselective hydrogenation. Optimization of the reaction conditions revealed that the hydrogenation in dioxane under the conditions of 2.0 MPa and 20 °C gave the 3*S*-lactone with an acceptable diastereomeric ratio of 87:13 (Tables S3 and S4). Both diastereomers (**18c** and **19c**)

could be separated by silica gel chromatography to isolate the enantiomerically pure forms.

Application to Wine Lactone Synthesis. With these methodologies for stereoselective access to fused lactones in hand, we finally set out to synthesize the naturally originated wine lactone (**6**) (Scheme ~~6~~5). Among the eight stereoisomers, we aimed to obtain the (3*S*, 3a*S*, 7a*R*)-form, which is found in red wine as a natural product and has the smallest threshold value of odor. The target substrate of racemic γ-keto acid (**23**) was easily prepared by the reaction of 3-methyl-2-cyclohexen-1-one (**21**) with *tert*-butyl bromoacetate (**22**) and sequential elimination of the *tert*-butyl group by treatment with trifluoroacetic acid. Considering the preferable edge-to-face interaction between the aryl groups of the substrate and the chiral oxo-tethered Ru(II) catalyst has been regarded as responsible for the high level of enantioselectivity, the following DKR-ATH of the nonaromatic ketone substrate (**23**) seemed to be very challenging.[8a]

Scheme 5. Synthesis of Wine Lactone (6) by a Combination of ATH-DKR/Lactonization with Diastereoselective Hydrogenation



Actually, ATH/lactonization with (*R*,*R*)-**3** afforded the target lactone (**24**) with only 55% ee. By judicious choice of the catalyst and reaction conditions (Tables S5–S7), however, a newly designed oxo-tethered Ru(II) complex bearing a 2,4,6-triisopropylbenzenesulfonyl substituent, (*R*,*R*)-**5**, proved to be a highly competent catalyst, and the ATH conducted with a mixture of formic acid and DABCO in CH_3CN led to a satisfactory enantioselectivity of 92% ee in 70% isolated yield. Subsequent conversion to the corresponding fused α-methylene-γ-butyrolactone by the established method gave the desired product (**25**) in 90% yield. The application of the (*R*)-H_8-BINAP/Ru-catalyzed hydrogenation gave the target (3*S*,3a*S*,7a*R*)-lactone (**6**) as a major isomer (dr = 7:3) with amplification to perfect enantioselectivity (>99.9% ee). These diastereomers were easily separated by silica gel column chromatography and rendered to be the diastereomerically and enantiomerically pure natural-type wine lactone, (3*S*)-**6**. The outcome of the established (3a*S*,7a*R*) stereochemistry ensures that the ATH catalyst (*R*,*R*)-**5** can discriminate the prochiral face of cyclohexenone due to an attractive interaction between the arene ligand and the alkene moiety, as depicted in Figure 5. A complementary synthesis of the epimer (3*R*)-**6** was also achieved with a diastereomeric ratio of >99/1 using (*S*)-SEGPHOS as well for the hydrogenation of the aromatic substrate **20** (see the Supporting information). Furthermore, aside from the diastereoselective hydrogenation protocols, a simple methylation of chiral lactone (**24**) with LDA and CH_3I could be alternatively utilized for the synthesis of the desired wine lactone (**6**) with perfect diastereoselectivity (dr = >99/1) and high yield (95%) while retaining the optical purity of 92% ee (Scheme ~~7~~6).

Scheme ~~6~~. Synthesis of Wine Lactone (6) by a Combination of ATH-DKR/Lactonization with Diastereoselective Hydrogenation

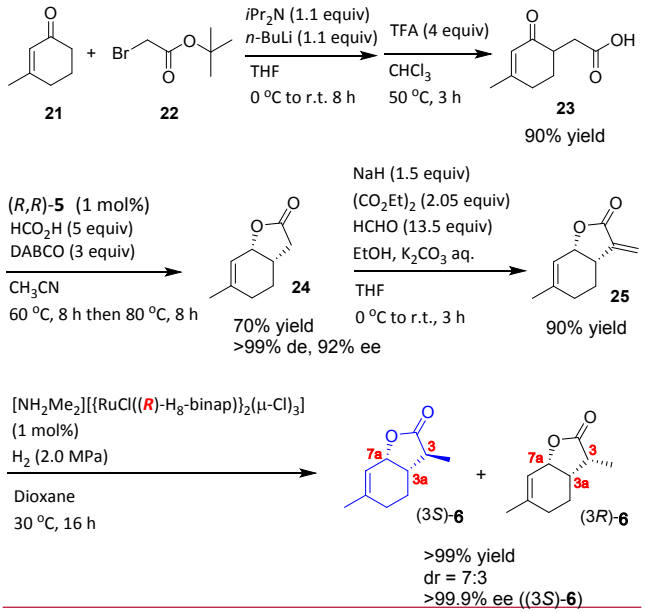
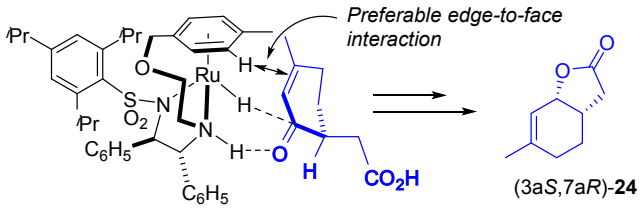
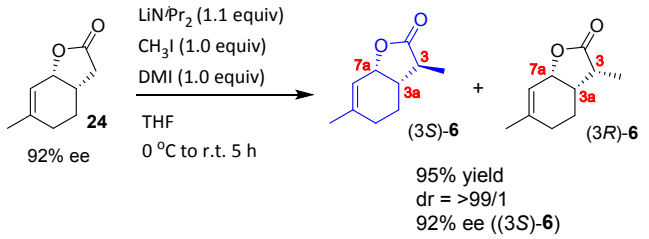


Figure 5. Proposed transition state for the DKR-ATH of **23**.



Scheme ~~7~~6. Synthesis of Wine Lactone (6) by Methylation with CH_3I



CONCLUSION

In conclusion, we successfully developed a versatile methodology for the asymmetric synthesis of chiral γ- and δ-lactones containing multiple contiguous stereocenters from racemic keto acids in a single step. This approach relies on (1) a DKR-ATH reaction mediated by the oxo-tethered Ru(II) complexes and the subsequent *syn*-selective lactonization or (2) the combination of a DKR-ATH/lactonization sequence with asymmetric hydrogenation catalyzed by the reputable chiral phosphine-Ru system. These protocols were successfully demonstrated in the synthesis of optically active fused lactones including natural wine lactone with excellent diastereo- and enantioselectivity. The cascade processes delineated in this study will contribute to the further innovation of stereoconvergent and abbreviated constructions of chiral polycyclic frameworks.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.

Experimental details and compound characterization data (PDF).

Crystallographic data for **13c**, **13d**, **15a**, **15e**, **15f**, **15g**, **7**, **18b**, **18c**, **19c**, and **20** (CIF).

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Notes

The authors declare no competing interest.

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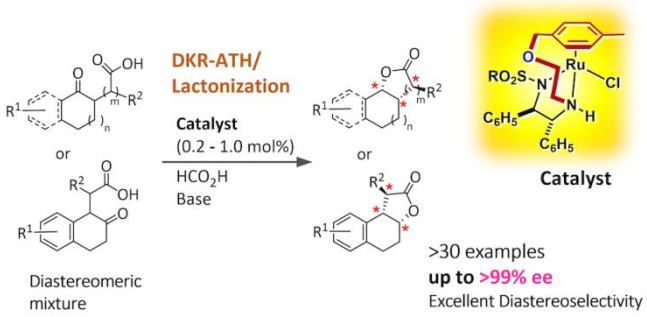

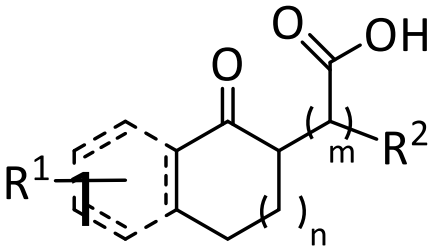

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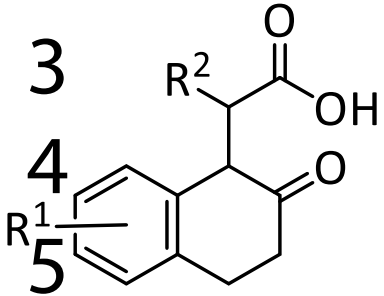
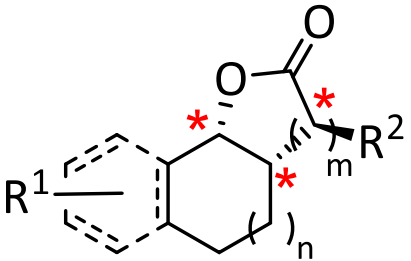


Diastereomeric mixture

DKR-ATH/ Lactonization

Catalyst
(0.2 - 1.0 mol%)

HCO_2H
Base



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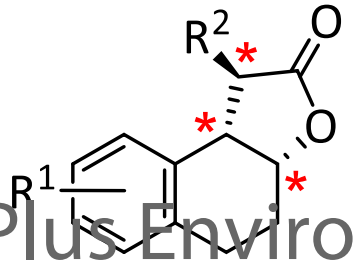

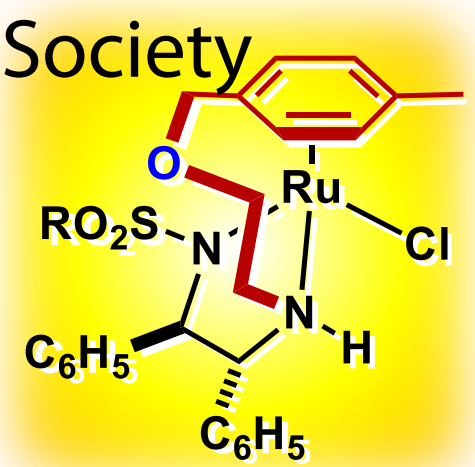

Catalyst

>30 examples

up to >99% ee

Excellent Diastereoselectivity