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Dynamic Kinetic Resolution of α-Keto Esters via Asymmetric Transfer Hydrogenation

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Supporting Information

ABSTRACT: The dynamic kinetic resolution of β-aryl α-keto esters has been accomplished using a newly designed (arene)RuCl(monosulfonamide) transfer hydrogenation catalyst. This dynamic process generates three contiguous stereocenters with remarkable diastereoselectivity through a reduction/lactonization sequence. The resulting enantioenriched, densely functionalized γ-butyrolactones are of high synthetic utility, as highlighted by several secondary derivatizations.

The conversion of racemic compounds into enantiomerically enriched products via a dynamic kinetic transformation is a powerful approach to asymmetric synthesis.[1] The advantages of this technique are fully realized when the racemic starting materials are trivial to access and a racemization pathway is simple to implement. As such, the asymmetric hydrogenation of configurationally labile α-substituted β-keto esters (Figure 1a) remains the archetypal dynamic kinetic resolution (DKR);[2] this process is used to create >100 tons of enantioenriched material each year.[3] The success of the reaction relies upon the acidity of the carbon acid that facilitates interconversion of the two enantiomers through the achiral enol. In contrast, the analogous resolution of less acidic α-keto esters has remained essentially undeveloped,[4] despite its enormous potential synthetic utility and complementary nature of the products (Figure 1b). Herein we describe the first highly enantioselective dynamic kinetic asymmetric transfer hydrogenation (DKR-ATH) of β-aryl α-keto esters, a transformation that (1) allows direct access to trisubstituted γ-butyrolactones, (2) establishes three contiguous stereocenters with complete diastereocontrol, (3) employs a newly designed ruthenium catalyst, (4) exhibits high catalyst efficiency, and (5) utilizes readily available starting materials.

At the reaction design stage, we applied the self-imposed constraint to not only establish a convenient and scalable route to the α-keto ester precursors but also strategically incorporate structural elements that would allow us to productively merge a dynamic process with downstream complexity-building events. Specifically, we envisioned a diastereoselective dynamic reduction of α-keto ester **1** to create the α- and β-stereocenters; the incorporation of a diester at the γ-position was projected to facilitate substrate synthesis and also allow a third stereocenter to be established by concomitant lactonization of the nascent hydroxyl group (Figure 1c). The functionality presented in α-keto ester **1** collectively constitutes a retron for a carbene-catalyzed Stetter addition between ethyl glyoxylate and readily

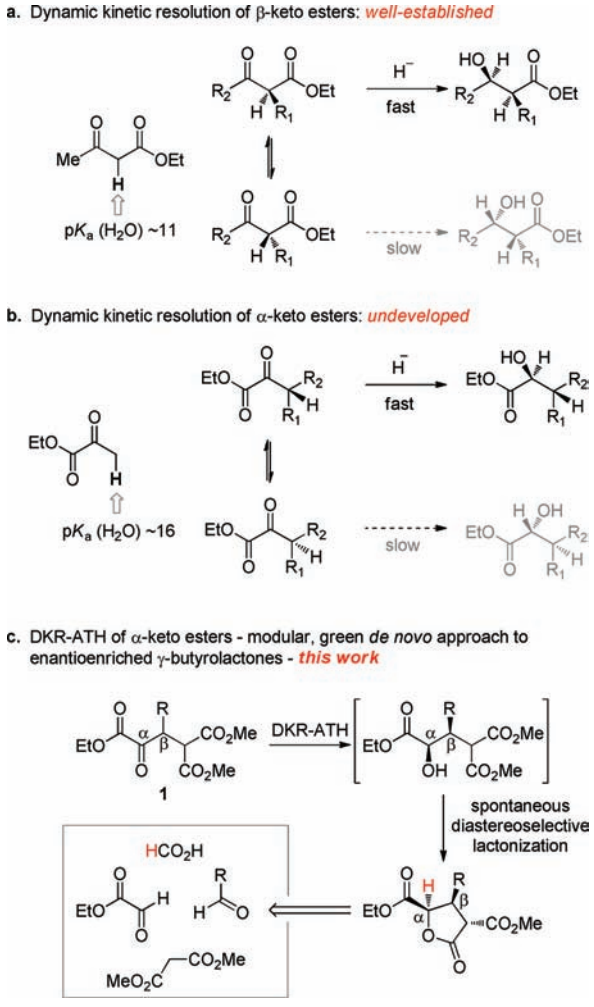

Figure 1. Dynamic kinetic resolution of keto esters.

available benzylidene malonate derivatives.[5] The implementation of the strategy outlined in Figure 1c would provide direct access to synthetically useful enantioenriched γ-butyrolactones, which notably would arise from four commercial reagents (aldehyde, dimethyl malonate, ethyl glyoxylate, and formic acid) and three catalytic steps (Knoevenagel reaction, Stetter reaction, DKR/lactonization). As revealed by Table 1, the new glyoxylate Stetter reaction catalyzed by the Rovis triazolium

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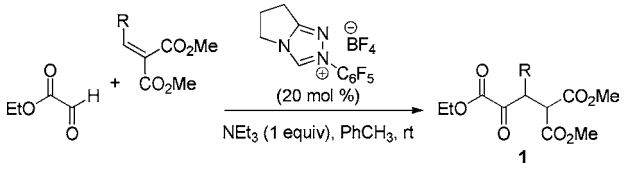
Table 1. Glyoxylate Stetter Reaction Substrate Scope[a]



entry	R	product	% yield[b]
1	C_6H_5	**1a**	96
2	4Cl-C_6H_5	**1b**	95
3	4Me-C_6H_5	**1c**	92
4	4MeO-C_6H_5	**1d**	93
5	4NC-C_6H_5	**1e**	90
6	2Me-C_6H_5	**1f**	78
7[c]	piperonyl	**1g**	91
8	2-furyl	**1h**	87
9	3-*N*-TsIndole	**1i**	89
10	3-*N*-BocIndole	**1j**	84
11	CH_2CHPh	**1k**	93

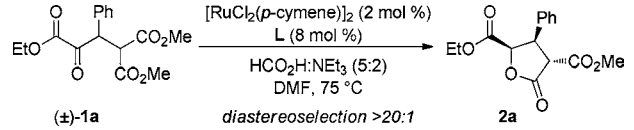
[a]Conditions: Unless otherwise noted, all reactions were performed on a 2.0 mmol scale in $PhCH_3$ (4 mL) at ambient temperature for 16 h. [b]Isolated yield. [c]Reaction performed on a 10 mmol scale.

carbene[5c] is efficient for a number of substrates and can be performed on a multigram scale. A major challenge associated with stereoselective carbonyl umpolung catalysis, viz., the configurational vulnerability of the stereocenter next to the ketone, is rendered moot here since the racemate is the desired product.

Our point of departure for this study with respect to catalyst development was Noyori's (arene)RuCl(monosulfonamide-DPEN),[6] a catalyst that has tremendous efficacy in both the asymmetric reduction of simple ketones[7] and the dynamic reduction of α-substituted β-keto esters and amides.[8] We elected to employ formic acid as the organic reductant and triethylamine as the base using **1a** as the test substrate. Initial studies identified $[RuCl_2(p\text{-cymene})]_2$ as the optimal precatalyst,[9] and a number of chiral 1,2-diaminoethane monosulfonamide ligands were screened for selectivity (Table 2). Subjecting **1a** to 2 mol % of the ruthenium dimer and Noyori's ligand **L1** (Ru atom:**L** mole ratio 1:2) in DMF at 70 °C provided the desired γ-butyrolactone in high yield (90%) and diastereoselectivity (>20:1 dr), but with low levels of enantiocontrol (57:43 er, entry 1). A significant increase in the enantioselectivity was observed by modification of the sulfonamide (**L2**–**L4**), but desirable levels of selectivity were not obtained (entries 2–4). Employing 1,2-diaminocyclohexane and 1,2-aminoindanol to serve as the chiral backbone (**L5** and **L6**) yielded comparable results (entries 5 and 6).

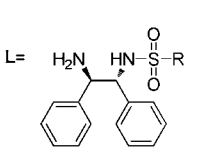
Based on these observations, it was clear that a new chiral ligand would need to be identified to achieve high levels of enantiocontrol. The development of the "mother diamine"/diaza-Cope approach to the synthesis of C_2-symmetric 1,2-diamines[10] allowed facile screening of a number of chiral diamine backbones. We found that the α-naphthyl/triisopropylbenzenesulfonamide ligand **L7** considerably increased the selectivity (Table 2, 88:12 er, entry 7). To further optimize the ligand structure, perturbations of the sulfonamide were examined due to its apparent ability to directly impact the chiral environment (entry 1 vs entry 2). A number of diverse sulfonyl chlorides were accessed through a one-pot double alkylation/sulfonylation of 1,3-dichlorobenzene.[11] The simplest

Table 2. Evaluation of Chiral Diamine Ligands[a]

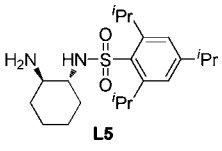


(±)-1a — *diastereoselection >20:1* — **2a**

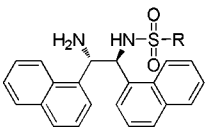
entry	ligand	% yield	er
1	**L1**	90	57:43
2	**L2**	87	70:30
3	**L3**	84	70:30
4	**L4**	84	72:28
5	**L5**	73	73:27
6	**L6**	88	60:40
7	**L7**	82	88:12
8	**L8**	92	94:6



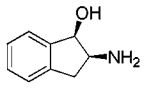
L1: R = 4-MePh
L2: R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
L3: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
L4: R = 2,6-Ph$_2$C$_6$H$_3$



L5



L7: R = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
L8: R = 2,6-Ph$_2$C$_6$H$_3$



L6

[a]Conditions: **2a** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.02 equiv), **L** (0.08 equiv), $[\mathbf{2a}]_0$ = 0.1 M in DMF, 70 °C, 16 h.

m-terphenyl sulfonamide variant, **L8**, distinguished itself as being uniquely effective for providing high levels of enantioselectivity for the title reaction (94:6 er, entry 8). The α-naphthyl backbone and *m*-terphenylsulfonamide operate synergistically; no improvement in enantiocontrol with the DPEN/*m*-terphenylsulfonamide ligand **L4** was observed. The α-naphthylethylenediamine backbone has been used sporadically in asymmetric synthesis, and the use of the *m*-terphenylsulfonamide for enantioselective catalysis is rarer still.[12]

As outlined in Table 3, we have found this DKR-ATH to be broad in scope for a number of β-aryl α-keto esters.[13] High yields and enantioselectivities (up to 94% yield and 96.5:3.5 er) were obtained for substrates incorporating electron-rich, electron-poor, and heteroaryl substituents at the β-position. The product lactones exhibit high incidence of crystallinity. The *syn,anti*-relationship of the trisubstituted γ-butyrolactone products was determined by NOESY experiments, and the absolute configuration was established by X-ray crystallographic analysis of **2b**.[14]

To demonstrate the synthetic utility and catalytic efficiency of this method, the reaction was performed on multigram scale (Scheme 1). Additional experimentation revealed that the catalyst loading could be lowered to 1 mol % with no loss in reaction efficiency. The reduction was trivially performed on a 10 g scale with **1g**, yielding lactone **2g** (er 95:5); recrystallization yielded enantiomerically pure lactone in 72% yield.

The reduction products present functionality immediately amenable to further manipulation (Scheme 2). Lactone **2a** undergoes facile diastereoselective alkylation upon treatment with allyl bromide and DBU, yielding tetrasubstituted lactone **3a** bearing an all-carbon quaternary carbon center (94% yield). Krapcho decarboxylation[15] afforded α-unsubstituted lactone **3b** (86% yield), which is primed to undergo further enolate-based

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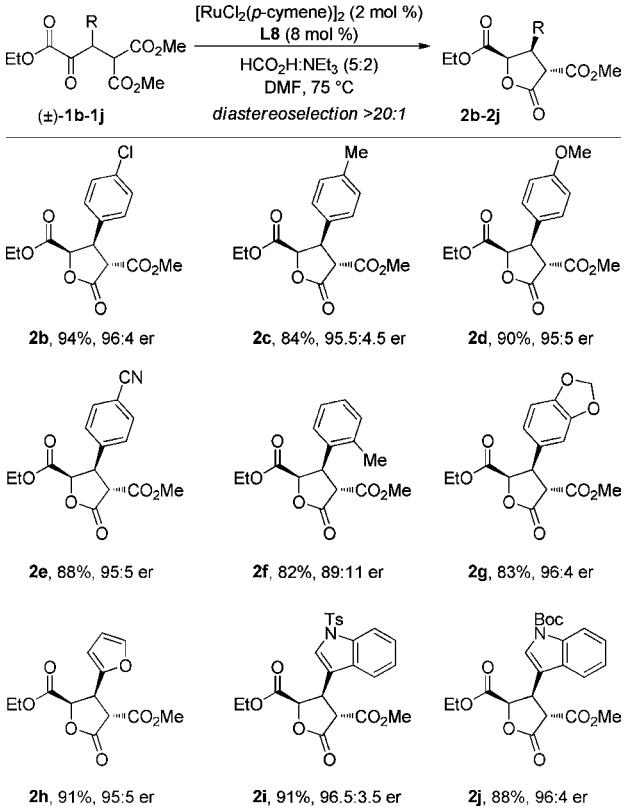
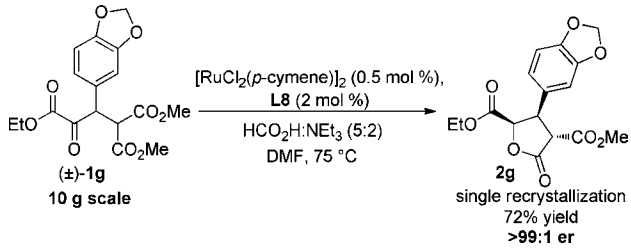
Table 3. DKR-ATH Substrate Scope[a]



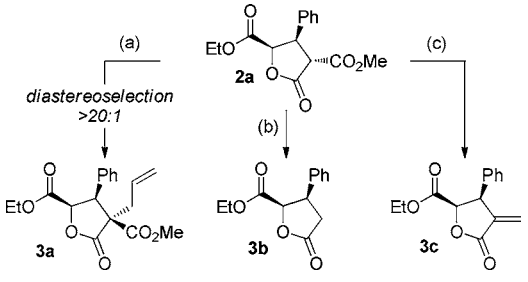
[a]Conditions: as described for Table 2.

Scheme 1. Catalyst Efficiency and Scalability



bond constructions. Of particular importance, alkylation with dibromomethane followed by dehalodecarboxylation[16] afforded α-alkylidene γ-butyrolactone **3c**. This substructure is featured in 3% of all known natural products, and members of this subclass exhibit a wide range of biological activity.[17] Due to the versatility of the product classes obtainable, we expect this method to be of significant value in the areas of both natural product and medicinal agent synthesis.

Scheme 2. Synthetic Utility of Lactone Products[a]



[a]Conditions: (a) allyl bromide (2 equiv), DBU (2 equiv), THF, rt, 2 h, 94%; (b) LiCl, DMSO, 140 °C, 87%; (c) (i) K_2CO_3, dibromomethane, 84%, (ii) LiCl, DMSO, 140 °C, 87%.

In summary, we have designed a new asymmetric transfer hydrogenation catalyst that has led to the successful development of the first dynamic kinetic resolution of β-aryl α-keto esters. Under the reaction conditions, spontaneous lactonization of the α-hydroxyl group onto the pendant ester occurs to provide trisubstituted γ-butyrolactones with complete diastereocontrol. With respect to the rubric of green chemistry, it is instructive to inventory the three steps that lead to the lactones **2**: (i) the Knoevenagel condensation is amine-catalyzed and generates water as the byproduct; (ii) the glyoxylate Stetter addition is carbene-catalyzed and is 100% atom economical, generating no stoichiometric byproducts; (iii) the DKR-ATH reaction uses a chiral ruthenium catalyst and formic acid as the reductant and generates only CO_2 and CH_3OH as byproducts. Further studies to understand the origin of selectivity, extend this method to other β-stereogenic α-keto esters, and identify other green, dynamic transformations with α-keto esters are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral, HPLC, and crystallographic (CIF) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Subjecting ketone **1k** to the reaction conditions in Table 3 afforded the corresponding γ-butyrolactone in 67:33 er. Studies are ongoing to optimize the DKR-ATH to include β-alkyl α-keto ester substrates.
(14) CCDC 871630 contains the crystallographic data for this paper (also available as Supporting Information). These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.
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