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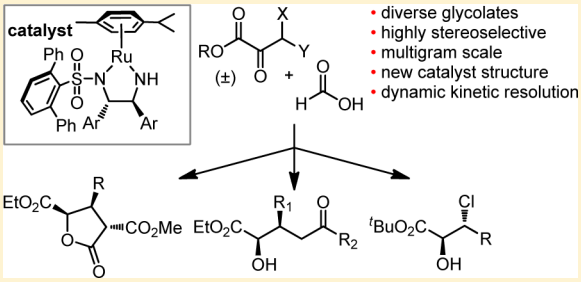
Asymmetric Synthesis of Diverse Glycolic Acid Scaffolds via Dynamic Kinetic Resolution of α-Keto Esters

Kimberly M. Steward,[†] Michael T. Corbett,[†] C. Guy Goodman, and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Supporting Information

ABSTRACT: The dynamic kinetic resolution of α-keto esters via asymmetric transfer hydrogenation has been developed as a technique for the highly stereoselective construction of structurally diverse β-substituted-α-hydroxy carboxylic acid derivatives. Through the development of a privileged *m*-terphenylsulfonamide for (arene)RuCl(monosulfonamide) complexes with a high affinity for selective α-keto ester reduction, excellent levels of chemo-, diastereo-, and enantiocontrol can be realized in the reduction of β-aryl- and β-chloro-α-keto esters.

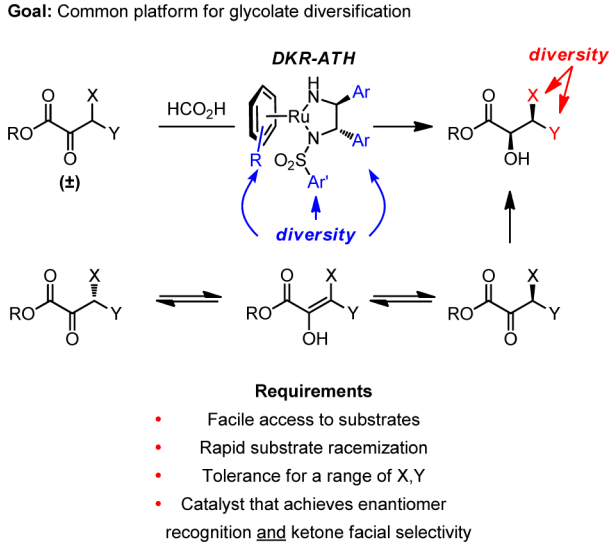


1. INTRODUCTION

The enantioselective construction of α-hydroxy carboxylic acids remains an active area of research due to their prevalence in biologically active molecules[1] and use in asymmetric synthesis.[2] Reliable methods to prepare these compounds include enantioselective glycolate aldol and alkylation reactions,[3,4] reduction or alkylation of α-keto esters,[5] Passerini-type reactions,[6] asymmetric cyanohydrin synthesis,[7] and ester enolate oxygenations.[8] Despite advances in these methodologies, the preparation of β-stereogenic glycolic acid derivatives remains much more challenging, highlighting the importance of a generalizable strategy to access these substructures.

The reduction of α-keto esters to give β-stereogenic-α-hydroxy esters has largely been limited to the diastereoselective reduction of enantioenriched substrates.[9] A more direct, efficient reaction manifold might arise from the asymmetric catalyst-controlled reduction of configurationally labile racemic β-substituted-α-keto esters. Such a reaction could in principle proceed with concomitant formation of two (or more) stereogenic centers in a single step and provide access to a number of functionalized glycolic acid derivatives (Scheme 1).[10] This strategy presupposes the application of a dynamic kinetic resolution (DKR), a powerful tool for the conversion of racemic materials into enantiomerically enriched products.[11] In light of the prominence and utility of DKR reactions of α-stereogenic-β-keto esters, the absence of complementary isomeric variants from racemic α-keto esters was surprising. As part of our laboratory's continued interest in glycolic acid synthesis,[12] we have recently developed a highly stereoselective dynamic kinetic resolution of β-stereogenic-α-keto esters via asymmetric transfer hydrogenation (DKR-ATH), yielding trisubstituted γ-butyrolactones (vide infra).[13] It occurred to us that substantial product diversity might arise from a common mechanistic platform simply by varying the identities of the nonhydrogen substituents (X and Y) at the β-carbon. The successful creation of an attractive synthetic protocol would require: (1) simple routes to the needed racemic

Scheme 1. β-Stereogenic Glycolic Acid Derivatives via Reduction



α-keto ester substrates; (2) reaction conditions that achieve rapid substrate racemization; and (3) the identification of a reduction catalyst that is enantiomer-selective, provides strong facial bias during the diastereoselective reduction, and can be applied to functionally diverse substrates. The subject of this Article is the evaluation of this strategy and the presentation of a new (arene)Ru catalyst system for the asymmetric dynamic reduction of a range of racemic β-stereogenic-α-keto esters. The chemistry to be detailed was enabled by a seemingly trivial, yet ultimately crucial deviation from established art in asymmetric Ru-catalyzed transfer hydrogenation.

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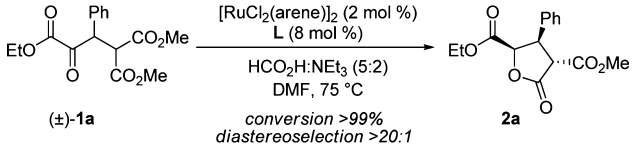
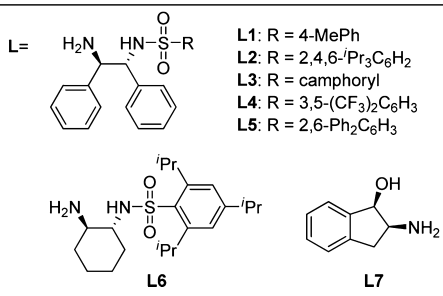
2. RESULTS AND DISCUSSION

2.1. Ligand/Catalyst Design. Inspired by the efficacy of Noyori's (arene)RuCl(monosulfonamide-DPEN)[14] in both the asymmetric reduction of simple ketones[15] and the dynamic reduction of α-substituted β-keto esters and amides,[16] we took this complex as our point of departure in ligand/catalyst design. Utilizing formic acid:triethylamine (5:2 mixture)[17] as the organic reductant and **1a** as a test substrate, a screen of ligands and precatalysts was undertaken (Table 1). Initial studies looked at

Table 1. Evaluation of Chiral Diamine Ligands[a]



entry	L	arene	er
1	**L1**	*p*-cymene	57:43
2	**L2**	*p*-cymene	70:30
3	**L3**	*p*-cymene	62:38
4	**L4**	*p*-cymene	70:30
5	**L5**	*p*-cymene	72:28
6	**L2**	C_6Me_6	62:38
7	**L2**	benzene	71:29
8	**L6**	*p*-cymene	73:27
9	**L7**	*p*-cymene	60:40

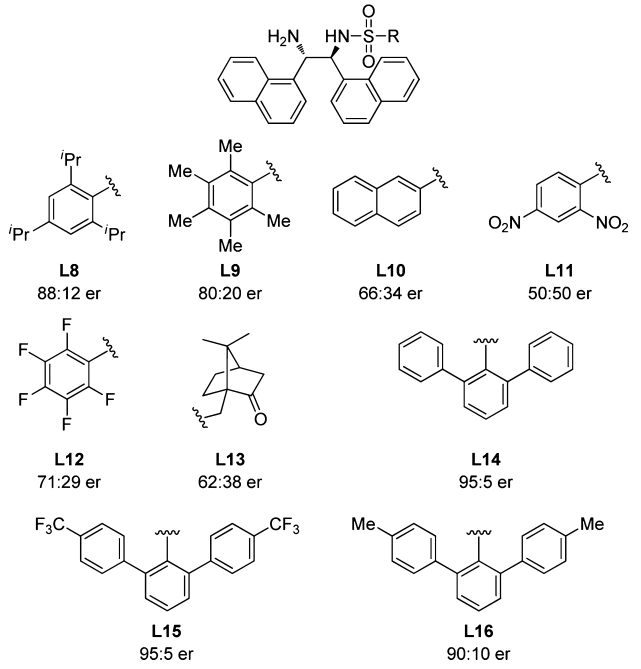


[a]Conditions: **1a** (1.0 equiv), $[RuCl_2(arene)]_2$ (0.02 equiv), **L** (0.08 equiv), HCO_2H:NEt_3 (5.0 equiv), $[\mathbf{1a}]_0$ = 0.1 M in DMF, 75 °C, 16 h.

the steric effects of the sulfonamide in Ru(II)-complexes possessing a (1*S*,2*S*)-diphenylethylenediamine (DPEN) backbone. Subjecting **1a** to 2 mol % of the ruthenium dimer $[RuCl_2(arene)]_2$ and Noyori's ligand **L1** (Ru atom:**L** mole ratio 1:2) in DMF at 75 °C[18] 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). DPEN-based ligands featuring bulkier sulfonamides (**L2**−**L5**) provided only modestly higher levels of selectivity (entries 2−5). Employing **L2**, a screen of (arene)Ru(II)-precatalysts was conducted to determine the role of the arene in the stereoselectivity of the reduction; however, no improvements were observed moving away from $[RuCl_2(p\text{-cymene})]_2$ (entries 6 and 7). In addition to DPEN, 1,2-diaminocyclohexane and 1,2-aminoindanol were also investigated as chiral backbones (**L6** and **L7**), but yielded comparable results (entries 8 and 9).

On the basis of these preliminary findings that asymmetric transfer hydrogenation catalysts from this family present in the literature were found to provide inadequate levels of selectivity, it became clear that new chiral space would need to be explored to achieve high levels of enantiocontrol. Utilizing the "mother diamine"/diaza-Cope approach to the synthesis of C_2-symmetric 1,2-diamines,[19] screening of a number of chiral diamine backbones was conducted. The α-naphthyl/triisopropylbenzenesulfonamide ligand **L8** considerably increased the selectivity (88:12 er, Table 2). To further optimize the ligand structure,

Table 2. Evaluation of Sulfonamides on α-Naphthyl Backbone[a]



[a]Conditions: As described for Table 1.

perturbations of the sulfonamide were examined due to its apparent ability to directly impact the chiral environment (Table 1, **L1** vs **L2**). Because less sterically encumbering sulfonamides (**L9**−**L12**) resulted in erosions in selectivity, we sought to synthesize bulkier sulfonamides by exploring new chiral space at the 2,6-positions of the arylsulfonamide.[20] A number of diverse sulfonyl chlorides were synthesized through a one-pot double alkylation/sulfonylation of 1,3-dichlorobenzene.[21] The simplest *m*-terphenyl sulfonamide variant **L14** distinguished itself as being uniquely effective for providing high levels of enantioselectivity for the title reaction (95:5 er). The use of electron-withdrawing (**L15**) or -releasing substituents (**L16**) provided no improvement in selectivity. The α-naphthyl backbone and *m*-terphenylsulfonamide operate synergistically; no improvement in enantiocontrol with the DPEN/*m*-terphenylsulfonamide ligand **L5** was observed (Table 1, entry 5). The α-naphthyl ethylenediamine backbone has been used sporadically in asymmetric synthesis, and the use of the *m*-terphenylsulfonamide for enantioselective catalysis is rarer still.[22]

2.2. Synthesis of Trisubstituted γ-Butyrolactones. This DKR-ATH was found to be applicable for a range of β-aryl α-keto esters (Table 3).[13] Electron-rich, electron-poor, and heteroaryl substituents were tolerated at the β-position providing γ-butyrolactone products in high yield and enantioselectivity.[23] Additionally, the reduction of **1g** was performed on a 10 g scale employing reduced catalyst loading (1 mol % Ru) yielding enantiopure lactone **2g** in 72% yield following a single

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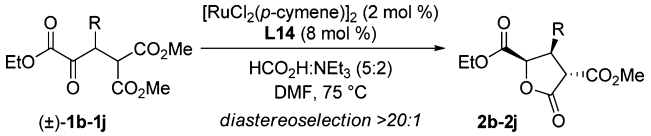
Table 3. DKR-ATH Substrate Scope[a]



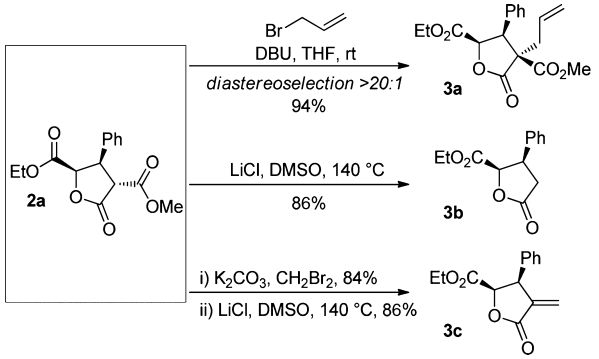
entry	R^2	2	yield (%)[b]	er[c]
1	4-Cl-C_6H_4	**2b**	94	96:4
2	4-Me-C_6H_4	**2c**	84	95.5:4.5
3	4-MeO-C_6H_5	**2d**	90	95:5
4	4-CN-C_6H_5	**2e**	88	95:5
5	2-Me-C_6H_5	**2f**	82	89:11
6[d]	piperonyl	**2g**	72	95:5
7	2-furyl	**2h**	91	95:5
8	*N*-Ts-indol-3-yl	**2i**	91	96.5:3.5
9	*N*-Boc-indol-3-yl	**2j**	88	96:4

[a]Conditions: As described for Table 1. [b]Isolated yield. [c]Enantiomeric ratio determined by HPLC/SFC analysis. [d][$RuCl_2$(*p*-cymene)]$_2$ (0.5 mol %), **L14** (2 mol %), 10 g scale, >99.5:0.5 er recrystallized.

recrystallization. The absolute stereochemistry of the trisubstituted γ-butyrolactone products was determined by X-ray crystallographic analysis of **2b**.[24]

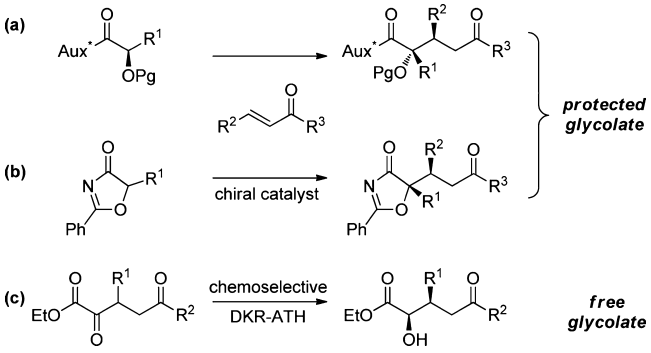
The obtained functionally rich γ-butyrolactones can be deployed in secondary transformations (Scheme 2). Diastereoselective alkylation of **2a** employing allyl bromide and DBU provided tetrasubstituted lactone **3a** bearing an all-carbon quaternary center in high yield. Krapcho decarboxylation[25] gave access to α-unsubstituted lactone **3b** (86% yield) that formally arises from cinnamic acid. When decarboxylation was preceded by alkylation with dibromomethane, dehalodecarboxylation[26] resulted and afforded α-alkylidene γ-butyrolactone **3c**. This substructure is prominent in natural product chemistry, and bioactivities within this subclass are well documented.[27]

Scheme 2. Reactions of Lactone Reduction Product 2a



2.3. "Free" Glycolate Michael Adducts Using Chemoselective DKR-ATH of α,δ-Diketo Esters. *2.3.1. DKR-ATH Approach to "Free" Glycolate Michael Adducts.* Access to δ-oxygenated glycolic acid derivatives via asymmetric glycolate Michael reactions is limited. The most common approach to this class of compounds is the addition of stoichiometric chiral glycolate enolates to α,β-unsaturated ketones and esters,[28] and in each case the protected glycolate is obtained (Scheme 3a). Only recently has a catalytic enantioselective variant been disclosed; that method uses oxazolones as the α-hydroxy acid surrogate (Scheme 3b).[29] To the best of our knowledge, no catalytic enantioselective Michael addition of a free glycolate enolate has been reported.[30]

Scheme 3. Approaches to δ-Oxygenated Glycolic Acid Derivatives



Based on the success of the DKR-ATH of γ,γ-dicarboalkoxy-α-keto esters (**1**, vide supra), we postulated that β-substituted-δ-keto-α-hydroxy esters might be accessible via a chemoselective dynamic reduction of α,δ-diketo esters directly delivering the formal "free" glycolate Michael adducts. Implicit in this analysis is the need for complete site selectivity in the reduction. Methods for the selective reduction of an aldehyde in the presence of less reactive carbonyls, that is, ketones and esters, are well-established.[31] While significant progress has been made in achieving the inverse process, the selective reduction of a ketone in the presence of an aldehyde,[32] the discrimination between two ketones remains a challenging task. Examples of the latter include the chemoselective reduction of 2,4-diketo acid derivatives using rhodium-aminophosphane-phosphinite catalysts[33] or baker's yeast[34] and aluminum-mediated selective reductions of diaryl ketones.[35] Our tactic takes advantage of the heightened reactivity enjoyed by α-dicarbonyls and establishes a simple catalytic method for achieving the formal asymmetric glycolate Michael construction without recourse to auxiliary control or protection of the hydroxyl group (Scheme 3c).

2.3.2. Glyoxylate Stetter Addition with Enones. Indirect methods for the preparation of the requisite α,δ-diketo esters **5** have been reported by us[10b] and others,[36] but the most direct and atom economical approach to these substrates would be a new Stetter reaction between commercial ethyl glyoxylate and α,β-enones.[37] This reaction was previously reported to be unsuccessful with thiazolium carbenes,[36c] but we have found that effective catalysis can be realized by employing the Rovis triazolium carbene derived from salt **4**.[38] As outlined in Table 4, this glyoxylate Stetter addition is highly efficient, tolerant of a number of ketonic substrates and substituents at the β-position, and can be performed on a multigram scale (entry 1). Notably, with the 1,4-dien-3-one dibenzylideneacetone, exclusive mono-addition was observed (entry 5).

2.3.3. Chemoselective DKR-ATH of α,δ-Diketo Esters. Our investigation into the chemoselective DKR-ATH began with an examination of the reduction of α,δ-diketo ester **5a**. As shown in Table 5, our initial studies confirmed the feasibility of selectively reducing the α-keto ester in the presence of an aryl ketone, as we observed exclusive formation of δ-keto-α-hydroxy ester **6a** as a single diastereomer. Subjecting **5a** to our previously optimized reaction conditions, 2 mol % of [$RuCl_2$(*p*-cymene)]$_2$ and diamine ligand **L14** (Ru atom:L mole ratio 1:2) in DMF at 70 °C using HCO_2H/Et_3N as the reductant, provided **6a** in 96% yield and a 91:9 er (entry 1). Lower levels of selectivity were

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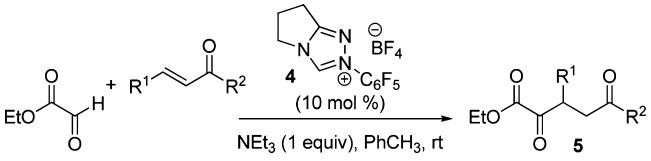
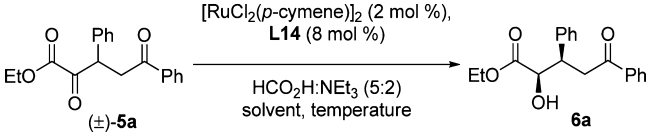
Table 4. Scope of the Glyoxylate Stetter Addition with Enones[a]



entry	R^1	R^2	5	yield (%)[b]
1[c]	C_6H_5	C_6H_5	**5a**	97
2	C_6H_5	4-I-C_6H_4	**5b**	95
3	C_6H_5	4-MeO-C_6H_5	**5c**	86
4	C_6H_5	Me	**5d**	72
5	C_6H_5	(*E*)-CH=CHPh	**5e**	91
6	C_6H_5	piperonyl	**5f**	92
7	4-Cl-C_6H_4	C_6H_5	**5g**	94
8	4-MeO-C_6H_4	C_6H_5	**5h**	96
9	2-Me-C_6H_4	C_6H_5	**5i**	70
10	3-Me-C_6H_4	C_6H_5	**5j**	93
11	4-Me- C_6H_4	C_6H_5	**5k**	95
12	CO_2Et	C_6H_5	**5l**	92
13	piperonyl	C_6H_5	**5m**	94
14	*N*-Boc-indol-3-yl	C_6H_5	**5n**	74

[a]Conditions: Unless otherwise noted, all reactions were performed on a 2.0 mmol scale in $PhCH_3$ (4 mL) at ambient temperature. [b]Isolated yield. [c]Reaction performed on a 20 mmol scale.

Table 5. Chemoselective DKR-ATH: Reaction Optimization[a]



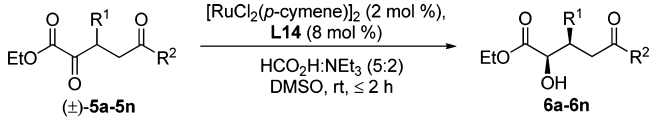
entry	solvent	*T* (°C)	yield (%)[b]	er[c]
1	DMF	70	94	91:9
2	DMF	rt	93	87:13
3	2-MeTHF	70	90	65:35
4	DCE	70	91	78:22
5	DMSO	70	96	97:3
6	DMSO	rt	98	97:3

[a]Conditions: **5a** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.02 equiv), **L14** (0.08 equiv), HCO_2H:NEt_3 (5.0 equiv), $[\mathbf{5a}]_0$ = 0.1 M, 16 h. [b]Isolated yield. [c]Enantiomeric ratio determined by SFC analysis.

observed when the reduction was conducted at room temperature (87:13 er, entry 2). Further optimization revealed that high levels of enantioselectivity (97:3 er) could be obtained by performing the reaction in DMSO at room temperature (entry 6). The chemoselectivity observed is remarkable in light of the extensive use of (arene)RuCl(sulfonamide) complexes for asymmetric transfer hydrogenation of aryl ketones.[14,15,17]

With optimal reaction conditions in hand, we next explored other substrates in the chemoselective dynamic reduction (Table 6). For all substrates examined, exclusive reduction of the α-keto ester was observed, irrespective of the electronic characteristics of the δ-ketone. High yields and enantioselectivities were obtained for substrates incorporating electron-rich, electron-poor, and heteroaryl substituents at the β-position. The level of selectivity for **6l** (entry 12, 91:9 er) is noteworthy as this demonstrates that the scope is not limited to β-aryl substrates (vide infra).[39] Additionally, other reducible functional groups remained intact: the retention of the α,β-enone in **6e** under the

Table 6. Chemoselective Dynamic Reduction Scope[a]



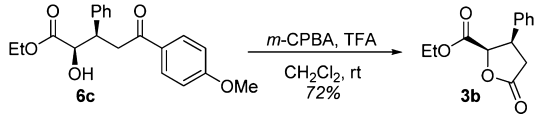
entry	R^1	R^2	6	yield (%)[b]	er[c]
1[d]	C_6H_5	C_6H_5	**6a**	97	98:2
2	C_6H_5	4-I-C_6H_4	**6b**	95	96:4
3	C_6H_5	4-MeO-C_6H_5	**6c**	86	96:4
4	C_6H_5	Me	**6d**	72	93:7
5	C_6H_5	(*E*)-CH=CHPh	**6e**	91	99:1
6	C_6H_5	piperonyl	**6f**	92	99:1
7	4-Cl-C_6H_4	C_6H_5	**6g**	94	98:2
8	4-MeO-C_6H_4	C_6H_5	**6h**	96	96:4
9	2-Me-C_6H_4	C_6H_5	**6i**	70	83:17
10	3-Me-C_6H_4	C_6H_5	**6j**	93	98:2
11	4-Me-C_6H_4	C_6H_5	**6k**	95	98:2
12	CO_2Et	C_6H_5	**6l**	92	91:9
13	piperonyl	C_6H_5	**6m**	94	97:3
14	*N*-Boc-indol-3-yl	C_6H_5	**6n**	95	98:2

[a]Conditions: As described for Table 5. [b]Isolated yield. [c]Enantiomeric ratio determined by SFC analysis. [d]Reaction performed using 0.05 mol % $[RuCl_2(p\text{-cymene})]_2$.

reaction conditions further highlights the catalyst's strong preference for the α-keto ester (entry 5). Aryl halides were also tolerated (entries 2,7). To evaluate the catalytic efficiency of this system, the reduction of **5a** was performed using 0.05 mol % of $[RuCl_2(p\text{-cymene})]_2$; no loss in reaction efficiency was observed as **6a** was obtained in 98:2 er (entry 1).

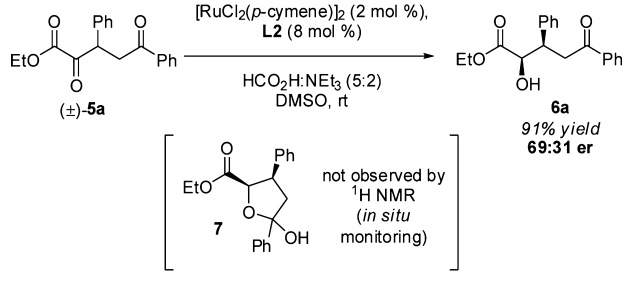
The absolute configuration and *syn*-stereochemical relationship of the α-hydroxy ester products were determined by converting **6c** to lactone **3b** via a Baeyer–Villiger oxidation followed by in situ lactonization; spectral data and optical rotation were in agreement with those previously obtained by us for **3b** (Scheme 4).[13]

Scheme 4. Stereochemical Analysis of δ-Keto-α-hydroxy Esters



To determine if the $[RuCl_2(p\text{-cymene})]_2$/**L14** catalyst system was uniquely effective for the reduction of α-keto esters, the chemoselectivity of transfer hydrogenation catalysts known to reduce simple ketones was evaluated with **5a** (Scheme 5). The

Scheme 5. Investigations into the Observed Chemoselectivity



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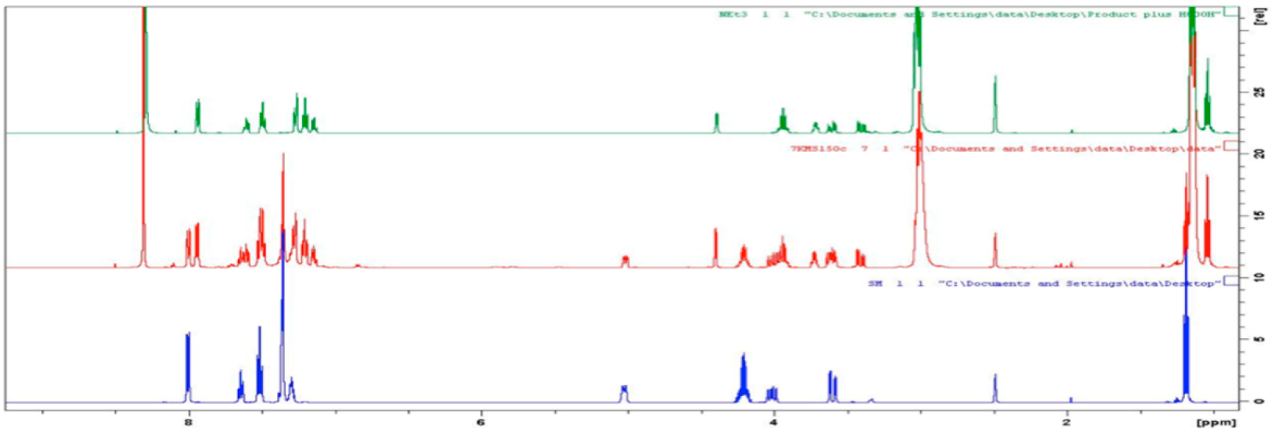
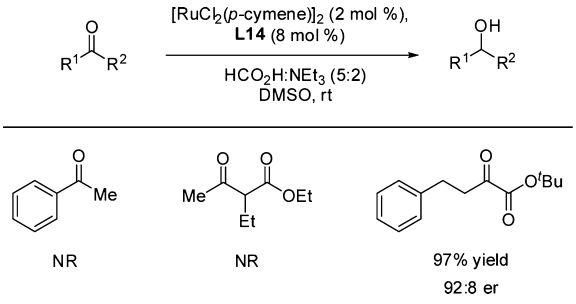


Figure 1. In situ monitoring of the reduction of (±)-**5a** by ^{1}H NMR spectroscopy in DMSO-d_6. Blue panel, α,δ-diketo ester **5a**; red panel, in situ monitoring of reduction of α,δ-diketo ester **5a** to **6a** (~50% conversion); green panel, α-hydroxy-δ-keto ester **6a** (with added HCO_2H/Et_3N).

use of ligand **L2** in the reduction, which is known to reduce acetophenone,[40] also afforded **6a** as the sole product, albeit with lower levels of enantioselectivity (69:31 er). This result caused us to wonder if the δ-ketone was possibly undergoing in situ "protection" as the lactol **7** following reduction of the α-keto ester and that this intermediate masked the δ-ketone from further reduction. To test this hypothesis, the reduction was monitored by ^{1}H NMR spectroscopy in DMSO-d_6, but **7** was not detected: only the diketo ester **5a** and hydroxy ester **6a** were observed (Figure 1).

We then examined the transfer hydrogenation of several other ketone substrates using the standard reaction conditions used in Table 6 (Scheme 6). Interestingly, acetophenone and ethyl 2-

Scheme 6. Other Keto Ester Reductions



ethyl-3-oxobutanoate, which are prototypical test substrates for new transfer hydrogenation catalysts, are not reduced with this catalyst system. This lack of reactivity further highlights the unique preference for α-keto esters conferred by the newly developed terphenylsulfonamide/di-α-napthylethylenediamine ligand. Reducing *tert*-butyl 2-oxo-4-phenylbutanoate under the standard conditions proceeded efficiently, imparting good levels of enantioselection and highlighting the potential applicability of this catalyst for simple α-keto esters.

2.4. Chlorohydrin Synthesis. *2.4.1. DKR-ATH Approach to Optically Active Chlorohydrins.* The investigations described above provide simple access to useful enantiomerically enriched glycolate building blocks, but Scheme 1 implies a goal of diversification in product structures that had not yet been realized. In considering new substrates that might be useful for DKR-ATH reactions, the potential integration of β-halo substituents was appealing on several levels. Optically active halohydrins are fundamental building blocks in organic chemistry, and these functional arrays can be converted to their derived enantioenriched epoxides or engage in nucleophilic substitution to provide a variety of functionalized product classes. The emergence of halohydrin dehalogenase (HheC), an enzyme produced by *Agrobacterium radiobacter* AD1, as a biocatalyst for the kinetic resolution of racemic haloalcohols highlights the importance of methods for the preparation of optically pure terminal halohydrins.[41] The catalytic asymmetric preparation of halohydrins has been limited principally to desymmetrization reactions of epoxides[42] and alkenes[43] or kinetic resolution of terminal epoxides.[42d,g,l,m,44] Methodology designed to directly access internal halohydrins from unsymmetrical precursors is largely underdeveloped (vide infra). We sought to develop a stereoselective Ru-catalyzed dynamic kinetic resolution of β-chloro-α-keto esters that would provide an efficient route to β-chloro-α-hydroxy esters.

Access to chiral β-chloro glycolic acid derivatives is currently limited to enzymatic processes or stereospecific opening of glycidic esters with strong acids. While enzymatic reductions[45] and kinetic resolutions[46] have been shown to impart good levels of diastereo- and enantioselectivity, these processes are substrate limited and lack generality. Chloride addition to optically pure glycidic esters often necessitates harsh reaction conditions, suffers from nonideal regio- and stereoselectivity, and lacks significant precedent for aliphatic substrates.[47] The dynamic kinetic resolution of α-chloro-β-keto esters has been developed for some time,[48] but the dynamic kinetic resolution of β-chloro-α-keto esters that would provide isomeric products is heretofore unknown. Thus, we sought to develop a simple, flexible synthesis of β-chloro glycolic acid derivatives employing a dynamic kinetic resolution asymmetric transfer hydrogenation (DKR-ATH) of β-chloro-α-keto esters (Figure 2).

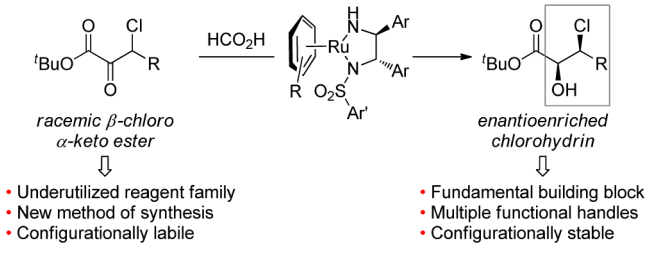


Figure 2. Dynamic kinetic resolution of β-chloro-α-keto esters.

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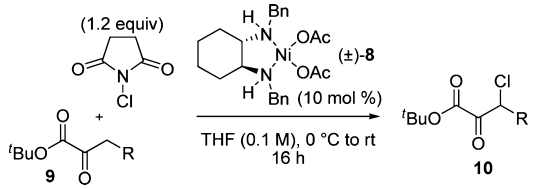
2.4.2. Direct Catalytic β-Chlorination of α-Keto Esters. The relative dearth of direct, catalytic β-functionalizations of α-keto esters presented an obstacle to the implementation of this synthetic plan; in particular, methods for the direct β-halogenation of α-keto esters are scarce.[9k,45b,c,49] Only two examples of the direct β-chlorination of singly activated α-keto esters have been reported, and those require either long reaction times or harsh reaction conditions.[45b,49a] To synthesize the requisite β-chloro substrates for the anticipated DKR-ATH, the development of a mild chlorination reaction of α-keto esters was pursued. A screen of various Cu(II)-diamine and Ni(II)-diamine complexes led to the identification of Sodeoka's $Ni(OAc)_2$-diamine complex **8**[9i] as an effective catalyst for the β-chlorination of α-keto esters **9** using *N*-chlorosuccinimide (NCS) under mild reaction conditions.[50] As outlined in Table 7, the chlorination proceeds with good selectivity for the singly halogenated product, is tolerant of a variety of functionalized aliphatic substrates, and can be performed on a multigram scale (entry 1). The elevated acidity of β-aryl substrates favored dichlorination (entry 9); therefore, the requisite β-aryl substrates were prepared via Darzens reaction.[51]

Table 7. Ni(II)-Catalyzed β-Chlorination of α-Keto Esters[a]



entry	R	10	mono:di[b]	yield (%)[c]
1[d]	$-CH_2Ph$	**10a**	9:1	81
2	$-CH_2p$-ClPh	**10b**	10:1	83
3	$-CH_2p$-MeOPh	**10c**	12:1	84
4	$-CH_2CH_2Ph$	**10d**	8:1	78
5	$-CH_2CH{=}CH_2$	**10e**	13:1	86
6	$-CH_2C{\equiv}CTMS$	**10f**	10:1	79
7	$-(CH_2)_2CH_3$	**10g**	13:1	87
8	$-(CH_2)_3OBn$	**10h**	13:1	86
9	−Ph	**10i**	1:>20	trace

[a]Unless otherwise noted, all reactions were performed on a 1.0 mmol scale. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield. [d]Performed on 8.0 mmol scale.

2.4.3. DKR-ATH of β-Chloro-α-keto Esters. The reduction of β-chloro-α-keto esters with $NaBH_4$ proceeds with high levels of diastereoselectivity to afford the *syn*-diastereomer via Felkin−Ahn control.[46a] Initial investigations into the DKR-ATH of **10a** revealed that ethylenediamine-derived **11a** also afforded excellent levels of *syn*-selectivity (Figure 3); however, the diastereochemical outcome was powerfully influenced by ligand selection. Upon switching to Noyori's parent Ru(II)-complex possessing a (1*S*,2*S*)-diphenylethylenediamine (DPEN) backbone (**11b**),[14] a significant erosion in *syn*-diastereoselection was observed, albeit with promising levels of enantioselectivity. The bulkier triisopropyl-DPEN ligand (**11c**) gave modest *anti*-diastereoselection with improved enantiocontrol. Exploiting the unique properties associated with the terphenylsulfonamide (vide supra), the DPEN-derivative **11d** led to appreciable ligand-controlled diastereoselection providing *anti*-**12a** with excellent levels of enantioselectivity. The α-naphthyl backbone (**11e**) employed in the reduction of β-aryl-α-keto esters was found to provide slightly higher levels of diastereoselection albeit with a small loss in enantioselectivity. The diastereoselectivity and enantioselectivity were further improved in DMF at 0 °C employing only 1 mol % of the Ru catalyst (in this case, the conveniently prepared and stored dehydrohalogenated variant of **11d**). Considering diastereoselectivity only, the continuum expressed by Figure 3 (>20:1 syn:anti → 1:9 syn:anti at 298 K) represents approximately 2.5 kcal/mol modulation of diastereomeric transition states through simple substituent modifications on a common ligand framework.

With optimized reaction conditions in hand, the relationship between α-keto ester structure and reaction stereoselectivity was assayed (Table 8). A variety of aliphatic substrates were found to be amenable to the reaction conditions providing β-chloro α-hydroxy esters with excellent levels of diastereo- and

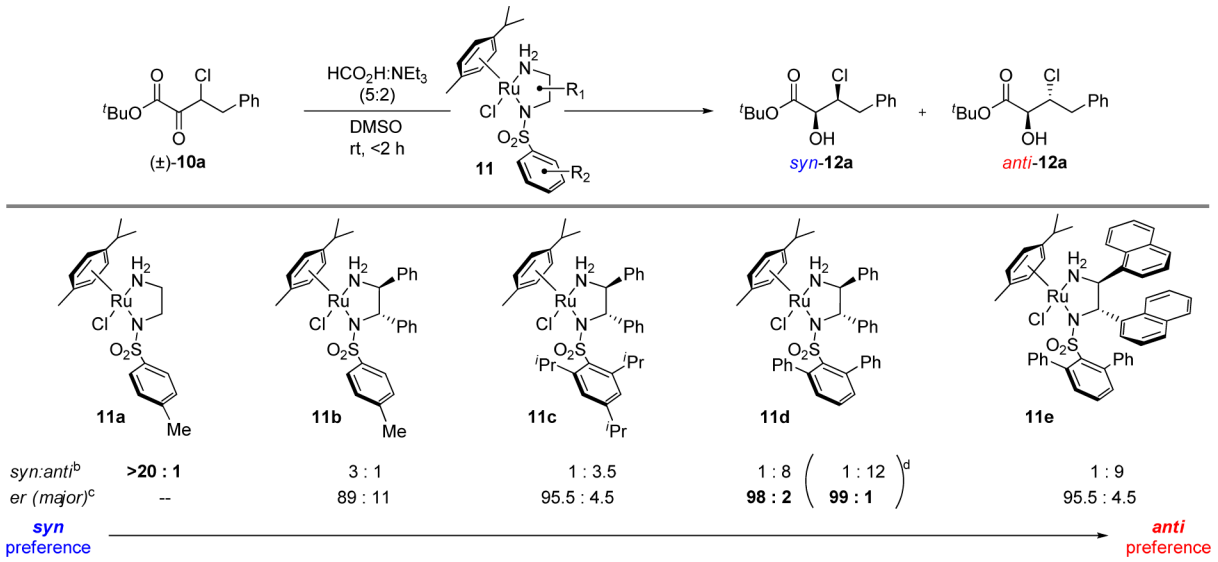


Figure 3. Ligand-controlled switch in diastereoselectivity. (a) Reactions were performed on 0.155 mmol scale employing 5 equiv of HCO_2H:NEt_3 (5:2). (b) Determined by ^1H NMR analysis of the crude reaction mixture. (c) Determined by chiral SFC analysis. (d) Performed with 1 mol % catalyst in DMF (0.1 M) at 0 °C for 10 h. Complex **11da** is the dehydrohalogenated variant of **11d**; the structure is illustrated in Table 8.

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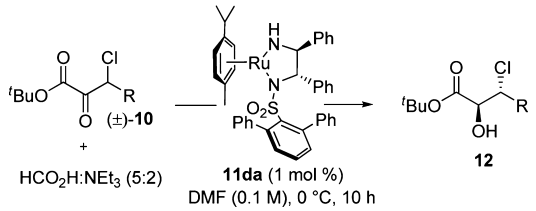
Table 8. β-Aliphatic Substrates in the DKR-ATH[a]



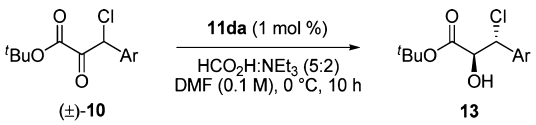
entry	R	12	yield (%)[b]	dr[c]	er[d]
1[e]	$-CH_2Ph$	**12a**	89	12:1	99:1
2	$-CH_2p$-ClPh	**12b**	90	16:1	99.5:0.5
3	$-CH_2p$-MeOPh	**12c**	93	20:1	98.5:1.5
4	$-CH_2CH_2Ph$	**12d**	93	16:1	98.5:1.5
5	$-CH_2CH{=}CH_2$	**12e**	95	>20:1	98:2[f]
6[g]	$-CH_2C{\equiv}CTMS$	**12f**	91	>20:1	96.5:3.5[f]
7	$-(CH_2)_2CH_3$	**12g**	94	>20:1	98.5:1.5[f]
8	$-(CH_2)_3OBn$	**12h**	91	18:1	98:2

[a]Unless otherwise noted, all reactions were performed on 0.155 mmol scale employing 5 equiv of HCO_2H:NEt_3 (5:2). [b]Isolated yield of *anti*-diastereomer. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by chiral SFC/HPLC analysis. [e]Performed on 6.5 mmol scale. [f]Determined following conversion to the benzoate (see the Supporting Information). [g]Performed at 23 °C for 10 h.

enantioselection. Alkene, alkyne, and benzyloxy functionality was tolerated under the reaction conditions offering value-added functional handles. The method was also scalable (entry 1). The efficiency of these aliphatic substrates under the DKR-ATH reaction conditions is a marked structural departure from the β-aryl and β-ester requirements in antecedent work from our group and the paradigm that aryl groups are necessary for high levels of enantiocontrol due to ligand/substrate π/C−H interactions.[52]

Compatibility with β-aryl substrates was also demonstrated under the optimized reaction conditions, providing adducts with excellent levels of enantioselectivity (Table 9). The electronic character of the aromatic ring was found to significantly impact the diastereoselectivity of the reaction. Electron-releasing groups engendered excellent diastereocontrol (entries 2, 3, and 10),

Table 9. Scope of β-Aryl Substrates in the DKR-ATH[a]



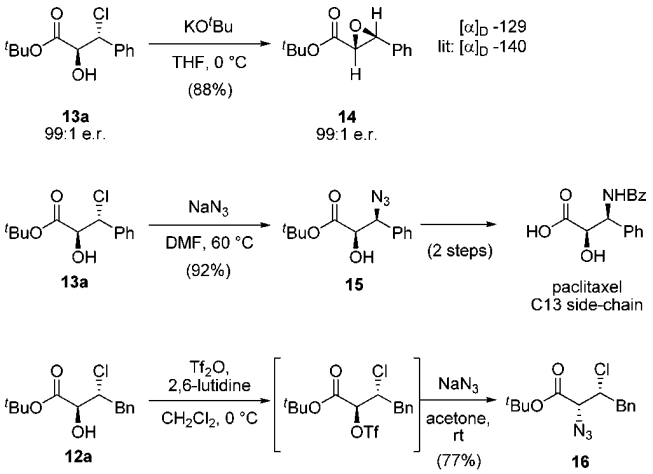
entry	Ar	13	yield (%)[b]	dr[c]	er[d]
1	Ph	**13a**	93	14:1	99.5:0.5
2	*o*-MeOPh	**13b**	95	>20:1	99:1
3	*m*-MeOPh	**13c**	94	19:1	99.5:0.5
4	*m*-NO_2Ph	**13d**	74	5:1	97.5:2.5
5	*p*-ClPh	**13e**	85	10:1	98.5:1.5
6	*p*-CF_3Ph	**13f**	80	8:1	98.5:1.5
7	*p*-CNPh	**13g**	82	6:1	98:2
8	*p*-NO_2Ph	**13h**	73	4:1	99:1
9	*p*-MePh	**13i**	91	14:1	99.5:0.5
10	*p*-MeOPh	**13j**	93	>20:1	99:1

[a]Reactions were performed on 0.155 mmol scale employing 5 equiv of HCO_2H:NEt_3 (5:2). [b]Isolated yield of *anti*-diastereomer. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by chiral SFC/HPLC analysis.

whereas electron-withdrawing groups provided somewhat lower diastereoselection (entries 4, 7, and 8).

The absolute stereochemistry of the products was determined by comparison to the known epoxide (2*R*,3*S*)-**14**,[53] which was synthesized from chlorohydrin (2*S*,3*R*)-**13a** upon exposure to KO^{t}Bu (Scheme 7). To highlight the synthetic utility of the

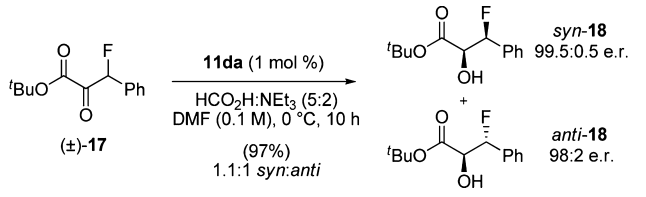
Scheme 7. Secondary Transformations of Chlorohydrin Products



enantioenriched chlorohydrins as synthetic building blocks, illustrative secondary transformations were pursued. Treatment of chlorohydrin **13a** with NaN_3 afforded the azido alcohol **15** representing a formal synthesis of the paclitaxel C13 side-chain.[47b] Notably, the *syn*-product **15** is stereocomplementary to the *anti* diastereomer obtained from the glycidic esters that one might derive from Darzens or Weitz−Scheffer reactions. Following triflate formation of chloroalcohol **12a**, chemoselective displacement with NaN_3 affords α-azido-β-chloro ester **16** providing access to β-chloro-α-amino acid derivatives.

The DKR-ATH is also amenable to the reduction of β-fluoro-α-keto esters. Preliminary investigations have revealed that ketone **17** can be reduced under the optimized reaction conditions to afford the derived fluorohydrin **18** in excellent yield as a mixture of diastereomers (Scheme 8). Despite the lack

Scheme 8. DKR-ATH of β-Fluoro-α-keto Ester 17



of diastereocontrol in the reaction,[54] excellent levels of enantioinduction were observed for both diastereomers. This initial finding is quite encouraging in light of the responsiveness of diastereocontrol to ligand structure in this reaction family (vide supra).

3. CONCLUSIONS

In summary, we have designed new (arene)Ru(monosulfonamide) asymmetric transfer hydrogenation catalysts that have led to the successful development of a highly modular dynamic kinetic resolution of β-substituted-α-keto

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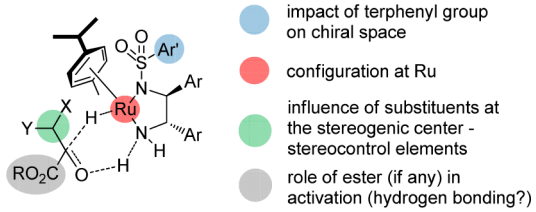
esters. The productive merger of a common mechanistic framework and a new *m*-terphenylsulfonamide-based catalyst system allows for rapid, atom-economical construction of highly functionalized glycolic acid derivatives with excellent levels of chemo-, diastereo-, and enantioselectivity.

A formal asymmetric glycolate Michael reaction has been established via a catalytic asymmetric chemoselective dynamic reduction of α,δ-diketo esters. The latter are prepared via a new atom economical carbene-catalyzed Stetter reaction between commercial ethyl glyoxylate and α,β-enones. The enantioselective reduction proceeds with high enantio- and diastereoselectivity for a number of substrates. Initial investigations into the origin of the observed selectivity suggest that the $[RuCl_2(p\text{-cymene})]_2$/**L14** catalyst system is uniquely effective for the reduction of α-keto esters, as other ketone substrates (even acetophenone) are unreactive under the standard reaction conditions.

Additionally, a highly stereoselective synthesis of β-chloro glycolic acid derivatives via asymmetric transfer hydrogenation was developed. A Ni(II)-catalyzed chlorination of aliphatic α-keto esters was developed to provide the requisite β-chloro-α-keto esters. In the reduction of these ketones, careful catalyst tuning allows for a remarkable ligand-controlled inversion of the preference for *syn*-selectivity to provide access to *anti*-chlorohydrins. The DKR-ATH proceeds with high levels of diastereo- and enantioselectivity for a number of aliphatic and aromatic substrates. The obtained chlorohydrins are versatile chemical building blocks for valuable secondary transformations.

These studies collectively provide diverse glycolate-based building blocks for synthesis. This study has highlighted some of the preparative and practical aspects of these reactions, but open questions with respect to mechanism clearly remain (Scheme 9).

Scheme 9. Open Mechanistic Questions



Additional studies to understand the catalyst–substrate interactions that account for the high levels of selectivity observed are ongoing, with the goal of utilizing this information in extensions to the dynamic kinetic resolution of other useful frameworks.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

jsj@unc.edu

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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