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Asymmetric Synthesis of *anti*-β-Amino-α-Hydroxy Esters via Dynamic Kinetic Resolution of β-Amino-α-Keto Esters

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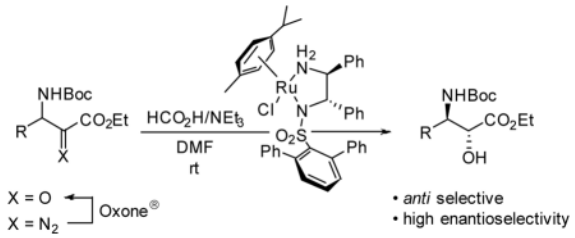
Abstract



A method for the asymmetric synthesis of enantioenriched *anti*-α-hydroxy-β-amino acid derivatives by enantioconvergent reduction of the corresponding racemic α-keto esters is presented. The requisite α-keto esters are prepared via Mannich addition of ethyl diazoacetate to imines followed by oxidation of the diazo group with Oxone®. Implementation of a recently-developed dynamic kinetic resolution of β-substituted-α-keto esters via Ru(II)-catalyzed asymmetric transfer hydrogenation provides the title motif in routinely high diastereo- and enantioselectivity.

The presence of α-hydroxy-β-amino acids in high value compounds is well-documented[1] and as a consequence, methods that provide access to this structural motif are in continual demand. Numerous methods of accessing enantioenriched forms of these products have been reported. Included among them are transformations that use alkene derivatives such as nucleophilic addition to chiral epoxides,[2] oxyaminations of alkenes using Sharpless conditions,[3] and asymmetric hydrosilylation of α-acetoxy-β-enamino esters.[4] In addition, a number of methods exist to access such substrates from non-alkene starting materials. These include oxidation and subsequent reduction of chiral β-amino-α-diazo esters,[5] asymmetric Henry reactions with subsequent nitro-group reduction,[6] asymmetric "glycolate" Mannich reactions,[7] β-amination of α-keto esters,[8] among others.[9]

In assessing various methods, we noticed that few methods provided products with easily manipulated protecting groups while simultaneously setting both stereocenters in a single transformation. We believed that these synthetic issues might be addressable using chemistry previously developed in our laboratories. Herein we describe the application of a recently discovered ruthenium catalyzed dynamic kinetic resolution-asymmetric transfer

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at: http:/pubs.acs.org

hydrogenation (DKR-ATH) that provides facile access to enantioenriched β-amino-α-hydroxy esters.

Our group has shown that various β-substituted-α-keto esters are reduced with high stereoselectivity under DKR-ATH conditions.[10] These examples provided the basis of a hypothesis that β-amino-α-hydroxy-esters could be accessed from racemic β-amino-α-keto esters via dynamic kinetic resolution (Scheme 1). Such reactions are well-established for the isomeric α-amino-β-keto esters and in fact comprise prototypical examples of DKR,[11] but extensions to the β-amino-α-keto esters remain limited to enzymatic catalysis.[12]

In principle, the most atom-efficient route towards the requisite β-amino-α-keto esters would be to use a glyoxylate aza-benzoin reaction mediated by an *N*-heterocyclic carbene (NHC) catalyst. This umpolung reactivity has precedent,[13] but it has not been demonstrated using glyoxylate as the nucleophile. Starting from readily accessed amido-sulfones **1**[14] and using the triazolium carbene derived from **2**,[15] we observed Mannich addition of ethyl glyoxylate into *in situ* formed imines (Scheme 2). The requisite carbamates **3a** and **3b** were obtained in low and variable yields.[16]

Although inefficient at the present level of optimization, this method provided us with sufficient amounts of material with which to examine the DKR-ATH for proof of concept. Guided by our previous work,[10] we began by screening catalyst complexes **5–7** which arise from diarylethylene diamine monosulfonamide ligands and $[RuCl_2(p\text{-cymene})]_2$.[17] The use of complex **5** afforded complete *anti* diastereoselection[18] but moderate enantioselectivity, necessitating a switch to ligands **6** and **7**, both of which bear a terphenyl sulfonamide. Complex **6** provided high stereoselectivity for both Cbz- and Boc-protected amines with Cbz providing slightly higher enantioselectivity (Table 1, entries 2 and 3). When the solvent was changed from DMSO to DMF, an increase in selectivity for the Boc protected substrate was observed (entry 4).

Searching for higher selectivity, we switched to ligand **7**, which provided **4a** in 99:1 er (Table 1, entry 5). We tested this same catalyst at 0 °C in an attempt to improve the yield by subverting retro-Mannich reactivity,[19] but this change resulted in decreased yield. The brief optimization study revealed that high levels of enantioselectivity can be obtained with two convenient carbamate protecting groups through judicious selection of catalyst. Due to the superior enantioselection provided by the Boc-protected amine, it was selected as the protecting group for further studies.

With proof of concept for the DKR-ATH established, attention returned to improving the synthesis of the requisite β-amino-α-keto esters. A survey of the literature revealed conditions reported by Wang and coworkers, which proved effective for generation of β-sulfonamido-α-keto esters.[20] This route employs *N*-sulfonyl imines in conjunction with ethyl diazoacetate to achieve a Mannich addition.[21] On the basis of precedent, subsequent oxidation was expected to furnish α-keto esters primed for reduction.[5,19] This general strategy has previously been exploited to access the title compounds via asymmetric Mannich addition followed by diastereoselective reduction.[5] Our hope was to provide a method in which both stereocenters would be set during the reduction from a racemic starting material.

The Mannich addition was conducted at room temperature for all aromatic substituted imines, and at −40 °C for aliphatic substrates to subvert enamine formation. With α-diazo esters in hand, we then turned to a two-step oxidation-reduction sequence (Figure 1).

We employed previously described conditions for oxidation of α-diazo esters to their corresponding α-keto esters using commercially available Oxone®.[5] The unpurified α-keto

esters were sufficiently pure to be used directly in the optimized reduction conditions: exposure of β-amino-α-keto esters (±)-**8** to Ru-complex **7** and HCO_2H/Et_3N provided products **4a–o** (Figure 2).

Our substrate scope sought to probe both electronic and steric controls for this reaction system. Heteroaromatic (**4l–4m)** as well as electron-rich (**4f–4h)** and -poor (**4g)** aromatic systems all provide high diastereomeric ratio (dr) and enantioselectivity. Additionally, **4j** showed only reduction of the α-ketone leaving the alkene intact, although the reaction proceeded with negligible diastereoselectivity. Products **4c–4e** showed that while steric encumbrance does affect the dr, enantioselectivity remains high. In testing **8o** for the application of this method towards aliphatic β-substitution, we observed full reduction of the ketone, albeit with low stereoselectivity. As was already noted, this reaction is tolerant to different amine protecting groups (**4a** and **4b)** providing further flexibility in substrate design. The resultant alcohols are often solids and a single recrystallization could regularly provide er values above 99.5:0.5 (parenthetical values in Table 3).

To determine the stereochemistry imparted by the DKR-ATH, (+)-**4b** was independently synthesized from the known enantioenriched epoxide **9** (Scheme 3A).[22] The stereochemistry was then assigned based on comparison of this product and (−)-**4b (**prepared by DKR-ATH, Table 3) using ^{1}H NMR and chiral SFC analysis. Lastly, the utility of Boc and Cbz protecting groups was demonstrated by the deprotection of **4a** under acidic conditions and **4b** with trimethylsilyl iodide, both of which result in free amine (−)-**10** (Scheme 3B).

Racemic β-amino-α-keto esters can be employed as an entry point for enantiomerically enriched *anti*-β-amino-α-hydroxy esters via DKR-ATH. The present work expands the product types that are accessible using terphenyl-based catalysts **6** and **7**, establishes both of the product's stereocenters in a single step, and delivers the amine in a conveniently configured form.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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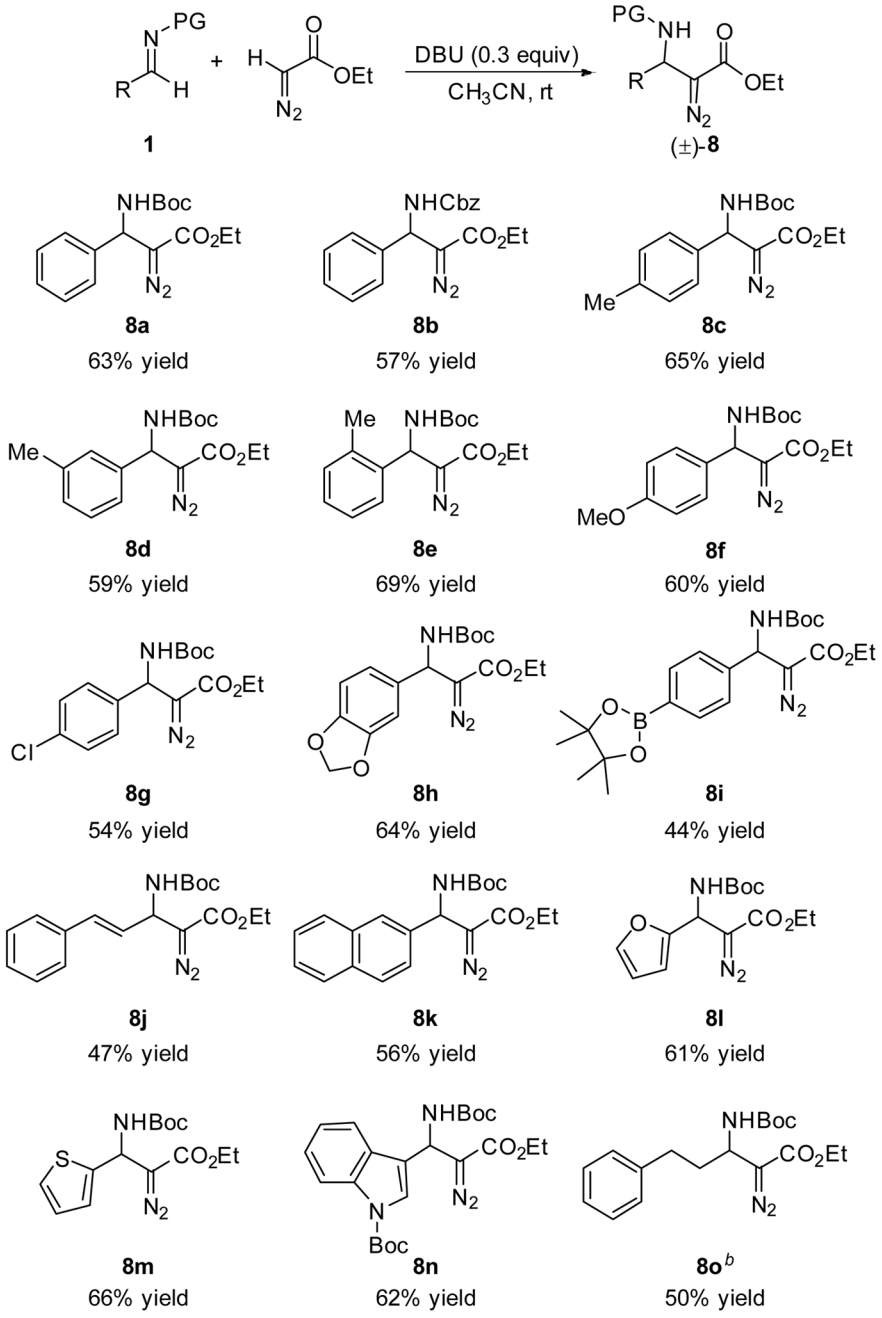


Figure 1.

Mannich addition of ethyl diazoacetate.[a]

[a)] The imine **1** was generated from the corresponding amido sulfone (see the Supporting Information for details). Isolated yields over the two steps are reported. [b)] Mannich addition conducted at −40 °C.

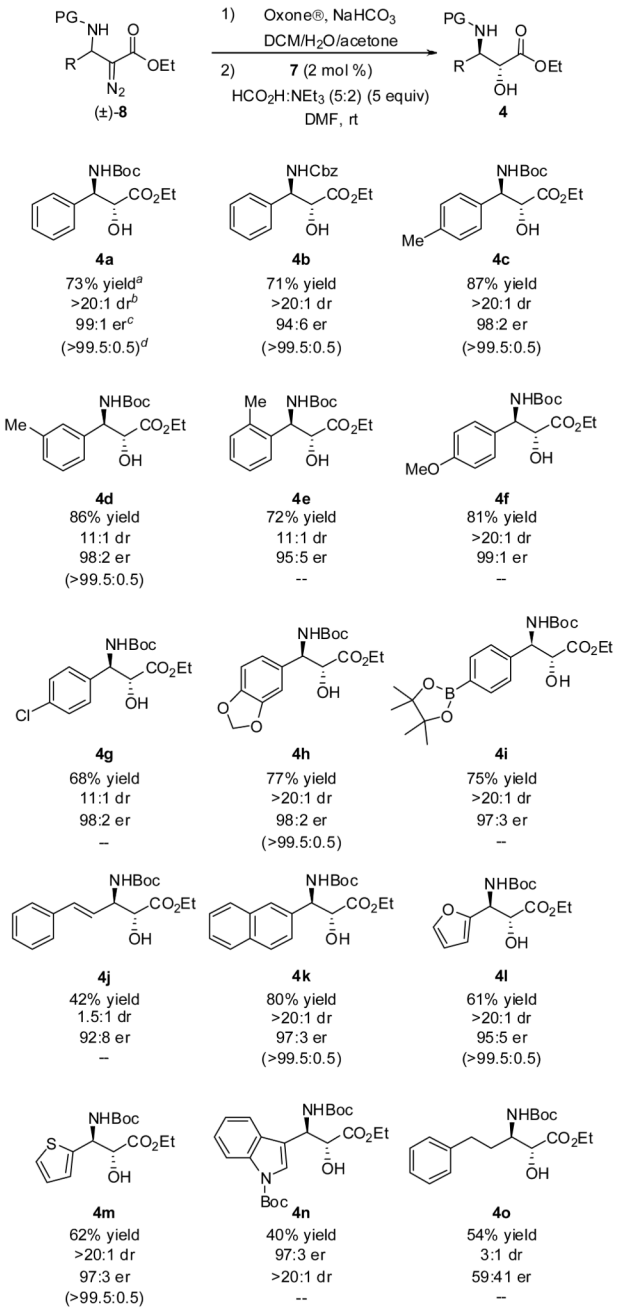
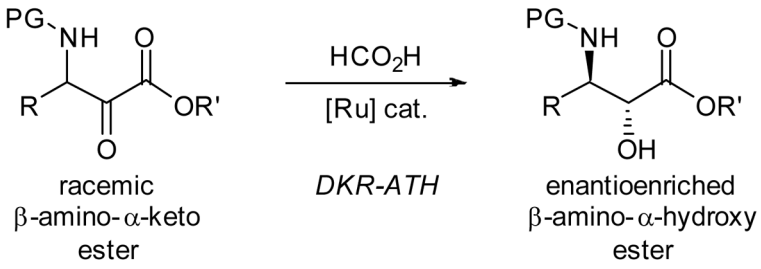


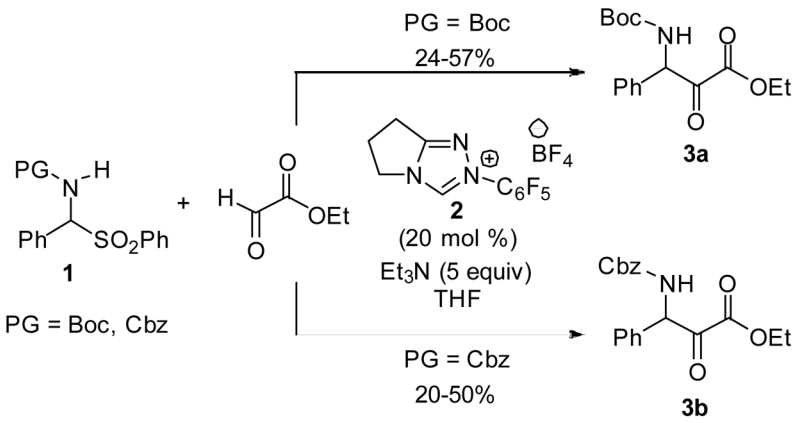
Figure 2.

Substrate scope for the ATH-DKR.

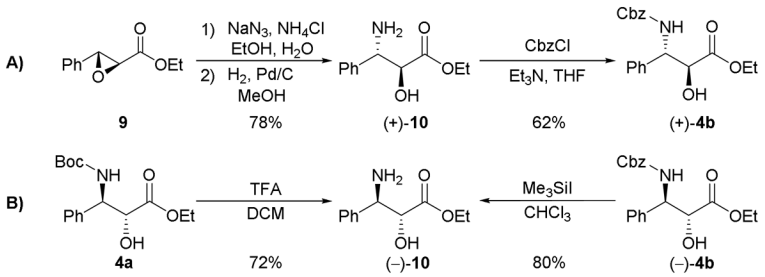
a) Isolated yields are reported. *b)*Determined by ^{1}H NMR analysis of crude reaction mixture. *c)*Determined by chiral HPLC or SFC analysis. *d)*Recrystallized er values are in parentheses



Scheme 1.
Proposed ATH-DKR of β-amino-α-keto esters



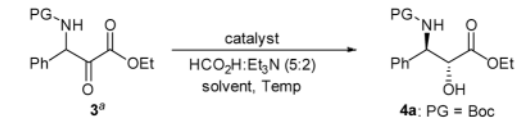
Scheme 2.
Aza-benzoin addition using ethyl glyoxylate

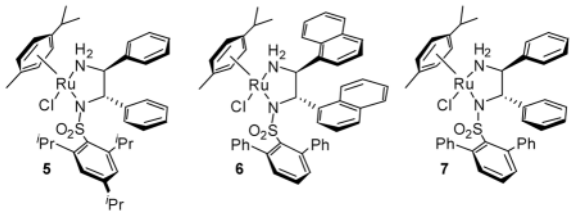


Scheme 3.
Determination of product stereochemistry.

Table 1

Optimization of ATH-DKR for β-amino-α-keto esters.





entry	PG	cat.	solvent	temp (°C)	yield[b] (%)	dr[c]	er[d]
1	Boc	**5**	DMSO	23	59	>20:1	77:23
2	Boc	**6**	DMSO	23	67	>20:1	94:6
3	Cbz	**6**	DMSO	23	77	>20:1	97:3
4	Boc	**6**	DMF	23	65	>20:1	97:3
5	Boc	**7**	DMF	23	73	>20:1	99:1
6	Boc	**7**	DMF	0	62	>20:1	98:2
7	Cbz	**7**	DMF	23	71	>20:1	94:6

[a] Reaction optimization took place using a crude mixture of compounds obtained via aza-benzoin reaction which included the desired starting material (cf. Scheme 2).

[b] Isolated yield calculated based on the assumption of pure α-keto ester starting material; actual yields are probably somewhat higher.

[c] Determined by ^{1}H NMR analysis of crude reaction mixture.

[d] Determined by chiral HPLC or SFC analysis.