Asymmetric Catalysis

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Dynamic Kinetic Asymmetric Transformations of β-Stereogenic α-Ketoesters by Direct Aldolization**

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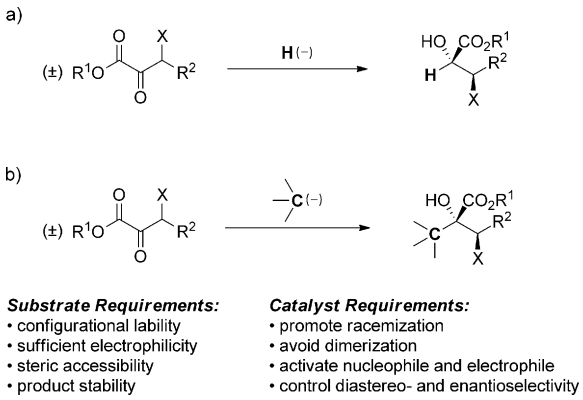
Abstract: *Dynamic kinetic asymmetric transformations (DyKAT) of racemic β-bromo-α-keto esters by direct aldolization of nitromethane and acetone provide access to fully substituted α-glycolic acid derivatives bearing a β-stereocenter. The aldol adducts are obtained in excellent yield with high relative and absolute stereocontrol under mild reaction conditions. Mechanistic studies determined that the reactions proceed through a facile catalyst-mediated racemization of the β-bromo-α-keto esters under a DyKAT Type I manifold.*

Deracemization is a valuable method for the generation of chiral molecules from simple racemic starting materials.[1] Although there are a plethora of reported dynamic kinetic processes, most are arguably either complexity-neutral transformations (hydrogenation, acylation, etc.) or generate a single stereogenic center. Dynamic kinetic asymmetric transformations (DyKAT) that utilize a C–C bond-forming step in the construction of multiple stereocenters are highly valuable synthetic strategies.[2] Herein, we describe dynamic kinetic asymmetric transformations of racemic β-bromo-α-ketoesters with both nitromethane and acetone through direct aldolization.[3]

On the basis of the pioneering work of Noyori and coworkers in the development of the dynamic kinetic resolution (DKR) of β-ketoesters by ruthenium-catalyzed hydrogenation,[4] our research group recently disclosed a protocol for ruthenium(II)-catalyzed dynamic kinetic reduction by the asymmetric transfer hydrogenation (DKR-ATH) of β-stereogenic α-ketoesters to afford secondary glycolic acid derivatives (Scheme 1 a).[5] Our group's longstanding interest in the synthesis of complex fully substituted glycolates[6] prompted us to investigate reaction manifolds for the dynamic addition of carbon nucleophiles to β-stereogenic α-ketoesters to provide access to products of this type (Scheme 1 b). For a DyKAT to be realized, a catalyst must be identified that can effectively racemize the α-ketoester without promoting self-condensation while also activating the nucleophile and delivering it with high stereoselectivity to a hindered ketone. We postulated that the identity of the β-substituent of the α-ketoester would be important in promoting the desired reactivity owing to its direct impact on both the β-C–H acidity and the steric environment about the ketone. To this end, we selected β-halo-α-ketoesters to investigate this potential reactivity profile owing to their successful previous use as substrates in DKR reactions.[5b,7]



Scheme 1. Development of a DyKAT of β-stereogenic α-ketoesters. a) Dynamic kinetic reduction by asymmetric transfer hydrogenation (DKR-ATH).[5] b) Dynamic kinetic asymmetric transformation (DyKAT) by direct aldolization.

We commenced our investigation by exploring the Henry addition of nitromethane to β-bromo-α-ketoesters **1** (Table 1). A number of methods have been reported for the Henry addition to pyruvates;[8] however, there is limited precedent for non-pyruvic alkyl α-ketoesters and β-branched substrates.[9] Quinidine (**I**) was found to catalyze the nitroaldol addition of (±)-**1a** in quantitative yield with good diastereoselectivity albeit poor enantioselectivity (Table 1, entry 1). Although bifunctional catalysts **II** and **III** only provided marginal improvements in enantioselectivity when CH_2Cl_2 was used (Table 1, entries 2 and 3), a solvent screen revealed that **III** in methyl *tert*-butyl ether (MTBE) provided **2a** with d.r. > 20:1 and e.r. 92.5:7.5 (Table 1, entry 6). Catalyst modifications to the secondary alcohol led to the identification of *o*-toluoyl-substituted **IV** as the optimized catalyst structure (Table 1, entry 7). Attempts to further enhance the selectivity through the addition of tetrabutylammonium bromide (TBABr)[7a] or lowering the reaction temperature to 0 °C provided no improvement (Table 1, entries 8 and 9). Gratifyingly, the *i*Pr ester (±)-**1b** was converted into **2b** with e.r. 96:4 as a single diastereomer when **IV** was employed in 2-methyltetrahydrofuran (2Me-THF; Table 1, entry 11). Under these optimized reaction

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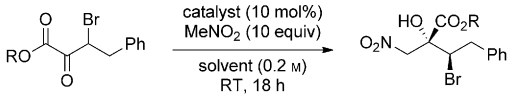
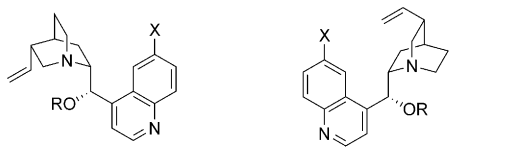
Table 1: Optimization of the Henry DyKAT.[a]



(±)-**1a**: R = Et
(±)-**1b**: R = *i*Pr

(2*R*,3*R*)-**2a**: R = Et
(2*R*,3*R*)-**2b**: R = *i*Pr



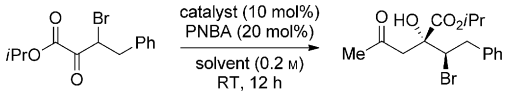
I: X = OMe, R = H
II: X = OH, R = H
III: X = OH, R = benzoyl
IV: X = OH, R = *o*-toluoyl

V: X = OH, R = *o*-toluoyl

Entry	**1**	Catalyst	Solvent	d.r.[b]	e.r.[c]
1	**1a**	**I**	CH_2Cl_2	13:1	62:38
2	**1a**	**II**	CH_2Cl_2	12:1	72:28
3	**1a**	**III**	CH_2Cl_2	11:1	80:20
4	**1a**	**III**	toluene	16:1	80.5:19.5
5	**1a**	**III**	MeCN	>20:1	88:12
6	**1a**	**III**	MTBE	>20:1	92.5:7.5
7	**1a**	**IV**	MTBE	>20:1	93:7
8[d]	**1a**	**IV**	MTBE	>20:1	93:7
9[e]	**1a**	**IV**	MTBE	>20:1	93:7
10	**1b**	**IV**	MTBE	>20:1	92:8
11	**1b**	**IV**	2Me-THF	>20:1	96:4
12	**1b**	**V**	2Me-THF	>20:1	13:87

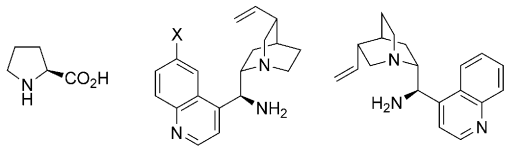
[a] Reactions were performed on a 0.20 mmol scale and proceeded to full conversion as adjudged by TLC. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] The enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was carried out with TBABr (10 mol%) as an additive. [e] The reaction was performed at 0°C for 30 h.

Table 2: Optimization of the acetone aldol DyKAT.[a]



(±)-**1b**

(2*R*,3*R*)-**3b**



A

B: X = H
C: X = OMe
D: X = OH

E

Entry	Catalyst	Solvent	d.r.[b]	e.r.[c]
1[d]	**A**	acetone	2:1	4:96
2	**B**	acetone/dioxane (1:9)	14:1	12:88
3	**B**	acetone/EtOAc (1:9)	8:1	19.5:80.5
4	**B**	acetone/MeCN (1:9)	5:1	16:84
5	**B**	acetone/DMF (1:9)	9:1	9.5:90.5
6	**B**	acetone	>20:1	4.5:95.5
7	**C**	acetone	>20:1	10.5:89.5
8	**D**	acetone	>20:1	14.5:85.5
9	**E**	acetone	>20:1	96:4

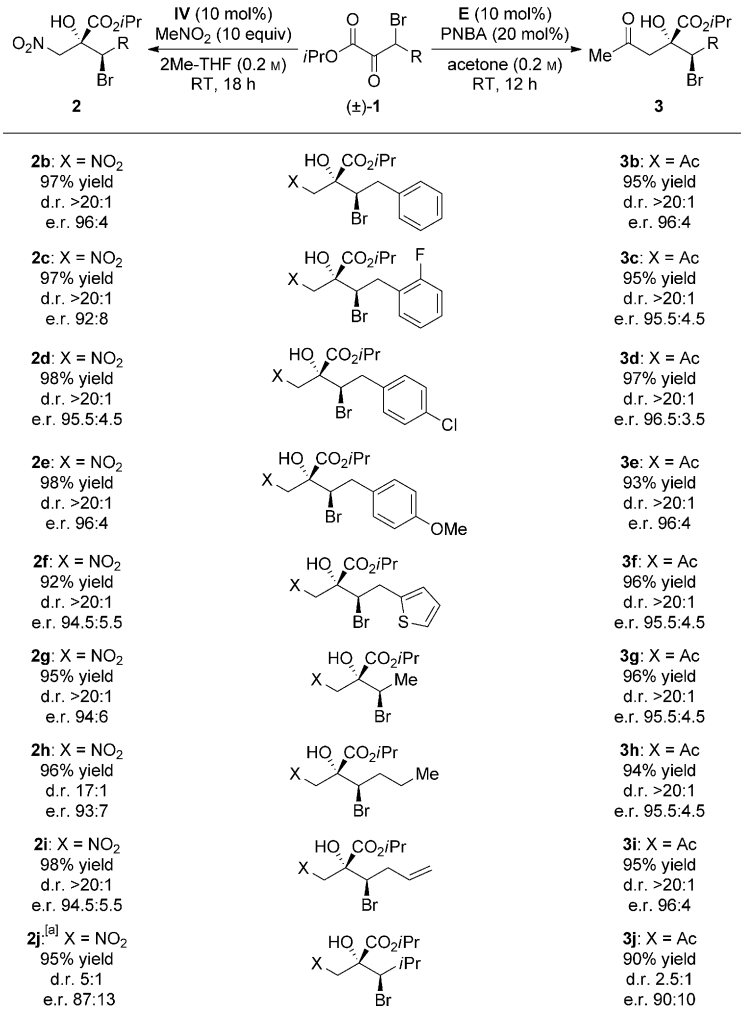
[a] Reactions were performed on a 0.20 mmol scale and proceeded to full conversion as adjudged by TLC. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] The enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed with **A** (20 mol%) in the absence of PNBA for 3 h. DMF = *N*,*N*-dimethylformamide.

conditions, *ent*-**2b** was obtained with d.r. > 20:1 and e.r. 87:13 with the pseudoenantiomeric catalyst **V** (Table 1, entry 12).

During the course of our optimization of the Henry reaction conditions, we observed that L-proline (**A**) catalyzed the addition of acetone to (±)-**1b** to provide *ent*-**3b** in quantitative yield with e.r. 96:4, albeit with low diastereoselectivity (Table 2, entry 1). Although related to the L-proline-catalyzed DKRs reported by Zhang and co-workers for highly activated 2-oxo-3-arylsuccinates and α,γ-diketoesters,[10] we sought to develop a DyKAT of the less-activated β-bromo-α-ketoester (±)-**1b**. A number of direct acetone aldolization reactions of α-ketoesters with a range of catalysts have been reported.[11,12] We chose to examine catalysts derived from the cinchona alkaloids on the basis of their efficiency in the Henry reaction (Table 1). The cinchonidine-derived primary-amine catalyst **B** with *p*-nitrobenzoic acid (PNBA) as a cocatalyst in acetone/dioxane (1:9) delivered *ent*-**3b** with good diastereo- and enantioselectivity (Table 2, entry 2). An examination of other polar solvents did not provide satisfactory improvement (Table 2, entries 3–5); however, a reaction run neat in acetone with **B** provided *ent*-**3b** with e.r. 95.5:4.5 as a single diastereomer (entry 6). Attempts to further increase the enantioselectivity by the use of either **C** or **D** proved ineffective (Table 2, entries 7 and 8), but pseudoenantiomeric **E** provided a slight improvement and delivered **3b** quantitatively with e.r. 96:4 as a single diastereomer (entry 9).

Having optimized the reaction conditions, we probed the scope of both the direct Henry and acetone-aldolization DyKAT of β-bromo-α-ketoesters (Scheme 2). In addition to a phenyl group (products **2b** and **3b**), the reactions were tolerant of both *ortho*- and *para*-substituted aryl groups at the γ-position and provided aldol adducts **2b–e** and **3b–e** in high yield and selectivity. Heteroaryl (±)-**1f** also reacted efficiently under the reaction conditions to cleanly provide **2f** and **3f**. A range of linear alkyl substrates underwent aldolization with no loss in selectivity to provide **2g–i** and **3g–i** with similarly high efficiency, thus indicating that aromatic interactions between the substrate and the catalyst are not required for high levels of selectivity. The increased steric requirements of γ-branching resulted in low diastereoselectivity and moderate enantioselectivity in the formation of **2j** and **3j**. The absolute configuration of (2*R*,3*R*)-**2b** and (2*R*,3*R*)-**3e** was in each case determined by X-ray crystallography, and the other products were assigned by analogy.[13]

Given that catalysts **IV** and **E** are derived from cinchona alkaloids, their pseudoenantiomeric catalysts **V** and **B** are readily available and provide access to both enantiomeric series of Henry and acetone-aldolization adducts. Although **V** provided *ent*-**2b** with only e.r. 87:13, a single recrystallization provided enantiomeric enrichment to e.r. 99:1 (Scheme 3). The utility of these reactions is highlighted not only by the mild, operationally simple reaction conditions, but by the near-quantitative yield of products following a simple filtra-

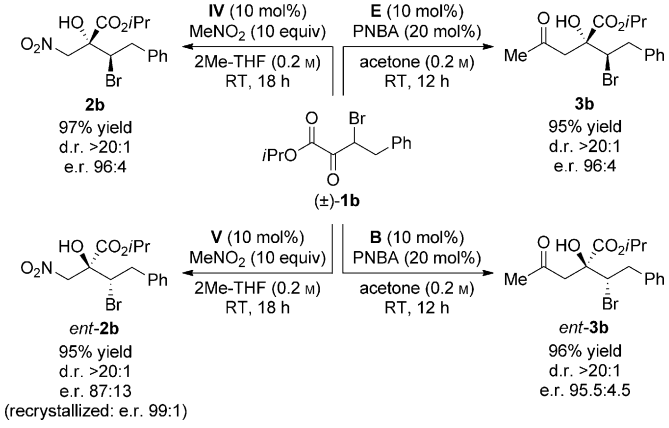


Scheme 2. Scope of the DyKATs. Reactions were performed on a 0.20 mmol scale. The yield of the isolated product is reported in each case. The diastereomeric ratio (d.r.) was determined by ^{1}H NMR spectroscopic analysis of the crude product. The enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral stationary phase. [a] The reaction was performed for 42 h.

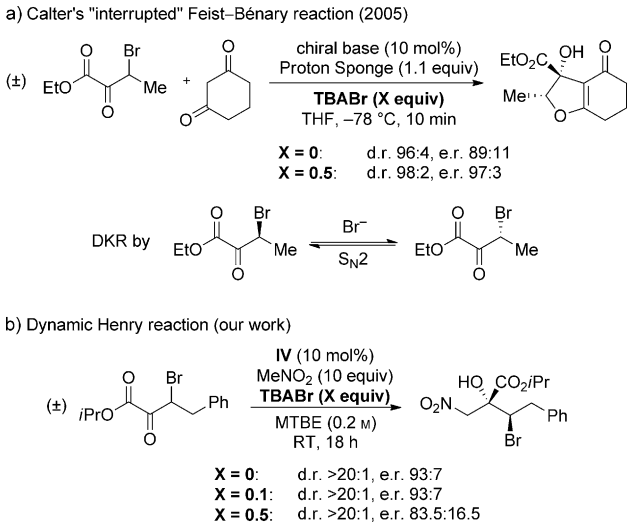
tion of the crude reaction mixtures through a plug of silica gel; no aqueous workup is required.

To better understand the mechanistic nuances of the DyKAT, we sought to elucidate the racemization pathway of this reaction. During the development of an "interrupted" Feist–Bénary reaction, Calter and co-workers proposed that the reaction of 1,3-diketones with β-bromo-α-ketoesters proceeds by DKR, in which the S_N2 halide displacement is promoted by TBABr or TBAI (Scheme 4a).[7] Since our reactions do not generate stoichiometric bromide and the addition of TBABr provided no improvement (Scheme 4b), we examined the nature of our dynamic system by studying the Henry reaction as a representative system.

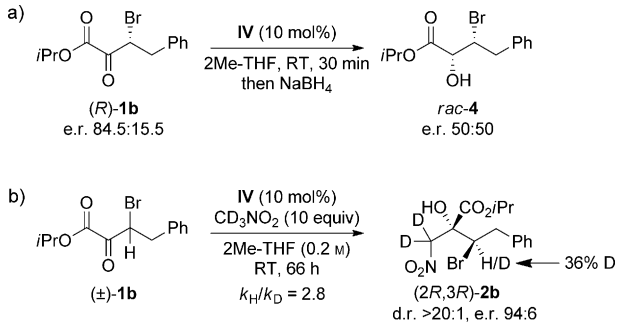
We began our studies by monitoring the enantiomeric compositions of both starting material and product during the course of the reaction of (*R*)-**1b**.[14] Although substrate racemization is obligatory for successful dynamic kinetic resolutions and certain DyKAT subtypes, this assay is seldom performed.[2e,15] This experiment confirmed that the product, (2*R*,3*R*)-**2b**, is obtained with uniform selectivity and that starting material remains racemic throughout the entire course of the reaction. Notably, (*R*)-**1b** was racemized in less than 30 min to (±)-**1b** in the presence of **IV**, thus highlighting the configurational lability of β-bromo-α-ketoesters under general base catalysis (Scheme 5a). When the catalyzed Henry addition was conducted with CD_3NO_2, a primary kinetic isotope effect ($k_H/k_D = 2.8$) and only 36% D incorporation at the β-position were observed (Scheme 5b).[16] These data suggest that racemization is at least partially an intimate ion process with protonation from the ammonium salt (protonated catalyst) rather than nitromethane, and generation of the reactive nitronate species contributes to the overall reaction rate. In situ monitoring of the



Scheme 3. Access to both enantiomeric series.



Scheme 4. Dynamic kinetic resolution through S_N2 halide displacement.

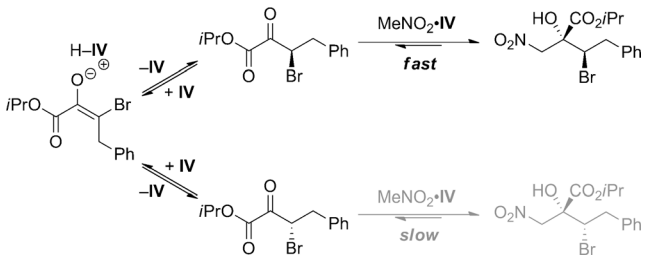


Scheme 5. Racemization and deuterium-labeling studies.

reaction by No-D ^{1}H NMR spectroscopy[17] in 2-MeTHF revealed no intermediates, thus confirming that the catalyst resting state is the neutral amine and corroborating the hypothesis that nitronate formation is an uphill process.

Since the racemization of **1b** is catalyst-mediated via a chiral onium enolate, the Henry addition proceeds through a DyKAT.[1c] The moderate deuterium incorporation excludes a DyKAT type II mechanism wherein the chiral onium enolate would directly participate in an ene-type reaction with *aci*-nitromethane.[18] Calter and co-workers employed a pyrimidinyl-bridged bisquinidine catalyst in their "interrupted" Feist–Bénary reaction to overcome poor selectivities observed with quinidine itself, thus suggesting that both chiral amines may be involved in the enantiodetermining step. Nonlinear effects have been studied only sparingly with cinchona-derived catalysts.[19] To elucidate whether a nonlinear effect was observed in our Henry reaction, we employed a mixture of the pseudoenantiomeric catalysts **IV** and **V**. The Henry reaction was found to exhibit a linear relationship between the diastereomeric composition of the catalyst and the reaction enantioselectivity ($R^2 = 0.997$), thus eliminating the possibility that a dimeric catalyst species operated by concomitant activation of electrophile and nucleophile (Figure 1). On the basis of these collective data, we propose that the reaction proceeds through a DyKAT type I manifold (Scheme 6).[20]

In conclusion, dynamic kinetic asymmetric transformations of β-bromo-α-ketoesters have been developed on the basis of the direct aldolization of nitromethane and acetone. The fully substituted β-bromo-α-glycolic acid derivatives were obtained with high levels of diastereo- and enantioselectivity in near-quantitative yield. The operationally simple protocols offer rapid generation of molecular complexity



Scheme 6. Proposed DyKAT mechanism.

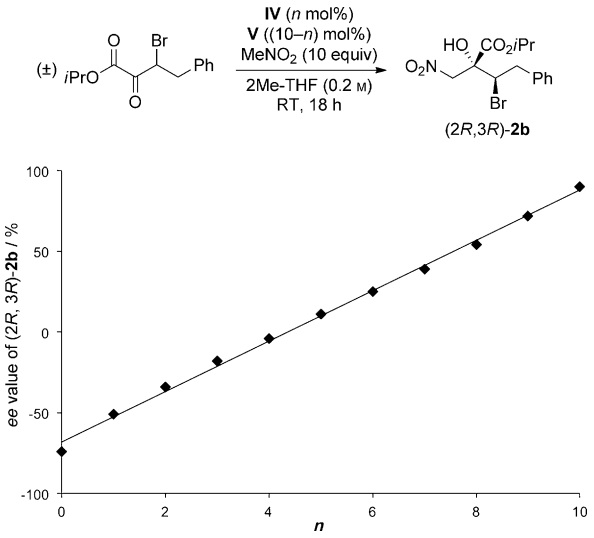


Figure 1. Evaluation of nonlinear effects in catalyzed Henry reactions.

through the formation of vicinal stereocenters in a single C–C bond-forming event. Mechanistic studies provided evidence for a DyKAT type I manifold in the Henry addition of nitromethane to β-bromo-α-ketoesters. Extensions of these transformations and the discovery of new dynamic reaction manifolds for α-labile carbonyl substrates are of ongoing interest in our research group.

Experimental Section

Henry aldol reaction: A 1 dram vial (1 dram = 3.697 mL) equipped with a magnetic stir bar was charged with β-bromo-α-ketoester **1b** (59.8 mg, 0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 μL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Catalyst **IV** (8.6 mg, 0.02 mmol, 0.1 equiv) was added, the vial was capped, and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then filtered through a 2 cm pad of SiO_2, washed through with Et_2O (5 × 2 mL), and concentrated in vacuo to afford analytically pure **2b** (69.9 mg, 97 % yield, d.r. > 20:1) as a white solid (m.p.: 113–116 °C).

Acetone aldol reaction: A 1 dram vial (1 dram = 3.697 mL) equipped with a magnetic stir bar was charged with β-bromo-α-ketoester **1b** (59.8 mg, 0.20 mmol, 1.0 equiv) in acetone (1.0 mL, 0.2 M). Catalyst **E** (5.9 mg, 0.02 mmol, 0.1 equiv) and PNBA (6.7 mg, 0.04 mmol, 0.2 equiv) were added, the vial was capped, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then filtered through a 2 cm pad of SiO_2, washed through with Et_2O (5 × 2 mL), and concentrated in vacuo to afford analytically pure **3b** (67.9 mg, 95 % yield, d.r. > 20:1) as a white solid (m.p.: 103–105 °C).

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[20] A reviewer pointed out that it might be simpler to classify these reactions as dynamic kinetic resolutions. Admittedly, the differences in the present case are subtle. According to the Steinreiber definition (reference [1c]), DyKAT reactions take place via interconverting diastereomeric complexes; thus, rate differences might reasonably be expected (or possible) for conversion of the enantiomeric starting materials into the "locally achiral" intermediate. This requirement is often taken to mean that the chiral catalyst that mediates the productive asymmetric transformation also catalyzes substrate racemization, a scenario that is certainly operative in the present case. We presume that diastereomeric precomplexes form between the substrate and the bifunctional catalyst prior to proton transfer, in analogy to soft enolization.

