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A Catalyst-Directed Remote Stereogenic Center Switch During the Site-Selective Aldol Desymmetrization of Cyclohexanone-Based Diketones

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Abstract: Site-selectivity, differentiating members of the same functional group type on one substrate, is an emerging tactic for shortened advanced building block and biomolecule synthesis. Despite its potential, site-selectivity remains less studied and especially so for ketone-based substrates. During this work ketone site-selectivity has been coupled with the chiral amine-catalyzed aldol desymmetrization of 4-keto-substituted cyclohexanones, allowing three stereogenic centers to form in the aldol product while leaving the acyclic ketone unreacted. Unique here, compared to all previous 4-substituted cyclohexanone desymmetrizations, is the first access to synthetically useful quantities of an epimeric (remote stereogenic center) aldol product. To demonstrate the value of these aldol products, we show their elaboration into eight keto-acetonide and one keto-lactone products. All compounds were isolated as single diastereomers and in high *ee* (≥96%). These efforts represent the first full characterization of aldol products with type III, Figure 2, relative stereochemistry, regardless of the enantiomer formed.

Keywords: aldols; desymmetrization; diketones; epimer switch; organocatalysis; site-selectivity

Ketone transformations are common, reliable, and represented by a large variety of reactions.[1] Nevertheless, the use of prochiral diketones for enantioselective synthesis is limited due to the difficulty of differentiating: (i) non-equivalent ketone carbonyl moieties, a topic of site-selectivity,[2,3a,c,e,4] or (ii) equivalent ketone carbonyl units, a topic of desymmetrization (Figure 1).[3a,b,d] Among diketone substrates, 1,2- and 1,3-diketones possess electronically interconnected carbonyl moieties making them susceptible to intra-

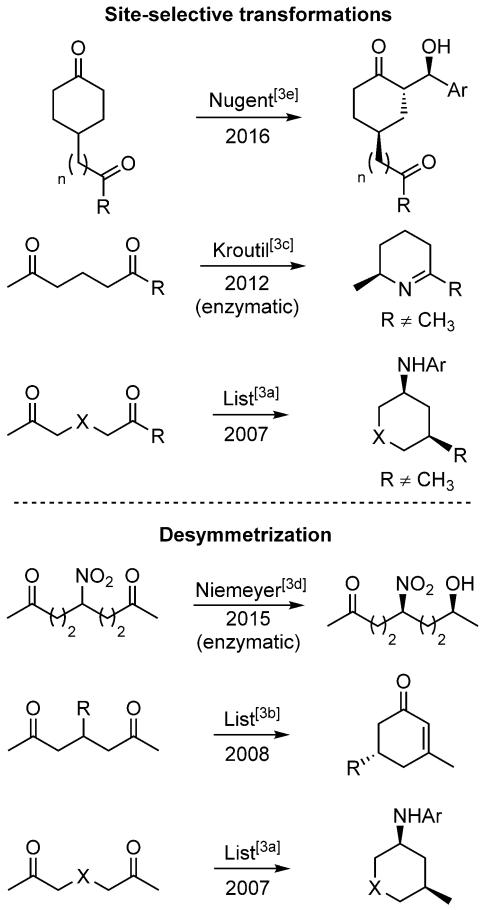


Figure 1. Prior examples of highly enantioselective diketone differentiation.[3]

molecular hydrogen bonding (enol-ketone), metal chelation control opportunities, and so forth. By contrast, 1,4- and higher diketones would generally lack these attributes, represent good prototypes for examining ketone carbonyl differentiation, and are the focus of this manuscript. From these diketones, we are aware of only five studies[3,4] that demonstrate highly enantioselective reactions while concomitantly illustrating site-selectivity or desymmetrization (Figure 1).[5,6]

The examples in Figure 1 show selective methyl ketone reactivity in the presence of internal acyclic ketones, and the enamine-based catalysis achievements therein may reflect Barbas' 2001 observation that 2-butanone has good reactivity under (*S*)-proline catalysis while an internal ketone, e.g., 3-pentanone, displayed a complete lack of reactivity.[7] In an effort to expand beyond methyl ketone site-selectivity, we recently demonstrated that cyclohexanone carbonyls can be reacted over methyl ketone carbonyl moieties in 4-keto-substituted cyclohexanones (Figure 1, Nugent, R = Me, n = 2).[3e] In doing so, we demonstrated the first examples in which a non-hindered methyl ketone remains unreacted. Here we detail an extension of that study in which an alternative amine catalyst, picolylamine (PicAm) **1** (Figure 2, left panel),[8] is used to form the first realistic quantities of a non-accessible epimeric aldol product (Figure 2, middle panel, type **III**).

All enantioselective transformations of mono-4-substituted cyclohexanones must concomitantly entail a desymmetrization (Figure 2, middle panel), and in 2007 Gong disclosed a highly selective aldol variant.[9] It used an efficient prolinamide catalyst **2** (Figure 2), and fifty-eight organocatalyst-based publications have followed in which the products, typically from 4-methyl,[10] 4-*tert*-butyl,[10b,d,11] or 4-phenylcyclohexanone[9,10b,11b,12] starting materials, have been benchmarked against each other under the use of alternative catalysts and reaction conditions. As such, our recent investigation of 4-keto-substituted cyclohexanone substrates **5**–**8** (Figure 2, right panel), under TBDPSO-4-hydroxyproline (**3**) catalysis (Figure 2, left panel),[3e] was unique because it was the first to show that diketones, based on 4-substituted cyclohexanones, can be site-selectively desymmetrized, but the product stereochemistry followed the same well-defined relative and absolute stereochemistry as noted for all previous aldol desymmetrizations of 4-substituted cyclohexanones.[9] Common to all prior studies, two dominant stereochemical outcomes were always noted as the relative stereochemistries of type **I** (major, often greater than 80% yield) and **II** (minor) aldol products,[13] see Figure 2 (middle panel). A small subset of the fifty eight publications describe and quantify other stereochemical outcomes as minor products, see aldol products **III** and **IV** of Figure 2.[10b,12b,14] From those studies, two reveal >5% yield for aldol products of type **III**,[14b,c] and the study by Plusquellec is the only one to indicate the formation of a type **IV** aldol product (8% yield).[14c] Specifically, in 2011 Córdova noted one example in which a 3:1 ratio of aldol **I** (68% yield) to aldol **III** (23%) products were found when examining the desymmetrization of 4-methylcyclohexanone (10 equiv.) with 4-nitrobenzaldehyde under 10 mol% TBSO-threonine catalysis (Figure 2, catalyst **4**).[14b] One year later, Plusquellec noted that 4-methylcyclohexanone (5 equiv.) could be desymmetrized with 3-nitrobenzaldehyde under 2 mol% (*R*)-3-pyrrolidinol (not shown) catalysis in a 1.0 M aqueous solution of a sugar derivative. During the Plusquellec study, the greatest aldol type **III** yield was 22%, while the type **IV** aldol product was noted, for the first time, in 8% yield. Unfortunately, both of those products were racemic.[15] Perhaps unsurprisingly, the low yields of these compounds precluded their isolation in pure form by Córdova or Plusquellec. As such, no aldol products of type **III** or **IV**, or analogs thereof, have ever been fully characterized.

In summary, regardless of the R substituent on a mono-4-substituted cyclohexanone (Figure 2, middle panel), their desymmetrization only infrequently provides aldol products **III** or **IV**, and then only in minor quantities. Furthermore, only when 4-methylcyclohex-

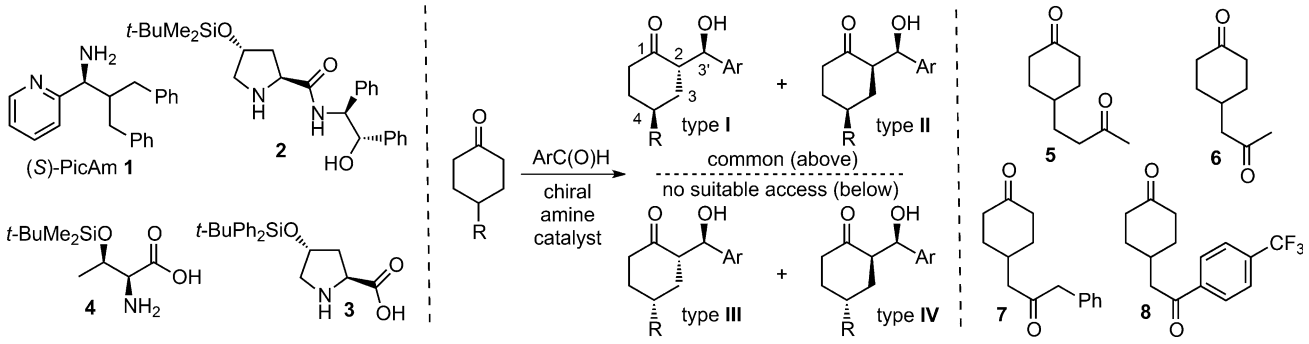


Figure 2. Left to right panels: catalysts (**1**–**4**), generic relative stereochemical outcomes for 4-substituted cyclohexanone desymmetrization (types **I**–**IV**), and diketones examined during this study (**5**–**8**).

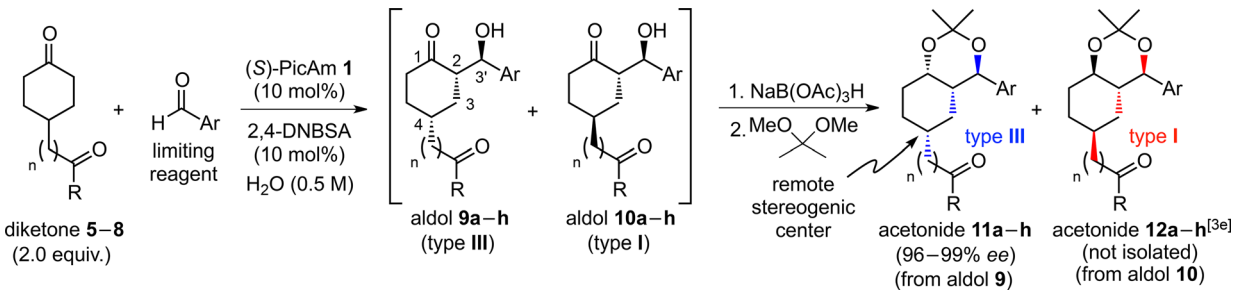
anone was used, were yields of up to 23% for aldol product **III** observed. There are no current examples with larger substituents, located at the 4-position, that provide >5% yield of type **III** relative stereochemistry products. In particular, we stress here that gaining access to these remote stereogeneric center epimeric products (**III** or **IV**) would be laboriously inefficient *via* (i) any other synthetic approach; (ii) post modification of aldol products **I** or **II**; or (iii) the application of an enantiomeric catalyst coupled with post modification.[16] With this communication, we change that dynamic by showing that useful, albeit modest, yields of pure type **III** relative stereochemistry compounds can now be accessed.

With that perspective, we begin our discussion by noting that picolyl amine (PicAm) catalyst **1** provides nearly equal quantities of two major aldol products, **9** and **10**, in combined yields of approximately 90% (^{1}H NMR analysis) during the enantioselective desymmetrization of diketones **5**–**8** (Scheme 1).[17] Aldol products **10a**–**h** contain the relative stereochemistry as found in all previous studies, that is, type **I**, and have been previously synthesized.[3e] They are consequently not a focus of this manuscript and are not further discussed. On the other hand, structures **9a**–**h** possess the difficult to access type **III** aldol stereochemistry and were readily isolated and characterized, albeit as their corresponding keto-acetonide (**11a**–**h**) and keto-lactone (**12**) products and are shortly discussed (Table 1). The PicAm **1** catalyst consequently permits an epimer switch, albeit non-selective, at the remote stereogenic center of the aldol product (Scheme 1).

Cyclohexanone-based aldol products, like aldol **9** and **10**, often undergo non-selective epimerization at their α-carbon (Scheme 1, carbon 2) upon exposure to silica gel.[18,19] Adding to this challenge, a majority of our *anti* and *syn* aldol products had very similar R_f values (TLC). As such, we found it practical to lock in the aldol stereochemical information by simply using the worked-up, crude, aldol products for our next reactions. In this manner, we showed that the aldol products can be elaborated into useful keto-acetonide building blocks as single diastereomers and in high *ee* (Table 1).[20]

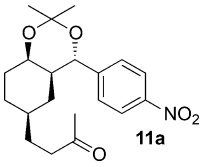
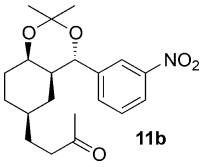
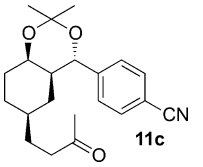
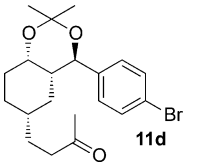
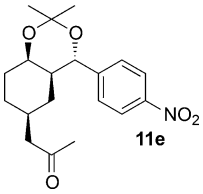
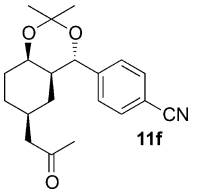
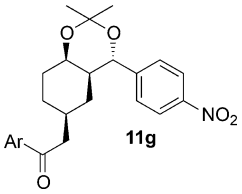
To gain access to the keto-acetonide products,[21] we took advantage of the well-known fact that β-hydroxy ketones are selectively reduced over simple ketones when employing $NaB(OAc)_3H$.[22] The stereochemical outcome of these type of reductions has been discussed elsewhere,[22] but it should be noted that carbonyl hydride delivery occurred, predominately, from the opposite face of the cyclohexanone ring for **9** versus **10**. The resultant keto-1,3-diols (not shown), were chromatographically unobtainable as pure diastereomers using EtOAc/petrol ether eluent systems, nonetheless, collection of the major diastereomer in mediocre diastereomeric and chemical purity, 85–90% after chromatography, did allow their conversion to keto-acetonides when treated with 2,2-dimethoxypropane (20–30 equiv.) under the mildly acidic conditions of catalytic pyridinium *p*-toluenesulfonate (5.0 to 7.5 mol%) in CH_2Cl_2.[23] The keto-acetonides attracted our attention because these structures always permitted chromatographic isolation of a single diastereomer that could be fully characterized.

As shown in Table 1, an array of 4-ketosubstituted cyclohexanone-based diketones (2.0 equiv.) reacted with a handful of aromatic aldehydes (1.0 equiv.) in the presence of 10 mol% of either (*R*)- or (*S*)-PicAm **1**. Note that most of the keto-acetonide products were synthesized with (*R*)-PicAm **1**, which produces the same relative stereochemistry as aldol type **III**, albeit for the opposite enantiomeric form. The overall yields, for the three step diketone to keto-acetonide transformations (Scheme 1), ranged from 25–34% (Table 1). At the low end, a 25% overall yield represents, on average, a 63% yield for each of the three reaction steps: aldol, reduction, and keto-acetonide formation. On the high end, a 34% overall yield represents a 70% yield for each reaction step. Placed in the context of no prior access, in pure form, to these highly enantioenriched compounds with four stereogenic centers, the current yields may be considered, if not yet practical, then perhaps as enabling the first speculative applications for natural product or medici-



Scheme 1. Aldol products **9** and **10** are formed in near equal quantities as the major reaction products under PicAm **1** catalysis. Keto-acetonides **11** were isolated and characterized, see Table 1. Note: 2,4-DNBSA = 2,4-dinitrobenzenesulfonic acid.

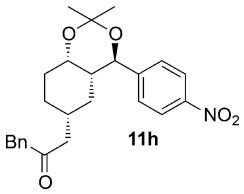
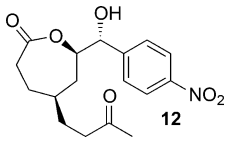
Table 1. Type **III** keto-acetonide and lactone products from (*R*)- or (*S*)-PicAm catalysis.[a]

Entry	Keto-acetonides (**11**)	Aldol product data[a]				Keto-acetonide product data	
		Reaction Time [h]	Conversion (^{1}H NMR)[b]	Aldol **9**/**10** (type **III** to **I**)[c,d]	*anti*/*syn* (type **I** & **III** to **II** & **IV**)[c]	Overall yield of **11** (from aldehyde)[e]	*ee*
1	 **11a**	28	96	1.00:1.20	>24:1	28	97
2	 **11b**	40	95	1.00:1.17	>24:1	27	>99
3	 **11c**	30	95	1.00:1.23	>24:1	32	97
4[f]	 **11d**	48	72	1.17:1.00	8:1	25	97
5	 **11e**	25	94	1.00:1.30	>24:1	30	>99
6	 **11f**	40	95	1.00:1.32	>24:1	32	96
7[g]	 **11g**	69	94	1.13:1.00	>24:1	34	96

nal chemistry goals. Of equal or higher significance, a convincing proof of concept for epimeric product formation has been established and opens a path, via catalyst refinement, for more selective epimer switches.

To establish that PicAm **1** can catalyze useful yields of type **III** aldol products, beyond those studied here: **5**–**8**, we additionally investigated the benchmark substrate 4-methylcyclohexanone.[24] Under unchanged reaction conditions a 1.2:1.0 ratio of **9i** (shown) to **10i** (not shown) was noted by crude ^{1}H NMR, and **9i** was isolated after silica gel chromatography in 46% yield (Scheme 2). This yield doubles the best previously reported for **9i**,[14b] and we have fully characterized this compound for the first time (see Section 5, Supporting Information). This result firmly establishes that

Table 1. (Continued)

Entry	Keto-acetonides (**11**)	Aldol product data[a]				Keto-acetonide product data	
		Reaction Time [h]	Conversion (^{1}H NMR)[b]	Aldol **9**/**10** (type **III** to **I**)[c,d]	*anti*/*syn* (type **I** & **III** to **II** & **IV**)[c]	Overall yield of **11** (from aldehyde)[e]	*ee*
8[f]	 **11h**	33	94	1.22:1.00	9:1	30	98
9[h]	 **12**	28	96	1.00:1.20	>24:1	31	98

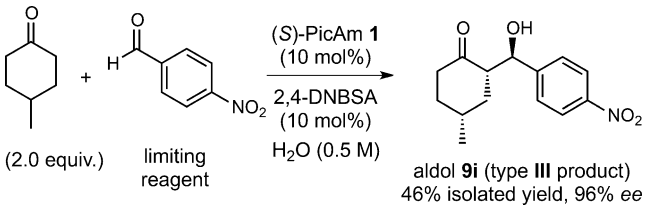
[a] The aldol reactions were performed with (*R*)-PicAm **1**, entries 4 and 8 used (*S*)-PicAm **1**. For reaction details, see Scheme 1 and the Supporting Information.
[b] Reaction aliquot (^{1}H NMR), integration of aldehydic (limiting reagent) resonance *versus* the combined integration for the benzylic resonances of all *anti*- and *syn*-aldol products.
[c] See Figure 2 for relative stereochemistry. Crude ^{1}H NMR data: ratio of the two major 2,3′-*anti* products **9** and **10**.
[d] Section 4 of the Supporting Information is dedicated to verifying the **9**/**10** ratios (^{1}H NMR expansions).
[e] The yield is the overall yield from three reaction steps: aldol, reduction, and keto-acetonide formation. Mmol of pure keto-acetonide product **11** *versus* mmol of the aldol limiting reagent (aldehyde) × 100%.
[f] (*S*)-PicAm **1** catalyzed the aldol reaction for this keto-acetonide. Note that the (*S*)-PicAm **1** catalyst provides the same enantiomer of **10**, a type **I** aldol product, as when the (2*S*,4*R*)-TBDPSO-4-hydroxyproline catalyst (Figure 2, catalyst **3**) is used.[3e]
[g] Ar equals *p*-trifluoromethylphenyl.
[h] Lactone formation occurred after treatment of aldol product **9a** with *m*CPBA (5.0 equiv.) in CH_2Cl_2, see Section 3 of the Supporting Information.

the noted epimer switch is a general phenomenon for 4-substituted cyclohexanones.

Finally, the syntheses of the diketone starting materials (**5**–**8**) are straight forward and proceed in good overall yields. We note that diketones **5** and **6** are synthesized after two reaction steps from commercially available phenols.[25]

As discussed earlier, aldol products of type **III** have been previously reported, but we know of no evidence that establishes their relative or absolute stereochemistry. We now rigorously address this point.

We were thwarted from a stereochemical assignment *via* X-ray analysis after several keto-acetonides



Scheme 2. Benchmark substrate (4-methylcyclohexanone) examination.

11 failed to form crystalline material. Aldol product **9i** is a solid but in our hands X-ray suitable crystals could not be formed. A stepwise approach was then taken to first confirm the relative stereochemistry by extensive NMR experiments (see the Supporting Information, Sections 6 and 7) and then establishing the absolute stereochemistry based on circular dichroism studies (see the Supporting Information, Section 8).

The short tether at the 4-position of keto-acetonide **11e** (Table 1, entry 5), in combination with the conformational rigidity imposed by the interlocked cyclohexane and acetonide rings of these compounds, made it a good candidate for determination of its relative stereochemistry *via* NMR measurements. To do so, first the proton and the carbon chemical shifts were assigned to the corresponding atom numbers of **11e** with the aid of the correlations in the COSY and the HSQC and by taking the measured shift values into account (see the Supporting Information, Sections 6 and 7). The two-dimensional structure of **11e** was then confirmed by analysis of the HMBC correlations. The relative stereochemistry of **11e** was elaborated by analysis of the $J_{H,H}$ coupling constants in the ^{1}H NMR and the COSY spectra and analysis of the

NOE correlations obtained from the NOESY experiment (see the Supporting Information, Section 5). The protons at carbons C-2 to C-7 of the cyclohexane ring show coupling constants typical of a chair conformation (Figure 3), since the protons are either axially

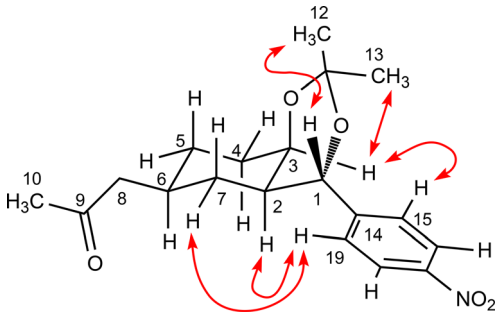


Figure 3. Selected NOE correlations and numbering of **11e**.

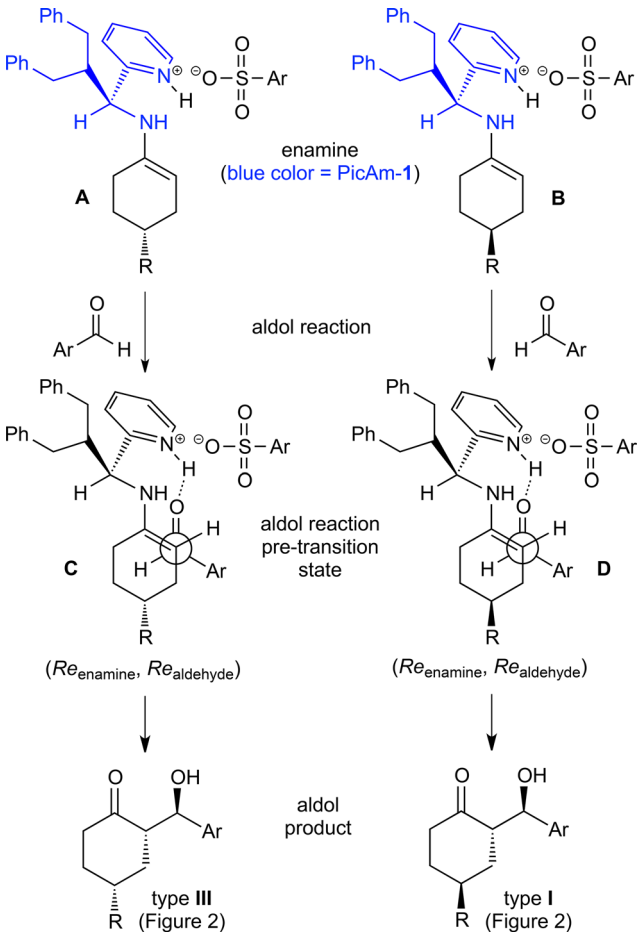
or equatorially oriented on account of their coupling constants. Proton H-1 couples to the axial proton H-2 with a coupling constant of $^{3}J_{H,H} = 6.2$ Hz, indicating that these protons are *gauche* oriented to each other. A characteristic NOE from H-1 to the methyl protons at C-12 and the absence of an NOE between H-1 and H-3 show that H-1 is not oriented in the same direction as H-3. Since there are key correlations between the protons H-15/19 of the aromatic ring and H-3_{eq}, H-2_{ax} and H-7_{eq} the six-membered ring containing the acetal moiety is most likely present in a boat like conformation and the aromatic ring is oriented as shown in Figure 3. This assignment is further supported by a key NOE correlation between the proton H-3_{eq} and those of the methyl group at C-13. Finally, the relative stereochemistry at C-6 is confirmed by the coupling pattern of H-6 which shows it to be axial.

The absolute stereochemistry was established by two different approaches. First, we generated the theoretical circular dichroism spectrum for the enantiomer represented by keto-acetonide **11e**. This was compared to the experimentally obtained circular dichroism spectrum, in *n*-pentane, and the two were found to be in general agreement regarding their absorption shifts, intensity, and positive or negative attributes about the x-axis, which displayed characteristic Cotton effects. This result supports the indicated absolute stereochemistry as shown in Figure 3 and Table 1 (entry 5). Section 8 of the Supporting Information is dedicated to a description of the CD study and the conclusions drawn here. In that section we also show the theoretical CD spectrums of related diastereomers so a comprehensive overview can be made.

The second piece of supportive evidence for this absolute stereochemistry is that (*S*)-PicAm **1** has been previously used to catalyze the reaction of cyclohexanone and 4-nitrobenzaldehyde. The aldol product thereof was unequivocally established as having the relative and absolute stereochemistry of *ent*-**11e**, albeit without the 4-substitutent and its associated remote stereogenic center.[19] During this current work, **11e** was formed with (*R*)-PicAm, thus the C-1 and C-2 stereogenic centers of the initial aldol products **9e** and **10e** should be *anti* and have the same stereogenicity as depicted for **11e** in Figure 3.

With the type **III** aldol product structure established, the next question was why PicAm-**1** catalyzes a significant increase in their formation. Scheme 3 depicts the expected enamine and aldol transition states that would provide the type **I** and **III** aldol products. Because aldol products **9** and **10** are formed in essentially equal quantities (Table 1), it seems logical that transition states **C** and **D** must be very similar in energy. Why this is true for PicAm-**1**, while proline-based catalysts overwhelmingly favor the corresponding transition states that would mimic **D** over **C**, is clearly the focus of a future computational study.

In conclusion, we have expanded the functional group diversity of these aldol products by demonstrating that 4-substituted, keto-carbonyl containing, cyclo-



Scheme 3. Possible transition states for type **I** and **III** aldol products from 4-substituted cyclohexanones.

hexanones (**5**–**8**) can be used as starting materials. Furthermore, we have shown that a non-selective epimer switch occurs and provides the first reasonable access to either enantiomeric form of a new relative stereochemistry for these aldol products. Their conversion to the corresponding acetonide (four stereogenic centers) and lactone (three stereogenic centers) products represents the first realistic starting point for their planned use in target-based synthesis. Furthermore, no other approaches, e.g., transition metal-mediated or enzyme-based, can currently surpass the organocatalyzed reaction results regardless of the desired stereochemical outcome (type **I**-**IV**).

Finally from a catalysis perspective, we have taken an obscure chemical observation, low yields of type **III** aldol product formation,[14b,c] to a level where it can now be imagined that a selective epimer switch, at the remote stereogenic center of these aldol products, is within reach *via* rational catalyst design. This is significant because there are no known step efficient replacements for the formation of these epimeric products.

Experimental Section

Experimental Details

Altogether112 pages of detailed Supporting Information are associated with this manuscript.

General Procedure for Aldol Products (9 and 10)

To a dry 2.0-mL screw-cap reaction vial were added diketone (1.0 mmol, 2.0 equiv.), aldehyde (0.5 mmol, 1.0 equiv.) and (*S*)- or (*R*)-PicAm **1** as a 2,4-dinitrobenzenesulfonic acid 1:1 salt (MW = 550.58 g mol^{-1}, 0.05 mmol, 10.0 mol%, 27.5 mg). After stirring for 5 min distilled water (0.50 mL) was added. This reaction mixture was then stirred and heated at 45 °C until a starting material conversion of ≥95% was noted unless otherwise stated. Reaction progress was monitored by aliquots (^{1}H NMR). Reaction conversion was determined by integrating the aldehydic resonance (singlet, ≈10.0 ppm) *versus* the combined integration of the benzylic proton resonance (doublets, both found between 4.50–5.50 ppm) of the *syn*- and *anti*-aldol products. Reaction times ranged from 25–69 h, see the individual descriptions for the specific reaction time.

Note: Extending the reaction time often results in decreased diastereoselectivity through α-keto epimerization.

Reaction work-up: The reaction mixture was transferred to a separatory funnel containing distilled water (25–35 mL) by excessive extractive addition of CH_2Cl_2 (9 × 1.5 mL) to the reaction vessel. After this initial extraction from water, the water was further extracted with CH_2Cl_2 (6 × 20 mL). Combined organic extract was dried (Na_2SO_4), filtered and concentrated (rotary evaporator bath temperature should not exceed 28 °C to minimize the risk of α-keto epimerization). The crude aldol product was then exposed to high vacuum drying and after 2–3 h the *dr*, *anti*/*syn* ratio (^{1}H NMR), was recorded. The aldol product was used in the next reaction step without further purification.

Note: Exposure to silica gel chromatography often results in reduced diastereoselectivity and aldol product yield and is discouraged.

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[15] See Table 3, entry 4 of ref.[14c]
[16] Related to this discussion, selective conversion of an *anti*-aldol product of type **I** to the corresponding *syn*-aldol product **II**, or *vice versa* has, to the best of our knowledge, never been demonstrated. See ref.[13] for further information.
[17] The remaining product balance in these aldol reactions is aldol products **II**, and **IV**, generally in a combined yield of $\leq$5% with approximately the another $\leq$5% of the limiting reagent remaining (the aldehyde).
[18] It is more often than not that cyclohexanone-based aldol products undergo partial, but non-selective epimerization, upon exposure to silica gel. See page 4 within the Supporting Information of ref.[19]
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[20] Only one lactone product is noted here (Table 1, entry 9). In fact we synthesized four more lactone products, but their isolation in greater than 90% chemical purity was not possible in our hands. We abandoned the further pursuit of these lactones because of these problems. We speculate that the ring opened forms may allow this problem to be circumvented, see ref.[3e] for an example during an Alzheimer drug candidate synthesis.
[21] Note that *ortho*-substituted aromatic aldehydes, for example, *o*-nitrobenzaldehyde, smoothly formed the corresponding aldol products, but those aldol products resisted reduction under our standard conditions with $NaB(OAc)_3H$.
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[24] Since Gong's 2007 disclosure of enantioselective organocatalytic aldol desymmetrization of mono-4-substituted cyclohexanone substrates, fifty-eight manuscripts based on the same subject have been published. From those, forty-eight describe the aldol desymmetrization of 4-methylcyclohexanone, making it the benchmark substrate.
[25] See the Supporting Information of ref.[3e]

A Catalyst-Directed Remote Stereogenic Center Switch During the Site-Selective Aldol Desymmetrization of Cyclohexanone-Based Diketones

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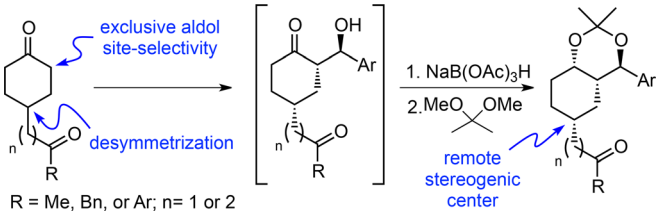

9