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Synthesis of Optically Active 4-Substituted 2-Cyclohexenones

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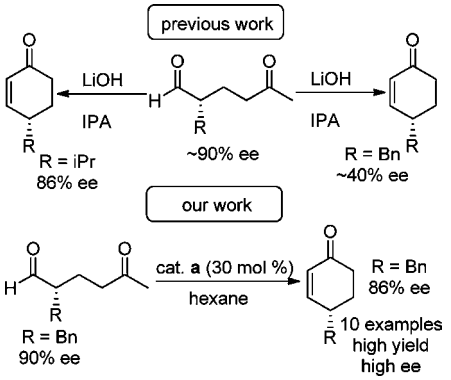
ABSTRACT



Recently, Nicolaou and Baran independently synthesized optically active 4-substituted 2-cyclohexenones via an efficient LiOH-mediated intramolecular aldol condensation. Thus far, application of their cyclization approach has been limited to ketoaldehydes where the R-group is branched. It is demonstrated that the LiOH-mediated cyclization, when applied to substrates containing unbranched R-groups, results in significant erosion of optical purity. A mechanistic justification is provided, and a set of neutral, organocatalyzed conditions is identified that enables cyclization with little loss in optical purity.

Optically active 4-substituted-2-cyclohexenones are both natural products and intermediates for the synthesis of complex molecules. An example is (*R*)-cryptone, an essential oil of *Eucalyptus cneorifolia*, that is used as a starting material for the synthesis of dihydrojunenol, faurinone, β-cadinene, and other natural products.[1,2]

Asymmetric routes into 4-substituted 2-cyclohexenones including cryptone have been relatively limited considering their wide use, although notable examples do exist.[3] For example, Koga et al. used optically active bases to deprotonate prochiral cyclohexanones followed by isomerization of the silyl enol ether to provide optically active cyclohexenones.[4] Later, Fuchs et al. introduced a multistep process starting with enantiopure epoxyvinyl sulfones[5] and Eloi et al. recently reported an approach using stoichiometric

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(1) For cryptone in synthesis: (a) Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738. (b) Findley, T.; Sucunza, D.; Miller, L.; Davies, D.; Procter, D. *Chem.—Eur. J.* **2008**, *14*, 6862. (c) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Ferreira, V.; Michelotti, E.; Porter, B.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 890. (d) Becker, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1654. (e) Ley, S. V.; Dixon, D. J.; Rodríguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2005**, *3*, 4095. (f) Mori, K. *Tetrahedron: Asymmetry* **2006**, *17*, 2133.

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(3) (a) Elliot, M. L.; Urban, F. J. *J. Org. Chem.* **1985**, *50*, 1752. (b) Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett.* **2005**, *7*, 4185. (c) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, H.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. (d) Rawal, V. H.; Kozmin, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 9562. (e) Asaoka, M.; Aida, T.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1989**, *30*, 7075.

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(5) Evarts, J.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 11093.

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chiral manganese complexes.[6] Despite these outstanding approaches, a simple catalytic method leading to 4-substituted cyclohexenones remains elusive. An excellent step forward was recently reported by both Baran and Nicolaou's groups. Nicolaou en route to *ent*-7-epizingiberene and Baran en route to dihydrojunenol used Robinson annulations employing an asymmetric Michael addition followed by a base-mediated ring closure (Figure 1).[7]

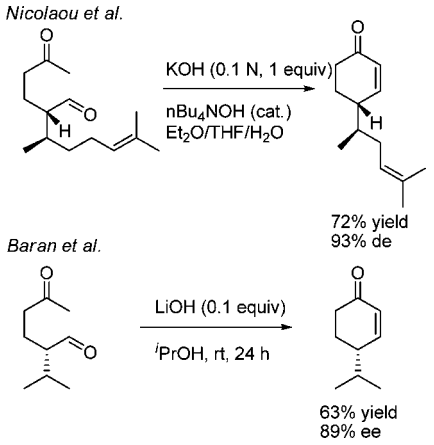


Figure 1. Baran's and Nicolaou's basic conditions for Robinson annulations.

In both cases, the asymmetric Michael addition was performed using an organocatalyst modeled after the pioneering work of Barbas et al. and other groups.[8] As shown in Figure 1, both Nicolaou and Baran's substrates featured β-branched substituents proximal to the chiral center. We wondered whether these conditions would function for unbranched substrates, as many optically active aldehydes are racemized under basic conditions.

We tested our curiosity by first preparing **1a** using Gellman's catalyst combined with methyl vinyl ketone and 3-phenylpropanal.[8f] The desired ketoaldehyde **1a** resulted in an 80% yield with 90% *ee*. Cyclization of **1a** under Baran's conditions provided cyclohexenone **2a** (Figure 2). We observed a steep initial decrease in optical purity concomitant with formation of product, but once the reaction is complete, the optical purity stays constant (Figure 2). We speculated that loss of optical purity was most likely to occur via two pathways as described in Scheme 1.

The first pathway is the reversible enolization of aldehyde (Scheme 1; $K_{eq\ 1} \geq K_{eq\ 2}$), leading to the loss of the

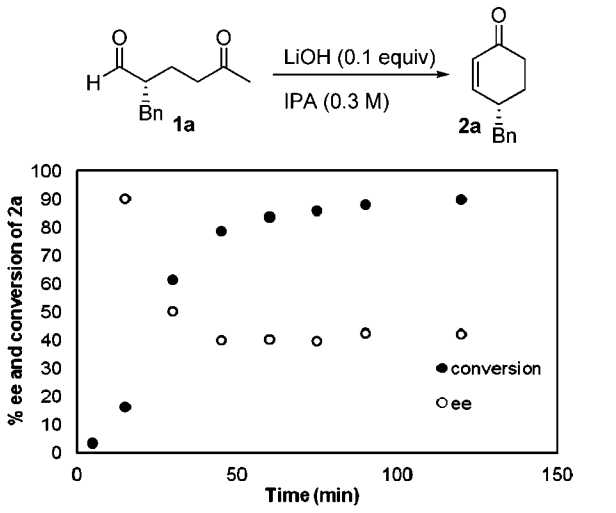
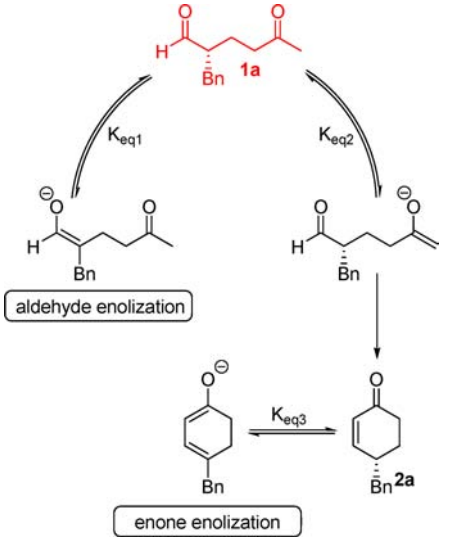


Figure 2. Plot of percent conversion and enantiomeric excess as a function of time for the base catalyzed aldol condensation of substrate **1a**.

stereoselectivity of the chiral ketoaldehyde *before undergoing the cyclization step*. The second possible pathway is the racemization of the product via conjugate enolization of the enone. Here the rate of epimerization of the aldehyde α-hydrogen is slow compared to the methyl hydrogen ($K_{eq\ 1} \ll K_{eq\ 2}$), but the chiral cyclohexenone produced undergoes an epimerization step at a faster or equal rate ($K_{eq\ 3} \geq K_{eq\ 2}$).

Scheme 1. Possible Epimerization Routes Leading to the Loss of Enantioselectivity



Based on the data presented in Figure 2, we predicted that the aldehyde enolization was the dominant origin, as optical purity stabilizes once the reaction is complete. To support our model further, we synthesized **2a** (83% *ee*) and

(7) (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (b) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4708. (c) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I.-H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6069.

(8) (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527. (c) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedon Lett.* **2001**, *42*, 4441. (d) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509. (f) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.

subjected the material to the LiOH reaction conditions of Baran (Figure 3). If the aldehyde enolization step is the main source of optical purity erosion, we expect to see little change in optical purity. We observe that the optical purity remains nearly constant over the 2 h period that we monitored, indicating that racemization of the product is too slow to explain the loss of optical purity.

Based on these observations, we further hypothesized that **1a** must exhibit rapid loss of optical purity for our model to be valid. We measured the *ee* of substrate **1a** while the reaction was still at low conversion (20 min into the reaction) (Figure 4) to test our hypothesis.

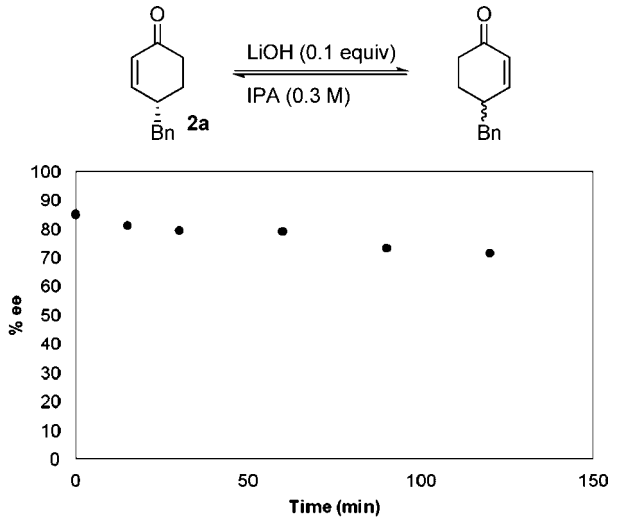


Figure 3. Plot of change in enantioselectivity of **2a** in presence of LiOH/IPA.

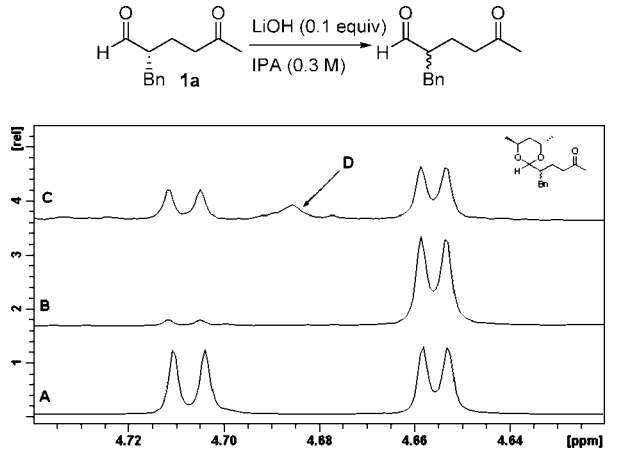
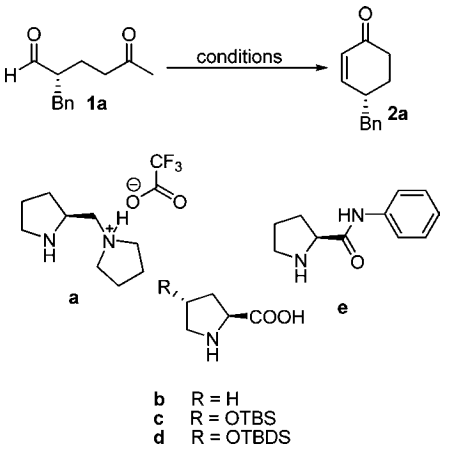


Figure 4. Enantioselectivity of the starting material **1a** as a function of reaction progress. Description of the experiment: enantiomeric excess was found using ^{1}H NMR spectrum of the acetal-protected product. Plot **A** represents the acetal doublets of the two enantiomers of the racemic **1a**. Plot **B** represents the doublets of the two enantiomers of the enantioselective **1a**. Plot **C** represents the doublets of **1a** after 20 min of the reaction with LiOH. **D** is a residue from the crude sample at 20 min, which contains the starting material, product, and the excess diol added together with the pTSA catalyst.

Table 1. Condition Screening for the Model Reaction[a]



entry	cat.	ee sm[b] (%)	yield[c] (%)	ee p[d] (%)	Δ ee
1	a[e]	90	87	87	3
2	a[f]	89	85	83	6
3	b	90	35	85	5
4	c	90	15	83	7
5	d	90	50	70	20
6	e	90	61	88	2

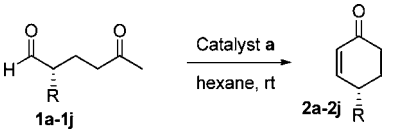
[a] Reaction conditions: **1a**, catalyst (30 mol %), rt, hexane, 2 h. [b] See Supporting Information. [c] Determined using GC analysis. [d] Determined by HPLC analysis using IA chiral column. [e] Reaction time is 1 h. [f] Opposite enantiomer of **1a** is used.

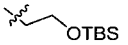
As shown in Figure 4, we observed that the *ee* of **1a** decreases from 89% to 35% in the first 20 min of reaction. This indicates that **1a** epimerizes faster than the rate of cyclization, leading to the loss of enantiopurity ($K_{eq\ 1} > K_{eq\ 2}$). Taking the initial rates of epimerization of **2a** from plots of Figures 2 and 3 into consideration, we conclude that $K_{eq\ 2}$ is 30-fold faster than $K_{eq\ 3}$. For branched substrates such as those used by Baran and Nicolaou, we predict that α-branched aldehydes have significantly slower rates of aldehyde enolization.

With **1a** speculated as an aberrant case, examination of the loss of optical purity on cyclization of **1b** (R = ethyl) confirmed that nonbranched substrates exhibit erosion of optical purity on cyclization. In the case of **1b**→**2b**, we observed a loss of optical purity from 88% *ee* in the starting material to 64% *ee* in the product similar to **1a**→**2a**. This led us to conclude that the base catalyzed conditions provide unsatisfactory results for substituents that do not

(9) For reviews, see: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron Asymmetry* **2007**, *18*, 2249. Other papers with cyclic ketoaldehydes: (c) Hayashi, Y.; Sekizawa, H.; Yamaguchi, J.; Gotoh, H. *J. Org. Chem.* **2007**, *72*, 6493. (d) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7613. (e) Burke, S. D.; Murtiashw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984**, *106*, 4558. (f) Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517.

Table 2. Substrate Scope[a]



entry	R (1a-1j)	ee sm (%)[b]	ee p (%)[c]	yield (%)[d]
1	benzyl	90	86	85
2	ethyl	90	81	95
3	isopropyl	87	83	95
4	methyl	ND[g]	80[e]	82
5		ND[g]	73[f]	70
6	4-chlorobenzyl	82	81	78
7	4-methylbenzyl	90	88	80
8	2-fluorobenzyl	90	88	81
9	2-methylbenzyl	90	84	75
10	2,4-dichlorobenzyl	89	81	72

[a] Reaction conditions: 30 mol % of catalyst **a**, hexane, rt, 1−1.5 h. [b] See Supporting Information. [c] Determined by HPLC analysis using IA column. [d] Isolated yield. [e] Determined by optical rotation. [f] Peaks were not fully separated (see Supporting Information). [g] Peaks of acetals were inseparable.

contain a β-branch. We sought a set of organocatalytic conditions that could fill this method's gap.

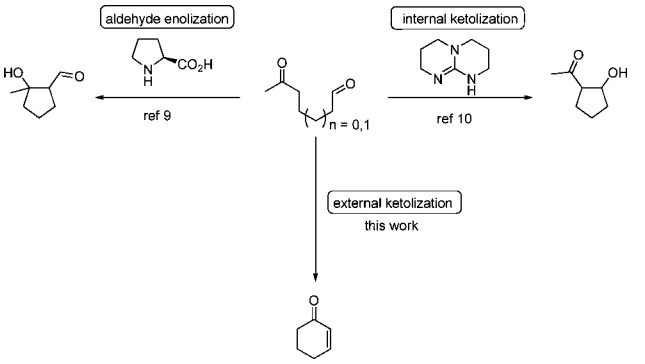
Identifying organocatalytic conditions to promote the desired cyclization is confounded by the observation that aldehyde enolization or internal ketone enolization is faster than enolization of the terminal ketone in most cases (Scheme 2).[9,10] This mechanistic detail might be one reason that asymmetric organocatalyzed 6-enol endo cyclizations where the aldehyde α center is tertiary are yet to be described.[11] We selected a range of pyrrolidine catalysts and screened them for capacity to enolize the ketone in favor of the aldehyde with the goal of producing 4-substituted-2-cyclohexenones without loss of optical purity (Table 1).

From our broader screen (see Supporting Information), it became clear that the acidity of the group pendant to the pyrrolidine was critical. Proline and similar derivatives containing carboxylic acid groups (entries 3 and 4) gave low yields or low *ee* (entry 5) and a poorly acidic amide

(10) (a) Hammar, P.; Ghobril, C.; Antheaume, C.; Wagner, A.; Baati, R.; Himo, F. *J. Org. Chem.* **2010**, *75*, 4728. (b) Ghobril, C.; Sabot, C.; Mioskowski, C.; Baati, R. *Eur. J. Org. Chem.* **2008**, 4104. (c) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785. (d) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656.

(11) (a) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616. (b) Yang, H.; Carter, R. G. *Org. Lett.* **2010**, *12*, 3108.

Scheme 2. Enolization Routes for Acyclic Ketoaldehydes Reported in Literature



(entry 6) afforded increased yields and *ee*, but the best results were obtained using a catalyst containing a pendant group with a pK_a of ~10 (entry 1). We propose that the matched acidity between the pendant group and the pyrrolidine amine is a critical attribute that promotes enolization of the ketone over the aldehyde.

As Table 2 shows, the identified conditions catalyzed cyclization of substrates containing both aromatic and aliphatic R-groups. The most significant loss of optical purity from starting material to product was observed with simple aliphatic and aromatic groups with substitution in the ortho position. Overall, the method appears to be successful with a wide range of substrates.

In conclusion, we have demonstrated that base mediated cyclization of 2-monosubstituted-5-oxohexanals requires branching of the substituent to prevent loss of optical purity. We provided evidence that the aldehyde enolization was responsible for this decrease in optical purity and not epimerization of the product. Using this gap as inspiration, we successfully identified organocatalyzed conditions to accomplish the aldol condensation reaction on unbranched substrates with minimal loss of optical purity. The method is successful on both aliphatic and aromatic substrates, yielding a wide range of 4-substituted 2-cyclohexenones with high yields and *ee*.

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

The authors declare no competing financial interest.