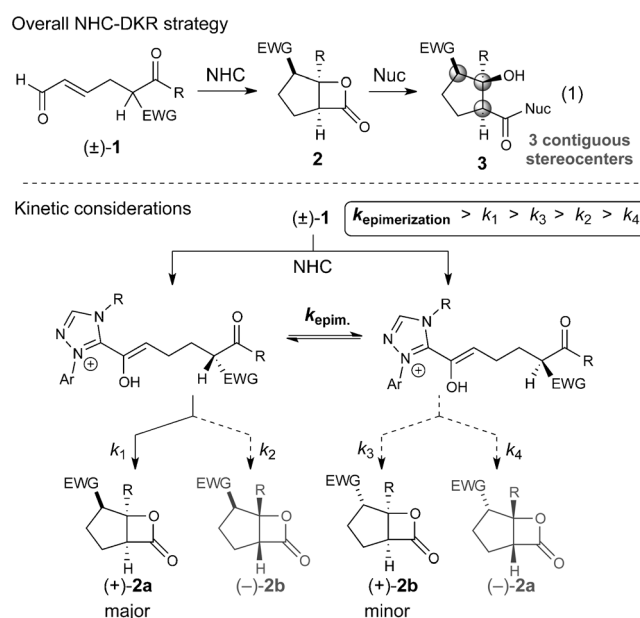


Catalytic Dynamic Kinetic Resolutions with N-Heterocyclic Carbenes: Asymmetric Synthesis of Highly Substituted β -Lactones**

Daniel T. Cohen, Chad C. Eichman, Eric M. Phillips, Emily R. Zarefsky, and Karl A. Scheidt*

The conversion of a racemic substrate to enantioenriched products, commonly referred to as a kinetic resolution, is an established method with broad applications.^[1,2] Due to the intrinsic lack of efficiency with this strategy where the theoretical yield is only 50 %, many creative *dynamic* kinetic resolutions (DKRs) have been developed in which > 99 % yields are possible.^[3] For these processes, the rapid interconversion between each enantiomer of a starting material provides an opportunity for a selective catalyst system^[4] to promote a desired reaction favoring only one enantiomer, assuming the interconversion is faster than the irreversible step. Both transition metal and enzyme-based DKR reactions have seen significant development over the past two decades.^[5] Dynamic kinetic resolutions based on organocatalysis are emerging as powerful and complementary approaches for the conversion of racemic substrates to products with high enantioselectivity. Organocatalytic DKRs have employed a wide variety of activation strategies, including Lewis bases,^[6] hydrogen bond donors,^[7] chiral Brønsted acids,^[8] enamine/iminium ions,^[9] and peptide-based biaryl oxidations.^[10] While N-heterocyclic carbene (NHC) catalysis has been used in very few cases of traditional kinetic resolutions^[11,12] or parallel kinetic resolutions, NHC-DKRs should provide significant new opportunities.^[13] Here, we report a new NHC-DKR with β -keto esters to generate highly substituted β -lactones^[14] with excellent levels of stereoselectivity (Scheme 1). This unique process leverages the basic conditions necessary to generate the NHC catalyst from the azolium salt to promote racemization of the substrates.

For a successful NHC-catalyzed DKR process, the racemic starting material must undergo facile epimerization under basic conditions typical with carbene generation. Given our experience with NHC-catalyzed homoenolate^[15] and enolate reactions^[16] we predicted that a similar approach could be



Scheme 1. NHC-catalyzed dynamic kinetic resolution.

applied to racemic α -substituted β -keto esters (**1**). The potential epimerization of the α -position under the basic reaction conditions could favor only one NHC-enol intermediate that would undergo the aldol/acylation (see below). A significant challenge for this process is controlling the selectivity to favor one of four potential diastereomeric products (Scheme 1). This approach provides access to cyclopentane-fused β -lactones (**2**) or substituted cyclopentanes (**3**) with three contiguous stereogenic centers [Scheme 1, Eq. (1)].

Our investigation began by treating racemic enals with an azolium salt (10 mol %) and a stoichiometric amount of Hünig's base (Table 1). Azolium precursors **A–D** furnished the product β -lactone with moderate diastereoselectivity but with little to no conversion (entries 1–4). Triazolium **E** gave complete conversion of starting material with a 7:1 d.r. and 90 % *ee*, but there was a significant amount of decarboxylation to the corresponding cyclopentene, with a 31 % yield of the isolated product lactone (entry 5).^[17,18] In this NHC-DKR process, the mitigation of the decarboxylation pathway is essential because complete decarboxylation of a 5:1 diastereomeric mixture of (+)-**2a** and (+)-**2b** would provide a cyclopentene product with only a ca. 65 % *ee*.

We explored azolium **F** which we have observed in previous carbene-catalyzed processes to provide high yields and selectivity.^[17e] Gratifyingly, this NHC catalyst afforded a reproducible increase in enantioselectivity (99 % *ee*) with

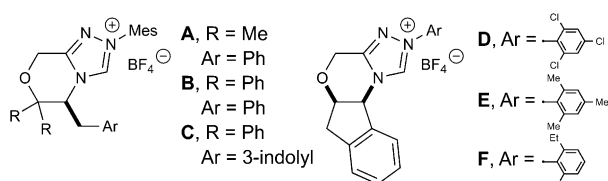
[*] D. T. Cohen, Dr. C. C. Eichman, E. M. Phillips, E. R. Zarefsky, Prof. K. A. Scheidt
Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Chemistry of Life Processes Institute
Northwestern University
2145 Sheridan Road, Evanston, IL 60208 (USA)
E-mail: scheidt@northwestern.edu

[**] Financial support has been generously provided by the NIH (NIGMS RO1-GM073072). D.T.C. thanks the ACS Division of Organic Chemistry for a 2011–12 Graduate Fellowship (sponsored by Organic Syntheses/Organic Reactions). E.M.P. also thanks the ACS Division of Organic Chemistry Graduate fellowship sponsored by Organic Reactions (2008–2009). We thank John M. Roberts (NU) and Dr. Amy A. Sarjeant for assistance with X-ray crystallography.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201203382>.

Table 1: Reaction optimization.^[a]

Entry	Variation of the standard conditions	P:SM ^[b]	d.r. ^[c]	ee [%] ^[d]
1	A , X = OEt	2:3	4:1	34
2	B , X = OEt	1.2:1	5:1	35
3	C , X = OEt	1:20	— ^[e]	52
4	D , X = OEt	1:3	4:1	70
5	E , X = OEt	> 20:1 (31) ^[f]	7:1	77
6	F , X = OEt	> 20:1 (72)	5:1	90
7	F , X = NBn ₂	> 20:1	1:1	35
8	F , X = SPh	— ^[g]	—	—
9	F , X = OCH ₂ CF ₃	> 20:1 (64)	8:1	99
10	F , X = OCH(CF ₃) ₂	1:1 ^[h]	—	—
11 ^[i]	F , X = OEt DCE, Cs ₂ CO ₃ (30 mol %)	> 20:1 (86)	6:1	98



[a] See the Supporting Information for details. [b] Ratio of product (P) to starting material (SM) determined by ¹H NMR spectroscopy (500 MHz). Number in parentheses is the isolated yield of both diastereomers (on a 0.4 mmol scale). [c] Ratio determined by ¹H NMR spectroscopy (500 MHz) prior to purification. [d] Enantiomeric excess of the major diastereomer determined by HPLC. [e] Starting material recovered. [f] Yield of major diastereomer only. [g] Full consumption of starting material but with no productive products observed. [h] Incomplete conversion. [i] 7 mol % catalyst loading.

a slight decrease in diastereoselectivity. More importantly, the use of azolium **F** provided a much-improved yield with trace amounts of decarboxylation (72% isolated yield, Table 1, entry 6). In an attempt to improve the diastereoselectivity of this process we examined other 1,3-dicarbonyl compounds (entries 6–10) with varying acidities at the α-position with the idea that different electron-withdrawing groups would perturb the acidity of the α-proton and thus increase the rate of enantiomer interconversion. With a β-ketoamide, the resultant lactone was formed in a 1:1 mixture of diastereomers, presumably due to the A^{1,3} strain created when tautomerizing to the enol form (entry 7).^[19] The β-keto thioester enal was not productive and only decomposed rapidly under the reaction conditions to unidentified products (entry 8). Fluorinated ester substrates were also investigated as a means to modulate the acidity of the α-proton. The trifluoroethyl ester gave an increase in diastereoselectivity (8:1 d.r.) with excellent enantioselectivity (99% ee) but with a decreased yield (64%) (entry 9). Increasing the acidity further by switching to the hexafluoroisopropyl ester gave incomplete conversion and unproductive products (entry 10). Other alkyl esters such as *tert*-butyl or benzyl gave similar or lower selectivities (not shown).

We also examined the effect of base and solvent on the ethyl ester substrate. Our goal was to increase the α-proton acidity through the use of a more polar solvent or stronger base. Coordinating polar aprotic solvents (i.e., THF, DMSO) provided sluggish reactions with poor selectivity while stronger bases resulted in starting material decomposition or poor reactivity. After screening a large array of solvent combinations and bases (not shown), it was determined that the most favorable conditions were observed when running the reaction in 1,2-dichloroethane (DCE) with cesium carbonate (30 mol %) as the base. Under these optimized conditions, the desired lactones were isolated in high yield (86%) with good diastereoselectivity (6:1 d.r.) and excellent enantioselectivity (Table 1, entry 11).

With the optimized reaction conditions established, we explored the scope of this NHC-catalyzed DKR (Table 2). Electron-deficient aromatic ketones led to desired lactones **6–12** in good yield (64–88%), with good diastereoselectivity, and excellent enantioselectivity (97–99%). Notably, the 2-

Table 2: Lactone substrate scope.^[a–d]

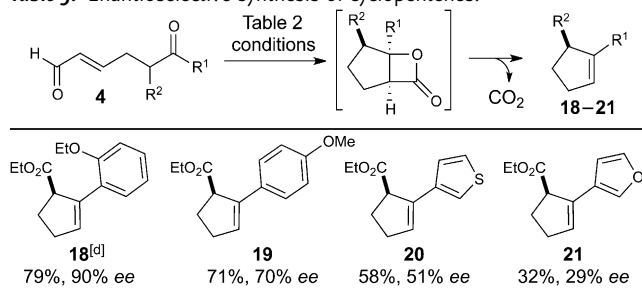
5	6	7	8^[e]	
84%, 6:1 d.r. 98% ee	86%, 6:1 d.r. 99% ee	81%, 6:1 d.r. 97% ee	88%, 5:1 d.r. 98% ee	
9	10	11	12	13^[f]
71%, 7:1 d.r. 99% ee	53%, 20:1 d.r. 98% ee	75%, 6:1 d.r. 98% ee	64%, 5:1 d.r. 99% ee	75%, 16:1 d.r. 97% ee
14^[f]	15^[f]	16^[f]	17^[g]	
72%, 13:1 d.r. 98% ee	77%, 6:1 d.r. 98% ee	73%, 7:1 d.r. 99% ee	51%, 20:1 d.r. 50% ee	

[a] 0.4 mmol scale. [b] Yields of isolated products are an average of two reactions. Diastereomers separable by column chromatography. Combined yield of both diastereomers is given. [c] Diastereomeric ratio determined by ¹H NMR spectroscopy (500 MHz) prior to purification. [d] Enantiomeric excess of the major diastereomer determined by HPLC. [e] 10 mol % **F**. [f] Yield of major diastereomer only. Minor not stable to column chromatography. [g] 30 mol % of **F**.

fluorophenyl substrate exhibited high diastereoselectivity (20:1) and enantioselectivity, but with a decreased yield. *Para*-phenyl substitution provided the lactone product (**13**) with excellent diastereoselectivity. Electron-donating substitution was tolerated in the *meta*-position furnishing lactone products **15** and **16** in high yield (73–77%) with good selectivities. Finally, the cyclopropyl ketone proceeded to furnish lactone **17** in moderate yield and enantioselectivity, but with excellent diastereoselectivity.^[20]

In this organocatalytic DKR process, electron-rich aryl ketones proceeded directly to the cyclopentene product (Table 3). Presumably, more available electron density pro-

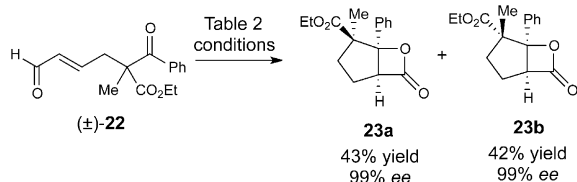
Table 3: Enantioselective synthesis of cyclopentenes.^[a–c]



[a] 0.4 mmol scale. [b] Yields of isolated products (average of two reactions). [c] *ee* determined by HPLC. [d] Lactone decarboxylated on SiO₂.

motes a facile decarboxylation. Unfortunately, along with this process comes an inherent decrease in enantioselectivity and investigations are underway to increase the selectivity. The 2-ethoxyphenyl ketone proceeded in high yield and enantioselectivity (90% *ee*). Other substrates, however, provided decreased yields and enantioselectivities of cyclopentene products **19–21**.^[21]

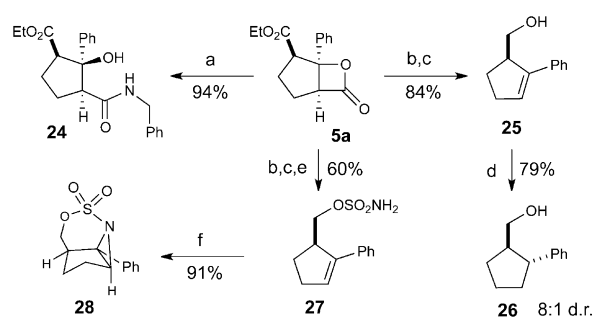
Given the highly selective nature of the method, we envisioned a stereodivergent parallel kinetic resolution (PKR) would be possible.^[22] In contrast to a standard kinetic resolution, a PKR converts both enantiomers of a starting material into two distinct products. For this process we employed a racemic substrate that is not epimerizable under the reaction conditions (Scheme 2). The reaction proceeded as planned with α -methylated β -keto ester **22** and complete



Scheme 2. Parallel kinetic resolution.

cyclization to diastereomeric β -lactone products **23** was achieved in excellent yield (50% theoretical yield for each) and enantioselectivity.

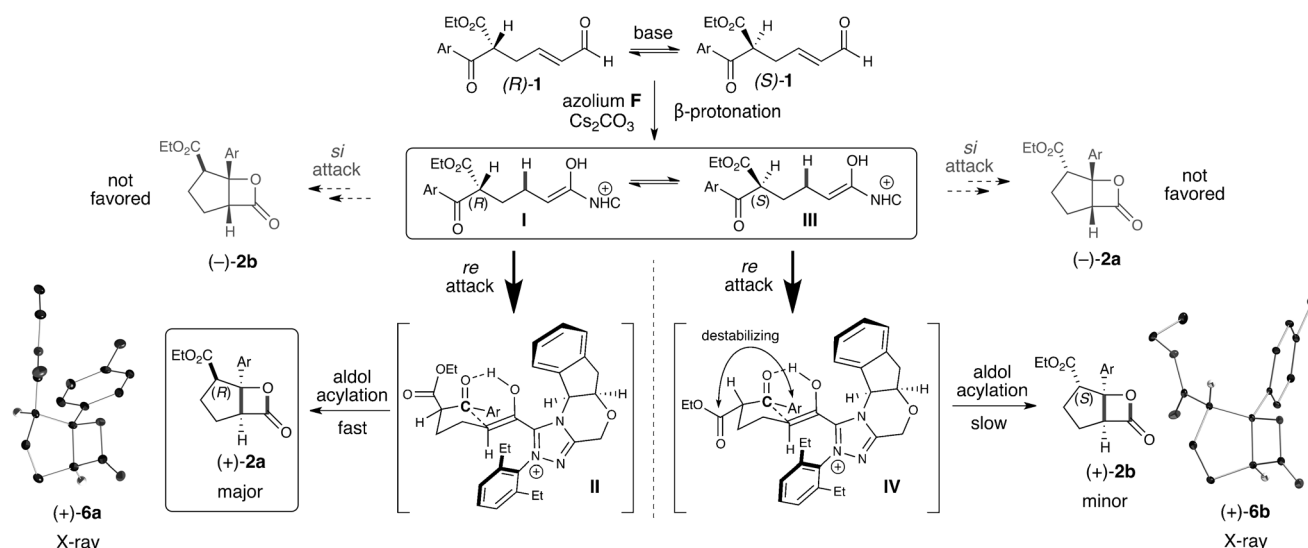
β -Lactones are highly useful building blocks for the synthesis of target compounds, especially in the area of



Scheme 3. Synthetic transformations (see the Supporting Information for details): a) PhCH₂NH₂, CH₂Cl₂, 23 °C; b) SiO₂, C₆H₆, 60 °C; c) LiAlH₄, Et₂O, 0 to 23 °C; d) [Ir(py)(cod)PCy₃], H₂, CH₂Cl₂, 23 °C; e) ClSO₂NH₂, pyridine, CH₂Cl₂, 0 to 23 °C; f) [Rh₂(OAc)₄], MgO, PhI(OAc)₂, CH₂Cl₂, 40 °C.

natural product synthesis.^[23] To demonstrate the potential utility of this DKR, we processed these β -lactones into diverse compounds (Scheme 3). The treatment of **5a** with benzylamine gave amide **24** in 94% yield while heating **5a** with SiO₂ at 60 °C^[24] followed by lithium aluminum hydride provided homoallylic alcohol **25** in 84% yield over two steps. A selective hydrogenation with Crabtree's catalyst^[25] afforded *trans*-cyclopentane **26** (79%, 8:1 d.r.), while 10% Pd/C hydrogenation favored the *cis*-cyclopentane (91%, 2.2:1 d.r., see the Supporting Information). Following a similar reaction sequence, sulfonamide **27** was prepared in three steps with a 60% overall yield. The exposure of **27** to Du Bois's conditions generated bicyclic aziridine **28** (91% yield).^[26]

Our current understanding of this DKR process is depicted in Scheme 4. Addition of the NHC to enal ($\pm$)-**1** induces the formation of the extended Breslow intermediate. The homoenolate undergoes β -protonation to form enols **I** and **III**. The mildly basic reaction conditions allow for these two intermediates to be in rapid equilibrium. Addition to the *re*-face of the enol is favored for both intermediates (**I** and **III**) due to a favorable hydrogen-bonding interaction between the NHC-enol and ketone forming a 6-membered transition state (**II** and **IV**). The importance of the hydrogen bonding is reinforced by the poor conversion observed with solvents that disturb this hydrogen-bonding interaction (coordinating polar aprotic). The major diastereomer ((+)-**2a**) arises from enol **II**, in which the ester is in a pseudo axial orientation. This conformation is more favorable than **IV**, which yields minor diastereomer ((+)-**2b**), due to destabilization created by a *gauche* interaction of the ethyl ester and the aryl group. This destabilization is increased with *ortho* substituted substrates (favoring intermediate **II**) and as a result virtually none of the minor diastereomer ((+)-**2b**) is observed (lactone **10** and cyclopentene **18**). The combination of a fast aldol addition with **II** compared to **IV** and the rapid equilibrium of **I** and **III** drives the reaction primarily in the direction of (+)-**2a** (97–99% *ee*). The rationale behind the absence of the corresponding enantiomer (–)-**2a** (which would arise from *si*-face attack of **III**) is twofold. First, there is an unfavorable arylester *syn* destabilization, and second, there is no hydrogen bonding to promote the aldol/acetylation. The minor diaste-



Scheme 4. Proposed reaction pathway.

reomer $(+)$ -2b (arising from intermediate **IV**) was likewise formed with high enantioselectivity (92–95% *ee*) (Table 2, lactones **5** and **6**, see the Supporting Information).

In conclusion, a new NHC-catalyzed dynamic kinetic resolution has been developed. This process takes advantage of the conditions necessary to generate the active NHC catalyst to simultaneously promote the epimerization of a β -ketoester substrate. The present study provides efficient access to highly enantioenriched β -lactones and cyclopentenones in good yield with good to excellent diastereoselectivity. With this blueprint for a new type of organocatalytic DKR process, further studies to probe the general reactivity, expand the substrate scope and application of this new NHC-DKR process in total synthesis are underway.

Experimental Section

In a nitrogen-filled dry box a screw-capped vial equipped with a magnetic stirbar was charged with the corresponding enal β -ketoester **4** (0.400 mmol), azolium pre-catalyst **F** (0.07 equiv), and cesium carbonate (0.30 equiv). The vial was capped with a septum cap, removed from the drybox and put under positive N_2 pressure. The heterogeneous mixture was then diluted with degassed 1,2-dichloroethane (12 mL, 0.033 M) and stirred for 12 h under static nitrogen pressure. Upon consumption of the aldehyde (all reactions were completed within 12 h) the reaction mixture was diluted with dichloromethane (5 mL) washed with brine (10 mL) and separated. The aqueous phase was back extracted with dichloromethane (5 mL). The combined organic layers were filtered through a Biotage Isololute phase separator, and the organic filtrate was concentrated. The material was purified by flash chromatography with EtOAc/hexanes to afford the corresponding β -lactone.

Received: May 2, 2012

Published online: ■ ■ ■ ■ ■ ■ ■ ■ ■ ■

Keywords: aldols · asymmetric synthesis · dynamic kinetic resolution · homoenolates · N-heterocyclic carbenes

- [1] a) H. B. Kagan, J. C. Fiaud, *Topics in Stereochemistry*, Wiley, **1988**, p. 249; b) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5; c) V. P. Krasnov, D. A. Gruzdev, G. L. Levit, *Eur. J. Org. Chem.* **2012**, 1471; d) C. E. Müller, P. R. Schreiner, *Angew. Chem.* **2011**, *123*, 6136; *Angew. Chem. Int. Ed.* **2011**, *50*, 6012; e) J. E. Taylor, S. D. Bull, J. M. J. Williams, *Chem. Soc. Rev.* **2012**, *41*, 2109; f) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.
- [2] For recent advances, see: a) A. Pesciulli, B. Procuranti, C. J. O'Connor, S. J. Connon, *Nat. Chem.* **2010**, *2*, 380; b) V. D. Bumbu, V. B. Birman, *J. Am. Chem. Soc.* **2011**, *133*, 13902; c) I. Čorić, B. List, *Nature* **2012**, *483*, 315; d) Y. Wang, K. Zheng, R. Hong, *J. Am. Chem. Soc.* **2012**, *134*, 4096.
- [3] a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; b) F. F. Huerta, A. B. E. Minidis, J. E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321; c) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621; d) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 659.
- [4] For dynamic kinetic resolutions using a chiral auxiliary, see: a) M. Amat, M. Cantó, N. Llor, V. Ponzio, M. Pérez, J. Bosch, *Angew. Chem.* **2002**, *114*, 345; *Angew. Chem. Int. Ed.* **2002**, *41*, 335; b) T. Ito, L. E. Overman, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 3272; c) J. I. Jang, S. Y. Kang, K. H. Kang, Y. S. Park, *Tetrahedron* **2011**, *67*, 6221.
- [5] For selected examples of metal-catalyzed DKRs, see: a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, *J. Am. Chem. Soc.* **1989**, *111*, 9134; b) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1993**, *115*, 144; c) B. M. Trost, N. G. Andersen, *J. Am. Chem. Soc.* **2002**, *124*, 14320; d) B. Martín-Matute, M. Edin, K. Bogár, F. B. Kaynak, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 8817; e) M. P. Rainka, J. E. Milne, S. L. Buchwald, *Angew. Chem.* **2005**, *117*, 6333; *Angew. Chem. Int. Ed.* **2005**, *44*, 6177.
- [6] a) J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154; b) L. Tang, L. Deng, *J. Am. Chem. Soc.* **2002**, *124*, 2870.
- [7] a) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817; *Angew. Chem. Int. Ed.* **2005**, *44*, 807; b) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; c) A. Pesciulli, C. Quigley, S. n. Tallon, Y. K. Gun'ko, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 6409; d) X. Yang, V. B. Birman, *Angew. Chem.* **2011**, *123*, 5667; *Angew. Chem. Int. Ed.* **2011**, *50*, 5553.

- [8] a) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; b) G. J. Lu, V. B. Birman, *Org. Lett.* **2011**, *13*, 356; c) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534.
- [9] a) D. E. Ward, V. Jheengut, O. T. Akinnusi, *Org. Lett.* **2005**, *7*, 1181; b) B.-C. Hong, R.-H. Jan, C.-W. Tsai, R. Y. Nimje, J.-H. Liao, G.-H. Lee, *Org. Lett.* **2009**, *11*, 5246; c) A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem.* **2011**, *123*, 1745; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707.
- [10] a) J. W. Evans, M. B. Fierman, S. J. Miller, J. A. Ellman, *J. Am. Chem. Soc.* **2004**, *126*, 8134; b) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251.
- [11] a) Y. Suzuki, K. Yamauchi, K. Muramatsu, M. Sato, *Chem. Commun.* **2004**, 2770; b) T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347; c) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; d) G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Adv. Synth. Catal.* **2008**, *350*, 1258; e) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Tetrahedron* **2009**, *65*, 3102; f) M. Binanzer, S.-Y. Hsieh, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 19698; g) S. De Sarkar, A. Biswas, C. H. Song, A. Studer, *Synthesis* **2011**, 1974.
- [12] For a DKR process involving sequential iminium ion catalysis and NHC catalysis, see: K. E. Ozboya, T. Rovis, *Chem. Sci.* **2011**, *2*, 1835. In this work, the NHC does not interact with a racemic mixture. Iminium ion catalysis presumably establishes the first stereocenter and the subsequent carbene catalysis step involves a second asymmetric, diastereoselective bond-forming event.
- [13] N. T. Reynolds, T. Rovis, *Tetrahedron* **2005**, *61*, 6368.
- [14] a) G. Liu, M. E. Shirley, D. Romo, *J. Org. Chem.* **2012**, *77*, 2496; b) C. A. Leverett, V. C. Purohit, D. Romo, *Angew. Chem.* **2010**, *122*, 9669; *Angew. Chem. Int. Ed.* **2010**, *49*, 9479; c) H. Henry-Riyad, C. Lee, V. C. Purohit, D. Romo, *Org. Lett.* **2006**, *8*, 4363.
- [15] a) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905; b) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334; c) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740; d) B. E. Maki, A. Chan, K. A. Scheidt, *Synthesis* **2008**, 1306; e) E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2416; f) B. E. Maki, E. V. Patterson, C. J. Cramer, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 3942; g) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766; h) D. T. Cohen, B. Cardinal-David, J. M. Roberts, A. A. Sarjeant, K. A. Scheidt, *Org. Lett.* **2011**, *13*, 1068; i) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem.* **2011**, *123*, 1716; *Angew. Chem. Int. Ed.* **2011**, *50*, 1678; j) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 5047; *Angew. Chem. Int. Ed.* **2012**, *51*, 4963.
- [16] a) E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 3167; *Angew. Chem. Int. Ed.* **2007**, *46*, 3107; b) Y. Kawanaka, E. M. Phillips, K. A. Scheidt, *J. Am. Chem. Soc.* **2009**, *131*, 18028; c) E. M. Phillips, M. Wadamoto, H. S. Roth, A. W. Ott, K. A. Scheidt, *Org. Lett.* **2009**, *11*, 105; d) E. M. Phillips, J. M. Roberts, K. A. Scheidt, *Org. Lett.* **2010**, *12*, 2830.
- [17] a) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; b) P. C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; c) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; d) E. M. Phillips, M. Wadamoto, K. A. Scheidt, *Synthesis* **2009**, 687; e) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345.
- [18] For computational studies involving this process, see: a) L. R. Domingo, R. J. Zaragoza, M. Arno, *Org. Biomol. Chem.* **2010**, *8*, 4884; b) L. R. Domingo, R. J. Zaragoza, M. Arno, *Org. Biomol. Chem.* **2011**, *9*, 6616; c) P. Verma, P. A. Patni, R. B. Sunoj, *J. Org. Chem.* **2011**, *76*, 5606.
- [19] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
- [20] Examination of other alkyl substrates provided unproductive products. Further studies are underway.
- [21] The observed enantioselectivity for these cyclopentenones is a due to the diastereoselectivity for the NHC-catalyzed process. These cyclopentenones are not epimerizable under reaction conditions. See the Supporting Information for details.
- [22] a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 2584; for a good review, see: b) L. C. Miller, R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550.
- [23] For selected examples of β -lactones in synthesis, see: a) R. L. Danheiser, J. S. Nowick, *J. Org. Chem.* **1991**, *56*, 1176; b) J. Taunton, J. L. Collins, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 10412; c) W. D. Schmitz, N. B. Messerschmidt, D. Romo, *J. Org. Chem.* **1998**, *63*, 2058; d) X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438; e) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478; f) B. Chandra, D. Fu, S. G. Nelson, *Angew. Chem.* **2010**, *122*, 2645; *Angew. Chem. Int. Ed.* **2010**, *49*, 2591; g) T. R. Vargo, J. S. Hale, S. G. Nelson, *Angew. Chem.* **2010**, *122*, 8860; *Angew. Chem. Int. Ed.* **2010**, *49*, 8678; h) G. Liu, D. Romo, *Angew. Chem.* **2011**, *123*, 7679; *Angew. Chem. Int. Ed.* **2011**, *50*, 7537.
- [24] The enantioselectivity was maintained following decarboxylation. See the Supporting Information for details.
- [25] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331.
- [26] a) K. Guthikonda, P. M. Wehn, B. J. Caliendo, J. Du Bois, *Tetrahedron* **2006**, *62*, 11331; b) P. M. Wehn, J. Du Bois, *Angew. Chem.* **2009**, *121*, 3860; *Angew. Chem. Int. Ed.* **2009**, *48*, 3802.

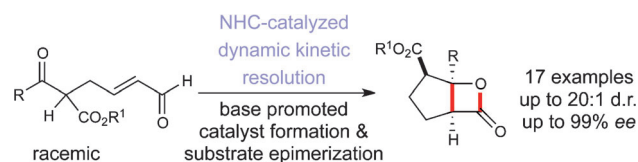
Communications



Asymmetric Catalysis

D. T. Cohen, C. C. Eichman, E. M. Phillips,
E. R. Zarefsky,
K. A. Scheidt* ————— ■■■■-■■■■

Catalytic Dynamic Kinetic Resolutions
with N-Heterocyclic Carbenes:
Asymmetric Synthesis of Highly
Substituted β -Lactones



New DKR type: An N-heterocyclic carbene (NHC)-catalyzed dynamic kinetic resolution of racemic α -substituted β -keto esters has been developed. This method relies on the epimerization of an

NHC-enol intermediate before subsequent aldol/acylation events. Highly substituted β -lactones are produced in good yield with good to excellent selectivities (see scheme).