Published in final edited form as:

Angew Chem Int Ed Engl. 2012 July 16; 51(29): 7309–7313. doi:10.1002/anie.201203382.

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

Daniel T. Cohen, Dr. Chad C. Eichman, Eric M. Phillips, Emily R. Zarefsky, and Prof. Karl 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)

Karl A. Scheidt: scheidt@northwestern.edu

Abstract

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 (50–88%) with good to excellent diastereoselectivity (5:1 to 20:1 dr) and excellent enantioselectivity (up to 99% ee).

Keywords

catalysis; asymmetric synthesis; *N*-heterocyclic carbene; homoenolate; dynamic kinetic resolution; aldol

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 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] In this communication, 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.

Correspondence to: Karl A. Scheidt, scheidt@northwestern.edu.

Supporting information for this article is available on the Web under <http://www.angewandte.org> or from the author.

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 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 (*vide infra*). 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 7:1 dr and 90% ee, but there was a significant amount of decarboxylation to the corresponding cyclopentene, with a 31% isolated yield of the 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 ~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 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, 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 alpha position with the idea that different electron withdrawing groups would perturb the acidity of the α -position 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 dr) 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 dr) and excellent enantioselectivity (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-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 promotes a facile decarboxylation. Unfortunately, along with this process comes an inherent decrease in enantioselectivity and investigations are underway to increase the selectivity. The 2-ethoxy-phenyl 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 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 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 2 steps. A selective hydrogenation with Crabtree's catalyst^[25] afforded *trans*-cyclopentane **26** (79%, 8:1 dr), while 10% Pd/C hydrogenation favored the *cis*-cyclopentane (91%, 2.2:1 dr, see supporting information). Following a similar reaction sequence, sulfonamide **27** was prepared in 3 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 aryl-ester *syn* destabilization, and second, there is no hydrogen bonding to promote the aldol/acetylation. The minor diastereomer (+)-**2b** (arising

from intermediate **IV**) was likewise formed with high enantioselectivity (92–95% ee) (Table 2, lactones **5** and **6**).

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 precatalyst **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 N₂ pressure. The heterogeneous mixture was then diluted with degassed 1,2-dichloroethane (12 mL, 0.033 M) and stirred for 12 hours under static nitrogen pressure. Upon consumption of the aldehyde (all reactions were completed within 12 hours) 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 ISOLUTE® phase separator, and the organic filtrate was concentrated. The material was purified by flash chromatography with EtOAc/hexanes to afford the corresponding β -lactone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 Synthesis/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.

References

1. a) Kagan, HB.; Fiaud, JC. Topics in Stereochemistry. John Wiley & Sons, Inc; 1988. p. 249b) Keith JM, Larrow JF, Jacobsen EN. Adv Synth Catal. 2001; 343:5.c) Krasnov VP, Gruzdev DA, Levit GL. Eur J Org Chem. 2012; 2012:1471.d) Müller CE, Schreiner PR. Angew Chem Int Ed. 2011; 50:6012.e) Taylor JE, Bull SD, Williams MJ. Chem Soc Rev. 2012; 41:2109. [PubMed: 22234578] f) Vedejs E, Jure M. Angew Chem Int Ed. 2005; 44:3974.
2. For recent advances, see: Peschiulli A, Procuranti B, Connor CJ, O'Connor SJ. Nat Chem. 2010; 2:380. [PubMed: 20414238] Bumbu VD, Birman VB. J Am Chem Soc. 2011; 133:13902. [PubMed: 21823609] Coric I, List B. Nature. 2012; 486:315. [PubMed: 22722174] Wang Y, Zheng K, Hong R. J Am Chem Soc. 2012; 134:4096. [PubMed: 22329839]
3. a) Noyori R, Tokunaga M, Kitamura M. Bull Chem Soc Jpn. 1995; 68:36.b) Huerta FF, Minidis ABE, Bäckvall JE. Chem Soc Rev. 2001; 30:321.c) Tian SK, Chen Y, Hang J, Tang L, McDaid P, Deng L. Acc Chem Res. 2004; 37:621. [PubMed: 15311961] d) Pellissier H. Adv Synth Catal. 2011; 353:659.

4. For dynamic kinetic resolutions using a chiral auxiliary, see: Amat M, Cantó M, Llor N, Ponzo V, Pérez M, Bosch J. *Angew Chem Int Ed*. 2002; 41:335. Ito T, Overman LE, Wang J. *J Am Chem Soc*. 2010; 132:3272. [PubMed: 20175519] Jang JI, Kang SY, Kang KH, Park YS. *Tetrahedron*. 2011; 67:6221.
5. For selected examples of metal-catalyzed DKRs, see: Noyori R, Ikeda T, Ohkuma T, Widhalm M, Kitamura M, Takaya H, Akutagawa S, Sayo N, Saito T. *J Am Chem Soc*. 1989; 111:9134. Kitamura M, Tokunaga M, Noyori R. *J Am Chem Soc*. 1993; 115:144. Trost BM, Andersen NG. *J Am Chem Soc*. 2002; 124:14320B. [PubMed: 12452702] Martín-Matute, Edin M, Bogár K, Kaynak FB, Bäckvall J-E. *J Am Chem Soc*. 2005; 127:8817. [PubMed: 15954789] Rainka MP, Milne JE, Buchwald SL. *Angew Chem Int Ed*. 2005; 44:6177.
6. a) Liang J, Ruble JC, Fu GC. *J Org Chem*. 1998; 63:3154. b) Tang L, Deng L. *J Am Chem Soc*. 2002; 124:2870. [PubMed: 11902867]
7. a) Berkessel A, Cleemann F, Mukherjee S, Müller TN, Lex J. *Angew Chem Int Ed*. 2005; 44:807. b) Lalonde MP, Chen Y, Jacobsen EN. *Angew Chem Int Ed*. 2006; 45:6366. c) Peschiulli A, Quigley C, Tallon Sn, Gun'ko YK, Connon SJ. *J Org Chem*. 2008; 73:6409. [PubMed: 18646859] d) Yang X, Birman VB. *Angew Chem Int Ed*. 2011; 50:5553.
8. a) Hoffmann S, Nicoletti M, List B. *J Am Chem Soc*. 2006; 128:13074. [PubMed: 17017786] b) Lu GJ, Birman VB. *Org Lett*. 2011; 13:356. [PubMed: 21175181] c) Müller S, Webber MJ, List B. *J Am Chem Soc*. 2011; 133:18534. [PubMed: 22044311]
9. a) Ward DE, Jheengut V, Akinnusi OT. *Org Lett*. 2005; 7:1181. [PubMed: 15760169] b) Hong BC, Jan RH, Tsai CW, Nimje RY, Liao JH, Lee GH. *Org Lett*. 2009; 11:5246. [PubMed: 19852490] c) Lee A, Michrowska A, Sulzer-Mosse S, List B. *Angew Chem Int Ed*. 2011; 50:1707.
10. a) Evans JW, Fierman MB, Miller SJ, Ellman JA. *J Am Chem Soc*. 2004; 126:8134. [PubMed: 15225052] b) Gustafson JL, Lim D, Miller SJ. *Science*. 2010; 328:1251. [PubMed: 20522769]
11. a) Suzuki Y, Yamauchi K, Muramatsu K, Sato M. *Chem Commun*. 2004:2770. b) Kano T, Sasaki K, Maruoka K. *Org Lett*. 2005; 7:1347. [PubMed: 15787503] c) Maki BE, Chan A, Phillips EM, Scheidt KA. *Org Lett*. 2007; 9:371. [PubMed: 17217307] d) Li GQ, Li Y, Dai LX, You SL. *Adv Synth Catal*. 2008; 350:1258. e) Maki BE, Chan A, Phillips EM, Scheidt KA. *Tetrahedron*. 2009; 65:3102. [PubMed: 20161230] f) Binanzer M, Hsieh SY, Bode JW. *J Am Chem Soc*. 2011; 133:19698. [PubMed: 22082205] g) De Sarkar S, Biswas A, Song CH, Studer A. *Synthesis*. 2011:1974.
12. For a DKR process involving sequential iminium ion catalysis and NHC catalysis, see: Ozboya KE, Rovis T. *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. [PubMed: 21927711]
13. Reynolds NT, Rovis T. *Tetrahedron*. 2005; 61:6368.
14. a) Liu G, Shirley ME, Romo D. *J Org Chem*. 2012; 77:2496. [PubMed: 22260519] b) Leverett CA, Purohit VC, Romo D. *Angew Chem Int Ed*. 2010; 49:9479. c) Henry-Riyad H, Lee C, Purohit VC, Romo D. *Org Lett*. 2006; 8:4363. [PubMed: 16956227]
15. a) Chan A, Scheidt KA. *Org Lett*. 2005; 7:905. [PubMed: 15727471] b) Chan A, Scheidt KA. *J Am Chem Soc*. 2007; 129:5334. [PubMed: 17407298] c) Chan A, Scheidt KA. *J Am Chem Soc*. 2008; 130:2740. [PubMed: 18260665] d) Maki BE, Chan A, Scheidt KA. *Synthesis*. 2008:1306. [PubMed: 22347730] e) Phillips EM, Reynolds TE, Scheidt KA. *J Am Chem Soc*. 2008; 130:2416. [PubMed: 18232690] f) Maki BE, Patterson EV, Cramer CJ, Scheidt KA. *Org Lett*. 2009; 11:3942. [PubMed: 19645427] g) Raup DEA, Cardinal-David B, Holte D, Scheidt KA. *Nat Chem*. 2010; 2:766. [PubMed: 20729898] h) Cohen DT, Cardinal-David B, Roberts JM, Sarjeant AA, Scheidt KA. *Org Lett*. 2011; 13:1068. [PubMed: 21271734] i) Cohen DT, Cardinal-David B, Scheidt KA. *Angew Chem Int Ed*. 2011; 50:1678. j) Dugal-Tessier J, O'Bryan EA, Schroeder TBH, Cohen DT, Scheidt KA. *Angew Chem Int Ed*. 2012; 51:4963.
16. a) Phillips EM, Wadamoto M, Chan A, Scheidt KA. *Angew Chem Int Ed*. 2007; 46:3107. b) Kawanaka Y, Phillips EM, Scheidt KA. *J Am Chem Soc*. 2009; 131:18028. [PubMed: 20000857] c) Phillips EM, Wadamoto M, Roth HS, Ott AW, Scheidt KA. *Org Lett*. 2009; 11:105. [PubMed: 19049403] d) Phillips EM, Roberts JM, Scheidt KA. *Org Lett*. 2010; 12:2830. [PubMed: 20469924]

17. a) Nair V, Vellalath S, Poonoth M, Suresh E. *J Am Chem Soc.* 2006; 128:8736. [PubMed: 16819860] b) Chiang PC, Kaeobamrung J, Bode JW. *J Am Chem Soc.* 2007; 129:3520. [PubMed: 17335218] c) Wadamoto M, Phillips EM, Reynolds TE, Scheidt KA. *J Am Chem Soc.* 2007; 129:10098. [PubMed: 17663558] d) Phillips EM, Wadamoto M, Scheidt KA. *Synthesis.* 2009:687. [PubMed: 21085623] e) Cardinal-David B, Raup DEA, Scheidt KA. *J Am Chem Soc.* 2010; 132:5345. [PubMed: 20345186]
18. For computational studies involving this process, see: Domingo LR, Zaragoza RJ, Arno M. *Org Biomol Chem.* 2010; 8:4884. [PubMed: 20740249] Domingo LR, Zaragoza RJ, Arno M. *Org Biomol Chem.* 2011; 9:6616. [PubMed: 21842074] Verma P, Patni PA, Sunoj RB. *J Org Chem.* 2011; 76:5606. [PubMed: 21627313]
19. Hoffmann RW. *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 due to the diastereoselectivity for the NHC-catalyzed process. These cyclopentenones are not epimerizable under reaction conditions. See Supporting Information for details.
22. a) Vedejs E, Chen X. *J Am Chem Soc.* 1997; 119:2584. For a good review, see: b) Miller LC, Sarpong R. *Chem Soc Rev.* 2011; 40:4550. [PubMed: 21629881]
23. For selected examples of β -lactones in synthesis, see: Danheiser RL, Nowick JS. *J Org Chem.* 1991; 56:1176. Taunton J, Collins JL, Schreiber SL. *J Am Chem Soc.* 1996; 118:10412. Schmitz WD, Messerschmidt NB, Romo D. *J Org Chem.* 1998; 63:2058. Shen X, Wasmuth AS, Zhao J, Zhu C, Nelson SG. *J Am Chem Soc.* 2006; 128:7438. [PubMed: 16756287] Purohit VC, Matla AS, Romo D. *J Am Chem Soc.* 2008; 130:10478. [PubMed: 18627148] Chandra B, Fu D, Nelson SG. *Angew Chem Int Ed.* 2010; 49:2591. Vargo TR, Hale JS, Nelson SG. *Angew Chem Int Ed.* 2010; 49:8678. Liu G, Romo D. *Angew Chem Int Ed.* 2011; 50:7537.
24. The enantioselectivity was maintained following decarboxylation. See Supporting Information for details.
25. Crabtree R. *Acc Chem Res.* 1979; 12:331.
26. a) Guthikonda K, Wehn PM, Caliendo BJ, Du Bois J. *Tetrahedron.* 2006; 62:11331. b) Wehn PM, Du Bois J. *Angew Chem Int Ed.* 2009; 48:3802.

Overall NHC-DKR Strategy

Kinetic Considerations

Scheme 1.
NHC-Catalyzed Dynamic Kinetic Resolution

Scheme 2.
Parallel Kinetic Resolution

Scheme 3.

Synthetic Transformations^[a]: [a] See supporting information for details. [b] PhCH₂NH₂, CH₂Cl₂, 23 °C. [c] SiO₂, C₆H₆, 60°C. [d] LiAlH₄, Et₂O, 0 to 23 °C. [e] Ir(py)codPCy₃, H₂, CH₂Cl₂, 23°C. [f] ClSO₂NH₂, pyridine, CH₂Cl₂, 0 to 23 °C. [g] Rh₂(OAc)₄, MgO, PhI(OAc)₂, CH₂Cl₂, 40 °C.

Scheme 4.
Proposed Reaction Pathway

Table 1

Reaction Optimization

entry	variation of the standard conditions	P:SM ^[b]	dr ^[c]	ee (%) ^[d]
1	A, X = OEt	2:3	4:1	ND
2	B, X = OEt	1.2:1	5:1	ND
3	C, X = OEt	1:20	— ^[e]	—
4	D, X = OEt	1:3	4:1	ND
5	E, X = OEt	>20:1 (31) ^[f]	7:1	90
6	F, X = OEt	>20:1 (72)	5:1	99
7	F, X = NtBu ₂	>20:1	1:1	ND
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 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.

\$watermark-text

\$watermark-text

\$watermark-text

[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]* mol % catalyst loading.

ND = not determined.

Table 2

Lactone Substrate Scope^[a] ^[a] 0.4 mmol scale.^[b] Isolated yields 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**.

Table 3

Enantioselective Synthesis of Cyclopentenes^[a-c] ^[a] 0.4 mmol scale.^[b] Isolated yields (average of two reactions).^[c] ee determined by HPLC.^[d] Lactone decarboxylated on SiO_2 .