Ring Contraction

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Ring-Contraction Strategy for the Practical, Scalable, Catalytic Asymmetric Synthesis of Versatile γ-Quaternary Acylcyclopentenes**

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Dedicated to Dr. Ahamindra Jain

Highly substituted cyclopentanes are a common structural motif integrated into thousands of natural products.[1] Selected examples of bioactive compounds containing this basic structural unit include the hamigerans (**2**),[2a] steroids (**3**),[2b] pleuromutilin antibiotics (**4**),[2c] cyathane diterpenoids (**5**),[2d] cyclic botryococcenes (**6**),[2e] and anti-HBV schisanwilsonenes (**7a–c**)[2f] (Figure 1). Synthetic methods for the asymmetric preparation of cyclopentanoid cores with multiple functional group handles are highly desirable because they allow for the strategic synthesis of these and other natural products.[3] Toward this goal, we envisioned that functionalized chiral units such as acylcyclopentene **1** could serve as valuable synthetic intermediates (Figure 1). Here, we describe a general and enantioselective preparation of versatile chiral acylcyclopentenes[4,5] that combines a catalytic asymmetric alkylation reaction[6] and a facile two-carbon ring contraction.

Our work in this area began with observation of the unusual reactivity of seven-membered ring vinylogous esters compared to their six-membered ring counterparts. Although

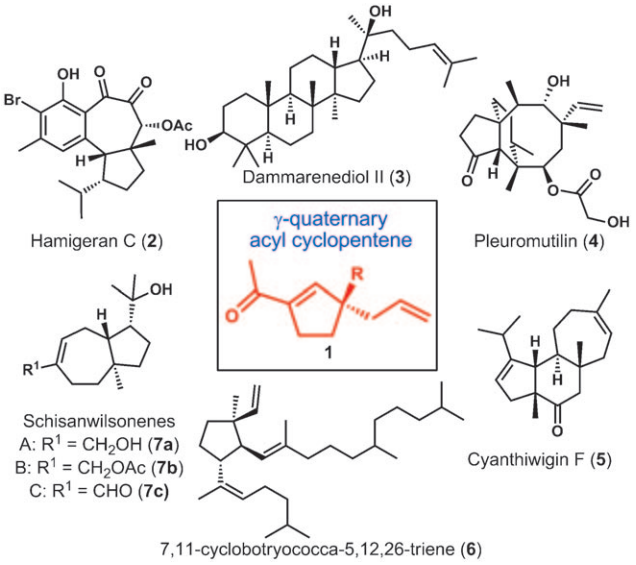
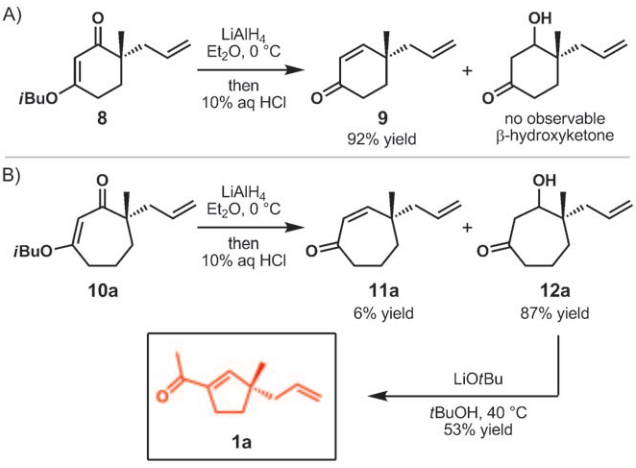


Figure 1. Representative natural products possessing cyclopentanoid core structures with quaternary stereocenters.

$LiAlH_4$ reduction of vinylogous ester **8** gave expected enone **9**[7] as the major product after acidic workup (Scheme 1 A), subjecting the analogous seven-membered ring vinylogous ester (**10a**) to identical reaction conditions led to cycloheptenone **11a** as only a minor product (Scheme 1 B). Interestingly, the major product was identified as stable β-



Scheme 1. Anomalous reactivity of seven-membered ring vinylogous esters and discovery of a ring-contraction reaction.

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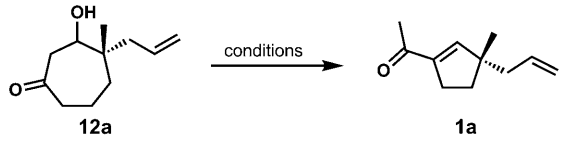
hydroxyketone **12a**.[8] The lack of appreciable β-elimination even under acidic conditions suggests that subtle, but fundamental differences in ring conformational preferences between six- and seven-membered rings may lead to the strikingly different product distributions.[9]

To further examine the inherent reactivity of β-hydroxyketone **12a**, we exposed the compound to a variety of basic reaction conditions. Treatment of β-hydroxyketone **12a** with LiO*t*Bu in *t*BuOH afforded acylcyclopentene **1a** in 53% yield without any evidence of direct β-hydroxy elimination to enone **11a** (Scheme 1). Overall, the reaction constitutes a two-carbon ring contraction that likely proceeds through a retro-aldol fragmentation/aldol cyclization pathway. Although some examples of the preparation of acylcyclopentenes from seven-membered rings[10] are known, general ring-contraction methods have not been demonstrated with γ-quaternary stereocenters and catalytic asymmetric routes are unprecedented.

Enticed by this initial finding, we investigated the effect of different bases on product formation (Table 1). Alcohol additives in combination with LiOH in THF improved the yield for the reaction (Table 1, entries 2–4), with CF_3CH_2OH[11] enabling the production of **1a** in 96% yield.[12] It is interesting to note that enone **11a** was not observed under any of the surveyed conditions. Among the conditions that promote the desired ring contraction, the combination of LiOH and CF_3CH_2OH in THF offered a mild, efficient, and selective method for further studies (Table 1, entry 4).

Table 1: Ring-contraction optimization.[a]

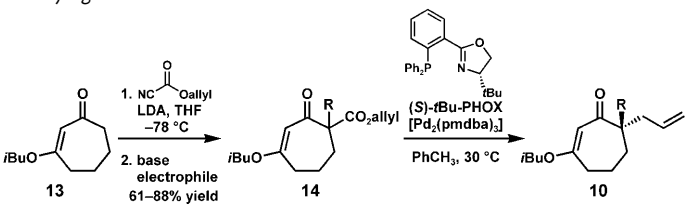


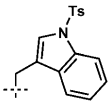
Entry	Base	Additive	Solvent	*T* [°C]	Yield [%][b]
1	LiO*t*Bu	none	*t*BuOH	40	71 (53)[c]
2	LiOH	*t*BuOH	THF	60	78
3	LiOH	HFIP[d]	THF	60	87
4	LiOH	CF_3CH_2OH	THF	60	96 (84)[c]

[a] Conditions: β-hydroxyketone (1.0 equiv), base (1.5 equiv), additive (1.5 equiv) in solvent (0.1 M) at indicated temperature for 9–24 h. [b] GC yield using an internal standard. [c] Yield of isolated products in parentheses. [d] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. THF = tetrahydrofuran.

With an optimized procedure for the ring contraction, we turned our attention to the asymmetric synthesis of various quaternary α-substituted vinylogous esters (e.g., **10**, Table 2).[13,14] A number of racemic β-ketoester substrates (e.g., **14**) for catalytic enantioselective alkylation could be obtained by acylation of parent vinylogous ester **13** with allyl cyanoformate[15] and trapping with a range of electrophiles under basic conditions.[16] Application of our standard enantioselective decarboxylative alkylation reaction conditions[6,13] to substrate **14a** produced chiral vinylogous ester **10a** in 91% yield and 88% *ee* (Table 2, entry 1).[17,18] Substituents such as ethyl, benzyl, propargyl, homoallyl, and 2,4-pentadienyl groups were well tolerated in the reaction, giving similarly high yields and enantioselectivity (Table 2, entries 2–6). A number of heteroatom-containing substrates were explored to test if more diverse functionality could be incorporated into our target acylcyclopentenes (Table 2, entries 7–11). β-Ketoesters bearing a 2-chloroallyl substitutent readily underwent the enantioselective alkylation reaction (Table 2, entry 7). Gratifyingly, compounds that possess Lewis basic moieties readily furnished the desired products without complications (Table 2, entries 8 and 9). Even indoles and free aldehydes could be incorporated into the cycloheptenone products (Table 2, entries 10 and 11).

Table 2: Scope of the Pd-catalyzed enantioselective alkylation of cyclic vinylogous esters.[a]

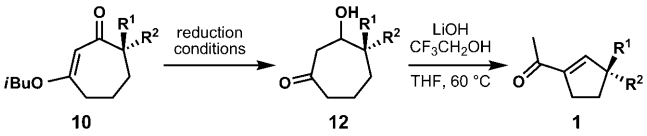


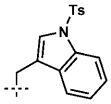
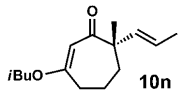
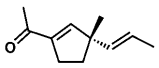
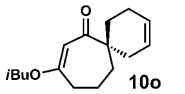
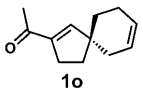
Entry	Substrate **14**	R	Product **10**	Yield [%][b]	*ee* [%][c]
1	**14a**	CH_3	**10a**	91	88
2	**14b**	CH_2CH_3	**10b**	89	92
3	**14c**	CH_2Ph	**10c**	98	86
4	**14d**	$CH_2C{\equiv}CH$	**10d**	88	89
5	**14e**	$CH_2CH_2CH{=}CH_2$	**10e**	95	87
6	**14f**		**10f**	90	90
7	**14g**		**10g**	99	86
8	**14h**	CH_2CH_2CN	**10h**	96	87
9	**14i**		**10i**	97	85
10	**14j**		**10j**	98	83
11	**14k**		**10k**	90	80

[a] Conditions: β-ketoester (1.0 equiv), $[Pd_2(pmdba)_3]$ (2.5 mol%), (*S*)-*t*Bu-PHOX (6.25 mol%) in $PhCH_3$ (0.1 M) at 30°C; pmdba = 4,4′-methoxydibenzylideneacetone. [b] Yield of isolated products. [c] Determined by HPLC or SFC analysis using a chiral column. LDA = lithium diisopropylamide, Ts = 4-toluenesulfonyl.

The chiral vinylogous esters (e.g., **10**) prepared above allowed us to examine the scope of the ring-contraction reaction (Table 3). Substrate reduction with $LiAlH_4$ and base-promoted rearrangement of vinylogous esters bearing γ-alkyl substituents provided access to the corresponding acylcyclopentenes in excellent yields over the two-step protocol

Table 3: Ring-contraction substrate scope.

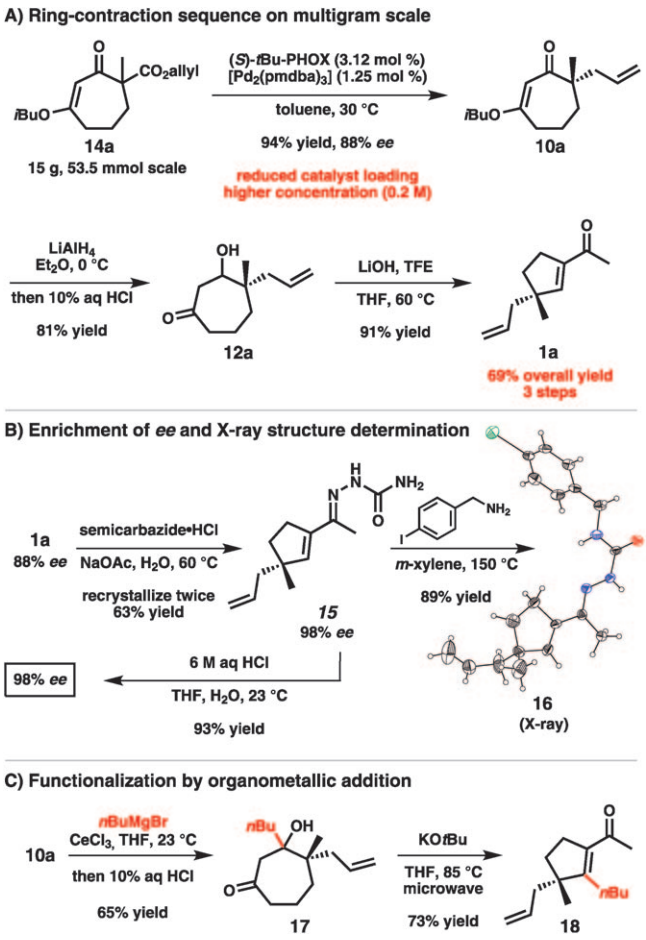


Entry	Substrate 10	R^1	R^2	Product 1	Overall Yield [%][e]
1[a,d]	**10a**	CH_3	$CH_2CH{=}CH_2$	**1a**	84
2[a,d]	**10b**	CH_2CH_3	$CH_2CH{=}CH_2$	**1b**	90
3[a,d]	**10c**	CH_2Ph	$CH_2CH{=}CH_2$	**1c**	86
4[a,d]	**10d**	$CH_2C{\equiv}CH$	$CH_2CH{=}CH_2$	**1d**	95
5[a,d]	**10e**	$CH_2CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	**1e**	87
6[a,d]	**10f**		$CH_2CH{=}CH_2$	**1f**	91
7[a,d]	**10g**		$CH_2CH{=}CH_2$	**1g**	92
8[a,d]	**10h**	CH_2CH_2CN	$CH_2CH{=}CH_2$	**1h**	85
9[b,d]	**10i**		$CH_2CH{=}CH_2$	**1i**	80
10[a,d]	**10j**		$CH_2CH{=}CH_2$	**1j**	87
11[c,d,f]	**10l**	$CH_2OTBDPS$	$CH_2CH{=}CH_2$	**1l**	91
12[c,d,g]	**10m**	$(CH_2)_3OTBDPS$	$CH_2CH{=}CH_2$	**1m**	85
13[a,d,h]					81
14[a,d,g]					87

[a] Reduction conditions A: vinylogous ester (1.0 equiv), $LiAlH_4$ (0.55 equiv) in Et_2O (0.2 M) at 0 °C, then 10% aqueous HCl quench. [b] Reduction conditions B: 1) vinylogous ester (1.0 equiv), DIBAL (1.2 equiv) in $PHCH_3$ (0.03 M) at −78 °C; 2) oxalic acid·$2H_2O$ in MeOH (0.02 M). [c] Reduction conditions C: vinylogous ester (1.0 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), $NaBH_4$ (3.0 equiv) in MeOH (0.02 M) at 0 °C, then 10% aqueous HCl in Et_2O at 0 °C. [d] Ring-contraction conditions: β-hydroxyketone (1.0 equiv), CF_3CH_2OH (1.5 equiv), LiOH (1.5 equiv) in THF (0.1 M) at 60 °C. [e] Yield of isolated products over 2–3 steps. [f] See the Supporting Information for experimental procedures for substrate synthesis. [g] Prepared from **14k**. See the Supporting Information. [h] Prepared from **14a**. See the Supporting Information. DIBAL = diisobutylaluminum hydride, TBDPS = *tert*-butyldiphenylsilyl.

(Table 3, entries 1–6). The chloroallyl-, nitrile-, and indole-containing substrates could be transformed with similarly high yields using the same conditions (Table 3, entries 7, 8, and 10). Alternatively, DIBAL allowed smooth conversion of vinylogous ester **10i** containing an N-basic pyridine (Table 3, entry 9). Milder reductions under Luche conditions enabled facile conversion of silyl ether substrates (Table 3, entries 11 and 12).[19] Furthermore, *trans*-propenyl substituted (Table 3, entry 13) and spirocyclic substrates (Table 3, entry 14) performed well in the ring-contraction chemistry. With the combination of asymmetric alkylation and ring contraction, we achieved a route to substituted acylcyclopentenes with a wide range of functionality at the γ-quaternary stereocenter.

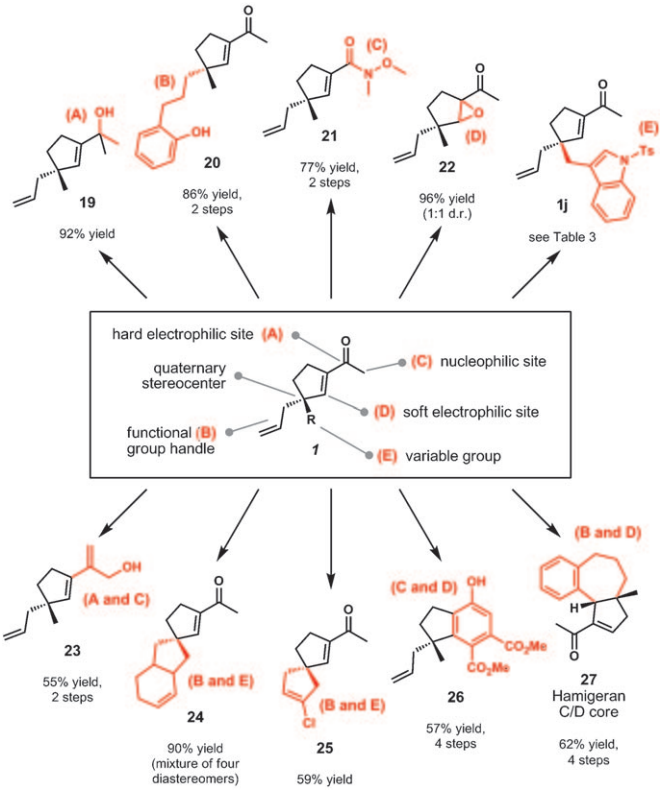
To demonstrate the practicality and scalability of the method, the α-methyl β-ketoester **14a** was converted to the corresponding acylcyclopentene **1a** in 69% yield over three steps on 15 g scale (Scheme 2A).[16] Notably, the multigram



Scheme 2. Multigram ring contraction, enrichment of *ee* values by recrystallization, and organometallic modified ring-contraction sequence. Color code for ORTEP plot of structure **16** in (B): green I, blue N, red O, gray C. TFE = 2,2,2-trifluoroethanol.

protocol proceeds with reduced catalyst loading and at higher reaction concentrations for the asymmetric alkylation step. Additionally, the enantiopurity of the acylcyclopentene **1a** can be increased to 98% *ee* by recrystallization of semicarbazone **15** (Scheme 2B).[16] Hydrolysis of semicarbazone **15** with aqueous HCl enabled facile recovery of **1a**. Further derivatization afforded X-ray quality crystals of **16** for verification of absolute configuration.[20] To enable access to β-substituted acylcyclopentenes, addition of *n*BuMgBr to **10a** resulted in formation of tertiary β-hydroxyketone **17** (Scheme 2C).[16] Application of modified ring-contraction conditions allowed access to acylcyclopentene **18**.

With a versatile, enantioselective synthesis of γ-quaternary acylcyclopentenes **1** in hand, we sought to demonstrate the further synthetic utility of these compounds. By combining site-selective manipulations in short reaction sequences (1–4 steps), any of five reactive handles present in acylcyclopentene **1** can be functionalized (Scheme 3, sites **A**–**E**).



Scheme 3. Versatility and synthetic utility of acylcyclopentenes.

Through careful implementation of these transformations, diverse monocarbocyclic (**1j**, **18**–**23**), spirocyclic (**24** and **25**), and fused polycyclic structures (**26** and **27**) can be obtained.[16]

In summary, we have developed a catalytic enantioselective synthesis for the preparation of densely functionalized chiral acylcyclopentenes in excellent yields and enantioselectivities. The protocol exploits a highly efficient Pd-catalyzed asymmetric alkylation reaction and a newly developed, mild two-carbon ring contraction. The important chiral building blocks formed using this method can undergo a variety of synthetic transformations and will serve as valuable intermediates for the total synthesis of natural products. Efforts directed toward these ends are currently underway and will be reported in due course.

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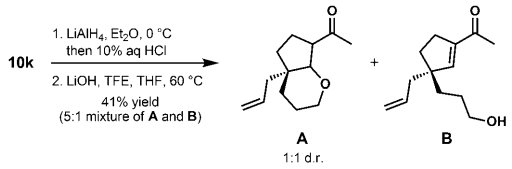
Keywords: aldol reaction · allylation · asymmetric catalysis · rearrangement reactions · ring contraction

[1] For a review of general methods for cyclopentane synthesis by ring contraction, see: L. F. Silva, Jr., *Tetrahedron* **2002**, *58*, 9137–9161.
[2] a) K. D. Wellington, R. C. Cambie, P. S. Rutledge, P. R. Bergquist, *J. Nat. Prod.* **2000**, *63*, 79–85; b) J. S. Mills, *J. Chem. Soc.* **1956**, 2196–2202; c) F. Kavanagh, A. Hervey, W. J. Robbins, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 570–574; d) J. Peng, K. Walsh, V. Weedman, J. D. Bergthold, J. Lynch, K. L. Lieu, I. A. Braude, M. Kelly, M. T. Hamann, *Tetrahedron* **2002**, *58*, 7809–7819; e) A. Behrens, P. Schaeffer, S. Bernasconi, P. Albrecht, *Org. Lett.* **2000**, *2*, 1271–1274; f) W.-H. Ma, H. Huang, P. Zhou, D.-F. Chen, *J. Nat. Prod.* **2009**, *72*, 676–678.
[3] For a review discussing our strategy of using natural product structures to drive the development of enantioselective catalysis, see: J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323–332.
[4] For an example of the preparation of substituted acylcyclopentenes from five-membered rings, see: B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174–184.
[5] For selected examples of the preparation of substituted acylcyclopentenes from six-membered rings, see: a) S. R. Wilson, R. B. Turner, *J. Org. Chem.* **1973**, *38*, 2870–2873; b) E. G. Gibbons, *J. Am. Chem. Soc.* **1982**, *104*, 1767–1769; c) L. A. Paquette, K. Dahnke, J. Doyon, W. He, K. Wyant, D. Friedrich, *J. Org. Chem.* **1991**, *56*, 6199–6205.
[6] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; c) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476–1491; d) M. Seto, J. L. Roizen, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 6979–6982; *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6876.
[7] G. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, *38*, 1775–1776.
[8] While a recent report shows a single example of a similar β-hydroxyketone, we believe the unusual reactivity and synthetic potential of these compounds has not been fully explored: H. Rinderhagen, J. Mattay, *Chem. Eur. J.* **2004**, *10*, 851–874.
[9] Differences in ring conformational preferences can also be observed in the ^{1}H NMR spectra of 1,3-cyclohexadione (exclusively ketoenol form) and 1,3-cycloheptadione (exclusively diketo form), see: N. Do, R. E. McDermott, J. A. Ragan, *Org. Synth.* **2008**, *85*, 138–146.
[10] For selected examples of the preparation of substituted acylcyclopentenes from seven-membered rings, see: a) J. J. Frankel, S. Julia, C. Richard-Neuville, *Bull. Soc. Chim. Fr.* **1968**, 4870–4875; b) C.-H. Jun, C. W. Moon, S.-G. Lim, H. Lee, *Org. Lett.* **2002**, *4*, 1595–1597.
[11] For a discussion of the properties of fluorinated alcohols and their use, see: J.-P. Begue, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18–29.
[12] a) A lithium alkoxide species is presumably generated in situ based on pK_a values, see: F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463; b) The use of $LiOCH_2CF_3$ as base provided comparable results (90% isolated yield), supporting the likelihood of its in situ formation under the reaction conditions.[16]
[13] For examples of the asymmetric alkylation of vinylogous esters or thioesters from our laboratory, see: a) D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810–811; b) S. R. Levine, M. R. Krout, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 289–292; c) K. V. Petrova, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 293–295.
[14] For a related example of the asymmetric alkylation of vinylogous thioesters, see: B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181–3184; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.

[15] a) L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1983**, *24*, 5425 – 5428; b) D. M. X. Donnelly, J.-P. Finet, B. A. Rattigan, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1729 – 1735.
[16] See Supporting Information for experimental procedures.
[17] a) K. Tani, D. C. Behenna, R. M. McFadden, B. M. Stoltz, *Org. Lett.* **2007**, *9*, 2529 – 2531; b) M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth.* **2009**, *82*, 181 – 193.
[18] $[Pd_2(pmdba)_3]$ is preferable to $[Pd_2(dba)_3]$ in this reaction for ease of separation of pmdba from the reaction products during purification. dba = dibenzylideneacetone.
[19] Exposure of aldehyde **10k** (Table 2, entry 11) to our standard reduction/ring contraction conditions produced a mixture of products as shown below:



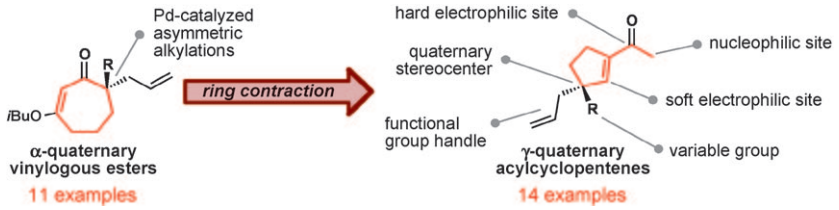
[20] CCDC 686849 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Ring Contraction

A. Y. Hong, M. R. Krout, T. Jensen, N. B. Bennett, A. M. Harned, B. M. Stoltz* _____ ■■■■–■■■■

Ring-Contraction Strategy for the Practical, Scalable, Catalytic Asymmetric Synthesis of Versatile γ-Quaternary Acylcyclopentenes



Contraction action! A simple protocol for the catalytic asymmetric synthesis of highly functionalized γ-quaternary acylcyclopentenes (see schematic) in up to 91% overall yield and 92% *ee* has been developed. The reaction sequence employs a palladium-catalyzed enantioselective alkylation reaction and exploits the unusual stability of β-hydroxy cycloheptanones to achieve a general and robust method for performing two-carbon ring contractions.