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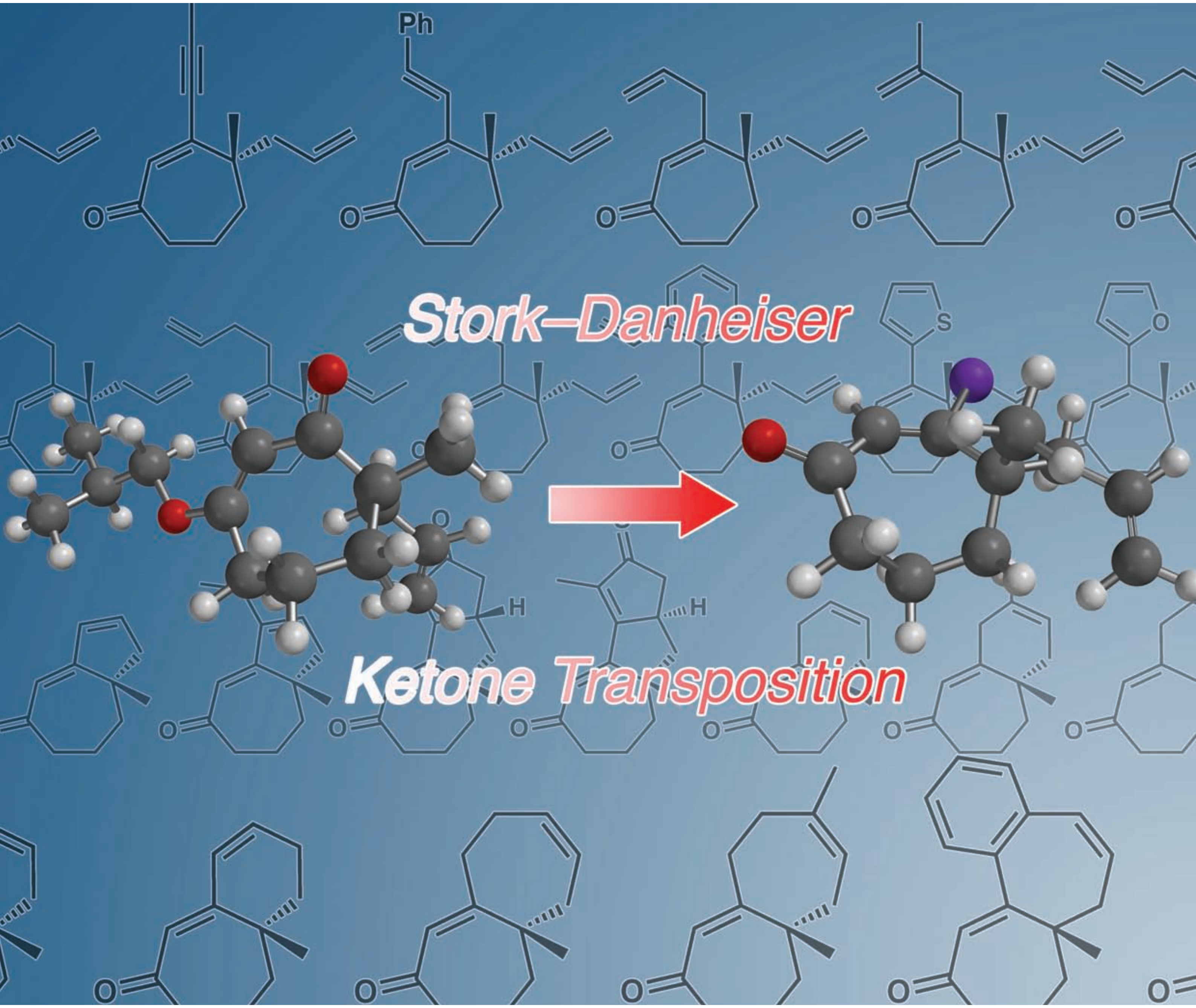

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FULL PAPER

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PAPER

Synthesis of enantioenriched γ-quaternary cycloheptenones using a combined allylic alkylation/Stork–Danheiser approach: preparation of mono-, bi-, and tricyclic systems†

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A general method for the synthesis of β-substituted and unsubstituted cycloheptenones bearing enantioenriched all-carbon γ-quaternary stereocenters is reported. Hydride or organometallic addition to a seven-membered ring vinylogous ester followed by finely tuned quenching parameters achieves elimination to the corresponding cycloheptenone. The resulting enones are elaborated to bi- and tricyclic compounds with potential for the preparation of non-natural analogs and whose structures are embedded in a number of cycloheptanoid natural products.

Introduction

Cycloheptanes bearing all-carbon quaternary stereocenters are incorporated into the polycyclic cores of many natural products including the daphnicyclidins (**2**),[1a] guanacastepenes (**3**),[1b–d] cyathins (**4**),[1e–i] dhilirolide D (**5**),[1j] tricholomalide B (**6**),[1k–l] miniolutelide A (**7**),[1m] and berkeleydione (**8**)[1m–o] (Fig. 1A). Due to the biological relevance and structural complexity of these compounds, we sought to develop a stereoselective approach to this quaternary carbon-containing cycloheptane motif. To this end, we envisioned cycloheptenone **1** as a promising synthetic intermediate. Additionally, we viewed enone **1** as an attractive scaffold for annulation strategies toward bi- and tricyclic structures potentially valuable in total synthesis and the preparation of non-natural analogs. Particularly attractive to us was the homologous structural relationship of the desired [7 – *n*] bicyclic scaffold to the classic [6 – 5] and [6 – 6] frameworks used in hundreds of approaches to natural products (Fig. 1B). Herein we describe a general enantioselective route to cycloheptenone **1** that allows for facile elaboration to bi- and tricyclic products.

Retrosynthetically, we planned to access cycloheptenone **1** using a Stork–Danheiser type transposition of vinylogous ester **9** (Scheme 1A). In this approach, the quaternary stereocenter of vinylogous ester **9** would be installed by employing our palladium-catalyzed asymmetric allylic alkylation methodology.[2,3] Toward this end, acylation and alkylation of vinylogous ester **10** generates racemic β-ketoester **11**, which under our standard decarboxylative alkylation conditions is converted to vinylogous ester **9** (Scheme 1B).[2d]

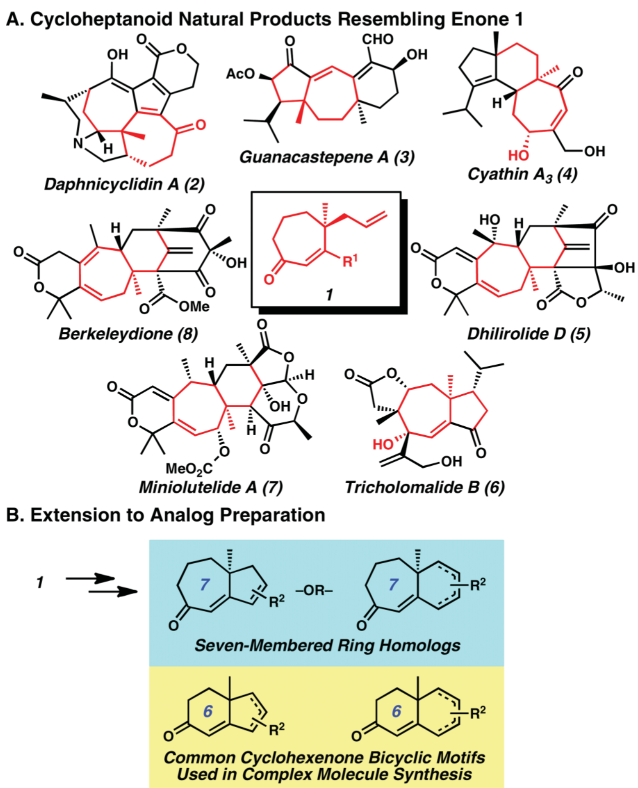

Fig. 1 Potential applications of cycloheptenone **1**.

As previously reported,[2d] initial efforts toward cycloheptenone **1** employing standard transposition conditions[4] were unsuccessful and led to the discovery of the unusual reactivity of vinylogous ester **9**. In contrast to the six-membered ring analog (**12**), both reduction and organometallic addition to vinylogous ester **9** followed by strong acidic work-up favor formation of the corresponding β-hydroxyketones (**14a** and **14b**) instead of the

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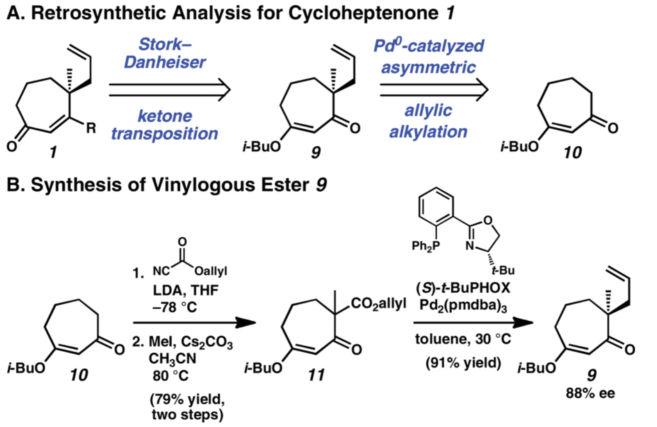
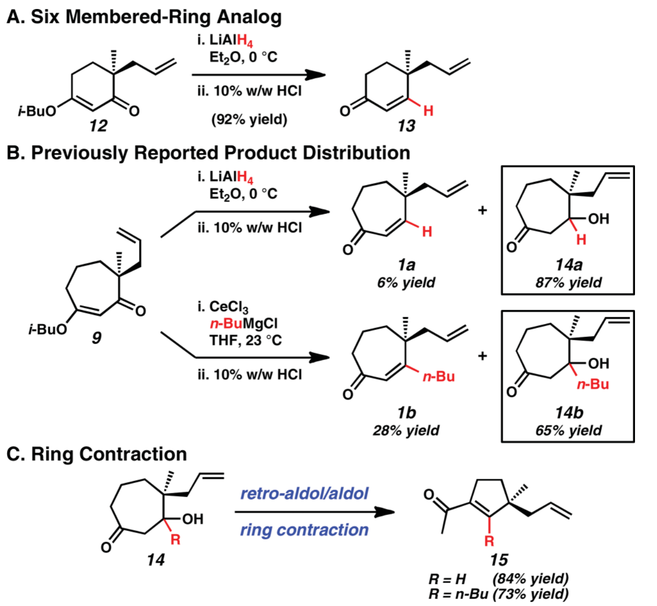
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, copies of NMR and IR spectra for compounds synthesized in this study. See DOI: 10.1039/c1ob06189e



Scheme 1 Retrosynthesis for cycloheptenone **1** and route to vinylogous ester **9**.

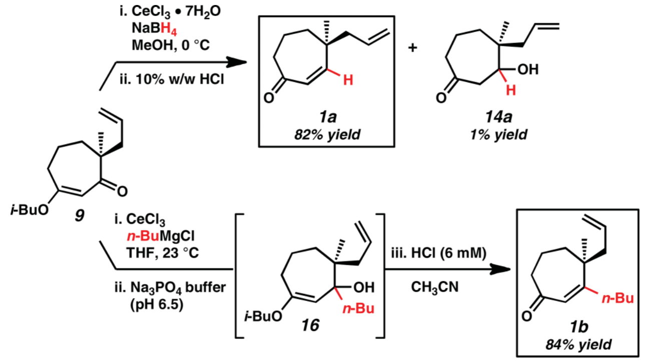
cycloheptenones (**1a** and **1b**) (Scheme 2A and B). Attempts to convert the β-hydroxyketones to enones resulted in an unexpected retro-aldol/aldol ring contraction that our lab has examined extensively (Scheme 2C).[2d] This unexpected reactivity prompted further investigation of the reaction sequence to develop new conditions for the efficient preparation of cycloheptenones.



Scheme 2 Previous investigation into reactivity of vinylogous ester **9** and β-hydroxyketone **14**.

Results and discussion

After some investigation, alternative reaction conditions enabled access to the elusive β-unsubstituted and substituted cycloheptenones. Gratifyingly, Luche reduction of vinylogous ester **9** followed by strong acidic work-up preferentially generated unsubstituted enone **1a** (Scheme 3).[5] Additionally, quenching the Grignard reaction of vinylogous ester **9** with a sodium phosphate buffer and treating the resulting crude oil with dilute acid in acetonitrile afforded substituted enone **1b**. Analysis of the initial crude material suggests that hydroxy enol ether **16** is formed



Scheme 3 Reduction and organometallic addition conditions favoring cycloheptenone formation.

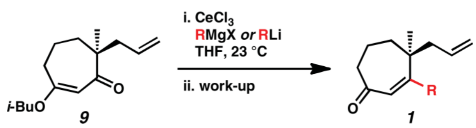
after the sodium phosphate buffer quench.[6] Subsequent acid treatment likely protonates alcohol **16**, which leads to dehydration *via* generation of the resonance stabilized tertiary carbocation and eventual collapse to enone **1b**. Overall, these modified conditions provide divergent routes to γ-quaternary cycloheptenones and acylcyclopentenes in conjunction with our preceding work.

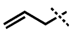
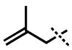
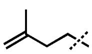
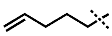
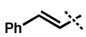
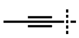
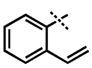
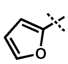
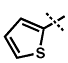
Based on these initial results, we examined the scope of β-substituted enones available from nucleophilic attack on vinylogous ester **9**. The buffer and dilute acid conditions described above (Table 1, method A) accommodate β-substituent groups initiating in sp^3 hybridization, producing allyl, homoallyl, and pentenyl substituted enones in moderate to excellent yield (entries 1–5). Attempts to apply this quenching sequence to reactions involving sp and sp^2 hybridized carbon nucleophiles resulted in complex reaction mixtures. Selectivity for the cycloheptenone was restored by quenching such reactions with a concentrated strong acid (*i.e.*, hydrochloric or sulfuric acid) and heating the resulting solutions at elevated temperature (Table 1, methods B and C). These conditions initially produce a mixture of β-hydroxyketone and enone that converges to the desired product over time.[7] In this manner, the synthesis of vinyl, alkynyl, aryl, and heteroaryl substituted enones is accomplished (entries 6–10). Of particular note is entry 8, in which an *ortho*-substituted aryl Grignard reagent can be incorporated to generate enone **1j**.[8] In general, application of the appropriate work-up conditions allows access to a variety of β-substituted γ-quaternary cycloheptenones.

With various cycloheptenones in hand, we sought to elaborate these compounds to bi- and tricyclic structures (Table 2). We first examined olefin metathesis reactions between the β-substituent and quaternary center allyl fragment to generate a number of [7 – 5], [7 – 6], [7 – 7], and [7 – 8] fused ring systems. Substrates possessing two terminal olefins lead to bicyclic products with high efficiency (entries 1, 3, 5, and 8). This process also accommodates the production of trisubstituted olefin products (*i.e.*, **17b**, **17d**, and **17f**) through ring-forming enyne metathesis (entry 2) or ring closing metathesis (entries 4 and 6). In addition, cycloheptenone **1j** is converted to the [7 – 7 – 6] tricyclic enone (**17g**) under the reaction conditions (entry 7). The ketone transposition/ring closing metathesis sequence is also amenable to *trans*-propenyl analog **18**,[9] producing the [7 – 6] system (**17i**) with the alkene adjacent to the quaternary center (Scheme 4A).

Having produced two [7 – 6] structures with variable olefin positions, we next investigated conditions to generate the conjugated dienone system. Interestingly, treatment of skipped diene **17c** with

Table 1 Scope of organometallic addition to vinylogous ester **9**[a]



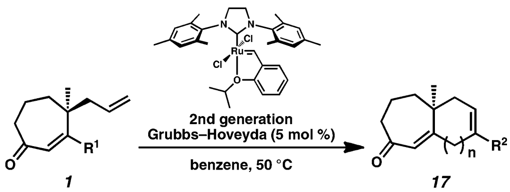
Entry	R	Work-up[b]	Product (*1*)	Yield (%)[c]
1		A	***1c***	73
2		A	***1d***	93
3		A	***1e***	90
4		A	***1f***	82
5		A	***1g***	92
6[d]		B	***1h***	84
7		C	***1i***	97
8[e]		C	***1j***	66
9		B	***1k***	72
10		B	***1l***	84

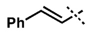
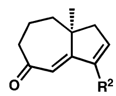
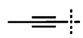
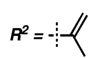
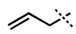
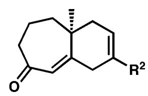
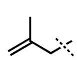
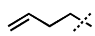
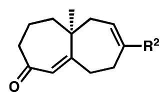
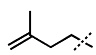
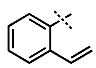
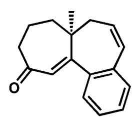
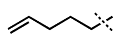
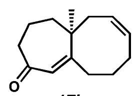
[a] Conditions: vinylogous ester **9** (1.0 equiv), $CeCl_3$ (2.5 equiv), RMgX or RLi (3.0 equiv) in THF, 23 °C then work-up by methods A, B, or C. [b] Method A: a) pH 6.5 Na_3PO_4 buffer b) 6 mM HCl, CH_3CN; Method B: 10% w/w aq HCl, 60 °C; Method C: 2 M H_2SO_4, 60 °C. [c] Yield of isolated product. [d] See Supporting Information for slightly different reaction parameters. [e] Product is 1.9 : 1 mixture of atropisomers.

base at ambient temperature migrated both olefins into the six-membered ring, producing diene **17j** (Scheme 4B). Alternatively, the alkenes can be migrated into conjugation with the carbonyl by microwave irradiation, affording diene **17k** (Scheme 4B).

Lastly, we envisioned enone **1i** as an ideal substrate for a Pauson–Khand reaction given the proximal enyne functionality. Treatment of **1i** with dicobalt octacarbonyl employing dimethyl-sulfoxide as an activating agent[10] produced the [7 – 5 – 5] tricycle in excellent yield with a 3 : 1 diastereomeric ratio of **19a** : **19b** (Scheme 4C).

Table 2 Ring closing metathesis on cycloheptenones to generate bi- and tricyclic products[a]



Entry	Substrate (*1*)	R[1]	Product (*17*)		Yield (%)[b]
1[c]	***1h***			***17a*** *R² = H*	93
2	***1i***			***17b*** 	99
3[d]	***1c***			***17c*** *R² = H*	91
4[d]	***1d***			***17d*** *R² = Me*	90
5	***1e***			***17e*** *R² = H*	90
6	***1f***			***17f*** *R² = Me*	98
7[e]	***1j***		 **17g**		96
8	***1g***		 **17h**		99

[a] Conditions: cycloheptenone **1** (1.0 equiv) and Grubbs–Hoveyda 2nd generation catalyst (5.0 mol%) in benzene, 50 °C. [b] Yield of isolated product. [c] See Supporting Information for alternative reaction parameters. [d] 1,4-benzoquinone (10 mol%) added. [e] Performed in toluene.

Conclusions

In summary, we have developed a method to access β-functionalized cycloheptenones (**1**) possessing a γ-quaternary stereocenter through a sequence involving asymmetric alkylation followed by addition of an organometallic reagent and acid-mediated ketone transposition. Subsequent manipulation of the newly incorporated β-substituents provides a number of bi- and tricyclic compounds with potential for the preparation of non-natural analogs and whose structure is present in cycloheptanoid natural products. Further efforts toward the total synthesis of such targets will be reported in due course.

Acknowledgements

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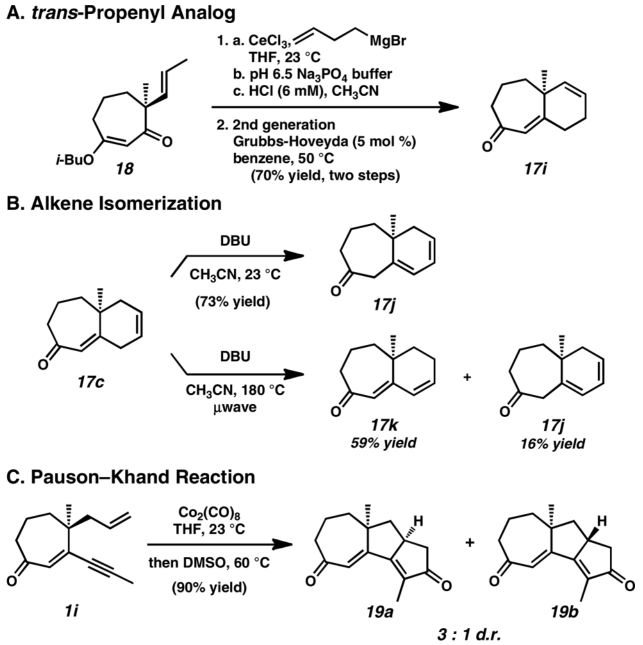

Scheme 4 Synthetic applications.

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2 (*a*) D. C. Behenna and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 15044; (*b*) J. T. Mohr, D. C. Behenna, A. M. Harned and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2005, **44**, 6924; (*c*) J. T. Mohr and B. M. Stoltz, *Chem.–Asian J.*, 2007, **2**, 1476; (*d*) A. Y. Hong, M. R. Krout, T. Jensen, N. B. Bennett, A. M. Harned and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2011, **50**, 2756; (*e*) D. E. White, I. C. Stewart, R. H. Grubbs and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 810; (*f*) J. A. Enquist Jr. and B. M. Stoltz, *Nature*, 2008, **453**, 1228; (*g*) S. R. Levine, M. R. Krout and B. M. Stoltz, *Org. Lett.*, 2009, **11**, 289; (*h*) K. V. Petrova, J. T. Mohr and B. M. Stoltz, *Org. Lett.*, 2009, **11**, 293.

3 Concurrent with our efforts, palladium-catalyzed asymmetric allylic alkylations to form enantioenriched α-quaternary vinylogous esters and thioesters have also been performed by Trost. See: (*a*) B. M. Trost, C. Pissot-Soldermann, I. Chen and G. M. Schroeder, *J. Am. Chem. Soc.*, 2004, **126**, 4480; (*b*) B. M. Trost and G. M. Schroeder, *Chem.–Eur. J.*, 2005, **11**, 174; (*c*) B. M. Trost, C. Pissot-Soldermann and I. Chen, *Chem.–Eur. J.*, 2005, **11**, 951; (*d*) B. M. Trost, R. N. Bream and J. Xu, *Angew. Chem., Int. Ed.*, 2006, **45**, 3109.

4 G. Stork and R. L. Danheiser, *J. Org. Chem.*, 1973, **38**, 1775.

5 Methanol likely plays a large role in selectivity inasmuch as exchanging the solvent to diethyl ether after Luche reduction and before acid treatment leads to the β-hydroxyketone preferentially. See ref. 2d.

6 Determined by ^{1}H NMR analysis of crude oil. Attempts to purify the crude material under several chromatography conditions resulted in decomposition to cycloheptenone **1b** and β-hydroxyketone **14b**.

7 Disappearance of β-hydroxyketone can be monitored by TLC analysis.

8 Cycloheptenone **1j** is formed as a 1.9 : 1 mixture of atropisomers. Broadening of the isomeric peaks was observed in a variable temperature ^{1}H NMR study. See Supporting Information.

9 *trans*-Propenyl analog **18** is prepared by palladium-catalyzed isomerization of terminal olefin **9**. See ref. 2d for details.

10 Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek and P. L. Pauson, *Organometallics*, 1993, **12**, 220.