CHAPTER 2

Palladium-Catalyzed Asymmetric Alkylation in the Synthesis of Cyclopentanoid and Cycloheptanoid Core Structures[†]

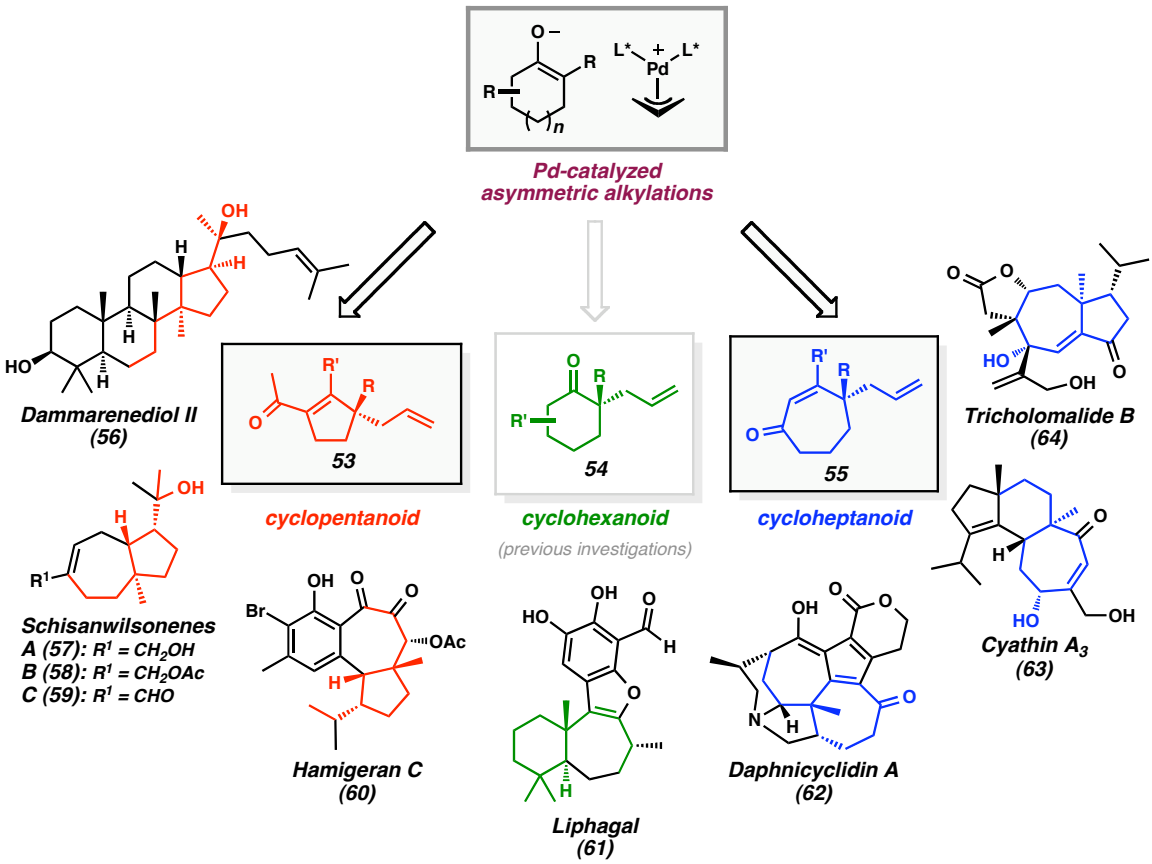
2.1 INTRODUCTION AND BACKGROUND

The stereoselective total synthesis of polycyclic natural products depends greatly on the available tools for the efficient preparation of small and medium sized rings in enantioenriched form.[1] Facile means to elaborate these monocyclic intermediates to fused, bridged, and spirocyclic architectures found within natural ring systems would significantly contribute to modern synthetic methods. While many strategies have been developed for the preparation of six-membered rings and their corresponding polycyclic derivatives, approaches toward the synthesis of five- and seven-membered rings would benefit from further development.

[†] This research was performed in collaboration with Drs. Allen Y. Hong, Michael R. Krout, Thomas Jensen, and Andrew M. Harned and has been published. This chapter was primarily derived from a published full paper (Ref. c). See: (a) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2756–2760. (b) Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56–59. (c) Hong, A. Y.; Bennett, N. B.; Krout, M. R.; Jensen, T.; Harned, A. M.; Stoltz, B. M. *Tetrahedron* **2011**, *67*, 10234–10248.

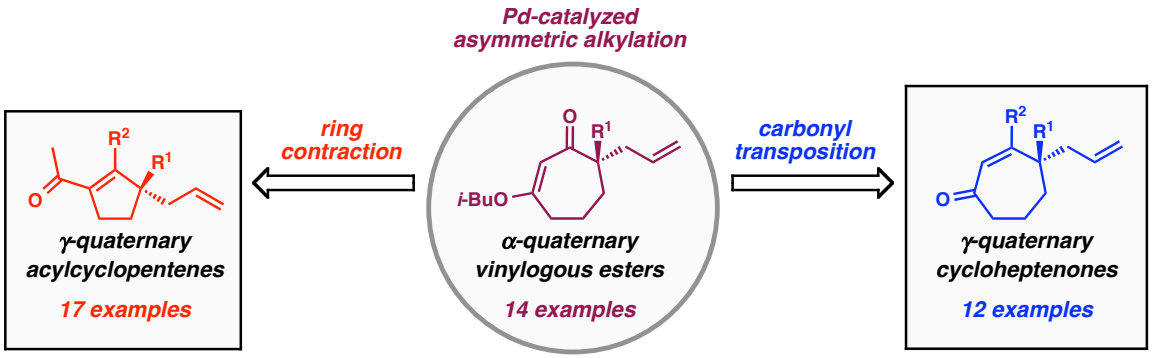
Guided by our continuing interest in the synthesis of polycyclic systems bearing all-carbon quaternary stereocenters using Pd-catalyzed asymmetric alkylation chemistry,[2,3,4,5,6] we sought to prepare various chiral cyclic ketone building blocks for total synthesis (Figure 2.1). Our investigation of six-membered ring substrates has previously enabeled the enantioselective total syntheses of a number of complex natural products (e.g., liphigal, **61**).[7] Given our earlier success, we aimed to generalize our approach to gain access to natural products containing chiral cyclopentanoid and cycloheptanoid ring systems as a part of a broader synthetic strategy.

Figure 2.1. Application of cyclopentanoid, cyclohexanoid, and cycloheptanoid cores toward stereoselective natural product synthesis.



Our efforts have led to the development of general strategies for the preparation of α-quaternary vinylogous esters and their conversion to γ-quaternary cycloheptenones using Stork–Danheiser transformations (Figure 2.2).[8] During the course of this work, we observed unusual reactivity with β-hydroxycycloheptanones and exploited a two-carbon ring contraction to provide a general synthesis of γ-quaternary acylcyclopentenes.[9] With access to the isomeric five- and seven-membered enones, we have prepared diverse synthetic derivatives and polycyclic systems that can potentially provide different entry points for synthetic routes toward complex natural products.

Figure 2.2. General access to enantioenriched cyclopentanoid and cyclohexanoid cores.

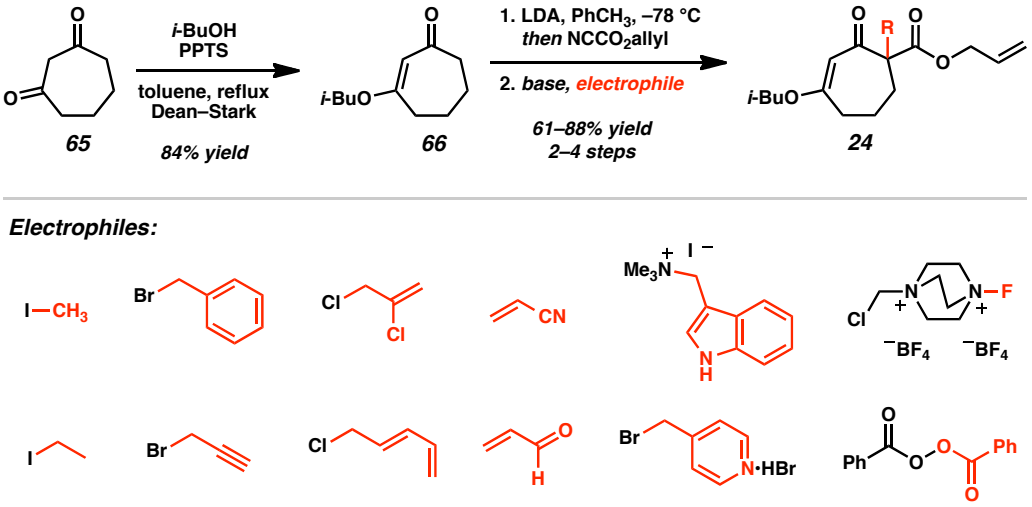


2.1 β-KETOESTER SYNTHESIS AND Pd-CATALYZED ASYMMETRIC ALKYLATION REACTIONS

Much of our past research on the asymmetric alkylation of cyclic ketones[2,3,7a,c,g–i,10d] and vinylogous esters[7b,d–f,10a–c,e] focused on six-membered rings, while transformations of larger rings were less thoroughly investigated. We hoped to expand our work by exploring asymmetric alkylations of seven-membered vinylogous esters.

The feasibility of various types of substrates for our asymmetric alkylation chemistry suggested that vinylogous ester **66** could be transformed into silyl enol ether, enol carbonate, or β-ketoester substrates, but we chose to prepare β-ketoesters due to their relative stability and ease of further functionalization. To access a variety of racemic α-quaternary β-ketoester substrates for Pd-catalyzed asymmetric alkylation reactions, we required multi-gram quantities of 1,3-cycloheptanedione (**65**). Dione **65** is commercially available,[11] but we typically prepare it from cyclopentanone by the route of Ragan and co-workers to facilitate large scale synthesis.[12] Treatment of **65** with *i*-BuOH and catalytic PPTS under Dean–Stark conditions produces vinylogous ester **66** (Scheme 2.1).[11] Acylation of **66** with allyl cyanoformate following deprotonation with LDA enables facile installation of the requisite allyl ester functionality. Subsequent enolate trapping with a variety of electrophiles under basic conditions provides substrates containing alkyl, alkyne, alkene, 1,3-diene, vinyl chloride, nitrile, heteroarene, aldehyde, fluoride, silyl ether, and ester functionalities in 61–88% yield over two to four steps (**24a**–**n**). With these quaternary β-ketoesters in hand, we evaluated the scope of Pd-catalyzed asymmetric alkylation reactions on seven-membered ring vinylogous ester substrates, focusing on methyl/allyl substituted **24a** for our initial optimization efforts.

Scheme 2.1. Synthesis of parent vinylogous ester ***66*** *and β-ketoester substrates* ***24****.*

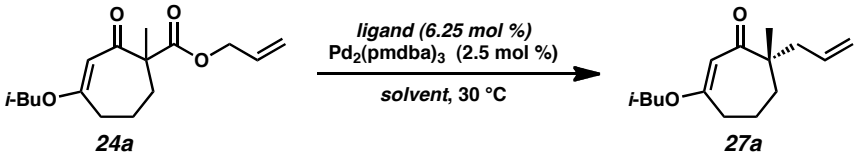


Optimal parameters for the asymmetric alkylation were identified with methyl-substituted β-ketoester **24a** by surveying several electronically differentiated PHOX ligands combined with $Pd_2(pmdba)_3$[13,14] in a number of solvents (Table 2.1). Our initial conditions employing (*S*)-*t*-BuPHOX[2,15] (**3**, 6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in THF give vinylogous ester **27a** in 94% yield and 84% ee (entry 1).[16] Application of the same catalyst system in other ethereal solvents, such as *p*-dioxane, 2-methyl THF, TBME, and Et_2O leads to only slight improvements in the enantioselectivity of the reaction to give the desired product in up to 86% ee (entries 2–5). Switching to aromatic solvents provides modest increases in asymmetric induction, furnishing **27a** in 91% yield and 88% ee in the case of toluene (entries 6 and 7).

We next examined the impact of other PHOX ligands (**8** and **67**) in this medium. Electron-deficient ligand **8**[7b,f,17] improves enantioselectivity at the cost of higher catalyst loading and lower yield (entry 8). Structural modification of the aryl phosphine

backbone was evaluated with ligand **67**, but this proved less effective, giving reduced yield and ee (entry 9). Of the three ligands, **3** furnishes the best overall results.

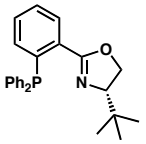
Table 2.1. Solvent and ligand effects on enantioselective decarboxylative allylation.[a]



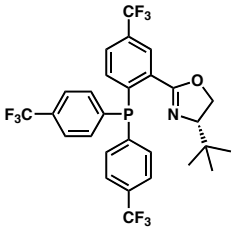
24a ***27a***

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	*13*	THF[e]	94	84
2	*13*	*p*-dioxane	86	84
3	*13*	2-methyl THF[e]	75	85
4	*13*	TBME[e]	88	85
5	*13*	Et_2O	93	86
6	*13*	benzene	84	86
7	*13*	toluene	91	88
8[d]	*14*	toluene	57	90
9	*150*	toluene	77	72

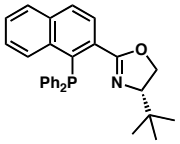
[a] *Conditions*: β-ketoester **24a** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), ligand (6.25 mol %) in solvent (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Increased catalyst loadings were required to achieve full conversion: $Pd_2(pmdba)_3$ (5 mol %), **8** (12.5 mol %). [e] THF = tetrahydrofuran, 2-methyl THF = 2-methyl tetrahydrofuran, TBME = *tert*-butyl methyl ether.



***(S)-t*-BuPHOX (*3*)**



(S)*-$(CF_3)_3$-*t*-BuPHOX *(8)

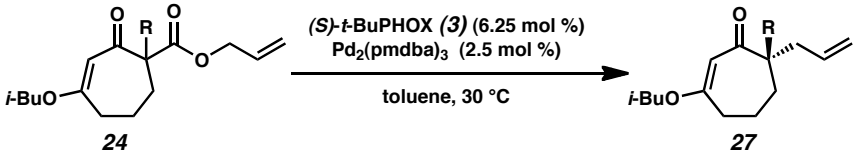


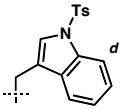
67

With optimal ligand and solvent conditions in hand, we explored asymmetric alkylation of a variety of α-substituted β-ketoesters (Table 2.2). Simple alkyl substitution perform well under our standard conditions (entries 1 and 2), as did a variety of aromatic and heteroaromatic groups (entries 3, 9–10). Additionally, unsaturated functionality such as alkynes, alkenes, and 1,3-dienes do not suffer from competitive reaction pathways (entries 4–6). In the case of vinyl chloride **24g**, no products derived from oxidative addition into the C–Cl bond are observed (entry 7). Gratifyingly, *N*-basic

functionality such as nitriles and pyridines can be carried through the reaction without noticeable catalyst poisoning (entries 8 and 9). Perhaps the most intriguing result is the observation that substrate **24k** with an unprotected aldehyde can be converted to the enantioenriched product **27k** in 90% yield and 80% ee, highlighting the essentially neutral character of the reaction conditions (entry 11). Tertiary fluoride products can also be obtained efficiently in 94% yield and 91% ee (entry 12). Although most β-ketoesters undergo smooth asymmetric alkylation, several products such as silyl ether **27m**[18] and benzoate ester **27n**[19] are not formed as efficiently due to unproductive side reactions (entries 13–14).

Table 2.2. Scope of the Pd-catalyzed enantioselective alkylation of cyclic vinylogous esters.[a]



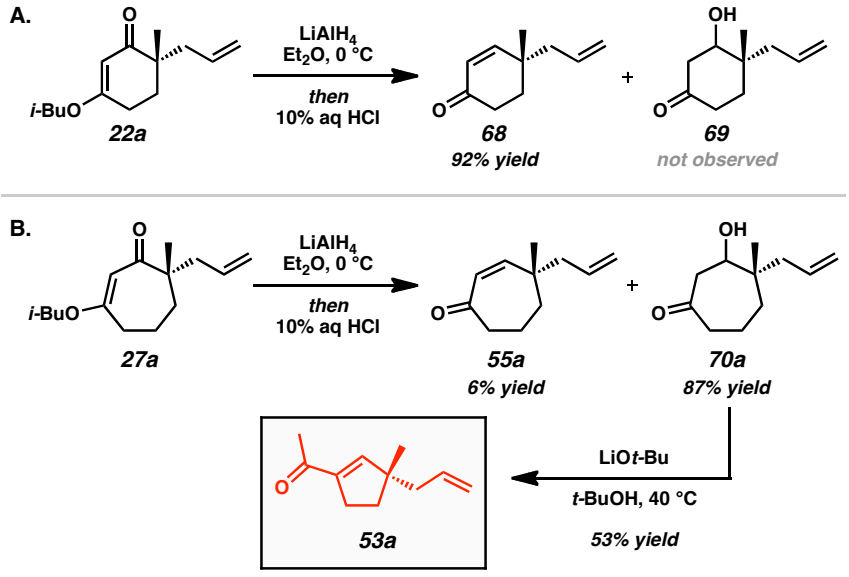
entry	substrate *24*	R	product *27*	yield (%)[b]	ee (%)[c]	entry	substrate *24*	R	product *27*	yield (%)[b]	ee (%)[c]
1	*24a*	$-CH_3$	*27a*	91	88	9	*24i*		*27i*	97	85
2	*24b*	$-CH_2CH_3$	*27b*	89	92						
3	*24c*	$-CH_2Ph$	*27c*	98	86	10	*24j*		*27j*	98	83
4	*24d*	$-CH_2C{\equiv}CH$	*27d*	88	89						
5	*24e*	$-CH_2CH_2CH{=}CH_2$	*27e*	95	87						
6	*24f*		*27f*	90	90	11	*24k*		*27k*	90	80
						12	*24l*	–F	*27l*	94	91
7	*24g*		*27g*	99	86	13	*24m*	$-CH_2OTBDPS$[d]	*27m*	66	58
8	*24h*	$-CH_2CH_2CN$	*27h*	96	87	14	*24n*		*27n*	75	57

[a] *Conditions*: β-ketoester **24** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), *(S)-t*-BuPHOX (**3**) (6.25 mol %) in toluene (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC or SFC. [d] Ts = 4-toluenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

2.1 UNUSUAL REACTIVITY OF β-HYDROXYCYCLOHEPTANONES

With an assortment of asymmetric alkylation products in hand, we next sought to perform a carbonyl transposition using methods developed by Stork and Danheiser.[20] Hydride reduction of six-membered vinylogous ester **22a** with subsequent acid treatment gives enone **68** as expected (Scheme 2.2A). To our surprise, application of identical reaction conditions to the seven-membered analog (**27a**) provides poor yield of cycloheptenone **55a** (Scheme 2.2B). Only minor quantities of elimination product are observed even after prolonged stirring with 10% aqueous HCl. Closer inspection of the reaction mixture revealed β-hydroxyketone **70a** as the major product, suggesting that these seven-membered ring compounds display unique and unusual reactivity compared to their cyclohexyl counterparts.[21,22,23]

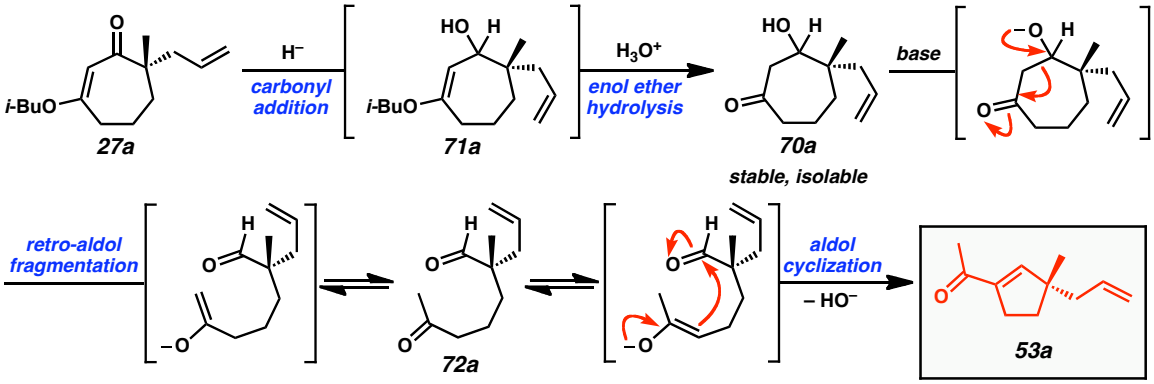
Scheme 2.2. Observation of the unusual reactivity of β-hydroxycycloheptanone ***70a****.*



Without initial success using acidic conditions, we reasoned that β-hydroxyketone **70a**[24] could potentially provide cycloheptenone **55a** under basic conditions through a β-elimination pathway (Scheme 2.2B). However, attempts in this regard did not produce enone **55a**, but instead generated isomeric enone **53a** that appeared to be formed through an unexpected ring contraction pathway. Notably, this transformation serves as a rare example of a two-carbon ring contraction.[22,25,26]

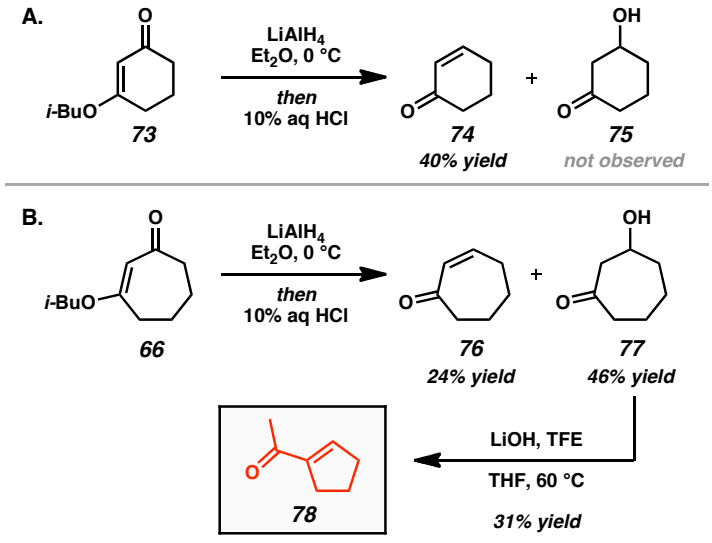
Upon consideration of the reaction mechanism, we believe this process occurs through an initial deprotonation of the hydroxy moiety, followed by retro-aldol ring fragmentation to a ketoaldehyde enolate (Scheme 2.3). Subsequent isomerization to the more substituted enolate and aldol cyclization could lead to the observed two-carbon ring contraction product **53a**. Attempts to isolate the intermediate ketoaldehyde **72a** were unsuccessful, but aldehyde peaks could be observed by ^{1}H NMR in reactions that did not proceed to full conversion. Subsequent experiments on more substituted β-hydroxyketones enabled isolation of linear uncyclized intermediates and provided additional support for this reaction mechanism (Scheme 2.6).

Scheme 2.3. Proposed ring contraction mechanism.



To explore the general stability and reactivity of β-hydroxycycloheptanones, we briefly examined simplified analogs that do not possess the α-quaternary stereocenter (Scheme 2.4). Following hydride reduction, elimination to cyclohexenone **74** is observed for the six-membered vinylogous ester **73**, while β-hydroxycycloheptanone **77** and volatile cycloheptenone **76** are observed for cycloheptyl analog **66**. In the seven-membered ring case, a higher proportion of elimination product is observed when compared to the substituted analog **27a**. A milder aqueous acid work-up may suffice to hydrolyze the isobutyl enol ether and enable isolation of the β-hydroxyketone in higher yield in this case. Ring contraction of β-hydroxycycloheptanone **77** under basic conditions proceeds smoothly to give volatile acylcyclopentene **78**. These observations suggest that the unusual two-carbon ring contraction appears to be a reactivity trend associated with seven-membered rings and motivated the development of the ring contraction methodology as a general approach to chiral acylcyclopentenes.

Scheme 2.4. Attempted Stork–Danheiser manipulations on unsubstituted rings.



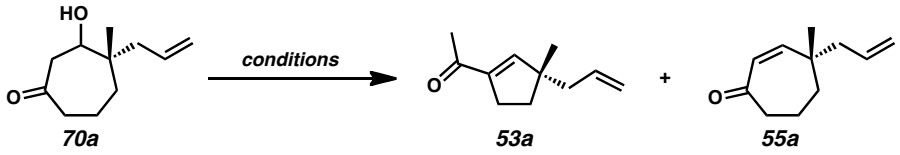
2.1 RING CONTRACTION STRATEGY FOR PREPARING γ-QUATERNARY ACYLCYCLOPENTENES

Intrigued by our findings, we sought to develop a robust route to γ-quaternary acylcyclopentenes with many substitution patterns. Exploration of a number of bases, additives, solvents, and temperatures for the ring contraction of β-hydroxyketone **70a** provided optimal parameters for the transformation (Table 2.3). Given our early result using LiO*t*-Bu, we examined a number of other aldol cyclization conditions with a variety of non-nucleophilic bases. We observed that several *tert*-butoxides in *t*-BuOH and THF provide conversion to the desired product (**53a**) in good yields (entries 1–4), but noted that the rate of product formation is comparatively slower with LiO*t*-Bu than with NaO*t*-Bu or KO*t*-Bu. The use of various hydroxides reveals a similar trend, where NaOH and KOH generate acylcyclopentene **53a** in 4 hours with improved yields over the respective *tert*-butoxides (entries 5 and 6). The relatively sluggish reactivity of LiOH may be due to the lower solubility of this base in THF, providing **53a** in low yield with the formation of various intermediates (entry 7).

To improve the yield of the reaction with LiOH as base, we investigated alcohol additives that facilitate the production of mild, organic-soluble bases under the reaction conditions. The combination of *t*-BuOH and LiOH in THF increases the yield of **53a** to a similar level as that observed with LiO*t*-Bu, although the reaction still proceeds slowly (entry 8). More acidic, non-nucleophilic alcohols such as hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) demonstrate exceptional reactivity in combination with LiOH and efficiently afford **53a** in high yields (entries 9 and 10).[27] In particular, TFE enables the production of **53a** in 96% yield. Comparable results with preformed

$LiOCH_2CF_3$[28] suggest this alkoxide could be the active base under the LiOH/TFE ring contraction conditions (entry 11).

Table 2.3. Ring contraction optimization.[a]



70a ***53a*** ***55a*** ***not observed***

entry	base	additive	solvent	T (°C)	conversion (%)	time (h)	yield (%)[b]
1	LiO*t*-Bu	—	*t*-BuOH	40	100	9	71
2	LiO*t*-Bu	—	THF	40	100	8	60
3	NaO*t*-Bu	—	THF	40	100	5	81
4	KO*t*-Bu	—	THF	40	100	5	85
5	NaOH	—	THF	60	100	4	89
6	KOH	—	THF	60	100	4	87
7	LiOH	—	THF	60	78	24	19[d]
8	LiOH	*t*-BuOH	THF	60	98	24	78
9	LiOH	HFIP[c]	THF	60	99	12.5	87
10	LiOH	TFE[c]	THF	60	99	12.5	96
11	$LiOCH_2CF_3$	—	THF	60	—	10	90[e]
12	$CsOH{\cdot}H_2O$	—	THF	60	100	4	48
13	Cs_2CO_3	—	THF	60	67	24	61[f]
14	Cs_2CO_3	TFE[c]	THF	60	100	12.5	86
15	Cs_2CO_3	TFE[c]	CH_3CN	60	100	12.5	100
16	NaO*t*-Bu	*t*-BuOH	THF	40	100	8	52
17	KO*t*-Bu	*t*-BuOH	THF	40	100	8	57
18	LiOH	*t*-BuOH	THF	40	87	24	77
19	LiOH	TFE[c]	THF	40	73	24	73
20	LiOH	HFIP[c]	THF	40	84	24	81
21	CsF	—	CH_3CN	60	86	24	10

[a] *Conditions*: β-hydroxyketone **70a** (1.0 equiv), additive (1.5 equiv), base (1.5 equiv), solvent (0.1 M) at indicated temperature for 9–24 h. [b] GC yield using an internal standard at ≥ 98% conversion unless otherwise stated. [c] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol. [d] Several reaction intermediates observed by TLC and GC analysis; proceeded to 78% conversion. [e] Isolated yield. [f] Reaction did not reach completion at 24 h; proceeded to 67% conversion.

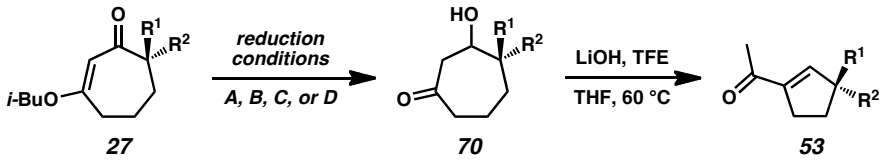
Concurrent investigation of cesium bases reinforced the importance of alcohol additives for the in situ formation of organic-soluble bases in the ring contraction transformation. With $CsOH{\cdot}H_2O$ and Cs_2CO_3, product formation is inefficient due to low

yield or sluggish reaction progress (entries 12 and 13). However, the addition of TFE affords acylcyclopentene **53a** in yields comparable to those of the LiOH/TFE conditions (entry 14). Notably, ring contraction with Cs_2CO_3/TFE can also be performed in acetonitrile as an alternative, non-ethereal solvent with high efficiency (entry 15). Additional combinations of bases, additives, solvents, and temperatures were evaluated, but these conditions were generally less effective (entries 16–21).[29]

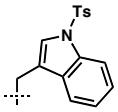
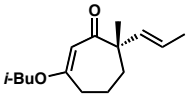
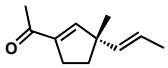
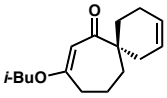
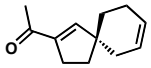
While a number of bases are effective for the production of **53a** in excellent yields, we selected the combination of LiOH/TFE as our standard conditions for reaction scope investigation due to the lower cost and greater availability of base. The data from our study further recognize the unique properties of these mild bases and suggest their application may be examined in a broader context.[30,31] Importantly, none of the conditions surveyed for the ring contraction studies generated the β-elimination product, cycloheptenone **55a**.

With optimal base-promoted conditions in hand, we investigated the scope of the ring contraction chemistry with a variety of substitution patterns[23] (Table 2.4). Simple alkyl, aromatic, and heteroaromatic functionalized substrates perform well under our standard parameters (Method A) in 84–95% yield (entries 1–6, 10). Additionally, vinyl chlorides, nitriles, and indoles can be incorporated into the target acylcyclopentenes in 85–92% yield (entries 7 and 8). Further studies revealed that DIBAL can alternatively be employed to generate the β-hydroxyketone by enabling more precise control of hydride stoichiometry. The use of these modified conditions followed by oxalic acid work-up in methanol (Method B) facilitates the preparation of pyridine-containing acylcyclopentene **53i** in higher yield compared to Method A (entry 9).

Table 2.4. Ring contraction substrate scope.[a–e]



27 **70** **53**

entry	substrate **27**	reduction conditions	R^1	R^2	product **53**[e]	yield (%)[f]
1	**27a**	A	$-CH_3$	$-CH_2CH{=}CH_2$	**53a**	84
2	**27b**	A	$-CH_2CH_3$	$-CH_2CH{=}CH_2$	**53b**	90
3	**27c**	A	$-CH_2Ph$	$-CH_2CH{=}CH_2$	**53c**	86
4	**27d**	A	$-CH_2C{\equiv}CH$	$-CH_2CH{=}CH_2$	**53d**	95
5	**27e**	A	$-CH_2CH_2CH{=}CH_2$	$-CH_2CH{=}CH_2$	**53e**	87
6	**27f**	A		$-CH_2CH{=}CH_2$	**53f**	91
7	**27g**	A		$-CH_2CH{=}CH_2$	**53g**	92
8	**27h**	A	$-CH_2CH_2CN$	$-CH_2CH{=}CH_2$	**53h**	85
9	**27i**	B		$-CH_2CH{=}CH_2$	**53i**	80
10	**27j**	A		$-CH_2CH{=}CH_2$	**53j**	87
11	**27m**	C	$-CH_2OTBDPS$[i]	$-CH_2CH{=}CH_2$	**53m**	91
12	**27o**[g]	C	$-(CH_2)_3OTBDPS$[i]	$-CH_2CH{=}CH_2$	**53o**	85
13	**27p**[h]	A			**53p**	81
14	**27q**[g]	A			**53q**	87
15	**27n**	D	–OH	$-CH_2CH{=}CH_2$	**53n**	25
16	**27l**	A	–F	$-CH_2CH{=}CH_2$	**53l**	0

[a] *Reduction Conditions A*: vinylogous ester **27** (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 **27** (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 **27** (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] *Reduction Conditions D*: (1) vinylogous ester **27** (1.0 equiv), DIBAL (3.3 equiv) in $PhCH_3$ (0.03 M) at –78 °C; (2) 10% aqueous HCl in Et_2O at 0 °C. [e] *Ring Contraction Conditions E*: β-hydroxyketone **70** (1.0 equiv), TFE (1.5 equiv), LiOH (1.5 equiv) in THF (0.1 M) at 60 °C. [f] Isolated yield over 2–3 steps. [g] Prepared from **27k**. See Experimental Section. [h] Prepared from **27a**. See Experimental Section. [i] Ts = 4-toluenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl, DIBAL = diisobutylaluminum hydride.

While various compounds undergo the ring contraction sequence with high efficiency, other substrates with more sensitive functionality require modification of the reaction conditions. To this end, we investigated the use of milder reduction conditions developed by Luche[32] to further increase the reaction scope. Silyl ether substrate **27m**[33] can be converted to the corresponding acylcyclopentene **53m** in 86% yield using the $LiAlH_4$ protocol (Method A), but application of Luche reaction conditions using (Method C) enables improvement to 91% yield (entry 11). The same conditions provide the related silyl ether-containing acylcyclopentene **53o** with a longer carbon chain in 85% yield (entry 12).

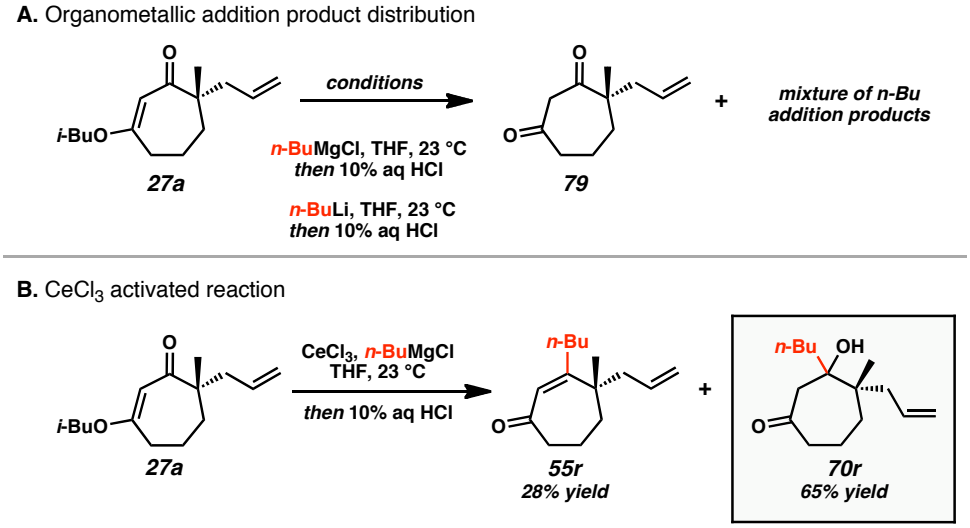
Our success in performing the ring contraction with a variety of substituents at the quaternary stereocenter encouraged studies aimed at determining whether additional substitution patterns could be introduced into the acylcyclopentene products. While most substrates involve a variable group and an allyl fragment positioned on the quaternary center, we were intrigued by the possibility of performing the ring contraction with other groups. Investigation of *trans*-propenyl substituted vinylogous ester **27p** using the standard LiOH/TFE conditions showed that the chemistry is unaffected by modification of the allyl fragment, generating product in 81% yield (entry 13). Additionally, the reaction of spirocycle **27q** also proceeds without complication and affords the desired acylcyclopentene in 87% yield (entry 14).

Although many compounds perform well in the ring contraction sequence, certain substrates pose significant challenges. DIBAL reduction with a 10% aqueous HCl work-up (Method D) and ensuing ring contraction of α-benzoate ester **27n** provides tertiary hydroxyl acylcyclopentene **53n**, but the yield is relatively low compared to other

substrates (entry 15). Attempts to prepare the corresponding tertiary fluoride **27l** were unsuccessful as no desired product was observed (entry 16). Under the reaction conditions, both vinylogous esters lead to more complex product mixtures from unproductive side reactions in contrast to the typically high yielding transformations observed for other substrates.

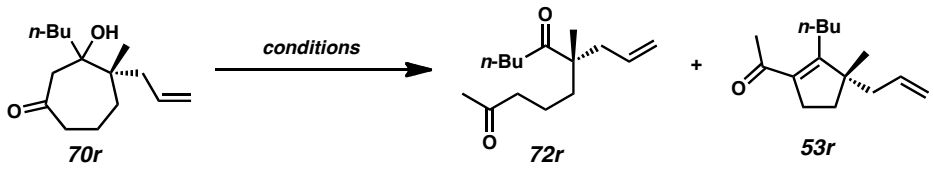
To obtain more functionalized acylcyclopentene products and extend our methodology, we sought access to β-substituted acylcyclopentenes by replacing the hydride reduction step with the addition of an organometallic reagent and applying the ring contraction chemistry on the resulting tertiary β-hydroxyketones. We selected a simple system for our initial investigations and evaluated the reaction of *n*-butyl nucleophiles with vinylogous ester **27a**. Unfortunately, the addition of *n*-BuMgCl or *n*-BuLi affords a complex mixture of products and proceeds slowly without reaching completion, consequently converting unreacted starting material to dione **79** upon work-up with strong acid (Scheme 2.5A).[34] This low reactivity can be understood from the electron-rich and sterically-crowded nature of the carbonyl electrophile. Gratifyingly, excellent reactivity is achieved by introducing $CeCl_3$ to the reaction with the Grignard reagent,[35] although a fair amount of the corresponding enone is produced in the transformation (Scheme 2.5B).[36] Nevertheless, the $CeCl_3$-supplemented addition furnishes a significantly improved overall yield of addition products with good selectivity for β-hydroxyketone **70r**.

Scheme 2.5. Organometallic addition to vinylogous ester ***27a***.



We next examined the ring contraction sequence with β-hydroxyketone **70r** (Scheme 2.6). Treatment of alcohol **70r** with the optimized ring contraction conditions using LiOH/TFE yields linear dione **72r** without any of the γ-substituted acylcyclopentene. Even though the conditions do not afford the desired product, the isolation of stable uncyclized intermediate **72r** supports our proposed retro-aldol fragmentation/aldol cyclization mechanism (Scheme 2.3). By employing a stronger base such as KO*t*-Bu, both steps of the rearrangement can be achieved to give acylcyclopentene **53r**. Furthermore, significantly higher yields and reduced reaction times are obtained with microwave irradiation.

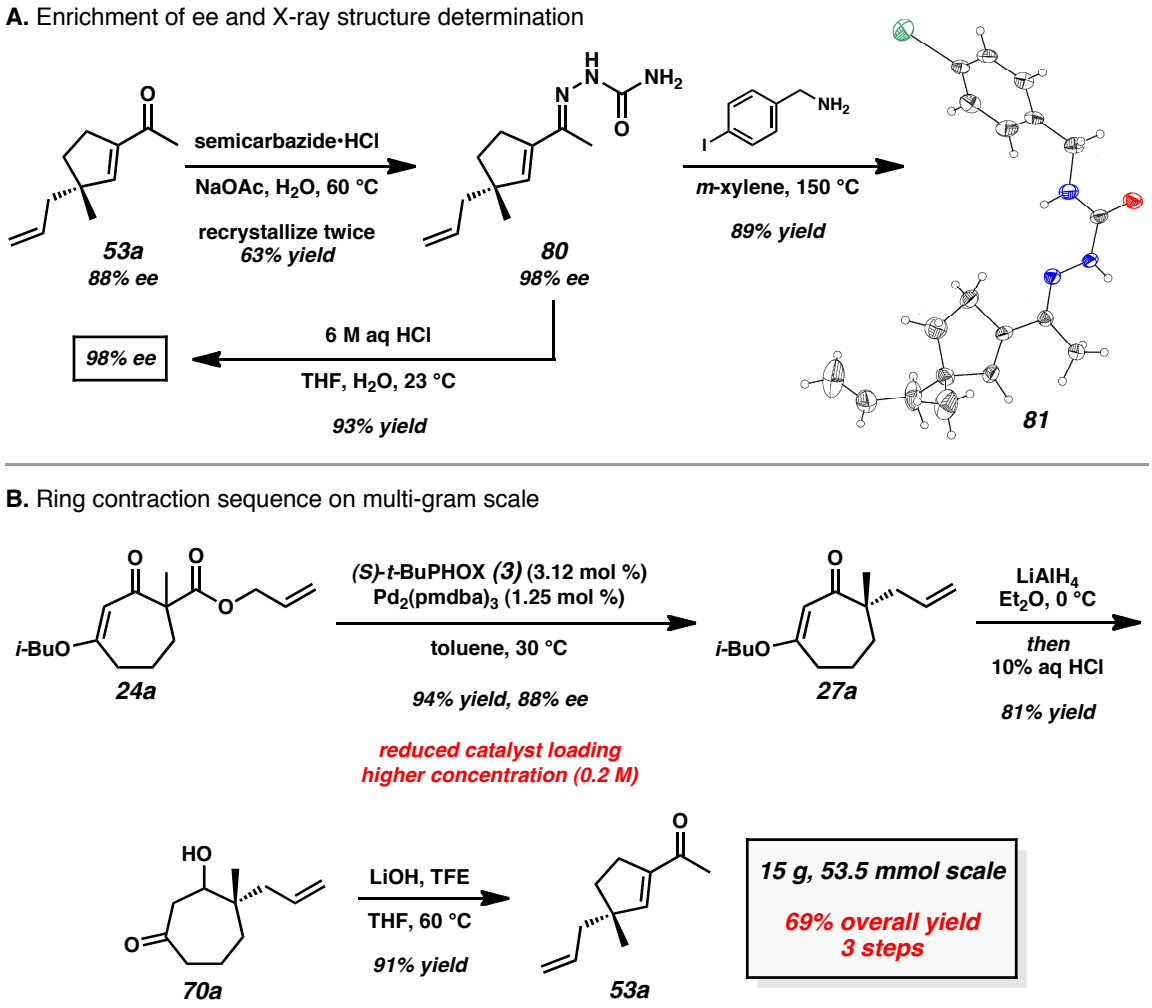
*Scheme 2.6. Ring contraction screen on β-hydroxyketone **70r**.*



LiOH, TFE, THF, 60 °C, 3 h	*71% yield*	*not observed*
KO*t*-Bu, THF, 60 °C, 22 h	*not observed*	*65% yield*
KO*t*-Bu, THF, 85 °C, μwaves, 5 min	*not observed*	*73% yield*

With a route to form a variety of acylcyclopentenes that possess different substitution patterns, we were interested in increasing the enantiopurity of these potentially useful intermediates. Formation of the corresponding semicarbazone **80** enables us to obtain material in 98% ee after two recrystallizations (Scheme 2.7A). A high yielding hydrolysis affords enantioenriched acylcyclopentene **53a**. Further functionalization of semicarbazone **80** with 4-iodobenzylamine provided crystals that allowed verification of absolute stereochemistry by X-ray crystallography.[37] To demonstrate the viability of our method for large-scale enantioselective synthesis, we performed the asymmetric alkylation and ring contraction transformations on multi-gram scale (Scheme 2.7B). Gratifyingly, our route proved to be robust and reliable. Using 50 mmol of substrate (15 g), we are able to achieve a 94% yield and 88% ee of our desired asymmetric alkylation product. Notably, the increased reaction scale permits reduced catalyst loadings (1.25 mol % $Pd_2(pmdba)_3$ and 3.12 mol % (*S*)-*t*-BuPHOX, **3**) and higher substrate concentrations (0.2 M). β-Ketoester **24a** undergoes the asymmetric alkylation and ring contraction protocol to furnish the desired acylcyclopentene in 69% overall yield over the three step sequence.

Scheme 2.7. Confirmation of absolute stereochemistry and multi-gram scale reactions.



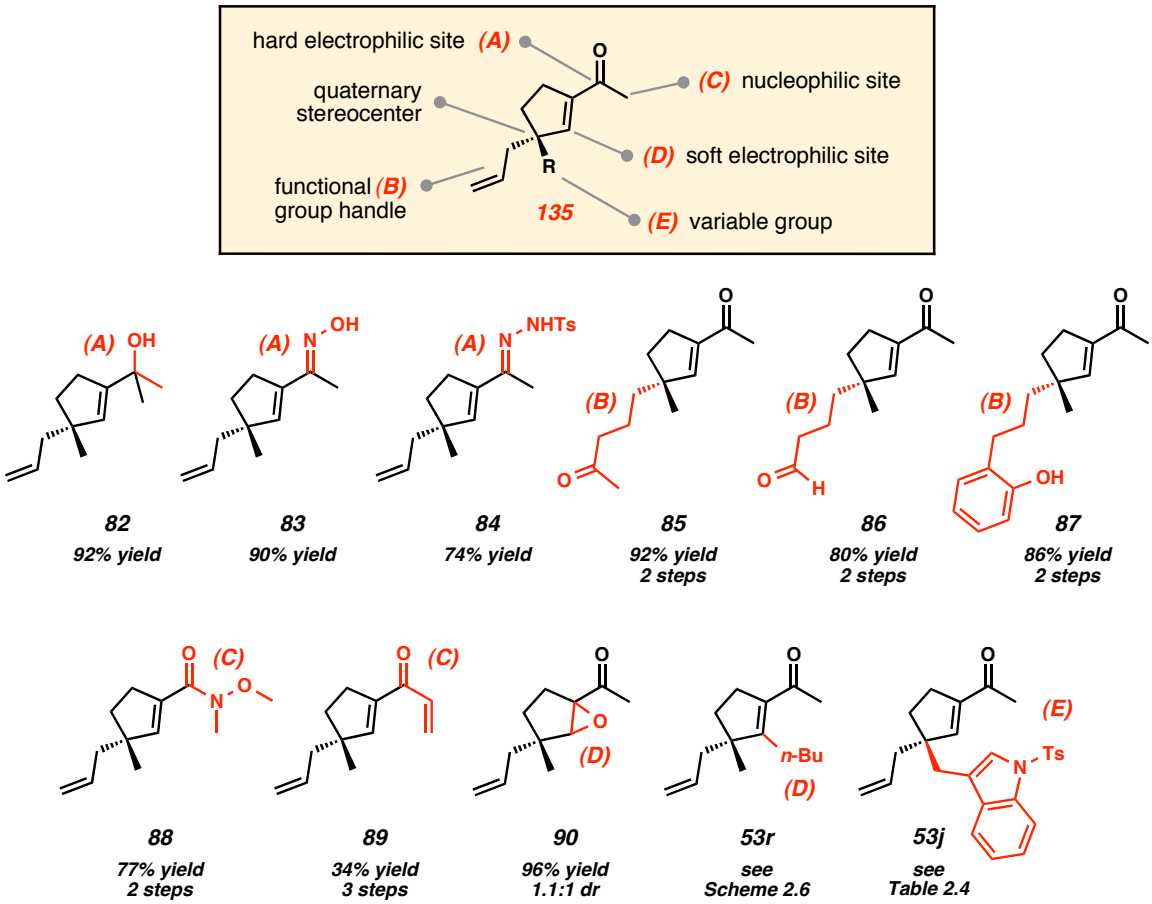
2.2 SYNTHESIS OF ACYLCYCLOPENTENE DERIVATIVES USING SITE-SELECTIVE TRANSFORMATIONS

With the ultimate goal of applying our methodology toward the total synthesis of complex natural products, we set out to probe the synthetic utility of various acylcyclopentenes prepared using our ring contraction strategy. While these acylcyclopentenes (**53**) are chiral fragments with low molecular weights, they possess an array of useful functionality that can be exploited for synthetic applications through site-

selective manipulations (Figure 2.3). Acylcyclopentene **53** contains hard and soft electrophilic sites, a nucleophilic site, a functional group handle in the form of an allyl group, and a variable group that is installed through asymmetric alkylation. Additionally, all of the acylcyclopentenes we have prepared bear an all-carbon quaternary stereocenter or a fully substituted tertiary center.

We aimed to perform site-selective functionalizations to demonstrate that a variety of derivatives could be prepared by recognizing the rich functionality present in acylcyclopentene **53** (Figure 2.3). Selective derivatization of site A enables access to tertiary alcohols, oximes, and hydrazones in 74–92% yield (**82**–**84**). Manipulation of site B through olefin methathesis with methyl vinyl ketone or crotonaldehyde provides intermediate bis-enone or enone-enal compounds in 90–95% yield as *trans* olefin isomers. Chemoselective hydrogenation with Wilkinson's catalyst reduces the less substituted and less sterically hindered olefin in these systems to form mono-enones **85** and **86** in 90–93% yield. Using the insights gathered from these manipulations, we performed chemoselective Heck and hydrogenation reactions to provide acylcyclopentene **87** bearing a pendant phenol in 86% yield over two steps. Through modification of site C, access to Weinreb amides and divinyl ketones can be achieved (**88**–**89**). Additionally, manipulation of site D gives rise to epoxide **90**. Functionalization of this site was also demonstrated with β-substituted acylcyclopentene **53r** (Scheme 2.6). Lastly, variations at site E are accomplished by installing the appropriate groups at an early stage during the asymmetric alkylation step (Scheme 2.1 and Table 2.2).

*Figure 2.3. Selective functionalizations on sites A–E of acylcyclopentenes (**53**).*

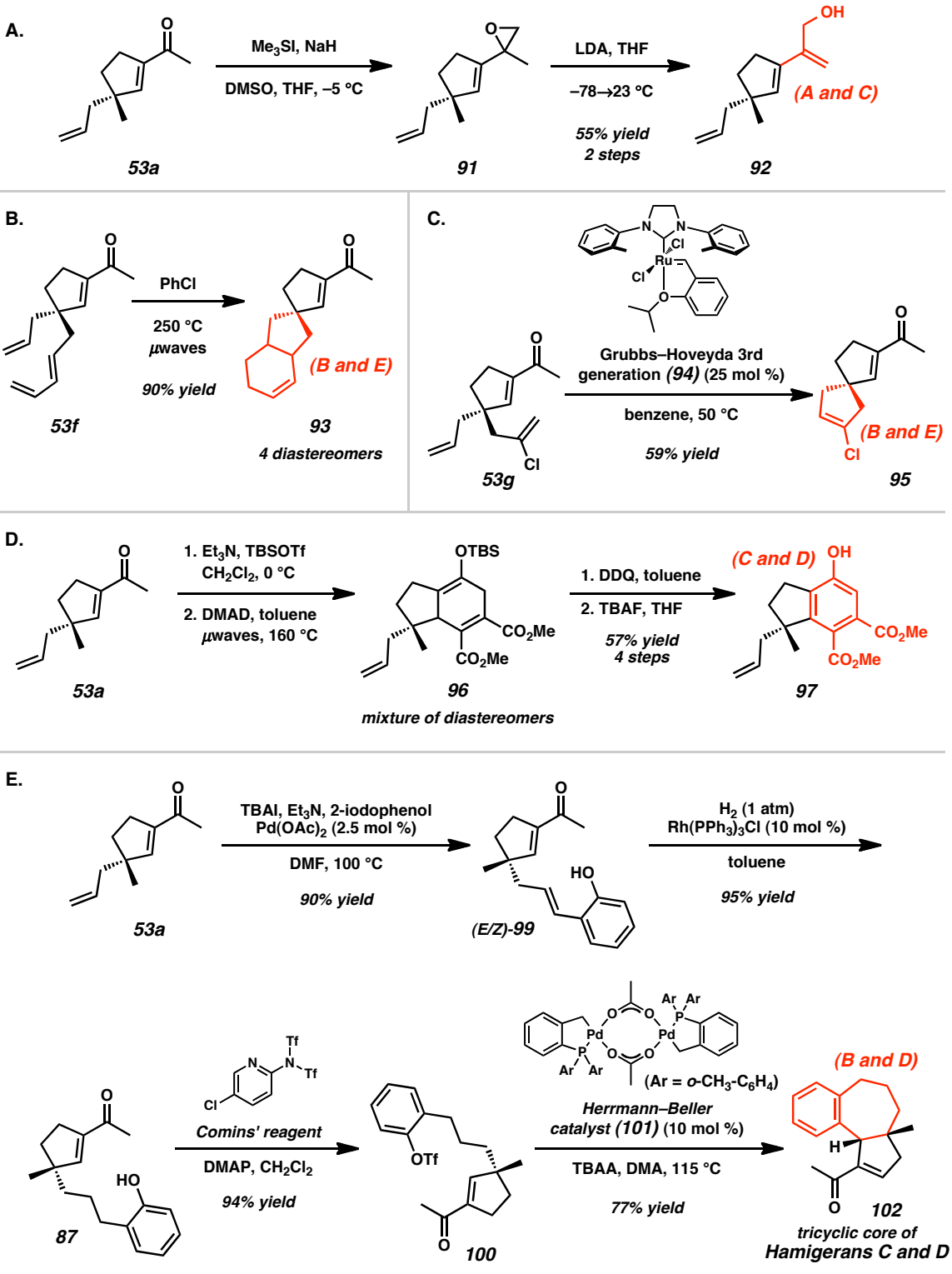


To further increase the potential of these chiral building blocks, we performed manipulations on a combination of reactive sites to arrive at more advanced synthetic intermediates (Scheme 2.8). Hydroxydiene **92** is obtained in 55% yield over two steps from acylcyclopentene **53a** by performing a carbonyl epoxidation followed by fragmentation (Scheme 2.8A). Spirocyclic systems such as enones **93** and **95** are obtained by performing an intramolecular Diels–Alder using **53f** or a ring-closing metathesis of **53g** using Grubbs–Hoveyda 3rd generation catalyst (Scheme 2.8B and Scheme 2.8C). Additionally, phenolic indane **97** is generated in 57% yield over four steps by exploiting an intermolecular Diels–Alder reaction with DMAD (Scheme 2.8D).

To arrive at intermediates that bear a stronger resemblance to natural products, we formed the triflate of Heck product **87** using Comins' reagent[38] and subjected the compound to a subsequent intramolecular Heck reaction using the Herrmann–Beller palladacycle **101**[39] to obtain tricycle **102** with the *cis*-ring fusion (Scheme 2.8E). This key tricycle contains all of the carbocyclic core of hamigerans C and D with the correct stereochemistry at the ring fusions.

Overall, our general strategy enables the synthesis of valuable chiral building blocks by taking advantage of the rich functional group content embedded in acylcyclopentenes (**53**). Site-selective manipulations at regions A–E produce monocyclic and polycyclic compounds with a large degree of structural variation. Our studies provide valuable insight into the nature of these compounds, and we aim to apply our knowledge of these promising intermediates in the total synthesis of complex natural products.

Scheme 2.8. Functionalization of multiple acylcyclopentene reactive sites.

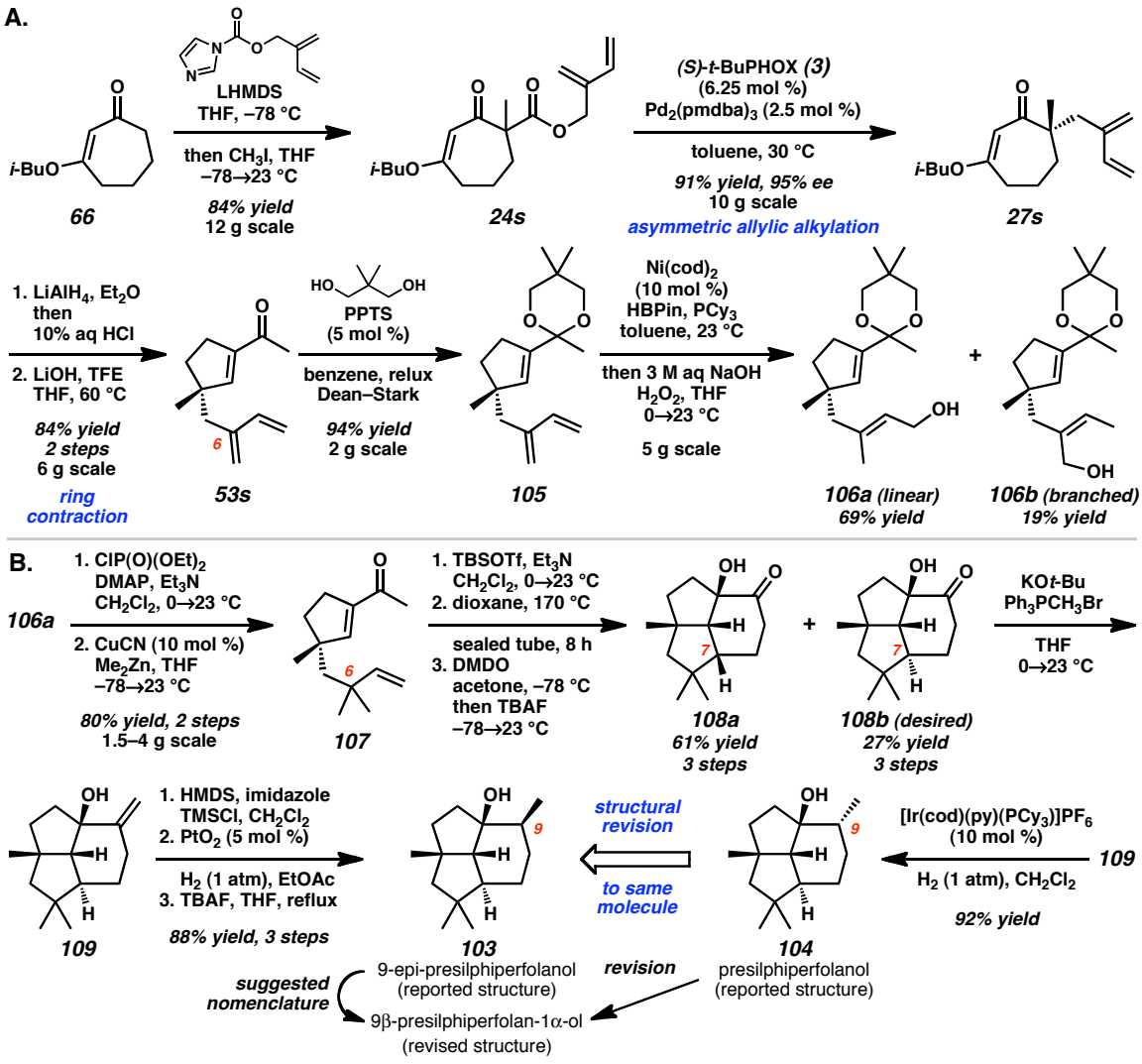


2.1.1 Application of Ring Contraction Toward (–)-9-epi-Presilphiperfolan-1-ol and (–)-Presilphiperfolan-1-ol[40]

In 2012, our group employed the ring contraction strategy toward the total synthesis of the reported structures of (–)-9-epi-presilphiperfolan-1-ol (**103**) and (–)-presilphiperfolan-1-ol (**104**).[41] In this route, vinylogous ester **66** is acylated and alkylated in a single step to afford vinylogous ester **24s** (Scheme 2.9A). Asymmetric allylic alkylation of this molecule under our standard Pd-catalyzed conditions affords α-quaternary vinylogous ester **27s** in excellent yield and 95% ee. Notably, no side products arising from a Heck or Diels–Alder pathway are observed in this transformation. The ring contraction process also proceeds well with this substrate, generating acylcyclopentene **53s** in 84% yield over two steps. A four step protection, hydroboration, phosphorylation, and S_N2' displacement sequence installs the geminal methyls at C(6) to furnish acylcyclopentene **107** (Scheme 2.9A and B). The tricyclic core of the natural product is assembled via a Diels–Alder cycloaddition, although a mixture of C(7) diastereomers is produced. Ensuing Rubottom oxidation selectivity forms the hydroxy group on the convex face of both diastereomeric tricycles to ultimately afford α-hydroxyketones **108a** and **b** (Scheme 2.9B). The desired ketone (**108b**) is olefinated with the standard Wittig ylide to give allylic alcohol **109**. Subsequent hydrogenation completes the synthesis by installing the C(9) methyl group selectively through either a steric (three step) or directing group (Crabtree's catalyst) approach. Analysis of the reported and synthetic structures of 9-epi-presilphiperfolan-1-ol (**103**) and presilphiperfolan-1-ol (**104**) suggest that the latter is not actually a natural product as the structure was originally misassigned. The spectral data of isolated **103** and **104** match

closely, and upon consideration of the biosynthetic pathway, we determined that isolated presilphiperfolan-1-ol (**104**) is actually 9-epi-presilphiperfolan-1-ol (**103**). To avoid future confusion, we propose that the name 9β-presilphiperfolan-1α-ol be used instead to describe this molecule.

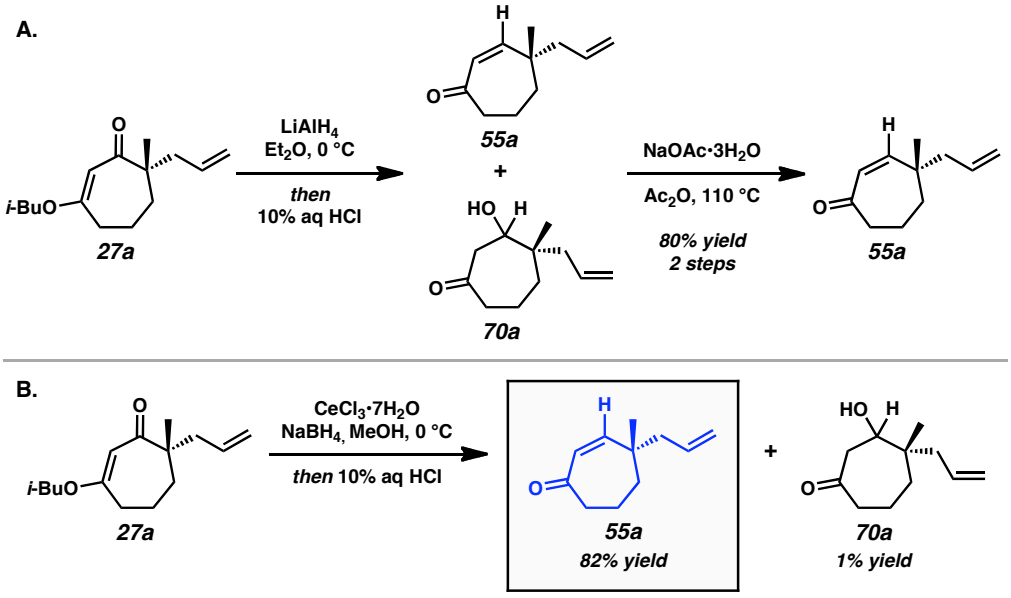
*Scheme 2.9. Route to (–)-9-epi-presilphiperfolan-1-ol (**103**) and (–)-presilphiperfolan-1-ol (**104**).*



2.3 CARBONYL TRANSPOSITION APPROACH TO γ-QUATERNARY CYCLOHEPTENONES

While pleased to discover the unusual reactivity of vinylogous esters **27** that led to the synthesis of various acylcyclopentenes, we maintained our original interest in preparing enantioenriched γ-quaternary cycloheptenones (**55**) and began reexamining reaction parameters to this end. Initially, we identified conditions to obtain cycloheptenone **55a** in two steps by activation and elimination of the hydroxy group at elevated temperatures, but ultimately desired a more direct route from vinylogous ester **27a** (Scheme 2.10A). After considerable experimentation, we fortuitously discovered that reduction and elimination using Luche conditions effectively furnished enone **55a** with minimal β-hydroxyketone **70a** (Scheme 2.10B). A number of factors may contribute to the reversed product distribution, with methanol as solvent likely playing a large role.[42] With an effective route to enone **55a**, we also sought to prepare β-substituted cycloheptenones through the 1,2-addition of organometallic reagents.

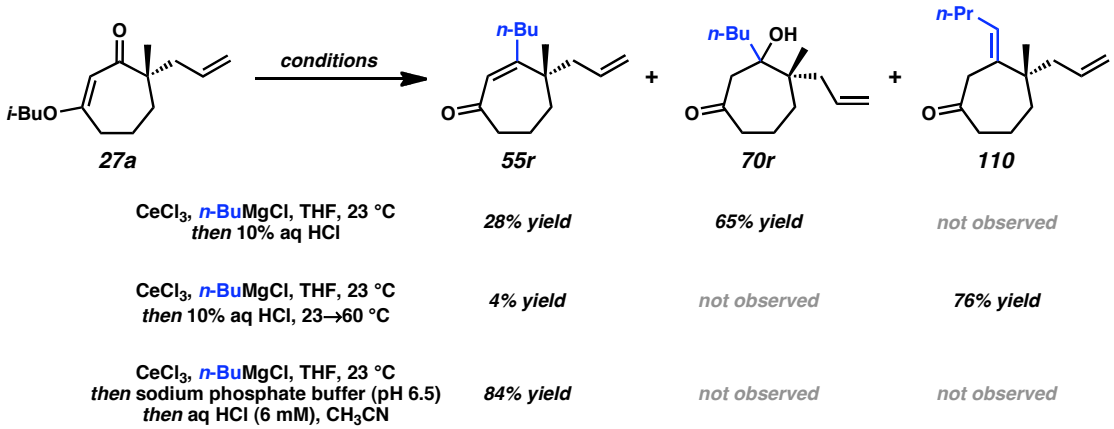
Scheme 2.10. Stepwise and one-pot formation of cycloheptenone ***55a****.*



We again investigated the addition of *n*-BuMgCl to vinylogous ester **27a** with $CeCl_3$ additive, focusing on the impact of various quenching parameters. While our previous studies showed that the formation of β-hydroxyketone **70r** is favored over cycloheptenone **55r** (Scheme 2.11, and Scheme 2.12, path a vs path b), we reasoned that elevated temperatures would promote dehydration of β-hydroxyketone **70** to form cycloheptenone **55** as the major product and simplify the product mixture (Scheme 2.12, path c). Subsequent heating of the reaction to 60 °C after acid quench leads to complete consumption of β-hydroxyketone (Scheme 2.11). However, the desired cycloheptenone **55r** is isolated as a minor product along with the non-conjugated enone **110** in 76% yield as a single olefin isomer. The prevalence of non-conjugated enone **110** again emphasizes the unusual reactivity of these seven-membered ring systems. To revise our approach, we extensively screened mild acidic work-up conditions to minimize the formation of

side products such as isomer **110**. We ultimately discovered that a sodium phosphate buffer quench followed by treatment of the crude enol ether[43] with dilute HCl in acetonitrile exclusively affords desired cycloheptenone **55r** (Scheme 2.11). Gratifyingly, a number of sp^3-hybridized carbon nucleophiles can be employed under these conditions, permitting the preparation of allyl,[44] homoallyl, and pentenyl substituted cycloheptenones (Table 2.5, entries 1–6, Method F).

Scheme 2.11. Synthesis of β-substituted cycloheptenones.



Scheme 2.12. General reaction mechanism for carbonyl transposition.

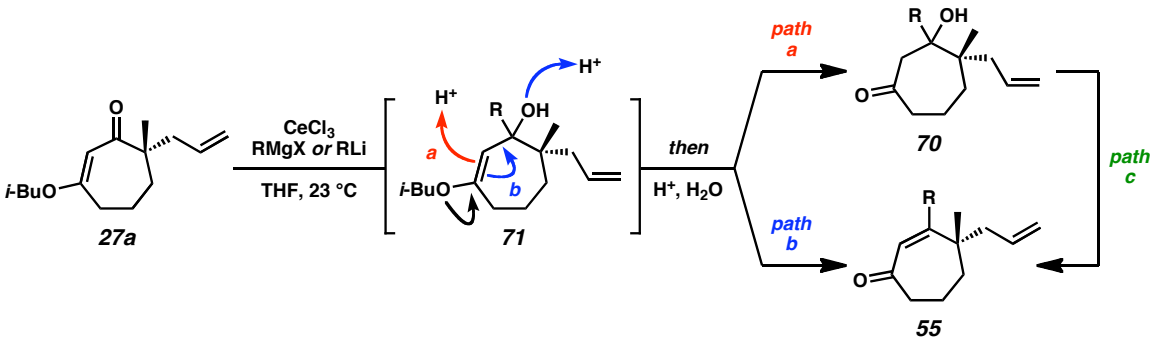
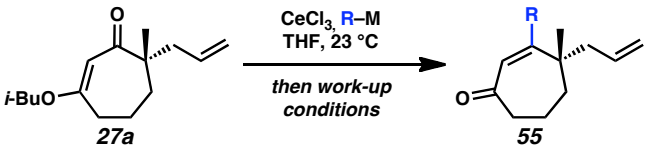
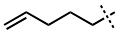


Table 2.5. Scope of organometallic addition/elimination.[a]



entry	R	M	work-up conditions[b]	product *55*	yield (%)[c]
1		–MgCl	F	*55r*	84
2		–MgBr	F	*55t*	73
3		–MgBr	F	*55u*	93
4		–MgBr	F	*55v*	90
5		–MgBr	F	*55w*	82
6		–MgBr	F	*55x*	92
7[d]		–Li	G	*55y*	84
8		–MgBr	H	*55z*	97
9[e]		–MgBr	H	*55aa*	66
10		–Li	G	*55ab*	72
11		–MgCl	G	*55ac*	84

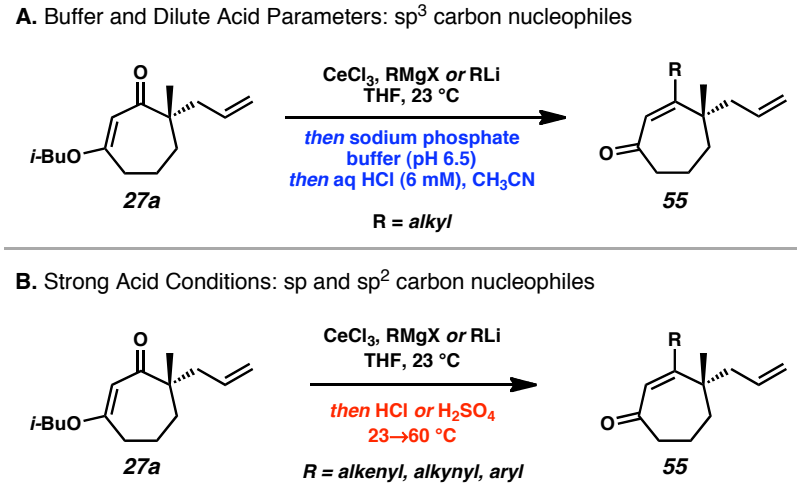
[a] *Conditions*: vinylogous ester **27a** (1.0 equiv), $CeCl_3$ (2.5 equiv), RMgX or RLi (3.0 equiv) in THF, 23 °C then work-up by Method F, G, or H. [b] *Method F*: (1) pH 6.5 sodium phosphate buffer; (2) 6 mM HCl, CH_3CN; *Method G*: 10% w/w aqueous HCl, 60 °C; Method H: 2 M H_2SO_4, 60 °C. [c] Yield of isolated product. [d] Performed without $CeCl_3$ additive. [e] Product was a 1.9:1 mixture of atropisomers.

We then turned our attention to sp- and sp^2-hybridized carbon nucleophiles as part of our goal to prepare variably substituted cycloheptenones (**55**). Attempts to apply the buffer and dilute acid quenching parameters provided poor selectivity and often led to complex mixtures of products. A thorough evaluation of work-up conditions revealed that the desired unsaturated β-substituted cycloheptenones could be obtained by quenching the reactions with concentrated strong acid followed by stirring at elevated

temperatures. Although investigated unsuccessfully for sp^3-hybridized carbon nucleophiles, the strong acid work-up conditions are more suitable for these reactions because the only possible elimination pathway leads to conjugated enone **55**. In this manner, the initial mixture of enone and β-hydroxyketone is funneled to the desired product (Scheme 2.12, paths b and c). By employing a HCl (Method G) or H_2SO_4 (Method H) quench, the synthesis of vinyl,[45] alkynyl,[46] aryl, and heteroaryl substituted enones was achieved in moderate to excellent yield (Table 2.5, entries 7–11). Particularly noteworthy is entry 9, where addition of an *ortho*-substituted Grignard reagent produces sterically congested cycloheptenone **55aa**.[47]

These results demonstrate that application of the appropriate quenching parameters based on the type of carbon nucleophile is required for successful carbonyl transposition to the cycloheptenone (Scheme 2.13). For sp^3-hybridized carbon nucleophiles, reaction work-up with buffer and dilute acid maximizes enone yield and minimizes formation of non-conjugated enone isomers. In contrast, reactions using sp- and sp^2-hybridized carbon nucleophiles require strong acidic work-up with heating for best results. Careful application of these general protocols (Methods F–H) provides access to diverse β-substituted γ-quaternary cycloheptenones (**55**).

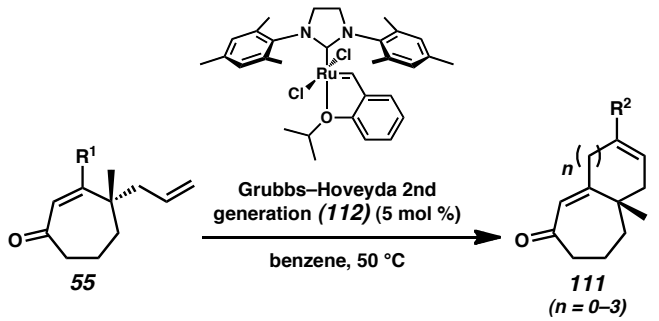
Scheme 2.13. Different work-up conditions for carbonyl transposition employing sp^3 versus sp/sp^2 carbon nucleophiles.



2.4 SYNTHESIS OF CYCLOHEPTENONE DERIVATIVES USING TRANSITION METAL-CATALYZED CYCLIZATIONS

Having produced a variety of cycloheptenones, we next turned our attention to the preparation of a series of bi- and tricyclic structures that would be valuable for total synthesis applications. The incorporation of alkene functionality at the β-position allows rapid access to a series of [7–*n*] fused ring systems through ring-closing metathesis with the γ-allyl fragment (Table 2.6). This transformation enables the formation of disubstituted bicycles (**111y**, **111t**, **111v**, and **111x**) from terminal alkenes in excellent yields (entries 1, 3, 5, and 8). Trisubstituted bicycles (**111z**, **111u**, and **111w**) are also accessible through enyne ring-forming metathesis (entry 2) and ring-closing metathesis with 1,1-disubstituted alkene β-substituents (entries 4 and 6). Additionally, both atropisomers of cycloheptenone **55aa** converge to the [7–7–6] tricyclic enone (**111aa**) under the reaction conditions (entry 7).

Table 2.6. Formation of bi- and tricyclic systems through ring-closing metathesis.[a]



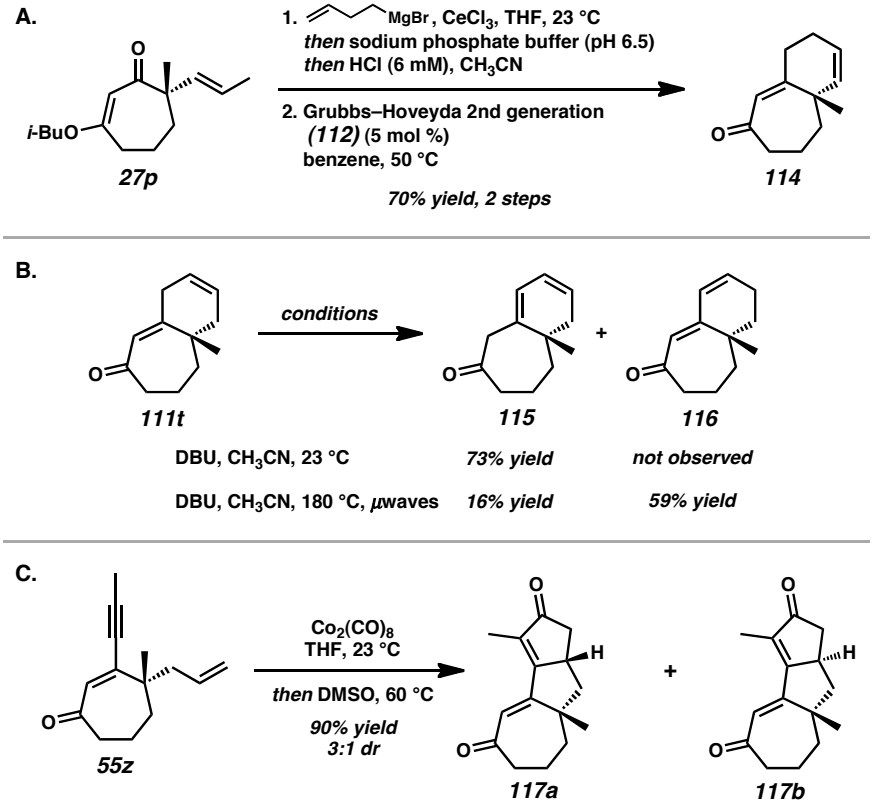
entry	substrate *55*	R^1	product *111*	R^2	yield (%)[b]
1[c]	*55y*	Ph	*111y*	R^2 = H	93
2	*55z*		*111z*	R^2 =	99
3[d]	*55t*		*111t*	R^2 = H	91
4[d]	*55u*		*111u*	R^2 = CH_3	90
5	*55v*		*111v*	R^2 = H	90
6	*55w*		*111w*	R^2 = CH_3	98
7[e]	*55aa*		*111aa*	—	96
8	*55x*		*111x*	—	99

[a] *Conditions*: cycloheptenone **55** (1.0 equiv) and Grubbs–Hoveyda 2nd generation catalyst (**112**, 5.0 mol %) in benzene, 50 °C. [b] Yield of isolated product. [c] *Conditions*: cycloheptenone **55** (1.0 equiv) and Grubbs 2nd generation catalyst (**113**, 0.2 mol %) in CH_2Cl_2, reflux. [d] 1,4-benzoquinone (10 mol %) added. [e] Performed in $PhCH_3$.

With two [7–6] bicyclic structures in hand, we next investigated the preparation of other such bicycles with variable olefin positions. Addition of 3-butenylmagnesium bromide to *trans*-propenyl vinylogous ester **27p** followed by ring-closing metathesis

furnishes bicycle **114** with the alkene adjacent to the quaternary stereocenter (Scheme 2.14A). Following the precedent of Fuchs,[48] we envisioned accessing bicycle **116** through a base-mediated migration from enone **111t**. However, treatment of skipped diene **111t** with an amine base at ambient temperature unexpectedly affords diene **115** instead (Scheme 2.14B). In the end, the alkene can be migrated in the desired direction to generate diene **116** by performing the reaction under microwave irradiation. Overall, these methods allow the preparation of a number of [7–6] bicycles with variable olefin substitution.

Scheme 2.14. Synthesis of additional [7–6] bicycles and [7–5–5] tricycles.



Recognition of the proximal enyne functionality of cycloheptenone **55z** prompted an investigation of a Pauson–Khand reaction to form more complex ring systems. Treatment of enone **55z** with dicobalt octacarbonyl in the presence of dimethylsulfoxide[49] generates the [7–5–5] tricycles **117a** to **117b** in a 3:1 diastereomeric ratio (Scheme 2.14C). Overall, our organometallic addition and elimination strategy combined with the appropriate work-up conditions facilitates the preparation of numerous bi- and tricyclic systems with a wide array of substitution patterns that may prove useful in the context of natural product synthesis.

2.5 UNIFIED STRATEGY FOR THE SYNTHESIS OF COMPLEX POLYCYCLIC NATURAL PRODUCTS

Our divergent approaches to the synthesis of acylcyclopentenes (**53**) and cycloheptenones (**55**) from enantioenriched vinylogous esters (**27**) have provided the foundation for the preparation of complex polycyclic molecules based on cyclopentanoid and cycloheptanoid core structures (Figure 2.4). Both [5–6] and [5–6–7] fused polycyclic molecules can be obtained from acylcyclopentenes. Synthetic elaboration of cycloheptenones provides access to [7–5], [7–6], [7–7], [7–8], [7–7–6], and [7–5–5] fused motifs. Additionally, [5–5], [5–6], and [7–6] spirocyclic structures can be prepared using our synthetic routes. These examples significantly add to the collection of polycyclic architectures accessible by elaboration of chiral six-membered ring carbocycles or heterocycles (**54**).[2,3] We have applied previously developed methodology toward a number of polycyclic cyclohexanoid natural products[7] (Figure 2.5) and similarly plan to exploit the ring contraction and ketone transposition methodology in future efforts

toward cyclopentanoid and cycloheptanoid natural products. The work presented in this chapter provides the foundation for future efforts and enables a broader synthetic approach to complex natural product targets.

Figure 2.4. Chiral fused and spirocyclic structures prepared by asymmetric allylic alkylation.

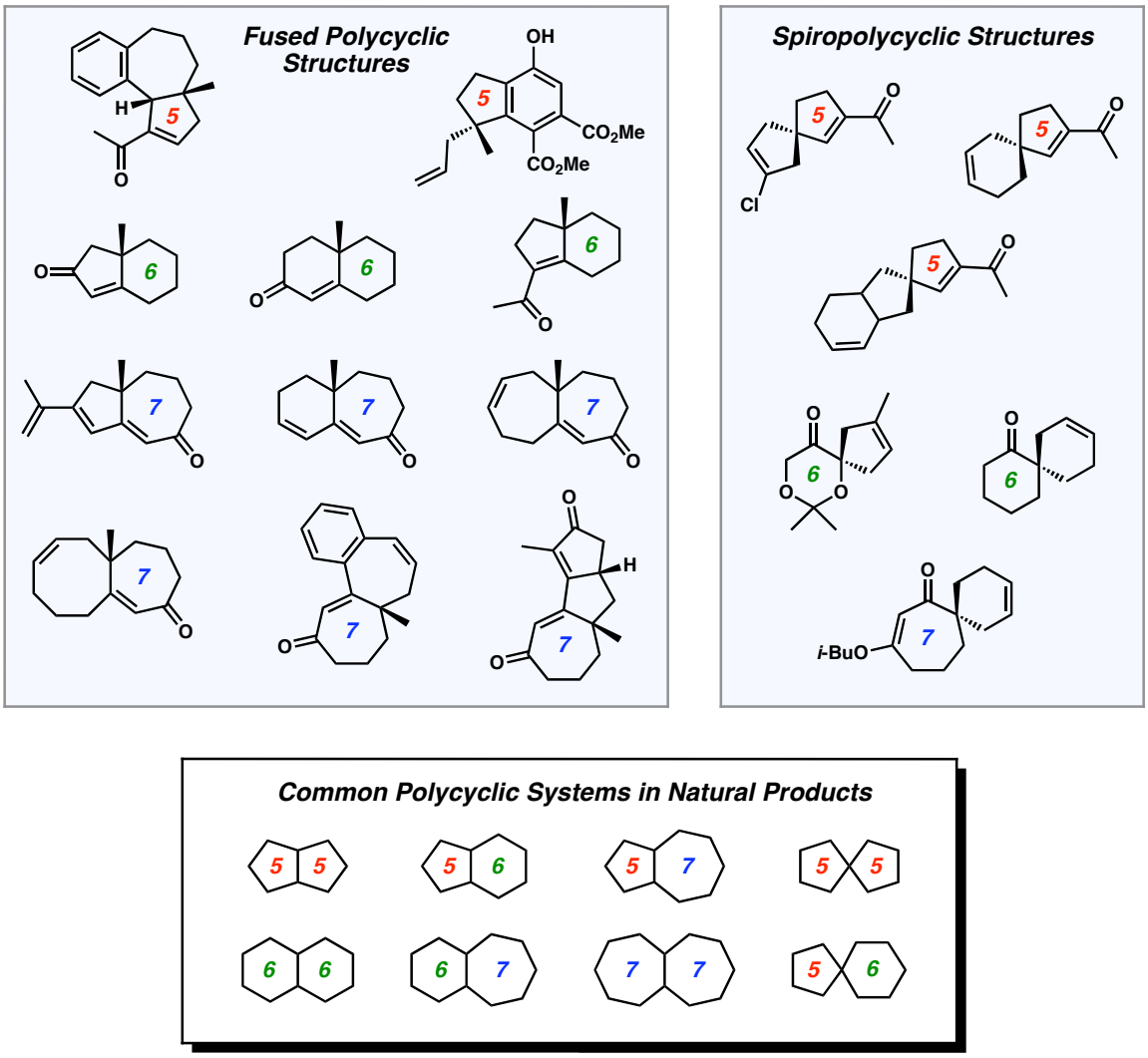
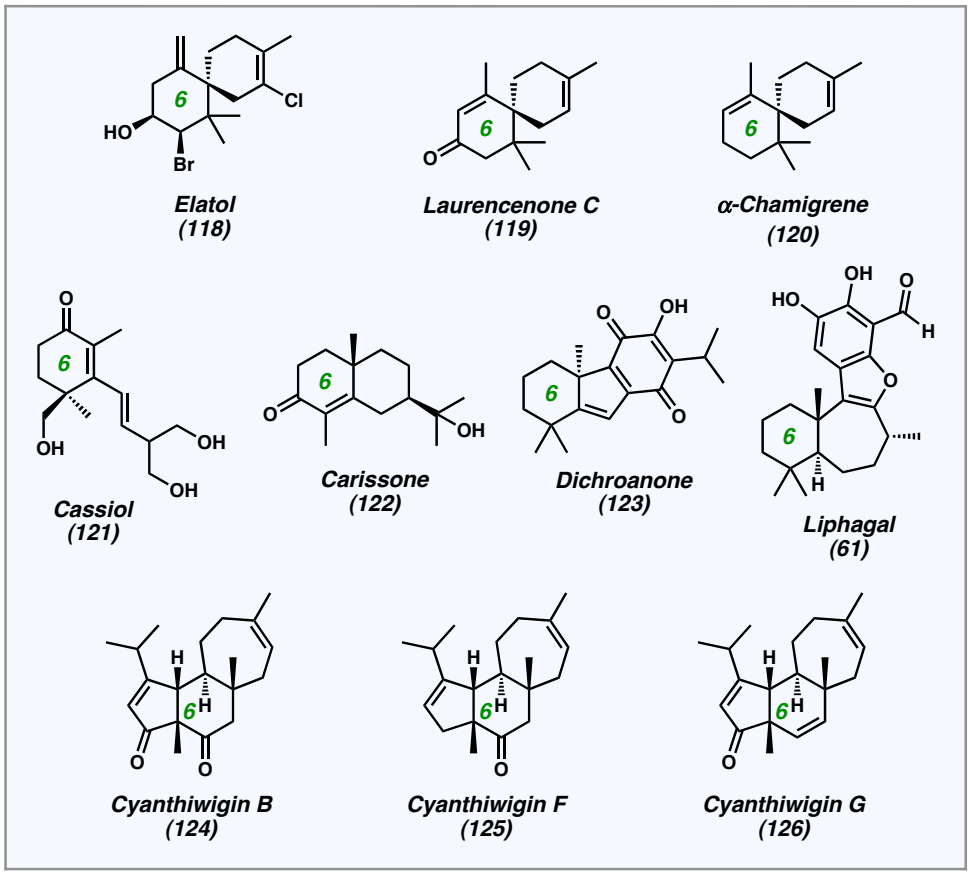


Figure 2.5. Pd-catalyzed asymmetric allylic alkylation in the total synthesis of cyclohexanoid natural products.



2.6 CONCLUDING REMARKS

We have successfully developed general, enantioselective synthetic routes toward γ-quaternary acylcyclopentenes (**53**) and cycloheptenones (**55**). The key stereoselective component unifying this chemistry is the Pd-catalyzed asymmetric alkylation of seven-membered vinylogous ester substrates to form α-quaternary vinylogous esters, for which we have demonstrated a broad substrate scope with a variety of all-carbon and heteroatom-containing functionality. These enantioenriched products were transformed in a divergent manner to either facilitate a two-carbon ring contraction to

acylcyclopentenes or a carbonyl transposition to cycloheptenones. Further synthetic elaboration of these products has enabled access to five- and seven-membered ring systems that are poised for further functionalization to bi- and tricyclic ring systems. Overall, the described strategies provide broader access to polycyclic ring systems and thus complement our previous work with six-membered ring building blocks. Efforts to expand the scope of these reactions, understand the key reaction mechanisms, and apply the chiral products to the total synthesis of natural products are the subject of future studies.

2.7 EXPERIMENTAL SECTION

2.7.1 MATERIALS AND METHODS

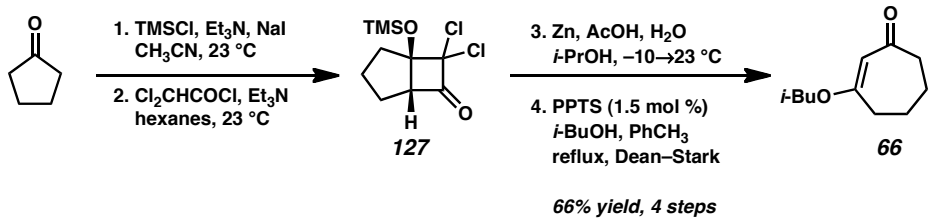
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. THF was distilled over sodium/fluorenone or dried by passage through an activated alumina column under argon[50] prior to use. *p*-Dioxane was distilled over sodium or dried by passage through an activated alumina column under argon prior to use. Methanol was distilled over $Mg(OMe)_2$ prior to use. Other solvents were dried by passage through an activated alumina column under argon. Diisopropylamine and triethylamine were distilled over CaH_2 prior to use. Iodomethane, iodoethane, acrylonitrile, methyl vinyl ketone, and acrolein were distilled prior to use. Furan was distilled over KOH and hydroquinone prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. $MePh_3PBr$ was purchased from Sigma-Aldrich and stored in a glove box prior to use. NaH (60% wt. dispersion in mineral oil) was purchased from Sigma-Aldrich and purified by trituration with hexanes under a N_2 atmosphere and removal of residual solvent under vacuum. Grignard and organolithium reagents were purchased from Sigma-Aldrich unless otherwise stated and titrated according to the method of Love.[51] $LiOCH_2CF_3$ was prepared according to the method of Shreeve.[52] Allyl cyanoformate was prepared according to the method of Mander[53a] or Rattigan.[51b] Gramine methiodide was prepared according to the method of Armen.[54] The procedure of Maruyama and Naruta was used to prepare 1-chloro-2,4-pentadiene (92:8 *E*:*Z*).[55] Phosphinooxazoline (PHOX) ligands (*S*)-*t*-BuPHOX (**3**)[56] and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[57] were prepared by methods described

in our previous work. Tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) ($Pd_2(pmdba)_3$) was prepared according to the method of Ibers[58] or Fairlamb.[56b] Herrmann–Beller's catalyst (**101**) was prepared according to a literature procedure.[59] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) or ICN silica gel (particle size 0.032–0.0653 mm) was used for flash column chromatography. Automated flash column chromatography was performed on a Teledyne Isco CombiFlash R_f system. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6H_6 (δ 7.16 ppm). Variable temperature ^{1}H NMR experiments were performed on a Varian Inova 500 MHz spectrometer and are reported relative to residual DMSO (δ 2.50 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer (at 75 MHz, 100 MHz, and 125 MHz respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6H_6 (δ 128.06 ppm). ^{19}F spectra were recorded on a Varian Mercury 300 MHz or a Varian Inova 500 MHz spectrometer (at 282 MHz and 470 MHz respectively) and are reported without the use of

a reference peak. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 or Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 or Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as follows: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, ee). Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel AD or OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral SFC was performed with a Mettler Toledo SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm) with visualization at 254 nm/210 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+ or FAB+) or on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

2.7.2 PREPARATIVE PROCEDURES

2.7.2.1 PREPARATION OF PARENT VINYLOGOUS ESTER 66



Vinylogous ester 66. NaI (157 g, 1.05 mol, 1.25 equiv) was placed in a 3 L 3-neck round-bottom flask, dried under high vacuum at 90 °C for 12 h, and allowed to cool to ambient temperature under N_2. CH_3CN (1.3 L) was added to dissolve the NaI. To the solution was added cyclopentanone (74.3 mL, 0.84 mol, 1.00 equiv), followed by Et_3N (146 mL, 1.05 mol, 1.25 equiv). The flask was fitted with an addition funnel, and the funnel was charged with TMSCl (122 mL, 0.96 mmol, 1.14 equiv), which was added dropwise over 30 min. The resulting suspension was stirred for an additional 1 h at ambient temperature. Pentane (1.0 L) was added, and the biphasic system was stirred vigorously for 10 min. The phases were separated and the CH_3CN layer was extracted with pentane (3 x 400 mL). The combined pentane phases were washed with H_2O (2 x 500 mL) and brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product (131 g, quantitative) as a colorless oil.

A portion of the above trimethylsilyl ether (89.7 g, 0.57 mol, 1.00 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a stopper, an addition funnel, and an overhead stirrer. Hexanes (900 mL) was added, followed by Et_3N (111 mL, 0.80 mol, 1.39 equiv). Dichloroacetyl chloride (66.4 mL, 0.69 mol, 1.21 equiv) was dissolved in hexanes (400 mL) and added dropwise over 9.5 h. After 18 h of stirring at ambient

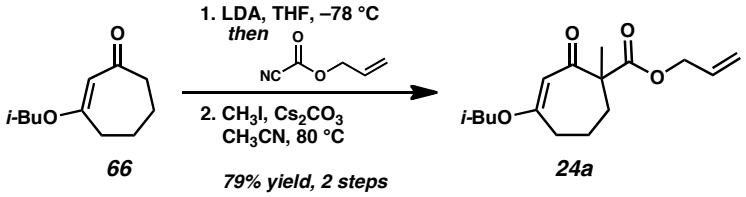
temperature, the brown suspension was filtered, rinsing with EtOAc (3 x 500 mL). The clear brown solution was concentrated under reduced pressure and then filtered through a pad of Al_2O_3 (7 x 18 cm, neutral) using EtOAc as eluent. The solution was concentrated under reduced pressure to afford the desired product (125 g, 0.47 mol, 82% yield) as a brown oil that crystallized in the freezer (–20 °C).

A portion of the above dichlorocyclobutanone (53.4 g, 0.20 mol, 1.00 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a thermometer, an addition funnel, and an overhead stirrer. Isopropyl alcohol and purified water (170 mL each) were added and the suspension was cooled to –10 °C (internal temperature) using a MeOH/ice bath. Zn dust (58.8 g, 0.90 mol, 4.50 equiv) was added in four portions (5 min between each) and AcOH (63 mL, 1.10 mol, 5.50 equiv) dissolved in H_2O (130 mL) was added dropwise while keeping the internal temperature below 0 °C (usually added over 1.5 h). The reaction was stirred for an additional 30 min at –10 °C (internal temperature) before the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. After 8.5 h, the reaction was filtered, rinsing with isopropyl alcohol (100 mL). The mixture was cooled to 0 °C and neutralized by portionwise addition of K_2CO_3 (74.6 g, 0.54 mol, 5.50 equiv). The viscous suspension was filtered, rinsing with H_2O (100 mL) and EtOAc (300 mL). The biphasic system was concentrated under reduced pressure to ca. 200 mL and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired product (24.2 g, 0.19 mol, 96% yield) as a pale orange oil.

To a solution of 1,3-cycloheptanedione (35.8 g, 0.28 mol, 1.00 equiv) in toluene (280 mL) in a 1 L flask fitted with a reflux condenser and Dean–Stark trap was added

isobutanol (208 mL, 2.27 mol, 8.11 equiv) and pyridinium *p*-toluenesulfonate (1.07 g, 4.26 mmol, 1.50 mol %). The solution was immersed in an oil bath at 130 °C and monitored by TLC. When the starting material was consumed (typically within 4–6 h), the reaction was allowed to cool to ambient temperature. The resulting dark orange solution was washed with sat. aqueous $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a thick dark orange oil. The crude oil was flushed through a silica gel plug (SiO_2, 7 x 9 cm, 1:4→3:7→1:1 Et_2O-hexanes) to afford vinylogous ester **66** (43.5 g, 0.24 mol, 84% yield, 66% yield over 4 steps) as a pale orange oil; R_f = 0.22 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60–2.56 (m, 4H), 2.00 (sept, *J* = 6.6 Hz, 1H), 1.88–1.77 (m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1307; found 182.1310.

2.7.2.2 PREPARATION OF β-KETOESTERS 24

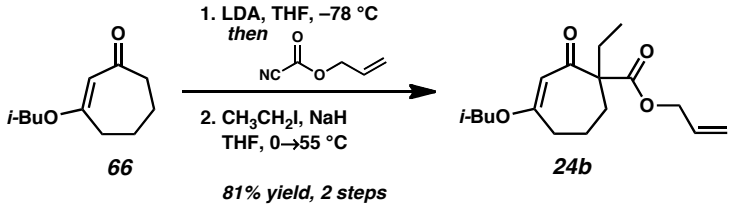


β-Ketoester 24a. To a solution of diisopropylamine (6.46 mL, 46.1 mmol, 1.20 equiv) in THF (180 mL) in a 500 mL round-bottom flask at 0 °C was added *n*-BuLi (17.2 mL, 44.2

mmol, 2.57 M in hexanes, 1.15 equiv) dropwise over 15 min using a syringe pump. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (7.01 g, 38.4 mmol, 1.00 equiv) in THF (20 mL) was added dropwise over 20 min using a syringe pump. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (4.60 mL, 42.2 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of sat. aqueous NH_4Cl and H_2O (30 mL each), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH_3CN (130 mL) in a 500 mL round-bottom flask and treated with CH_3I (7.2 mL, 115 mmol, 3.00 equiv) and Cs_2CO_3 (16.76 g, 49.9 mmol, 1.30 equiv). The flask was fitted with a condenser, immersed in an oil bath, and heated to 80 °C with vigorous stirring. After 12 h of stirring at 80 °C, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford an orange oil. The crude product was purified by flash column chromatography (SiO_2, 5 x 15 cm, 19:1→9:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-ketoester **24a** (8.51 g, 30.4 mmol, 79% yield over 2 steps) as a pale yellow oil; R_f = 0.43 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (app dq, *J* = 17.1, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.5, 1.4 Hz, 1H), 4.62 (dddd, *J* = 13.3, 5.6, 1.2, 1.2 Hz, 1H), 4.56 (dddd, *J* = 13.4, 5.6, 1.2, 1.2 Hz, 1H), 3.54–3.42 (m, 2H), 2.59

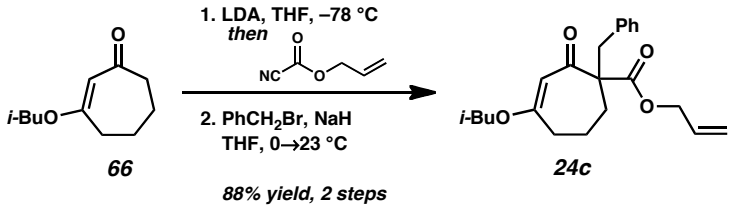
(ddd, J = 17.8, 9.8, 3.9 Hz, 1H), 2.45–2.38 (m, 2H), 2.02–1.94 (m, 2H), 1.84–1.75 (m, 1H), 1.70 (ddd, J = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{16}H_{24}O_4$ $[M]^{+\bullet}$: 280.1675; found 280.1686.



β-Ketoester 24b. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (158 mg, 6.58 mmol, 1.20 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. CH_3CH_2I (1.31 mL, 16.4 mmol, 3.00 equiv) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for 4.5 h. The mixture was heated to 45 °C and stirred for 1.5 h. Additional CH_3CH_2I (0.65 mL, 8.22 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at 45 °C for 6 h. A third portion of CH_3CH_2I (0.33 mL, 4.11 mmol, 0.75 equiv) was added dropwise and the reaction was warmed to 55 °C and stirred for 1.5 h. The flask was cooled to ambient temperature and quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 20 cm, 9:1→6:1→3:1→2:1 hexanes:EtOAc) to afford β-ketoester **24b** (1.31 g, 4.44 mmol, 81% yield over 2 steps) as a yellow oil; R_f = 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.5, 10.2, 5.7, 5.7 Hz, 1H), 5.35 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.62 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 4.54 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 3.57–3.34 (m, 2H), 2.60 (dddd, *J* = 17.9, 9.9, 3.7, 1.2 Hz, 1H), 2.49–2.26 (m, 2H), 2.12–1.85 (m, 4H), 1.85–1.57 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 173.7, 173.2, 132.0, 118.5, 105.5, 74.7, 65.7, 63.1, 34.1, 31.0, 30.6, 27.9, 22.0, 19.3, 9.0; IR (Neat Film NaCl) 3085, 2960, 2937, 2876, 1731, 1663, 1613, 1471, 1461, 1453, 1424, 1383, 1369, 1328, 1304,

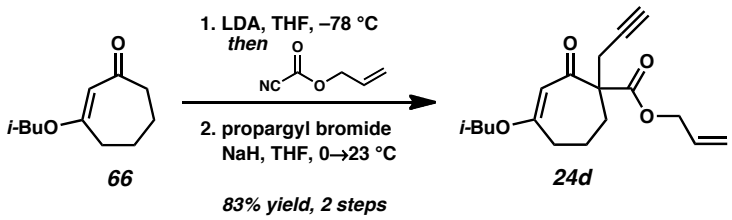
1278, 1229, 1199, 1170, 1121, 1006, 988, 931, 875, 858, 813 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1904; found 295.1918.



β-Ketoester 24c. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Benzyl bromide (1.96 mL, 16.44 mmol, 3.00 equiv) was added dropwise. The reaction was allowed to warm to

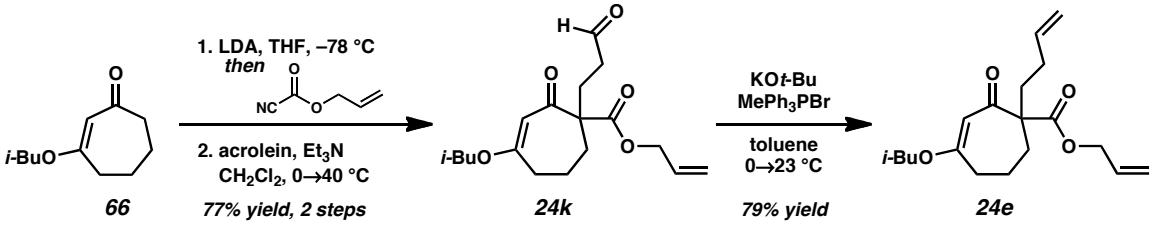
ambient temperature and stirred for 3 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 23 cm, hexanes→10:1 hexanes:EtOAc) to afford β-ketoester **24c** (1.72 g, 4.83 mmol, 88% yield over 2 steps) as a pale yellow oil; R_f = 0.26 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 3H), 7.15–7.06 (m, 2H), 5.85 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.36 (s, 1H), 5.30 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 (dddd, *J* = 13.2, 5.7, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 3.42 (d, *J* = 6.5 Hz, 2H), 3.30 (d, *J* = 13.5 Hz, 1H), 3.23 (d, *J* = 13.5 Hz, 1H), 2.54 (ddd, *J* = 12.1, 10.0, 3.5 Hz, 1H), 2.38–2.18 (m, 2H), 2.04–1.83 (m, 2H), 1.81–1.64 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 174.0, 172.7, 137.0, 131.8, 130.7, 128.1, 126.8, 118.8, 105.7, 74.8, 66.0, 64.0, 43.1, 34.0, 31.3, 27.9, 22.0, 19.2; IR (Neat Film NaCl) 3085, 3062, 3029, 2959, 2934, 2873, 1736, 1732, 1661, 1652, 1611, 1495, 1471, 1454, 1423, 1383, 1368, 1270, 1235, 1173, 1088, 1007, 957, 992, 930, 862, 815, 741 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{29}O_4$ $[M+H]^+$: 357.2060; found 357.2051.



β-Ketoester 24d. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.5 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Propargyl bromide (1.22 mL, 10.96 mmol, 80% wt in toluene, 2.00 equiv) was added dropwise and the reaction was allowed to warm to ambient temperature and stirred for 5.5 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic

phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 24 cm, hexanes→20:1→15:1→10:1 hexanes:EtOAc) to afford β-ketoester **24d** (1.38 g, 4.53 mmol, 83% yield over 2 steps) as a pale yellow oil; R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.38 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 (dddd, *J* = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 4.56 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 3.56–3.38 (m, 2H), 2.79 (dd, *J* = 2.7, 0.6 Hz, 1H), 2.72–2.32 (m, 4H), 2.15–1.89 (m, 4H), 1.89–1.71 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 174.8, 171.7, 131.7, 118.7, 105.0, 80.2, 74.9, 71.4, 66.1, 62.0, 34.3, 31.2, 27.9, 27.5, 21.7, 19.2; IR (Neat Film NaCl) 3289, 3085, 2959, 2933, 2874, 2120, 1740, 1735, 1654, 1649, 1470, 1452, 1424, 1402, 1384, 1369, 1309, 1291, 1272, 1232, 1187, 1173, 1133, 1085, 1066, 1007, 968, 930, 863, 820 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1753; found 305.1746.



β-Ketoester 24k. To a solution of diisopropylamine (1.49 mL, 10.63 mmol, 1.20 equiv) in THF (43 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (4.74 mL, 10.19 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A

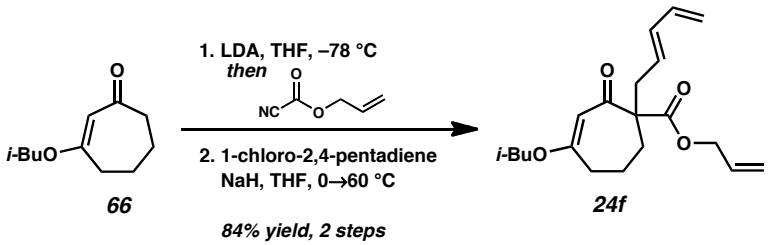
solution of vinylogous ester **66** (1.61 g, 8.86 mmol, 1.00 equiv) in THF (3 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.06 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (12.9 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 330 g column, hold 0% [3 min]→ramp to 20% [10 min]→hold 20% [10 min]→ramp to 50% [4 min]→hold 50% EtOAc in hexanes [5 min]) to afford the intermediate β-ketoester (2.02 g, 7.58 mmol, 86% yield).

A portion of the intermediate β-ketoester (990 mg, 3.72 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (10 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and treated with Et_3N (0.518 mL, 3.72 mmol, 1.00 equiv). Acrolein (0.248 mL, 3.72 mmol, 1.00 equiv) was added dropwise and the reaction was allowed to warm to ambient temperature. After 51 h, the reaction was cooled to 0 °C and an additional portion of acrolein (0.125 mL, 1.86 mmol, 0.50 equiv) was added. After 100 h, the reaction was concentrated under reduced pressure, dissolved in Et_2O, and filtered through a cotton plug to remove salts. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24k** (1.07 g, 3.34 mmol, 90% yield, 77% yield over

2 steps) as a clear oil; R_f = 0.23, broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.3 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.36 (s, 1H), 5.30 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.63 (dddd, *J* = 13.1, 5.7, 1.3, 1.3 Hz, 1H), 4.55 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 3.55–3.40 (m, 2H), 2.66–2.29 (m, 5H), 2.29–2.08 (m, 2H), 2.08–1.89 (m, 2H), 1.89–1.59 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 197.9, 173.9, 172.7, 131.7, 119.0, 105.3, 74.9, 66.0, 61.8, 39.7, 34.2, 32.1, 29.6, 27.9, 21.5, 19.2; IR (Neat Film NaCl) 3084, 2960, 2936, 2875, 2829, 2723, 1727, 1649, 1611, 1471, 1454, 1422, 1403, 1385, 1369, 1306, 1270, 1234, 1191, 1173, 1104, 1004, 990, 931, 877, 862, 822 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{27}O_5$ $[M+H]^+$: 323.1858; found 323.1860.

β-Ketoester 24e. $MePh_3PBr$ (1.33 g, 3.72 mmol, 1.26 equiv) was suspended in toluene (20 mL) in 100 mL round-bottom flask and cooled to 0 °C. KO*t*-Bu (0.348 g, 3.10 mmol, 1.05 equiv) was added in one portion and the bright yellow mixture was stirred at 0 °C for 30 min, warmed to ambient temperature, and stirred for an additional 2 h. The mixture was cooled to 0 °C and a solution of aldehyde **24k** (0.95 g, 2.94 mmol, 1.00 equiv) in toluene (2 mL) was added to the reaction using positive pressure cannulation. The mixture turned brown. The reaction was maintained at 0 °C for 1.5 h, warmed to ambient temperature, and stirred for 4 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc)

to afford β-ketoester **24e** (747 mg, 2.33 mmol, 79% yield) as a pale yellow oil; $R_f = 0.66$ (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.84–5.69 (m, 1H), 5.35 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 5.08–4.96 (m, 1H), 4.96–4.87 (m, 1H), 4.62 (dddd, *J* = 13.1, 5.7, 1.4, 1.4 Hz, 1H), 4.54 (dddd, *J* = 13.1, 5.7, 1.4, 1.4 Hz, 1H), 3.53–3.38 (m, 2H), 2.59 (dddd, *J* = 17.9, 9.8, 3.7, 1.1 Hz, 1H), 2.51–2.29 (m, 2H), 2.09–1.87 (m, 6H), 1.87–1.66 (m, 2H), 0.94 (d, *J* = 6.7, 3H), 0.94 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 173.7, 173.0, 138.2, 131.9, 118.6, 114.9, 105.4, 74.8, 65.8, 62.6, 36.8, 34.1, 31.5, 28.8, 27.9, 22.0, 19.3; IR (Neat Film NaCl) 3078, 2959, 2935, 2874, 1732, 1662, 1612, 1471, 1453, 1423, 1401, 1384, 1369, 1307, 1270, 1231, 1194, 1170, 1091, 993, 913, 874, 817, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{28}O_4$ $[M]^{+\bullet}$: 320.1988; found 320.1977.

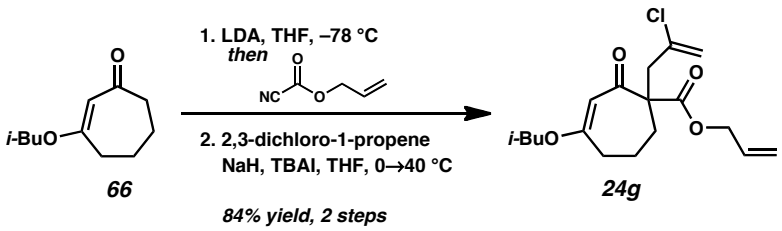


β-Ketoester 24f. To a solution of diisopropylamine (0.406 mL, 2.90 mmol, 1.20 equiv) in THF (12 mL) in a 50 mL round-bottom flask at 0 °C was added *n*-BuLi (1.10 mL, 2.77 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (0.44 g, 2.41 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.288 mL, 2.65 mmol, 1.10 equiv) was added dropwise over 10 min. The

mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (4 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 5 g loading cartridge, 40 g column, hold 0% [1 min]→ramp to 20% [8 min]→hold 20% [5 min]→ramp to 50% [4 min]→50% EtOAc in hexanes [6 min]) to afford the intermediate β-ketoester (590 mg, 2.21 mmol, 92% yield).

A portion of the intermediate β-ketoester (250 mg, 0.94 mmol, 1.00 equiv) was dissolved in THF (5 mL) in a 50 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (33.8 mg, 6.58 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. 1-chloro-2,4-pentadiene[53] (144 mg, 1.41 mmol, 1.50 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature and then heated to 40 °C. After 10.5 h, an additional portion of 1-chloro-2,4-pentadiene (144 mg, 1.41 mmol, 1.50 equiv) was added, and the reaction was heated at 50 °C for 11.5 h. The flask was cooled to ambient temperature and the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (2 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1→10:1 hexanes:EtOAc) to afford β-ketoester **24f** (286 mg,

0.86 mmol, 91% yield, 84% yield over 2 steps) as a pale yellow oil; R_f = 0.59 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (ddd, *J* = 16.7, 10.3, 10.3 Hz, 1H), 6.11–5.98 (m, 1H), 5.83 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.58 (ddd, *J* = 15.1, 7.7, 7.7 Hz, 1H), 5.36 (s, 1H), 5.27 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (app dq, *J* = 10.4, 1.2 Hz, 1H), 5.08 (dd, *J* = 16.9, 1.6 Hz, 1H), 4.96 (dd, J = 16.9, 1.6 Hz, 1H), 4.60 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 4.52 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 3.57–3.35 (m, 2H), 2.65 (d, *J* = 7.7 Hz, 2H), 2.56 (ddd, *J* = 12.7, 6.8, 2.3 Hz, 1H), 2.48–2.19 (m, 2H), 2.10–1.85 (m, 2H), 1.85–1.63 (m, 2H), 0.92 (d, *J* = 6.7, 3H), 0.92 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 174.0, 172.7, 136.9, 134.6, 131.9, 129.7, 118.6, 116.1, 105.4, 74.8, 65.9, 62.9, 41.0, 34.1, 31.4, 27.9, 21.8, 19.2; IR (Neat Film NaCl) 3085, 2959, 2933, 2874, 1733, 1650, 1612, 1471, 1453, 1434, 1402, 1384, 1369, 1307, 1272, 1234, 1194, 1171, 1093, 1006, 968, 955, 929, 900, 864, 822, 761 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2066; found 333.2052.

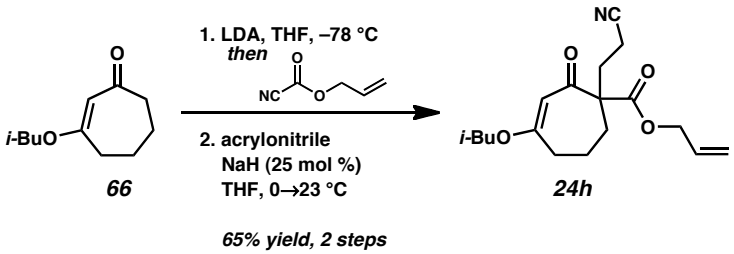


β-Ketoester 24g. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise

using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. 2,3-dichloro-1-propene (1.00 mL, 10.96 mmol, 2.0 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature. After 10 h, TBAI (202 mg, 0.548 mmol, 0.10 equiv) was added, and the reaction was heated to 40 °C. After 41 h, the reaction was cooled to ambient temperature and quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc) to afford β-ketoester **24g** (1.57 g, 4.61 mmol, 84% yield over 2 steps) as a yellow oil; R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.38–5.25 (m, 3H), 5.25–5.16 (m, 2H), 4.65 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.1, 5.8, 1.3, 1.3 Hz, 1H), 3.45 (ddd, *J* = 21.1, 9.3, 6.5 Hz, 2H), 3.04 (s,

2H), 2.71 (dddd, J = 18.2, 10.2, 3.0, 1.3 Hz, 1H), 2.62–2.47 (m, 1H), 2.39 (ddd, J = 17.2, 6.9, 2.6 Hz, 1H), 2.10–1.90 (m, 2H), 1.89–1.65 (m, 2H), 0.94 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 174.8, 172.1, 138.1, 131.7, 118.8, 117.1, 104.9, 74.8, 66.2, 62.2, 46.1, 33.9, 30.7, 27.8, 22.6, 19.2; IR (Neat Film NaCl) 3085, 2960, 2935, 2875, 1737, 1662, 1610, 1471, 1452, 1427, 1384, 1369, 1298, 1272, 1229, 1198, 1171, 1153, 1079, 1008, 967, 930, 890, 862, 813 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{18}H_{25}O_4$ $[M–Cl]^+$: 305.1753; found 305.1742.

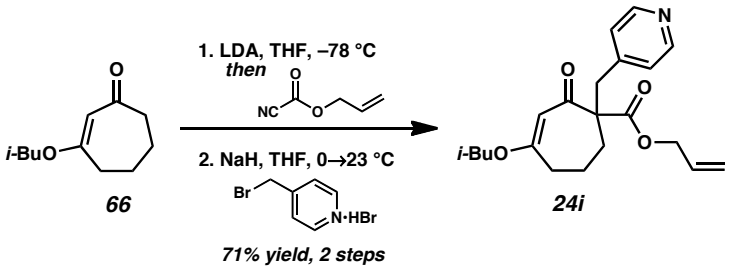


β-Ketoester 24h. To a solution of diisopropylamine (1.53 mL, 10.93 mmol, 1.20 equiv) in THF (45 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (4.17 mL, 10.47 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.66 g, 9.11 mmol, 1.00 equiv) in THF (2 mL) was added dropwise over 10 min. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.09 mL, 10.0 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (13.5 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 80 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [4 min]→hold 20% [15 min]→ramp to 50% [7 min]→hold 50% EtOAc in hexanes [5 min]) to afford the intermediate β-ketoester (2.08 g, 7.80 mmol, 86% yield).

One third of the intermediate β-ketoester (694 mg, 2.60 mmol, 1.00 equiv) was dissolved in THF (5 mL) in a 50 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (15.6 mg, 0.65 mmol, 0.25 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Acrylonitrile (0.256 mL, 3.90 mmol, 1.50 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature. After 40 h, the reaction was diluted with Et_2O (30 mL) and washed with H_2O (5 mL) and brine (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24h** (620 mg, 1.94 mmol, 75% yield, 65% yield over 2 steps) as a clear, colorless oil; R_f = 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 16.2, 10.4, 5.8, 5.8 Hz, 1H), 5.38 (s, 1H), 5.32 (app dq, *J* = 17.2, 1.4 Hz, 1H), 5.25 (app dq, *J* = 10.4, 1.1 Hz, 1H), 4.67 (dddd, *J* = 13.0, 5.8, 1.2, 1.2 Hz, 1H), 4.58 (dddd, *J* = 13.1, 5.9, 1.2, 1.2 Hz, 1H), 3.57–3.39 (m, 2H), 2.58 (ddd, *J* = 13.1, 9.6, 3.9 Hz, 1H), 2.51–2.32 (m, 4H), 2.32–2.11 (m, 2H), 2.11–1.90 (m, 2H), 1.90–1.64 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 196.9, 174.4, 172.0, 131.4, 119.7, 119.3, 105.1, 75.0, 66.3, 61.5, 34.1, 33.1, 32.0, 27.9, 21.4, 19.2, 13.3; IR (Neat Film NaCl) 3081, 2959, 2936, 2875, 2247, 1733, 1648, 1609, 1471, 1454, 1423, 1403, 1385, 1369, 1297, 1269, 1235, 1192, 1173, 1096, 996, 932, 874, 824, 764 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{25}O_4N$ $[M]^{+\bullet}$: 319.1784; found 319.1777.

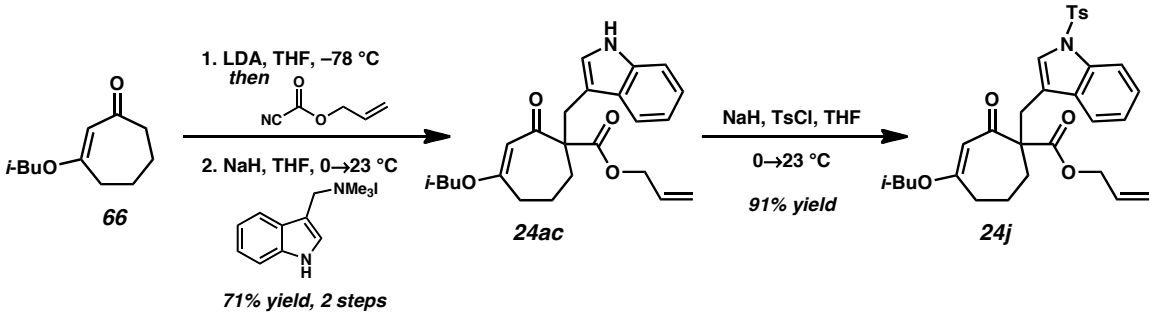


β-Ketoester 24i. To a solution of diisopropylamine (3.54 mL, 25.27 mmol, 1.20 equiv) in THF (108 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (10.26 mL, 24.22 mmol, 2.36 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (3.84 g, 21.06 mmol, 1.00 equiv) in THF (10 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (2.52 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (30.7 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a

Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 330 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [10 min]→hold 20% [6 min]→ramp to 50% [3 min]→hold 50% EtOAc in hexanes [11 min]) to afford the intermediate β-ketoester (4.66 g, 17.50 mmol, 83% yield) as a pale orange oil.

A portion of the intermediate β-ketoester (1.00 g, 3.75 mmol, 1.00 equiv) was dissolved in THF (25 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (90 mg, 3.75 mmol, 1.00 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Additional NaH (202 mg, 8.43 mmol, 2.25 equiv) was added, giving a thick yellow suspension. After 5 min, 4-(bromomethyl)pyridine hydrogen bromide (996 mg, 3.94 mmol, 1.05 equiv) was added portionwise, and the reaction was allowed to warm to ambient temperature. After 14 h, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (16 mL) to give a brown biphasic mixture. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 1:1→1:4 hexanes:EtOAc→EtOAc) to afford β-ketoester **24i** (1.16 g, 3.23 mmol, 86% yield, 71% yield over 2 steps) as a yellow oil; R_f = 0.28, broad (1:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.06 (dd, *J* = 4.4, 1.6 Hz, 2H), 5.82 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.37 (s, 1H), 5.28 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.61 (dddd, *J* = 13.1, 5.9, 1.3, 1.3 Hz, 1H), 4.50 (dddd, *J* = 13.1, 5.9, 1.3, 1.3 Hz, 1H), 3.42 (d, *J* = 6.5 Hz, 2H), 3.27 (d, *J* = 13.3 Hz, 1H), 3.18 (d, *J* = 13.3 Hz, 1H), 2.54 (ddd, *J* = 17.2,

9.3, 3.0 Hz, 1H), 2.38–2.21 (m, 2H), 2.03–1.86 (m, 2H), 1.83–1.59 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 174.3, 172.3, 149.6, 146.1, 131.4, 126.0, 119.2, 105.6, 74.9, 66.1, 63.5, 42.4, 33.9, 31.5, 27.8, 21.8, 19.2; IR (Neat Film NaCl) 3072, 3026, 2959, 2935, 2874, 1733, 1660, 1608, 1557, 1496, 1470, 1452, 1415, 1384, 1369, 1293, 1272, 1232, 1201, 1172, 1095, 1074, 1005, 994, 956, 935, 862, 823, 773 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{21}H_{27}O_4N$ $[M]^{+\bullet}$: 357.1940; found 357.1945.



Indolyl β-Ketoester 24ac. To a solution of diisopropylamine (3.54 mL, 25.27 mmol, 1.20 equiv) in THF (108 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (10.26 mL, 24.22 mmol, 2.36 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (3.84 g, 21.06 mmol, 1.00 equiv) in THF (10 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (2.52 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (30.7 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried

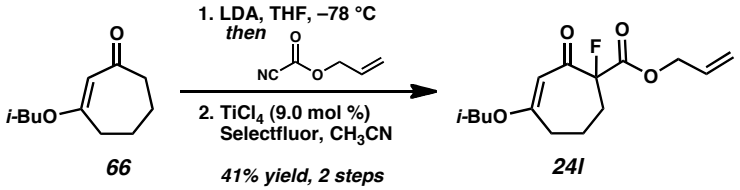
over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 330 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [10 min]→hold 20% [6 min]→ramp to 50% [3 min]→hold 50% EtOAc in hexanes [11 min]) to afford the intermediate β-ketoester (4.66 g, 17.50 mmol, 83% yield) as a pale orange oil.

A portion of the intermediate β-ketoester (0.85 g, 3.19 mmol, 1.00 equiv) was dissolved in THF (32 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (84 mg, 3.51 mmol, 1.10 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Gramine methiodide[52] (1.06 g, 3.35 mmol, 1.05 equiv) was added portionwise to give a suspension. After 11.5 h, the reaction was a brown-orange solution. Additional gramine methiodide (212 mg, 0.67 mmol, 0.31 equiv) was added. After 30 min, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (4.3 mL) to give a brown biphasic mixture. Volatiles were removed under reduced pressure. The residue was extracted with EtOAc (3 x 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in a minimal amount of 1:1 hexanes:EtOAc and filtered through a silica gel pad (1.5 x 10 cm, 1:1 hexanes:EtOAc). The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 20 cm, 6:1→4:1→2:1 hexanes:EtOAc) to afford β-ketoester **24ac** (1.09 g, 2.75 mmol, 86% yield, 71% yield over 2 steps) as an orange-brown semi-solid; R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.67–7.54 (m, 1H), 7.38–7.29 (m, 1H), 7.21–7.04 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 5.84 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.37 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.60 (dddd, *J* = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 4.50 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 3.52 (dd, *J* = 14.3, 0.5 Hz, 1H), 3.47–3.31 (m, 3H), 2.63–2.34 (m, 2H), 2.28 (ddd, *J* = 17.8, 7.7, 4.0 Hz, 1H), 2.02–1.63 (m, 4H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 173.7, 173.2, 135.8, 131.9, 128.8, 124.3, 121.8, 119.5, 119.2, 118.6, 111.1, 111.0, 106.0, 74.7, 65.9, 64.3, 34.0, 32.8, 31.6, 27.8, 21.7, 19.2; IR (Neat Film NaCl) 3785, 3584, 3392, 3079, 3057, 2958, 2930, 2874, 1729, 1641, 1607, 1457, 1457, 1433, 1423, 1384, 1368, 1341, 1233, 1191, 1174, 1127, 1085, 1010, 932, 879, 863, 822, 742 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{24}H_{29}O_4N$ $[M]^{+\bullet}$: 395.2097; found 395.2097.

Tosylindolyl β-Ketoester 24j. To a solution of indole **24ac** (250 mg, 0.63 mmol, 1.00 equiv) in THF (9 mL) in a 100 mL round-bottom flask was added TsCl (241 mg, 1.26 mmol, 2.00 equiv). The mixture was cooled to 0 °C and stirred vigorously as hexane-washed NaH (61 mg, 2.53 mmol, 4.00 equiv) was added in one portion. The reaction was maintained at 0 °C for 5 min before warming to ambient temperature. After 24 h, the white suspension was cooled to 0 °C and additional TsCl (241 mg, 1.26 mmol, 2.00 equiv) was added, followed by hexane-washed NaH (121 mg, 5.06 mmol, 8.00 equiv) in one portion. The reaction was allowed to warm to ambient temperature. After 46 h, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24j** (317 mg, 5.76 mmol, 91% yield) as a yellow foam; R_f = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 1H), 7.75–7.66 (m, 2H), 7.53–7.44 (m, 1H), 7.35 (s, 1H), 7.31–7.13 (m, 4H), 5.77 (dddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.39 (s, 1H), 5.25 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.52 (dddd, *J* = 13.1, 5.7, 1.3, 1.3 Hz, 1H), 4.42 (dddd, *J* = 13.2, 5.9, 1.3, 1.3 Hz, 1H), 3.48–3.32 (m, 3H), 3.26 (d, *J* = 14.4 Hz, 1H), 2.52 (ddd, *J* = 17.7, 9.2, 3.3 Hz, 1H), 2.41–2.19 (m, 5H), 2.02–1.82 (m, 2H), 1.78–1.58 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 174.0, 172.8, 144.8, 135.4, 134.9, 132.1, 131.6, 129.9, 127.0, 125.8, 124.6, 123.2, 119.9, 118.9, 118.0, 113.7, 105.9, 74.8, 66.1, 63.6, 34.1, 32.2, 31.7, 27.9, 21.7, 21.6, 19.2; IR (Neat Film NaCl) 3854, 3401, 2959, 2931, 2874, 1731, 1657, 1650, 1609, 1448, 1368, 1279, 1233, 1188, 1173, 1121, 1098, 1087, 1019, 1007, 992, 976, 938, 864, 813, 748 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{36}O_6N$ $[M+H]^+$: 550.2263; found 550.2250.

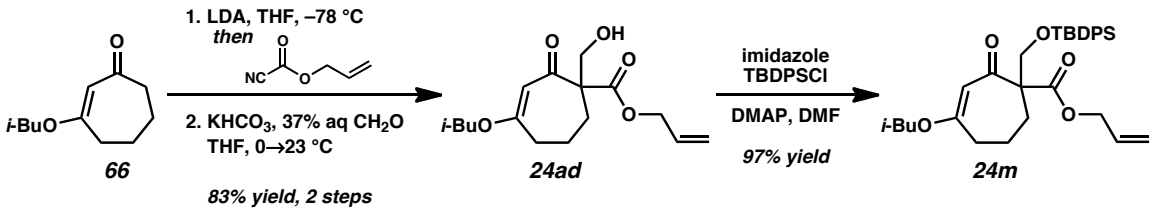


β-Ketoester 24l. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottomed flask at 0 °C in an ice/water bath was added *n*-BuLi (2.56 mL, 2.46 M in hexanes, 6.30 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv)

in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH_3CN (55 mL) in a 100 mL round-bottomed flask under N_2 and $TiCl_4$ (53.7 μL, 0.49 mmol, 9.0 mol %) was added dropwise, giving a dark purple-brown mixture. After 10 min, Selectfluor (2.33 g, 6.58 mmol, 1.20 equiv) was added in one portion. After 3.5 h, the reaction mixture was an orange suspension. The reaction was concentrated under reduced pressure and the orange residue was partitioned between water (25 mL) and Et_2O (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash column chromatography using Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 120 g column, 10% EtOAc in hexanes) to afford β-ketoester **24l** (639 mg, 2.25 mmol, 41% yield over 2 steps) as a pale yellow oil; R_f = 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.20 (app d, *J* = 10.5 Hz, 1H), 4.59 (dddd, *J* = 19.0, 13.2, 5.6, 1.2 Hz, 2H), 3.50 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.8, 9.8, 3.9 Hz, 1H),

2.45–2.38 (m, 2H), 2.02–1.94 (m, 1H), 1.84–1.75 (m, 1H), 1.70 (ddd, J = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1 (d, J_{CF} = 24.1 Hz), 178.0, 167.6 (d, J_{CF} = 25.4 Hz), 131.3, 119.0, 102.0 (d, J_{CF} = 1.1 Hz), 99.3 (d, J_{CF} = 193.5 Hz), 75.3, 66.6, 34.0 (d, J_{CF} = 2.1 Hz), 31.9 (d, J_{CF} = 22.5 Hz), 27.8, 20.7 (d, J_{CF} = 1.7 Hz), 19.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ –148.54 (dd, J = 35.4, 20.7 Hz); IR (Neat Film NaCl) 3086, 2960, 2938, 2876, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1045, 991, 953, 927, 874, 862, 843, 829, 795, 758 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{21}O_4F$ $[M]^{+\bullet}$: 284.1425; found 284.1424.

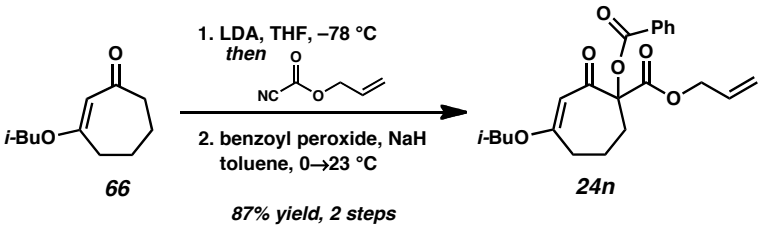


Hydroxy β-Ketoester 24ad. To a solution of diisopropylamine (1.84 mL, 13.15 mmol, 1.20 equiv) in THF (54 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (5.12 mL, 12.60 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (2.00 g, 10.96 mmol, 1.00 equiv) in THF (4 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.34 mL, 12.06 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (16 mL), and then allowed to warm to ambient temperature. The reaction

was diluted with Et_2O (200 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil (2.92 g).

Half of the crude oil (1.46 g) was dissolved in THF (10 mL) in a 50 mL round-bottom flask and cooled to 0 °C. $KHCO_3$ (1.65 g, 16.44 mmol, 3.00 equiv) and 37% wt. aqueous formaldehyde (2.81 mL, 37.73 mmol, 6.9 equiv) were added. The reaction was allowed to warm to ambient temperature. After 11 h, the reaction was diluted with H_2O and CH_2Cl_2 (25 mL each). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 12 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 4:1→ 2:1→1:1 hexanes:EtOAc) to afford β-ketoester **24ad** (1.35 g, 4.55 mmol, 83% yield over 2 steps) as a pale yellow oil; R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.43 (s, 1H), 5.32 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.23 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.76–4.54 (m, 2H), 3.93–3.72 (m, 2H), 3.51 (d, *J* = 6.5 Hz, 2H), 3.59–3.45 (m, 1H) 2.68–2.50 (m, 1H), 2.50–2.35 (m, 1H), 2.31–2.12 (m 1H), 2.10–1.91 (m, 2H), 1.91–1.71 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 175.1, 171.9, 131.6, 118.9, 105.6, 75.1, 68.7, 66.1, 63.6, 33.7, 28.6, 27.9, 20.9, 19.2; IR (Neat Film NaCl) 3448, 3083, 2959, 2937, 2875, 1733, 1646, 1608, 1471, 1457, 1420, 1404, 1385, 1369, 1298, 1235, 1195, 1171, 1099, 1044, 998, 928, 869, 825 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{25}O_5$ $[M+H]^+$: 297.1702; found 297.1715.

Siloxy β-Ketoester 24m. Alcohol **24ad** (895 mg, 3.02 mmol, 1.00 equiv), DMAP (553 mg, 4.53 mmol, 1.50 equiv), and imidazole (308 mg, 4.53 mmol, 1.50 equiv) were dissolved in DMF (11 mL) in a 20 mL scintillation vial with magnetic stir bar and septum fitted screw cap. TBDPSCl (0.942 mL, 3.62 mmol, 1.20 equiv) was added dropwise. The stirred mixture turned into a turbid white suspension within 5 min. After 54 h, the reaction was poured into H_2O (35 mL) and 2:1 CH_2Cl_2/hexanes (75 mL). The phases were separated and the aqueous layer was further extracted with 2:1 CH_2Cl_2/hexanes (4 x 35 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 25 cm, 40:1→20:1 hexanes:EtOAc) to afford siloxy β-ketoester **24m** (1.567 g, 2.93 mmol, 97% yield) as a clear, colorless oil; R_f = 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.61 (m, 4H), 7.47–7.32 (m, 6H), 5.86 (dddd, *J* = 17.1, 10.5, 5.7, 5.7 Hz, 1H), 5.39 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 (dddd, *J* = 13.2, 5.7, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.3, 5.7, 1.3, 1.3 Hz, 1H), 4.15 (d, *J* = 9.6 Hz, 1H), 4.05 (d, *J* = 9.6 Hz, 1H), 3.47 (d, *J* = 6.5 Hz, 2H), 2.80–2.51 (m, 2H), 2.43 (ddd, *J* = 11.0, 7.4, 2.9 Hz, 1H), 2.17–1.89 (m, 3H), 1.89–1.68 (m, 1H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 174.8, 171.6, 135.8, 135.7, 133.3, 133.2, 131.89, 129.8, 129.7, 127.8, 127.7, 118.5, 105.8, 74.8, 69.0, 65.9, 65.1, 34.5, 30.0, 27.8, 26.8, 21.9, 19.4, 19.2; IR (Neat Film NaCl) 3460, 3071, 3049, 2958, 2931, 2890, 2857, 1738, 1650, 1609, 1472, 1429, 1384, 1362, 1299, 1236, 1200, 1173, 1113, 1007, 998, 936, 864, 822, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{32}H_{43}O_5Si$ $[M+H]^+$: 535.2880; found 535.2880.



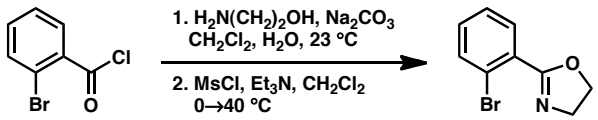
β-Ketoester 24n. To a solution of diisopropylamine (1.84 mL, 13.15 mmol, 1.20 equiv) in THF (54 mL) in a 250 mL round-bottomed flask at 0 °C in an ice/water bath was added *n*-BuLi (5.12 mL, 2.51 M in hexanes, 12.60 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (2.00 g, 10.96 mmol, 1.00 equiv) in THF (4 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.34 mL, 12.06 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (16 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (20 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil (2.92 g).

Half of the crude oil (1.46 g) was dissolved in toluene (30 mL) in a 100 mL round-bottomed flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min. Benzoyl peroxide (1.99 g, 8.22 mmol, 1.50 equiv) was added slowly portionwise, giving a thick, pasty suspension. The reaction was warmed to ambient temperature and diluted with toluene (20 mL) to give a more

freely stirring turbid yellow mixture. After 30 min, the reaction was diluted with toluene (50 mL) and washed with H_2O (2 x 5 mL) and brine (2 x 5 mL). The aqueous layers were combined and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 13 cm, 10:1 hexanes:EtOAc) to afford β-ketoester **24n** (1.85 g, 4.79 mmol, 87% yield over 2 steps) as a pale yellow oil; R_f = 0.46 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–7.99 (m, 2H), 7.64–7.53 (m, 1H), 7.50–7.38 (m, 2H), 5.89 (dddd, *J* = 17.2, 10.5, 5.7, 5.7 Hz, 1H), 5.42 (s, 1H), 5.31 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.80–4.62 (m, 2H), 3.57 (d, *J* = 6.5 Hz, 2H), 2.87–2.46 (m, 4H), 2.12–1.85 (m, 3H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 175.9, 168.0, 165.1, 133.6, 131.7, 130.0, 129.6, 128.6, 118.7, 102.2, 88.8, 75.2, 66.6, 33.8, 31.2, 27.9, 21.2, 19.2, 19.2; IR (Neat Film NaCl) 3070, 2960, 2937, 2875, 1753, 1727, 1661, 1605, 1471, 1452, 1423, 1384, 1369, 1315, 1280, 1222, 1206, 1175, 1107, 1097, 1070, 1044, 1026, 1002, 933, 849, 792 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{22}H_{26}O_6$ $[M]^{+\bullet}$: 386.1733; found 386.1729.

2.7.2.3 SYNTHESIS OF PHOX LIGANDS

Ligands (*S*)-*t*-BuPHOX (**3**)[54] and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[55] were prepared according to previously reported procedures. The preparation of ligands **128** and **67** are described below.

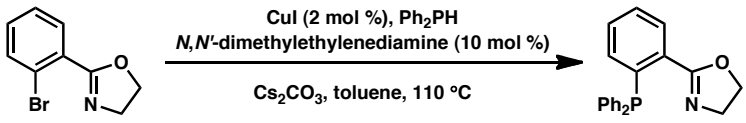


127

2-(2-Bromo-phenyl)-4,5-dihydrooxazole 127. To a solution of ethanolamine (1.32 mL, 21.9 mmol, 1.20 equiv) in CH_2Cl_2 (60 mL) in a 250 mL round-bottom flask was added a solution of Na_2CO_3 (5.80 g, 54.7 mmol, 3.00 equiv) in H_2O (45 mL). Neat 2-bromobenzoyl chloride (4.00 g, 2.38 mL, 18.2 mmol, 1.00 equiv) was added dropwise via syringe to the vigorously stirred biphasic system. The reaction flask was capped with a yellow plastic stopper and stirred for 7.5 h at 23 °C. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid. The crude product was dissolved in CH_2Cl_2 (50 mL) and hexanes (10 mL) was added. The solution was concentrated to ca. 25 mL under reduced pressure resulting in precipitation of the intermediate amide (4.02 g, 16.4 mmol, 90% yield) as a white solid.

The intermediate amide (2.0 g, 8.2 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (62 mL) in a 100 mL round-bottom flask equipped with a reflux condenser. Et_3N (3.43 mL, 24.5 mmol, 3.00 equiv) was added, and the solution was cooled to 0 °C by use of an ice/water bath. Methanesulfonyl chloride (952 μL, 12.3 mmol, 1.50 equiv) was added dropwise. The reaction was stirred at 0 °C for 30 min and heated to 40 °C in an oil bath. After 5 h of stirring, the resulting yellow solution was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (25 mL), and washed with H_2O (2 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a thick, pale yellow oil. The crude oil was purified by flash

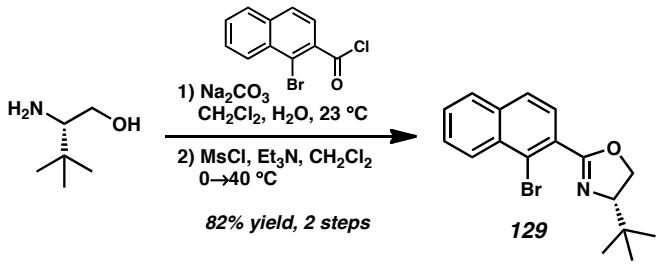
chromatography (SiO_2, 5 x 10 cm, 6:2:2 hexanes:EtOAc:toluene) to afford 2-(2-bromo-phenyl)-4,5-dihydrooxazole **127** (1.31 g, 5.79 mmol, 71% yield); R_f = 0.45 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.35 (app dt, *J* = 7.6, 1.2 Hz, 1H), 7.29 (app dt, *J* = 7.6, 1.7 Hz, 1H), 4.46 (t, *J* = 9.6 Hz, 2H), 4.12 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 134.1, 131.8, 131.5, 129.8, 127.2, 122.0, 67.8, 55.5; IR (Neat Film NaCl) 3390, 3070, 2966, 2904, 2868, 1729, 1646, 1589, 1432, 1362, 1328, 1272, 1243, 1093, 1026, 938 cm^{-1}; HRMS (EI+) *m/z* calc'd for C_9H_8BrNO $[M]^{+\bullet}$: 224.9789; found 224.9779.



127 ***86% yield*** ***128***

PHOX Ligand 128. A 250 mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol, 2 mol %), Ph_2PH (3.85 mL, 22.1 mmol, 1.25 equiv), *N,N'*-dimethylethylenediamine (191 mL, 1.77 mmol, 10 mol %), and toluene (18 mL). The solution was stirred at 23 °C for 20 min. 2-(2-Bromo-phenyl)-4,5-dihydrooxazole **127** (4.0 g, 17.7 mmol, 1.00 equiv) was azeotroped with toluene (2 x 5 mL) under reduced pressure, dissolved in toluene (18 mL), and transferred quantitatively to the Schlenk flask by use of positive pressure cannulation. Cs_2CO_3 (8.65 g, 26.5 mmol, 1.50 equiv) was added in one portion and the flask was evacuated/backfilled with Ar (three cycles). The teflon valve was sealed, and the yellow heterogeneous reaction mixture was stirred vigorously, immersed in an oil bath, and heated to 110 °C. After 20 h of stirring at 110 °C, the mixture was allowed to cool to ambient temperature and filtered through a pad of

Celite using CH_2Cl_2 (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford a clear orange oil. The crude oil was flushed through a plug of silica gel (SiO_2, 5 x 10 cm, hexanes→9:1 CH_2Cl_2:Et_2O) to afford PHOX ligand **128** (5.03 g, 15.2 mmol, 86% yield) as a colorless viscous oil that crystallized upon standing; R_f = 0.50 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 3.4 Hz, 1H), 7.37–7.26 (comp. m, 12H), 6.89 (dd, *J* = 4.1, 7.6 Hz, 1H), 4.08 (t, *J* = 9.5 Hz, 2H), 3.78 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (d, J_{CP} = 2.8 Hz), 139.1 (d, J_{CP} = 24.9 Hz), 138.0 (d, J_{CP} = 11.5 Hz), 134.1 (d, J_{CP} = 20.7 Hz), 133.7 (d, J_{CP} = 1.8 Hz), 131.9 (d, J_{CP} = 18.9 Hz), 130.5, 129.9 (d, J_{CP} = 2.8 Hz), 128.7, 128.5 (d, J_{CP} = 7.4 Hz), 128.1, 67.2, 55.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.99 (s); IR (Neat Film NaCl) 3053, 3000, 2971, 2901, 2876, 1650, 1585, 1562, 1478, 1434, 1354, 1326, 1248, 1133, 1089, 1070, 1041, 974, 942, 898, 743 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{19}NOP$ $[M+H]^+$: 332.1204; found 332.1218; mp = 99–101 °C.

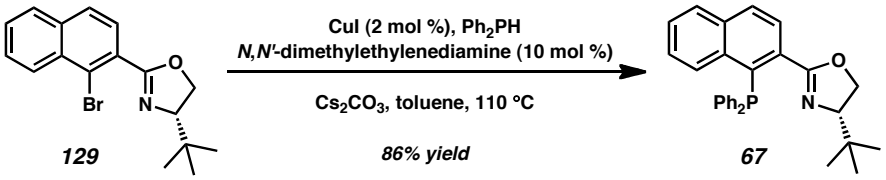


Dihydrooxazole 129. (*S*)-*tert*-Leucinol (1.02 g, 8.66 mmol, 1.00 equiv) was placed in a 250 mL round-bottom flask and dissolved in CH_2Cl_2 (14 mL). Na_2CO_3 (2.75 g, 26.0 mmol, 3.00 equiv) in H_2O (27.0 mL) was added dropwise via syringe to the vigorously stirred biphasic system. To the biphasic mixture was added a solution of 1-bromonaphthalene-2-carbonyl chloride (2.68 g, 9.96 mmol, 1.15 equiv) in CH_2Cl_2 (15

mL). The reaction was stirred vigorously at 23 °C for 9.5 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were stirred with KOH (10 mL, 10 mmol, 1.0 N in MeOH) for 30 min and then transferred to a separatory funnel. H_2O (10 mL) was added and the mixture was neutralized with HCl (6.0 M in H_2O). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford the intermediate amide (3.03 g) as a pale yellow solid.

The intermediate amide (3.03 g) was dissolved in CH_2Cl_2 (43.3 mL) in a 100 mL 3-neck round-bottom flask fitted with a reflux condenser. The solution was cooled to 0 °C by use of an ice/water bath and Et_3N (2.90 mL, 20.8 mmol, 2.40 equiv) was added. Methanesulfonyl chloride (0.77 mL, 9.96 mmol, 1.15 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and heated to 40 °C in a water bath. After 21 h of stirring, the mixture was allowed to cool to ambient temperature and saturated aqueous $NaHCO_3$ was added. The biphasic system was stirred vigorously for 5 min and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography (SiO_2, 3 x 15 cm, 9:1 hexanes:EtOAc) to afford **129** (2.36 g, 7.12 mmol, 82% yield over two steps) as a pale yellow oil that solidifies when placed in a –20 °C freezer; $R_f = 0.73$ (9:1 $CHCl_3$:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.85–7.81 (m, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.60 (app dt, *J* = 8.2, 1.3 Hz, 1H), 7.56 (app dt, *J* = 6.9, 1.3 Hz, 1H), 4.46 (dd, *J* = 10.4, 8.5 Hz, 1H),

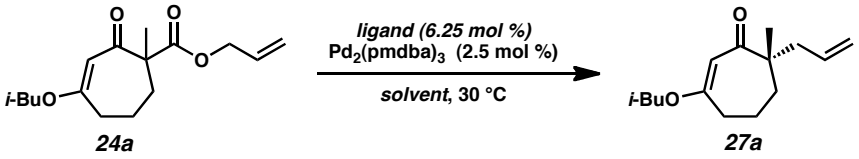
4.33 (dd, J = 8.5, 8.0 Hz, 1H), 4.17 (dd, J = 10.4, 8.2 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 134.9, 132.3, 128.8, 128.3, 128.3, 128.0, 127.8, 127.7, 126.9, 123.2, 76.9, 69.2, 34.1, 26.1; IR (Neat Film NaCl) 3065, 2956, 2899, 2863, 1667, 1620, 1594, 1556, 1499, 1476, 1463, 1393, 1372, 1362, 1339, 1321, 1300, 1238, 1264, 1210, 1161, 1104, 1024, 977, 956, 920, 817, 752 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{17}H_{18}ONBr$ $[M]^{+\bullet}$: 331.0572; found 331.0583; $[\alpha]_D^{20.0}$ –64.0 (c 0.92, $CHCl_3$); mp = 66–68 °C.



PHOX Ligand 67. Prepared by the typical method as described for **128** above by employing **129** (830.6 mg, 2.50 mmol). After 24 h of stirring, the reaction mixture was filtered through a plug of Celite, eluted with CH_2Cl_2 (2 x 25 mL), and concentrated under reduced pressure. The crude oil was passed through a short plug of silica (SiO_2, 2.5 x 8 cm, hexanes→9:1 CH_2Cl_2:Et_2O) to afford a bright yellow oil. The crude oil was purified by flash chromatography (SiO_2, 2.5 x 25 cm, 19:1 hexanes:acetone and then 2.5 x 21 cm, 9:1→6:1 hexanes:EtOAc) to afford PHOX ligand **67** (950.8 mg, 2.17 mmol, 87% yield) as a bright yellow foam; R_f = 0.21 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.72 (dd, J = 8.3, 2.9 Hz, 1H), 7.45 (app dt, J = 7.8, 1.7 Hz, 2H), 7.41–7.38 (m, 3H), 7.29–7.22 (m, 6H), 7.16 (ddd, J = 8.3, 6.9, 1.0 Hz, 1H), 4.17–4.15 (m, 2H), 3.91 (dd, J = 9.8, 8.8 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (d, J_{CP} = 5.1 Hz), 137.5 (d, J_{CP} = 33.1 Hz), 136.8, (d, J_{CP}

= 14.7 Hz), 136.5 (d, J_{CP} = 14.7), 134.9, 134.7 (d, J_{CP} = 33.6 Hz), 133.1 (d, J_{CP} = 26.7 Hz), 132.2 (d, J_{CP} = 17.5 Hz), 132.1 (d, J_{CP} = 17.5 Hz), 131.5 (d, J_{CP} = 0.9 Hz), 129.1 (d, J_{CP} = 7.4 Hz), 129.0, 128.4 (d, J_{CP} = 6.0 Hz), 127.8 (d, J_{CP} = 8.3 Hz), 126.6 (d, J_{CP} = 8.7 Hz), 126.4 (d, J_{CP} = 40.5 Hz), 76.8, 69.0, 34.1, 26.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ –9.33 (s); IR (Neat Film NaCl) 3054, 2954, 2867, 1665, 1584, 1478, 1434, 1364, 1244, 1094, 1026, 986, 962, 922, 824 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{29}H_{28}NOP$ $[M]^{+\bullet}$: 437.1908; found 437.1908; $[\alpha]_D^{26.1}$ –38.2 (*c* 1.59, *n*-hexane).

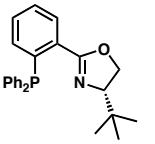
2.7.2.4 ENANTIOSELECTIVE Pd-CATALYZED DECARBOXYLATIVE ALKYLATION SCREENING PROTOCOL[a]



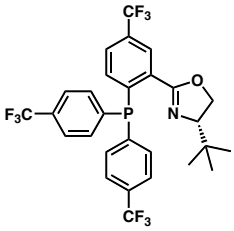
24a *27a*

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	*13*	THF[e]	94	84
2	*13*	*p*-dioxane	86	84
3	*13*	2-methyl THF[e]	75	85
4	*13*	TBME[e]	88	85
5	*13*	Et_2O	93	86
6	*13*	benzene	84	86
7	*13*	toluene	91	88
8[d]	*14*	toluene	57	90
9	*150*	toluene	77	72

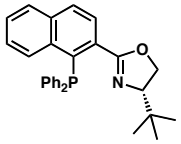
[a] *Conditions*: β-ketoester **24a** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), ligand (6.25 mol %) in solvent (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Increased catalyst loadings were required to achieve full conversion: $Pd_2(pmdba)_3$ (5 mol %), **8** (12.5 mol %). [e] THF = tetrahydrofuran, 2-methyl THF = 2-methyl tetrahydrofuran, TBME = *tert*-butyl methyl ether.



***(S)*-*t*-BuPHOX (*3*)**



(S)*-$(CF_3)_3$-*t*-BuPHOX *(8)



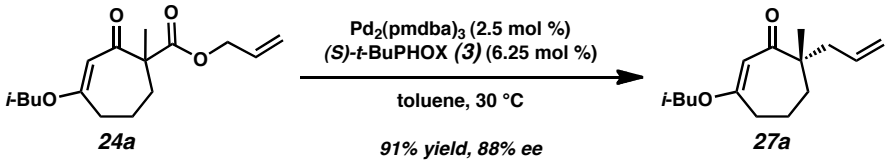
67

Enantioselective Allylation Screen to Produce Vinylogous Ester 27a *(0.20 mmol scale).* To a 25 mL flask was added $Pd_2(pmdba)_3$ (5.00 μmol, 2.5 mol %) and ligand (12.5 μmol, 6.25 mol %). The flask was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Solvent (most of total volume, 0.1 M final concentration) was added and the black suspension was stirred for 30 min at 30 °C using an oil bath. A solution of β-ketoester **24a** (0.20 mmol, 1.00 equiv) in solvent (remainder of total volume) was transferred to the catalyst solution using positive pressure cannulation. When judged complete by TLC analysis, the reaction was filtered through a small plug of SiO_2, eluted with Et_2O, and concentrated under reduced pressure. Purification by flash

column chromatography (SiO_2, 1.5 x 15 cm, 9:1→6:1 hexanes:EtOAc) or preparative TLC (SiO_2, 2:1 hexanes:EtOAc) provided vinylogous ester **27a** for analysis. HPLC conditions: 1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 6.30, minor = 7.26. (For characterization data, see p. 287)

2.7.2.5 PREPARATION OF CHIRAL VINYLOGOUS ESTERS 27

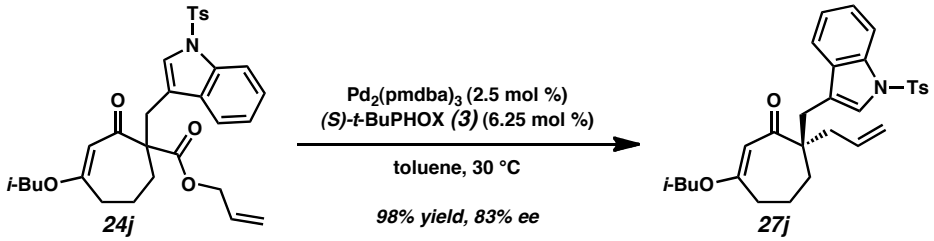
Non-enantioselective reactions were performed using $Pd(PPh_3)_4$ (5 mol %) or achiral PHOX ligand **128** (6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in toluene at 30 °C. For the synthesis of ligand **128**, see p. 277–283.



Schlenk Manifold Method: Asymmetric Allylic Alkylation

Vinylogous Ester 27a. $Pd_2(pmdba)_3$ (5.0 mg, 4.5 μmol, 2.5 mol %) and (*S*)-*t*-BuPHOX (4.4 mg, 11 μmol, 6.25 mol %) were placed in a 1 dram vial. The flask was evacuated/backfilled with N_2 (3 cycles, 10 min evacuation per cycle). Toluene (1.3 mL, sparged with N_2 for 1 h immediately before use) was added and the black suspension was immersed in an oil bath preheated to 30 °C. After 30 min of stirring, β-ketoester **24a** (50.7 mg, 0.181 mmol, 1.00 equiv) was added as a solution in toluene (0.5 mL, sparged with N_2 immediately before use) using positive pressure cannulation. The dark orange catalyst solution turned olive green immediately upon addition of β-ketoester **24a**. The

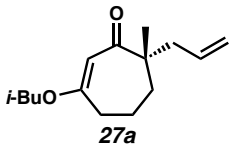
reaction was stirred at 30 °C for 21 h, allowed to cool to ambient temperature, filtered through a silica gel plug (2 x 2 cm, Et_2O), and concentrated under reduced pressure. The crude oil was purified by preparative TLC (SiO_2, 4:1 hexanes:EtOAc) to afford vinylogous ester **27a** (38.8 mg, 0.164 mmol, 91% yield, 88% ee) as a pale yellow oil. (For characterization data, see p. 287).



Glove Box Method: Asymmetric Allylic Alkylation

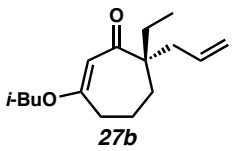
Vinylogous Ester 27j. A 20 mL scintillation vial was loaded with β-ketoester **24j** (447 mg, 0.81 mmol, 1.00 equiv). A separate 20 mL scintillation vial was loaded with $Pd_2(pmdba)_3$ (19.7 mg, 0.051 mmol, 6.25 mol %), (*S*)-*t*-BuPHOX (22.3 mg, 0.020 mmol, 2.5 mol %), and magnetic stir bar. The two vials and a teflon-lined hard cap were evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being trasnsferred into the glove box. Toluene (5 mL) was added to the vial containing $Pd_2(pmdba)_3$ and (*S*)-*t*-BuPHOX. The vial was capped and heated to 30 °C for 30 min. During this time, the mixture developed a dark orange color. β-Ketoester **24j** was dissolved in toluene (3 mL) and added to the catalyst solution dropwise, causing the solution to turn olive green. The solution was stirred at 30 °C in a heating block. The capped vial was removed from the glove box after 29 h of stirring. The crude product was concentrated under reduced pressure and purified by flash column chromatography

(SiO_2, 5 x 25 cm, 15:1→10:1→8:1→6:1 hexanes:EtOAc) to afford vinylogous ester **27j** (403 mg, 0.796 mmol, 98% yield, 82.9% ee) as a thick, white semi-solid. (For characterization data, see p. 294).



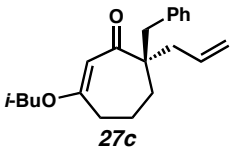
27a

Vinylogous Ester 27a ***(Table 2.1, entry 1).*** Prepared using Schlenk Manifold Method. 38.8 mg, 0.164 mmol, 91% yield. Preparative TLC (SiO_2, 4:1 hexanes:EtOAc). R_f = 0.31 (3:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05–5.00 (m, 2H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.53–2.42 (m, 2H), 2.38 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.98 (app sept, *J* = 6.6 Hz, 1H), 1.86–1.70 (m, 3H), 1.62–1.56 (m, 1H), 1.14 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 236.1776; found 236.1767; $[\alpha]_D^{25.6}$ –69.04 (*c* 1.08, $CHCl_3$, 88.0% ee); HPLC conditions: 1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 6.30, minor = 7.26.



27b

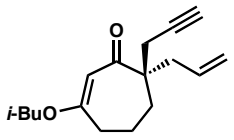
Vinylogous Ester 27b ***(Table 2.1, entry 2).*** Prepared using Schlenk Manifold Method. 226.3 mg, 0.90 mmol, 89% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.43 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82–5.62 (m, 1H), 5.29 (s, 1H), 5.06–4.98 (m, 2H), 3.48 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.45 (dd, *J* = 11.2, 6.6 Hz, 1H), 2.49–2.42 (m, 2H), 2.40 (dddd, *J* = 13.8, 7.1, 1.2 Hz, 1H), 2.23 (dddd, *J* = 13.8, 7.7, 1.1, 1.1 Hz, 1H), 1.97 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.44 (m, 6H), 0.98–0.91 (d, *J* = 6.7 Hz, 6H), 0.79 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 171.0, 135.1, 117.6, 105.5, 74.4, 54.8, 41.9, 36.1, 32.3, 31.3, 28.0, 20.0, 19.3, 8.6; IR (Neat Film NaCl) 3073, 2960, 2933, 2876, 1617, 1613, 1459, 1400, 1387, 1369, 1314, 1220, 1190, 1173, 996, 969, 954, 912, 883, 873, 856, 782 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{26}O_2$ $[M]^{+\bullet}$: 250.1933; found 250.1909; $[\alpha]_D^{25.0}$ +25.83 (*c* 1.04, $CHCl_3$, 91.6% ee); HPLC conditions: 0.25% IPA in hexanes, 1.0 mL/min, AD column, t_R (min): minor = 16.23, major = 18.08.



27c

Vinylogous Ester 27c ***(Table 2.1, entry 3).*** Prepared using Schlenk Manifold Method. 172.5 mg, 0.552 mmol, 98% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.50 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.14 (m, 3H), 7.14–7.08 (m, 2H), 5.85–5.68 (m, 1H), 5.31 (s, 1H),

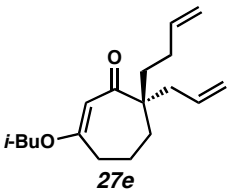
5.10–4.99 (m, 2H), 3.44 (dd, *J* = 14.7, 6.6 Hz, 1H), 3.41 (dd, *J* = 14.7, 6.6 Hz, 1H), 3.14 (d, *J* = 13.3 Hz, 1H), 2.71 (d, *J* = 13.3 Hz, 1H), 2.51 (dddd, *J* = 13.7, 6.8, 1.2, 1.2 Hz, 1H), 2.45–2.32 (m, 2H), 2.16 (dddd, *J* = 13.7, 7.9, 1.1, 1.1 Hz, 1H), 1.93 (app sept, *J* = 6.7 Hz, 1H), 1.83–1.56 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 171.4, 138.3, 134.5, 130.8, 128.0, 126.3, 118.2, 106.3, 74.5, 56.2, 44.1, 43.9, 36.3, 31.3, 27.9, 19.5, 19.3; IR (Neat Film NaCl) 3072, 3061, 3027, 3002, 2957, 2931, 2871, 1610, 1495, 1471, 1454, 1422, 1403, 1387, 1368, 1318, 1280, 1217, 1189, 1173, 1081, 1031, 1007, 969, 957, 913, 875, 856, 831, 760, 746, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{28}O_2$ $[M]^{+\bullet}$: 312.2089; found 312.2083; $[\alpha]_D^{25.0}$ +2.91 (*c* 0.98, $CHCl_3$, 86.3% ee); HPLC conditions: 0.5% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 13.96, major = 15.70.



27d

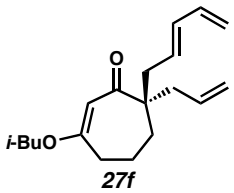
Vinylogous Ester 27d ***(Table 2.1, entry 4).*** Prepared using Schlenk Manifold Method. 224.7 mg, 0.86 mmol, 88% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.44 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.59 (m, 1H), 5.32 (s, 1H), 5.12–5.02 (m, 2H), 3.50 (dd, *J* = 14.9, 6.5 Hz, 1H), 3.47 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.53–2.48 (m, 4H), 2.46 (dddd, *J* = 13.7, 7.3, 1.2, 1.2 Hz, 1H), 2.35 (dddd, *J* = 13.7, 7.6, 1.1, 1.1 Hz, 1H), 2.09–1.67 (m, 5H), 1.57 (s, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 171.7, 133.7, 118.5, 105.0, 81.7, 74.6, 70.8, 54.2, 42.9, 36.1, 32.5, 28.0, 27.1, 20.0, 19.3; IR (Neat Film NaCl) 3301,

3075, 2957, 2930, 2873, 2116, 1612, 1471, 1457, 1435, 1423, 1402, 1387, 1368, 1320, 1221, 1191, 1175, 995, 969, 916, 874, 845 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{24}O_2$ $[M]^{+\bullet}$: 260.1776; found 260.1737; $[\alpha]_D^{25.0}$ –26.51 (*c* 1.03, $CHCl_3$, 88.5% ee); HPLC conditions: 0.5% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 12.35, minor = 13.43.



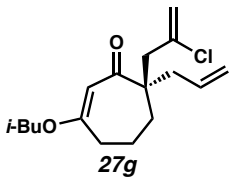
27e

Vinylogous Ester 27e ***(Table 2.1, entry 5).*** Prepared using Glove Box Method. 287.5 mg, 1.04 mmol, 95% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 20:1 hexanes:EtOAc). R_f = 0.44 (10:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84–5.64 (m, 2H), 5.30 (s, 1H), 5.09–4.87 (m, 4H), 3.49 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.46 (dd, *J* = 11.1, 6.6 Hz, 1H), 2.54–2.37 (m, 3H), 2.27 (dddd, *J* = 13.8, 7.7, 1.2, 1.2 Hz, 1H), 2.07–1.89 (m, 3H), 1.86–1.45 (m, 6H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 171.1, 138.9, 134.8, 117.9, 114.5, 105.5, 74.8, 54.4, 42.3, 38.0, 36.1, 32.7, 28.6, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3076, 2958, 2932, 2874, 1639, 1614, 1471, 1455, 1434, 1424, 1402, 1387, 1368, 1317, 1280, 1216, 1190, 1174, 1086, 996, 969, 955, 910, 878, 853, 829, 771 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{28}O_2$ $[M]^{+\bullet}$: 276.2089; found 276.2060; $[\alpha]_D^{25.0}$ +15.28 (*c* 0.97, $CHCl_3$, 86.9% ee); HPLC conditions: 0.8% IPA in hexanes, 2.0 mL/min, AD column, t_R (min): major = 5.03, minor = 6.06.



27f

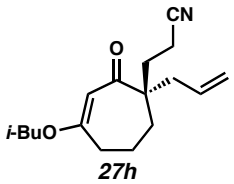
Vinylogous Ester 27f ***(Table 2.1, entry 6).*** Prepared using Schlenk Manifold Method. 232.9 mg, 0.81 mmol, 90% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.45 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.04 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.82–5.53 (m, 2H), 5.31 (s, 1H), 5.15–4.92 (m, 4H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.55–2.36 (m, 4H), 2.30–2.16 (m, 2H), 1.98 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.67 (m, 4H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.4, 137.2, 134.5, 134.1, 130.8, 118.0, 115.5, 105.5, 74.5, 55.1, 43.1, 41.6, 36.1, 32.5, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3075, 3036, 3007, 2958, 2931, 2873, 1726, 1635, 1611, 1471, 1456, 1436, 1402, 1387, 1368, 1312, 1277, 1219, 1190, 1173, 1085, 1005, 954, 911, 874, 831 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{29}O_2$ $[M+H]^+$: 289.2168; found 289.2172; $[\alpha]_D^{25.0}$ –20.62 (*c* 1.05, $CHCl_3$, 89.6% ee); SFC conditions: 5.0% IPA in hexanes, 2.5 mL/min, AD-H column, t_R (min): minor = 6.31, major = 6.99.



27g

Vinylogous Ester 27g ***(Table 2.1, entry 7).*** Prepared using Schlenk Manifold Method. 259.5 mg, 0.87 mmol, 99% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.36 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz,

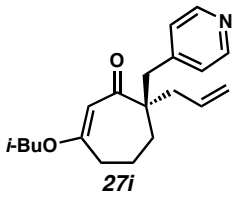
$CDCl_3$) δ 5.78–5.62 (m, 1H), 5.36 (s, 1H), 5.25 (s, 1H), 5.14 (s, 1H), 5.11–5.01 (m, 2H), 3.54–3.43 (m, 2H), 2.95 (dd, *J* = 14.4, 0.7 Hz, 1H), 2.54–2.41 (m, 4H), 2.25 (dddd, *J* = 13.9, 7.9, 1.1, 1.1 Hz, 1H), 2.07–1.89 (m, 2H), 1.88–1.70 (m, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 171.6, 139.4, 133.9, 118.7, 116.6, 105.9, 74.6, 54.7, 46.7, 43.7, 36.3, 31.5, 28.0, 19.6, 19.3; IR (Neat Film NaCl) 3075, 2958, 2934, 2874, 1612, 1471, 1458, 1424, 1403, 1388, 1368, 1339, 1321, 1297, 1222, 1192, 1175, 1082, 1010, 995, 968, 956, 916, 875, 847, 746 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{26}O_2Cl$ $[M+H]^+$: 297.1621; found 297.1623; $[\alpha]_D^{25.0}$ +4.20 (*c* 1.02, $CHCl_3$, 85.7% ee); HPLC conditions: 0.1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 24.19, major = 27.22.



27h

Vinylogous Ester 27h ***(Table 2.1, entry 8).*** Prepared using Schlenk Manifold Method. 292.8 mg, 1.06 mmol, 96% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→10:1→8:1→6:1 hexanes:EtOAc). R_f = 0.39 broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.58 (m, 1H), 5.31 (s, 1H), 5.15–5.04 (m, 2H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.1 Hz, 2H), 2.40 (dddd, *J* = 14.0, 7.0, 1.2, 1.2 Hz, 1H), 2.35–2.22 (m, 3H), 2.11–1.93 (m, 2H), 1.93–1.62 (m, 5H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 172.1, 133.1, 120.3, 119.2, 104.9, 74.7, 53.6, 41.8, 36.1, 33.9, 32.8, 28.0, 19.8, 19.3, 12.8; IR (Neat Film NaCl) 3076, 2958, 2933, 2874, 2246, 1635,

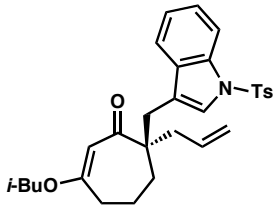
1609, 1472, 1458, 1420, 1404, 1388, 1368, 1319, 1281, 1214, 1192, 1175, 1084, 1003, 917, 880, 854, 827, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_2N$ $[M]^{+\bullet}$: 275.1885; found 275.1893; $[\alpha]_D^{25.0}$ –20.97 (*c* 1.06, $CHCl_3$, 87.4% ee); HPLC conditions: 5.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 10.67, minor = 14.66.



27i

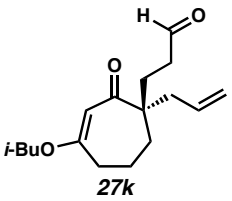
Vinylogous Ester 27i ***(Table 2.1, entry 9).*** Prepared using Glove Box Method. 339.6 mg, 1.08 mmol, 97% yield. Flash column chromatography (SiO_2, 3 x 20 cm, 1:1→1:4 hexanes:EtOAc→EtOAc). R_f = 0.28, broad (1:2 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.05 (dd, *J* = 4.5, 1.6 Hz, 2H), 5.84–5.66 (m, 1H), 5.31 (s, 1H), 5.15–5.02 (m, 2H), 3.44 (dd, *J* = 15.1, 6.3 Hz, 1H), 3.41 (dd, *J* = 15.0, 6.3 Hz, 1H), 3.20 (d, *J* = 12.9 Hz, 1H), 2.60 (d, *J* = 12.9 Hz, 1H), 2.48 (dddd, *J* = 13.8, 6.9, 1.2, 1.2 Hz, 1H), 2.43–2.29 (m, 2H), 2.23 (dddd, *J* = 13.8, 7.8, 1.1, 1.1 Hz, 1H), 1.94 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.67 (m, 2H), 1.67–1.51 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 171.8, 149.5, 147.6, 133.7, 126.2, 118.9, 106.0, 74.6, 55.8, 43.8, 43.5, 36.2, 31.5, 27.9, 19.4, 19.3; IR (Neat Film NaCl) 3072, 3024, 2957, 2931, 2873, 1608, 1558, 1496, 1471, 1458, 1438, 1415, 1388, 1368, 1320, 1220, 1190, 1173, 1072, 994, 957, 916, 876, 844, 796 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{27}O_2N$ $[M]^{+\bullet}$: 313.2042; found 313.2045; $[\alpha]_D^{25.0}$ +22.44 (*c* 1.16, $CHCl_3$, 84.6% ee);

HPLC conditions: 5.0% EtOH in hexanes, 1.0 mL/min, AD column, t_R (min): major = 13.22, minor = 15.13.



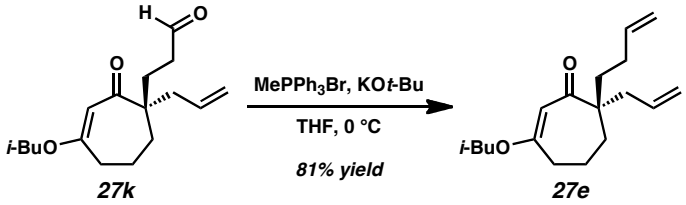
27j

Vinylogous Ester 27j ***(Table 2.1, entry 10).*** Prepared using Glove Box Method. 403 mg, 0.796 mmol, 98% yield. Flash column chromatography (SiO_2, 5 x 25 cm, 15:1→10:1→8:1→6:1 hexanes:EtOAc). R_f = 0.49 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dm, *J* = 8.4 Hz, 1H), 7.70 (dm, *J* = 8.4 Hz, 2H), 7.48 (dm, *J* = 7.9 Hz, 1H), 7.31–7.13 (m, 5H), 5.86–5.68 (m, 1H), 5.32 (s, 1H), 5.13–5.00 (m, 2H), 3.42 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.38 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.20 (dd, *J* = 14.2, 0.7 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.51 (dddd, *J* = 13.7, 6.9, 1.3, 1.3 Hz, 1H), 2.44–2.15 (m, 6H), 1.92 (app sept, *J* = 6.7 Hz, 1H), 1.76–1.46 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 171.7, 144.8, 135.4, 135.0, 134.1, 132.4, 129.8, 126.9, 125.4, 124.5, 123.2, 120.1, 119.6, 118.6, 113.8, 106.4, 74.6, 55.9, 44.1, 36.3, 33.0, 31.9, 27.9, 21.7, 19.5, 19.3; IR (Neat Film NaCl) 3584, 3401, 2068, 2958, 2930, 2873, 1609, 1494, 1470, 1448, 1422, 1402, 1368, 1306, 1279, 1215, 1188, 1174, 1120, 1097, 1020, 975, 916, 876, 813, 782, 747 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{30}H_{36}O_4NS$ $[M+H]^+$: 506.2365; found 506.2358; $[\alpha]_D^{25.0}$ +9.10 (*c* 1.00, $CHCl_3$, 82.9% ee); HPLC conditions: 5.0% EtOH in hexanes, 1.0 mL/min, AD column, t_R (min): major = 11.11, minor = 16.64.



27k

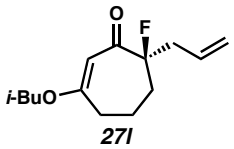
Vinylogous Ester 27k ***(Table 2.1, entry 11).*** Prepared using Glove Box Method. 77.3 mg, 0.278 mmol, 90% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.35, broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.5 Hz, 1H), 5.78–5.61 (m, 1H), 5.29 (s, 1H), 5.11–5.02 (m, 2H), 3.47 (m, 2H), 2.54–2.33 (m, 5H), 2.28 (dddd, *J* = 14.0, 7.6, 1.2, 1.2 Hz, 1H), 2.07–1.73 (m, 5H), 1.73–1.56 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 202.3, 171.7, 134.0, 118.5, 105.2, 74.6, 53.6, 42.1, 39.4, 36.1, 33.1, 30.3, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3075, 2958, 2931, 2719, 1724, 1611, 1471, 1458, 1421, 1403, 1388, 1368, 1213, 1191, 1175, 998, 915, 878 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{27}O_3$ $[M+H]^+$: 279.1960; found 279.1969; $[\alpha]_D^{25.0}$ +15.37 (*c* 1.03, $CHCl_3$, 79.5% ee); Compound **27k** was derivatized using procedure below to determine ee using the corresponding chiral HPLC assay for vinylogous ester **27e**.



27k ***27e***

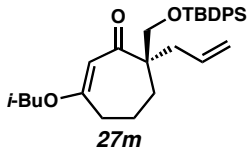
Vinylogous Ester 27e. To a solution of $MePh_3PBr$ (323.2 mg, 0.905 mmol, 0.84 equiv) in THF (14.0 mL) in a 50 mL round-bottom flask at 0 °C was added KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) to give a bright yellow suspension. Aldehyde **27k** (299.9 mg,

1.078 mmol, 1.00 equiv) in THF (2 mL) was added to the suspension using positive pressure cannulation and maintained at 0 °C. The reaction faded to an off-white suspension. After 1.5 h of stirring, an additional portion of Wittig reagent was prepared in a 20 mL scintillation vial. $MePPh_3Br$ (323.2 mg, 0.905 mmol, 0.84 equiv) was added to the vial. The vial was sealed with a septum, evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Anhydrous THF (3 mL) was added and the vial was cooled to 0 °C. KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) was added in one portion, giving a bright yellow suspension that was added to the reaction flask using positive pressure cannulation. The tan suspension was stirred at 0 °C for 1 h. An additional portion of Wittig reagent using $MePPh_3Br$ (323.2 mg, 0.905 mmol, 0.84 equiv), KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) and THF (3 mL) was prepared at 0 °C and added using positive pressure cannulation as previously described. The reaction showed a persistent yellow color. After 30 min of stirring at 0 °C, the reaction was quenched by addition of sat. aqueous NH_4Cl (5 mL) and stirred for 30 min while the mixture was allowed to warm to ambient temperature. The mixture was extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 1%→2%→3%→5% EtOAc in hexanes) to afford vinylogous ester **27e** (243.7 mg, 0.882 mmol, 81% yield) as a yellow liquid; HPLC conditions: 0.8% IPA in hexanes, 2.0 mL/min, AD column, t_R (min): major = 4.39, minor = 3.17. (For characterization data, see p. 290).



27l

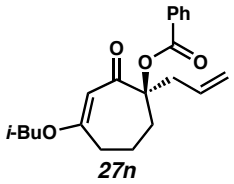
Vinylogous Ester 27l ***(Table 2.1, entry 12).*** Prepared using Schlenk Manifold Method. 172.5 mg, 0.552 mmol, 98% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.59 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.72 (m, 1H), 5.28 (s, 1H), 5.18–5.08 (m, 2H), 3.53 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.50 (dd, *J* = 10.6, 6.6 Hz, 1H), 2.80–2.46 (m, 3H), 2.46–2.33 (m, 1H), 2.22–1.67 (m, 5H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2 (d, J_{CF} = 24.9 Hz), 176.9 (d, J_{CF} = 1.8 Hz), 131.9 (d, J_{CF} = 4.4 Hz), 119.3, 101.7, 101.2 (d, J_{CF} = 180.6 Hz), 75.0, 42.1 (d, J_{CF} = 23.2 Hz), 34.4 (d, J_{CF} = 23.2 Hz), 34.1 (d, J_{CF} = 2.4 Hz), 27.9, 21.7 (d, J_{CF} = 2.1 Hz), 19.3, 19.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –145.81 (m); IR (Neat Film NaCl) 3086, 2960, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1066, 145, 991, 927, 873, 843, 795, 758 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{21}O_2F$ $[M]^{+\bullet}$: 240.1526; found 240.1524; $[\alpha]_D^{25.0}$ +0.61 (*c* 1.02, $CHCl_3$, 91.2% ee); HPLC conditions: 1.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 8.05, major = 8.80.



27m

Vinylogous Ester 27m ***(Table 2.1, entry 13).*** Prepared using Glove Box Method. 242.0 mg, 0.493 mmol, 66% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 2%→5%→10% EtOAc in hexanes). R_f = 0.44 (10:1 hexanes:EtOAc); ^{1}H NMR (300

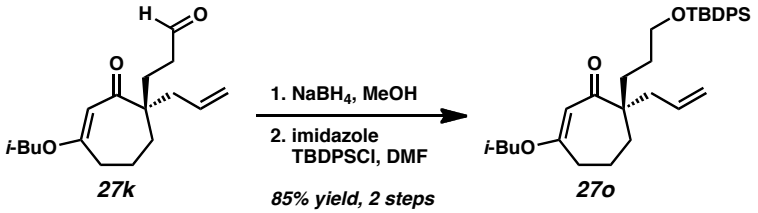
MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7.46–7.33 (m, 6H), 5.78–5.60 (m, 1H), 5.32 (s, 1H), 5.08–4.96 (m, 2H), 3.78 (d, *J* = 9.7 Hz, 1H), 3.67 (d, *J* = 9.7 Hz, 1H), 3.46 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.43 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.49 (dddd, *J* = 13.7, 6.6, 1.3, 1.3 Hz, 1H), 2.48–2.41 (m, 2H), 2.33 (dddd, *J* = 13.8, 7.8, 1.2, 1.2 Hz, 1H), 2.09–1.88 (m, 2H), 1.82–1.65 (m, 3H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 171.5, 135.9, 135.8, 134.7, 133.7, 133.5, 129.7, 127.8, 127.7, 117.8, 106.1, 74.5, 69.0, 57.4, 41.0, 36.3, 30.3, 28.0, 27.0, 20.0, 19.5, 19.3; IR (Neat Film NaCl) 3071, 3050, 2957, 2930, 2857, 1731, 1614, 1472, 1428, 1402, 1388, 1368, 1315, 1261, 1222, 1190, 1174, 1112, 1007, 998, 969, 955, 938, 914, 880, 824, 810, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2982; found 491.2993; $[\alpha]_D^{25.0}$ –6.72 (*c* 1.09, $CHCl_3$, 57.8% ee); HPLC conditions: 0.2% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 21.74, minor = 25.53.



27n

Vinylogous Ester 27n ***(Table 2.1, entry 14).*** Prepared using Schlenk Manifold Method. 589.8 mg, 1.72 mmol, 75% yield. Flash column chromatography (SiO_2, 5 x 13 cm, 20:1→15:1→10:1→6:1 hexanes:EtOAc). R_f = 0.57 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.96 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 5.96–5.78 (m, 1H), 5.27 (s, 1H), 5.19–5.08 (m, 2H), 3.42 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.39 (dd, *J* = 9.4, 6.5 Hz, 1H), 3.06 (dddd, *J* = 14.8, 6.7, 1.4, 1.4 Hz, 1H), 2.83–2.67 (m, 2H), 2.55–2.34 (m, 2H), 2.10–1.74 (m, 4H), 0.80 (dd, *J* = 6.6, 4.7 Hz, 6H); ^{13}C NMR (75

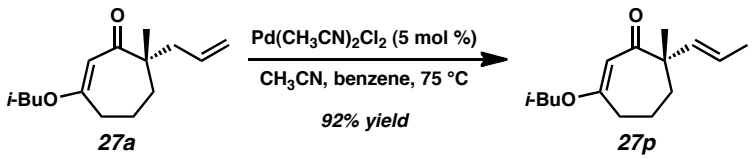
MHz, $CDCl_3$) δ 198.1, 174.3, 165.5, 133.1, 132.5, 130.6, 129.7, 128.5, 119.2, 102.1, 88.6, 74.9, 40.8, 34.0, 27.7, 21.9, 19.1, 19.0; IR (Neat Film NaCl) 3073, 2959, 2934, 2873, 1718, 1672, 1649, 1613, 1479, 1451, 1421, 1382, 1368, 1315, 1291, 1258, 1231, 1199, 1174, 1108, 1070, 1026, 1004, 919, 866, 820, 801, 762, 715 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{26}O_4$ $[M]^{+\bullet}$: 342.1815; found 342.1831; $[\alpha]_D^{25.0}$ +79.72 (*c* 1.02, $CHCl_3$, 57.1% ee); HPLC conditions: 1.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 18.28, minor = 22.01.



Vinylogous Ester 27o. A round-bottom flask with magnetic stir bar was charged with aldehyde **27k** (40.2 mg, 0.14 mmol, 1.00 equiv) and MeOH (3.0 mL). The flask was cooled to 0 °C and $NaBH_4$ (5.5 mg, 0.14 mmol, 1.00 equiv) was added slowly portionwise. The mixture was stirred for 1 h at 0 °C. Sat. aqueous $NaHCO_3$ (3 mL) was added, followed by CH_2Cl_2 (10 mL). The mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was used directly in the next step without further purification. R_f = 0.29 (2:1 hexanes:EtOAc).

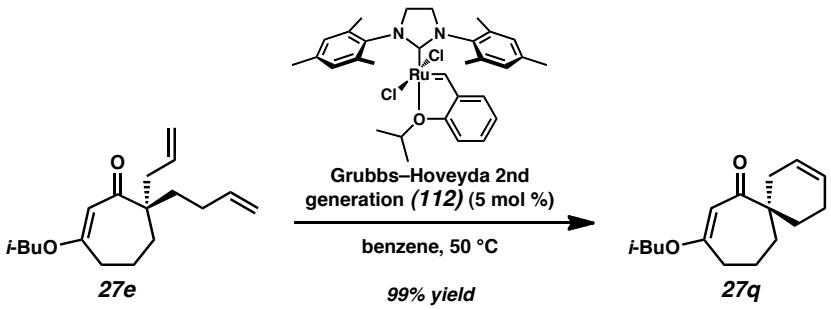
To a 2 dram vial with a solution of crude alcohol and imidazole (11.8 mg, 0.17 mmol, 1.20 equiv) in DMF (0.7 mL) at 0 °C was added TBDPSCl (39.6 μL, 0.14 mmol,

1.00 equiv) dropwise. After 2 h of stirring, the reaction was quenched by addition of H_2O (0.3 mL) and extracted with Et_2O (5 x 5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 12 g loading cartridge, 80 g column, multi-step gradient, hold 2% [2 min]→ramp to 5% [10 min]→hold 5% [10 min]→ramp to 10% [32 min]→hold 10% Et_2O in hexanes [5 min]) to afford vinylogous ester **27o** (63.3 mg, 0.12 mmol, 85% yield over 2 steps) as a pale, white oil; R_f = 0.42 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H), 7.46–7.33 (m, 6H), 5.82–5.62 (m, 1H), 5.29 (s, 1H), 5.08–4.96 (m, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.48 (dd, *J* = 13.7, 6.6 Hz, 1H), 3.45 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.50–2.43 (m, 2H), 2.40 (dddd, *J* = 13.8, 7.0, 1.2 Hz, 1H), 2.25 (dddd, *J* = 13.9, 7.8, 1.1 Hz, 1H), 1.98 (app sept, *J* = 6.7 Hz, 1H), 1.86–1.38 (m, 8H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 171.0, 135.7, 134.9, 134.1, 129.6, 127.7, 117.7, 105.2, 74.4, 64.4, 54.2, 42.1, 36.1, 34.8, 32.8, 28.0, 27.3, 27.0, 20.0, 19.3; IR (Neat Film NaCl) 3071, 3051, 3013, 2998, 2956, 2930, 2858, 1614, 1471, 1428, 1401, 1387, 1368, 1311, 1214, 1188, 1174, 1111, 1028, 1007, 998, 966, 913, 872, 823, 780, 740, 725 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{33}H_{47}O_3Si$ $[M+H]^+$: 519.3295; found 519.3275; $[\alpha]_D^{25.0}$ +9.06 (*c* 0.95, $CHCl_3$, 78.4% ee).



Vinylogous Ester 27p. $Pd(CH_3CN)_2Cl_2$ (49.1 mg, 0.189 mmol, 5 mol %) was placed in a 50 mL round-bottom Schlenk flask and evacuated/backfilled with N_2 (3 cycles, 5 min per cycle). Benzene (10 mL) was added, followed by acetonitrile (90 μL). A solution of vinylogous ester **27a** (895 mg, 3.79 mmol, 1.00 equiv) in benzene (5.0 mL) was added using positive pressure cannulation. The resulting orange solution was heated to 75 °C in an oil bath. After 11 h of stirring, the reaction was cooled to ambient temperature, filtered through a Celite plug (eluted with Et_2O), and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to afford a pale yellow oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 80 g column, linear gradient, 0→10% EtOAc in hexanes [33 min]) to afford vinylogous ester **27p** (823.6 mg, 3.48 mmol, 92% yield) in a 20:1 ratio to isomeric starting material **27a**. Analytically pure samples could be obtained using the above column conditions; R_f = 0.56 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (dq, *J* = 15.7, 1.4 Hz, 1H), 5.41 (dq, *J* = 15.7, 6.2, Hz, 1H), 5.34 (s, 1H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.63–2.33 (m, 2H), 2.04–1.91 (m, 1H), 1.90–1.70 (m, 4H), 1.67 (dd, *J* = 6.2, 1.4 Hz, 3H), 1.22 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.6, 136.5, 123.9, 105.2, 74.5, 53.9, 36.2, 33.3, 28.0, 27.2, 20.2, 19.3, 18.4; IR (Neat Film NaCl) 3022, 2960, 2873, 1614, 1471, 1455, 1423, 1402, 1387, 1370, 1212, 1192, 1173, 1120, 967, 883, 858,

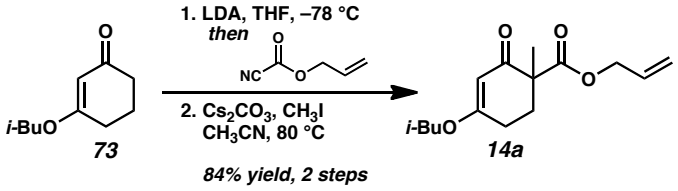
827 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O_2$ $[M+H]^+$: 237.1849; found 237.1848; $[\alpha]_D^{25.0}$ +4.05 (*c* 1.39, $CHCl_3$, 88.0 % ee).



Vinylogous Ester 27q. Vinylogous ester **27e** (100 mg, 0.362 mmol, 1.00 equiv) was added to a 50 mL 2-neck flask fitted with a rubber septum and oven-dried reflux condenser. The flask was evacuated/backfilled with Ar (3 cycles, 5 min evacuation per cycle). Dry degassed benzene (36.2 mL, sparged with N_2 for 1 h immediately before use) was added. Grubbs–Hoveyda 2nd generation catalyst (11.3 mg, 18.1 μmol, 5 mol %) was added to the reaction, giving the solution an olive green color. The mixture was kept under Ar, stirred until homogeneous, and heated to 50 °C using an oil bath. After 30 min of stirring, the reaction was cooled to ambient temperature and several drops of ethyl vinyl ether were added. After 30 min, the reaction developed a deep brown color. The mixture was concentrated under reduced pressure and filtered through a silica gel plug (3 x 5 cm, 1:1 hexanes:Et_2O). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1→10:1 hexanes:EtOAc) to afford vinylogous ester **27q** (89.2 mg, 0.359 mmol, 99% yield) as a white solid. R_f = 0.39 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69–5.58 (m, 2H), 5.30 (s, 1H), 3.49 (dd, *J* = 14.4, 6.5 Hz, 1H), 3.46 (dd, *J* =

14.3, 6.5 Hz, 1H), 2.70–2.57 (m, 1H), 2.54–2.44 (m, 2H), 2.08–1.91 (m, 3H), 1.91–1.57 (m, 7H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 171.3, 125.6, 125.4, 104.0, 74.4, 50.5, 35.9, 33.9, 32.3, 32.2, 28.0, 22.4, 20.6, 19.3; IR (Neat Film NaCl) 3050, 3023, 2981, 2958, 2928, 2890, 2874, 2837, 1726, 1633, 1610, 1470, 1457, 1435, 1416, 1406, 1392, 1364, 1327, 1295, 1270, 1218, 1178, 1189, 1117, 1096, 1045, 1028, 1003, 953, 935, 917, 888, 850, 837, 807, 758, 731 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{24}O_2$ $[M]^{+\bullet}$: 248.1776; found 248.1774; $[\alpha]_D^{25.0}$ –32.18 (*c* 0.97, $CHCl_3$, 78.4% ee).

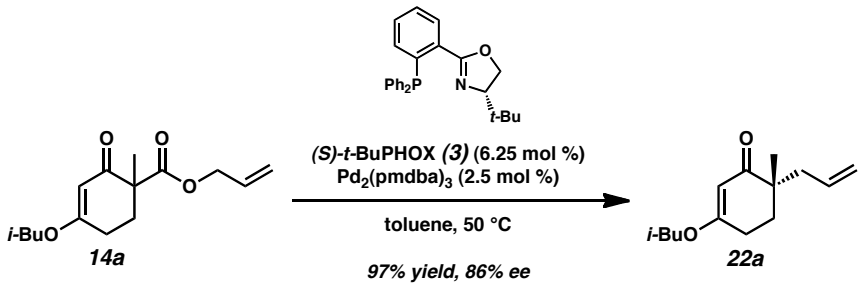
2.7.2.6 SYNTHETIC STUDIES ON THE REDUCTION/REARRANGEMENT OF SIX- AND SEVEN-MEMBERED VINYLOGOUS ESTERS



β-Ketoester 14a. To a solution of diisopropylamine (0.49 mL, 3.47 mmol, 1.17 equiv) in THF (10 mL) in a 50 mL round-bottom flask at 0 °C was added *n*-BuLi (1.70 mL, 3.40 mmol, 2.1 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the reaction was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **73**[60] (0.50 g, 2.97 mmol, 1.00 equiv) in THF (5.0 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.37 mL, 3.40 mmol, 1.15 equiv) was added dropwise. The reaction was stirred at –78 °C for 2.5 h, quenched by addition of sat. aqueous NH_4Cl and H_2O (5 mL each), and then allowed to warm to ambient temperature. The reaction was

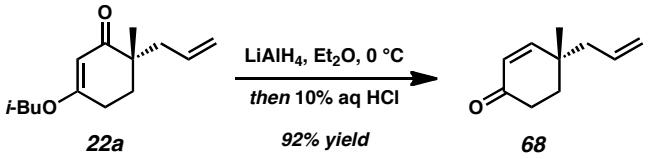
diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale red oil.

The crude oil was added to a 25 mL Schlenk flask and dissolved in CH_3CN (10 mL). CH_3I (0.56 mL, 8.90 mmol, 3.00 equiv) was added, followed by Cs_2CO_3 (1.26 g, 3.90 mmol, 1.30 equiv). The flask was sealed with a teflon valve, immersed in an oil bath, and heated to 80 °C. After 14 h of vigorous stirring, the suspension was allowed to cool to ambient temperature, diluted with EtOAc (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 20 cm, 19:1→9:1→4:1, hexanes:EtOAc) to afford β-ketoester **14a** (0.67 g, 2.52 mmol, 84% yield over 2 steps) as a pale yellow oil; $R_f = 0.36$ (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.2, 10.7, 5.5, 5.5 Hz, 1H), 5.30 (s, 1H), 5.22 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.14 (app dq, *J* = 10.5, 1.3 Hz, 1H), 4.65–4.46 (m, 2H), 3.55 (d, *J* = 6.5 Hz, 2H), 2.60–2.23 (m, 3H), 1.97 (app sept, *J* = 6.6 Hz, 1H), 1.89–1.70 (m, 1H), 1.35 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 176.7, 172.5, 131.9, 118.0, 101.7, 74.9, 65.5, 52.3, 31.7, 27.7, 26.3, 20.6, 19.0; IR (Neat Film NaCl) 2961, 2937, 2876, 1733, 1660, 1608, 1457, 1427, 1406, 1385, 1369, 1346, 1319, 1248, 1199, 1176, 1113, 1039, 991, 928, 837, 818, 772, 751 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{22}O_4$ $[M]^{+\bullet}$: 266.1518; found 266.1510.



Vinylogous Ester 151. β-Ketoester **14a** (180 mg, 0.68 mmol, 1.00 equiv) in a 20 mL scintillation vial and a septum-fitted screw cap were evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) in a glove box antechamber before being transferred into a glove box. A separate 20 mL scintillation vial in the glove box was loaded with (*S*)-*t*-BuPHOX (16.4 mg, 0.042 mmol, 6.25 mol %), $Pd_2(pmdba)_3$ (18.5 mg, 0.017 mmol, 2.5 mol %), and a magnetic stir bar. Toluene (4 mL) was added, and the black suspension was stirred at 30 °C in a heating block for 30 min. β-Ketoester **14a** was dissolved in toluene (2.8 mL) and added to the orange catalyst solution, causing an immediate color change to olive green. The vial was capped with the septum-fitted screw cap and the edges were sealed with electrical tape. The vial was removed from the glove box, connected to a N_2-filled Schlenk manifold, and immersed in a 50 °C oil bath. After 22 h, the reaction was an orange-brown solution. The mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 2 x 25 cm, 20:1→10:1, hexanes:EtOAc) to afford vinylogous ester **22a** (146 mg, 0.66 mmol, 97% yield) as a clear, colorless oil; R_f = 0.57 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81–5.63 (m, 1H), 5.22 (s, 1H), 5.08–4.98 (m, 2H), 3.56 (d, *J* = 6.5 Hz, 2H), 2.40 (app t, *J* = 6.4 Hz, 2H), 2.33 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 2.16 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 2.00 (app sept, *J* = 6.7 Hz, 1H), 1.90 (ddd, *J* = 13.4, 6.6, 6.6

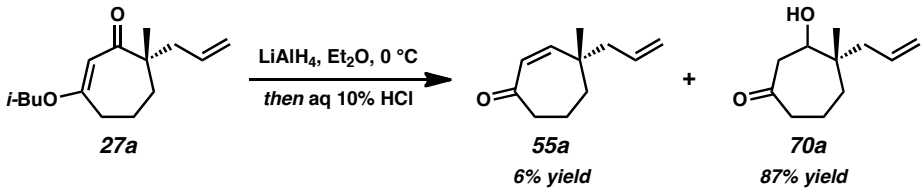
Hz, 1H), 1.68 (ddd, J = 13.6, 6.2, 6.2 Hz, 1H), 1.06 (s, 3H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 176.1, 134.4, 117.9, 101.4, 74.8, 43.3, 41.6, 31.9, 27.9, 26.0, 22.3, 19.2; IR (Neat Film NaCl) 3074, 2962, 2932, 2875, 1655, 1611, 1470, 1464, 1429, 1404, 1384, 1368, 1327, 1307, 1299, 1240, 1195, 1178, 1123, 1080, 1032, 996, 968, 951, 913, 862, 840, 806, 786, 736 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{22}O_2$ $[M]^{+\bullet}$: 222.1620; found 222.1627; $[\alpha]_D^{25.0}$ –10.67 (c 0.98, $CHCl_3$, 86.3% ee); HPLC conditions: 5% IPA in hexanes, OD-H column, t_R (min): major = 5.80, minor = 6.53.



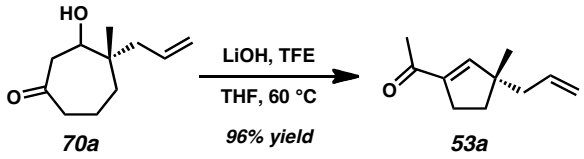
22a *68*

Cyclohexenone 68. A 50 mL round-bottom flask was charged with Et_2O (11.1 mL) and cooled to 0 °C in an ice/water bath. $LiAlH_4$ (13.6 mg, 0.36 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **22a** (146 mg, 0.66 mmol, 1.00 equiv) in Et_2O (2.0 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, an additional portion of $LiAlH_4$ (2.5 mg, 0.066 mmol, 0.10 equiv) was added. After 60 min of stirring, the reaction was quenched by slow addition of aqueous HCl (1.0 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→1:1→1:2 hexanes:Et_2O) to afford cyclohexenone **68** (90.5 mg, 0.60

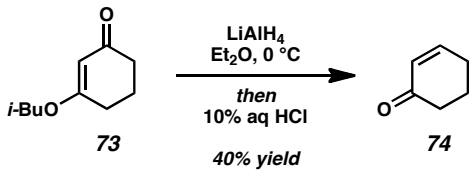
mmol, 92% yield) as a yellow oil; R_f = 0.51 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, *J* = 10.2 Hz, 1H), 5.88 (d, *J* = 10.2 Hz, 1H), 5.79 (dddd, *J* = 16.8, 10.3, 7.4, 7.4 Hz, 1H), 5.20–5.01 (m, 2H), 2.54–2.36 (m, 2H), 2.29–2.10 (m, 2H), 2.05–1.89 (m, 1H), 1.85–1.69 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 158.4, 133.4, 127.6, 118.6, 45.2, 35.7, 34.1, 33.6, 24.7; IR (Neat Film NaCl) 3077, 3005, 2960, 2917, 2868, 2849, 1682, 1639, 1616, 1459, 1419, 1390, 1373, 1332, 1250, 1223, 1193, 1115, 996, 961, 918, 871, 803, 757 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{10}H_{14}O$ $[M]^{+\bullet}$: 150.1045; found 150.1056; $[\alpha]_D^{25.0}$ +26.72 (*c* 1.02, $CHCl_3$, 86.3% ee).



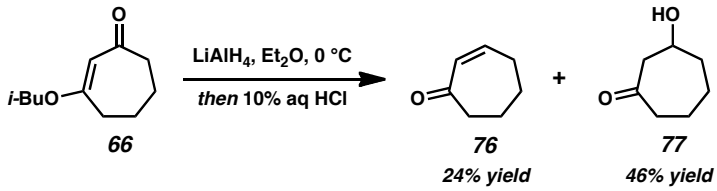
Cycloheptenone 55a and **β-Hydroxyketone 70a.** For procedure and characterization data, see General Method A (Section 2.10.2.8, p. 154–154).



Acylcyclopentene 53a. For procedure and characterization data, see General Method E (Section 2.10.2.8, p. 155).



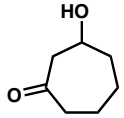
Cyclohexenone 74. A 25 mL round-bottom flask with magnetic stir bar and $LiAlH_4$ (22.8 mg, 0.60 mmol, 0.60 equiv) was charged with Et_2O (4 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester **73** (168.23 mg, 1.00 mmol, 1.00 equiv) in Et_2O (1 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (2.60 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product purified using flash column chromatography (SiO_2, 2 x 25 cm, 5:1→4:1 hexanes:EtOAc) to afford cyclohexenone **74** (39.4 mg, 0.41 mmol, 40% yield) as a volatile pale yellow oil. Spectra for the compound match data for commercially available material.



Cycloheptenone 76 and β-Hydroxyketone 77. A 50 mL round-bottom flask with magnetic stir bar and $LiAlH_4$ (806 mg, 21.2 mmol, 0.60 equiv) was charged with Et_2O (8 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester

66 (328.2 mg, 1.80 mmol, 1.00 equiv) in Et_2O (2 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (4.73 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product purified using flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1→2:1→1:1→1:2→1:4 hexanes:EtOAc) to afford β-hydroxyketone **77** (107.1 mg, 0.84 mmol, 46% yield) as a pale yellow oil and cycloheptenone **76** (47.9 mg, 0.44 mmol, 24% yield) as a colorless oil.

Cycloheptenone 76: Spectra for the compound match data for commercially available material.



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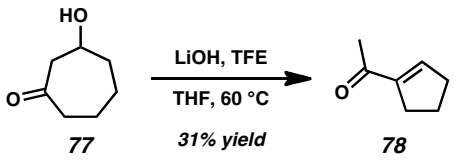
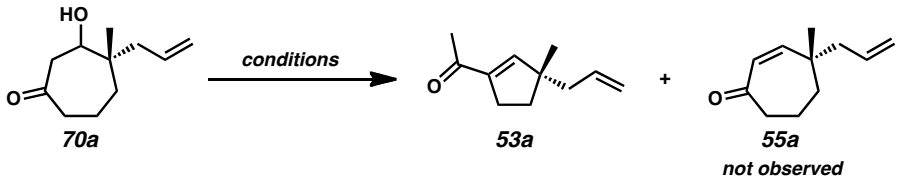
β-Hydroxyketone 77: R_f = 0.26 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18–3.97 (m, 1H), 2.89–2.67 (m, 2H), 2.55–2.35 (m, 2H), 2.10 (br s, 1H), 1.95–1.69 (m, 5H), 1.65–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 67.5, 51.8, 44.4, 38.8, 24.4, 23.8; IR (Neat Film NaCl) 3420, 2930, 2861, 1696, 1449, 1410, 1349, 1263, 1196, 1157, 1109, 1043, 1016, 929, 878, 829, 752, 710 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_{12}O_2$ $[M]^{+\bullet}$: 128.0837; found 128.0828.



Acylcyclopentene 78. Alcohol **77** (101.3 mg, 0.79 mmol, 1.00 equiv) was dissolved in THF (7.9 mL) in a 20 mL scintillation vial with magnetic stir bar. The solution was treated with 2,2,2-trifluoroethanol (86.4 μL, 1.19 mmol, 1.50 equiv) and anhydrous LiOH (28.4 mg, 1.19 mmol, 1.50 equiv). The headspace of the vial was purged with N_2 and the vial was capped with a teflon-lined hard cap and stirred at 60 °C in a heating block. After 16 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (150 mL), dried over Na_2SO_4 (30 min of stirring), filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product was purified using flash column chromatography (SiO_2, 2 x 20 cm, 15:1→10:1 hexanes:Et_2O) to afford acylcyclopentene **78** (27 mg, 0.25 mmol, 31% yield) as a colorless fragrant oil. Spectra for the compound match data for commercially available material.

2.7.2.7 RING CONTRACTION SCREENING PROTOCOL[a]



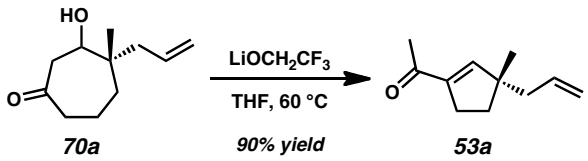
70a *53a* *55a* *not observed*

entry	base	additive	solvent	T (°C)	conversion (%)	time (h)	yield (%)[b]
1	LiO*t*-Bu	—	*t*-BuOH	40	100	9	71
2	LiO*t*-Bu	—	THF	40	100	8	60
3	NaO*t*-Bu	—	THF	40	100	5	81
4	KO*t*-Bu	—	THF	40	100	5	85
5	NaOH	—	THF	60	100	4	89
6	KOH	—	THF	60	100	4	87
7	LiOH	—	THF	60	78	24	19[d]
8	LiOH	*t*-BuOH	THF	60	98	24	78
9	LiOH	HFIP[c]	THF	60	99	12.5	87
10	LiOH	TFE[c]	THF	60	99	12.5	96
11	$LiOCH_2CF_3$	—	THF	60	—	10	90[e]
12	$CsOH{\cdot}H_2O$	—	THF	60	100	4	48
13	Cs_2CO_3	—	THF	60	67	24	61[f]
14	Cs_2CO_3	TFE[c]	THF	60	100	12.5	86
15	Cs_2CO_3	TFE[c]	CH_3CN	60	100	12.5	100
16	NaO*t*-Bu	*t*-BuOH	THF	40	100	8	52
17	KO*t*-Bu	*t*-BuOH	THF	40	100	8	57
18	LiOH	*t*-BuOH	THF	40	87	24	77
19	LiOH	TFE[c]	THF	40	73	24	73
20	LiOH	HFIP[c]	THF	40	84	24	81
21	CsF	—	CH_3CN	60	86	24	10

[a] *Conditions*: β-hydroxyketone **70a** (1.0 equiv), additive (1.5 equiv), base (1.5 equiv), solvent (0.1 M) at indicated temperature for 9–24 h. [b] GC yield using an internal standard at ≥ 98% conversion unless otherwise stated. [c] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol. [d] Several reaction intermediates observed by TLC and GC analysis; proceeded to 78% conversion. [e] Isolated yield. [f] Reaction did not reach completion at 24 h; proceeded to 67% conversion.

Ring Contraction Screen to Produce Acylcyclopentene 53a *(0.10 mmol scale, Table 2.3, entries 1–15).* A benzene solution of β-hydroxyketone **70a** was transferred to a dry 1 dram vial and concentrated under reduced pressure to obtain a starting mass. To this vial was added a magnetic stir bar and 1,4-diisopropylbenzene (internal standard). The contents were solvated in either *t*-BuOH or THF (0.1 M). After complete solvation, an appropriate additive (*t*-BuOH, TFE, or HFIP; 1.50 equiv) was added, followed by base (1.50 equiv). The head space of the vial was purged with N_2 and the vial was capped

with a teflon-lined hard cap and stirred at the appropriate temperature (40 or 60 °C) in a heating block. Reaction progress was initially followed by TLC analysis, and when necessary, aliquots were removed and flushed through a small SiO_2 plug with EtOAc for GC analysis. GC conditions: 90 °C isothermal for 5 min, then ramp 10 °C/min to 250 °C, DB-WAX column, t_R (min): 1,4-diisopropylbenzene = 5.3, acylcyclopentene **53a** = 9.3, β-hydroxyketone **70a** = 17.1 and 17.2 (two diastereomers). (For characterization data, see p. 319–321).



Ring Contraction using $LiOCH_2CF_3$ *(Table 2.3, entry 11).* β-Hydroxyketone **70a** (30.0 mg, 0.16 mmol, 1.00 equiv) was measured into a 1 dram vial with magnetic stir bar with a septum-fitted screw cap. $LiOCH_2CF_3$[50] (26.0 mg, 0.25 mmol, 1.50 equiv) was measured into a separate 1 dram vial, capped with a septum, evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle), and dissolved in THF (0.5 mL). The solution was cannulated into the vial containing β-hydroxyketone along with additional THF rinses (2 x 0.5 mL). The yellow solution was stirred at 60 °C in a heating block. After 10 h, the reaction was cooled to ambient temperature. The turbid brown solution was diluted with Et_2O and stirred with Na_2SO_4 for 30 min. The reaction was filtered and concentrated under reduced pressure at 0 °C in an ice/water bath. The residue was purified by flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O) to afford acylcyclopentene

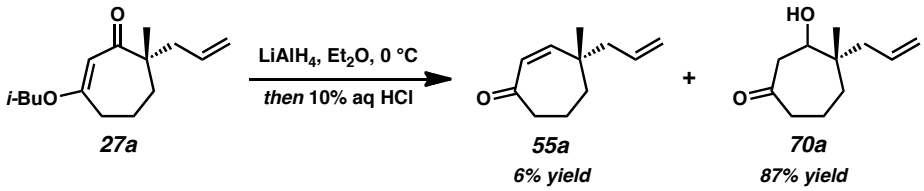
53a (24.4 mg, 0.149 mmol, 90% yield) as a clear, colorless oil. (For characterization data, see p. 320).

Additional Conditions. Additional reaction conditions are listed in Table 2.3, entries 16–21.

Unsuccessful Conditions. No reaction was observed using the following bases, with or without TFE additive: DBU, TMG, Na_2CO_3, K_2CO_3, $BaCO_3$, CaH_2. DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

2.7.2.8 PREPARATION OF β-HYDROXYKETONES AND ACYLCYCLOPENTENES

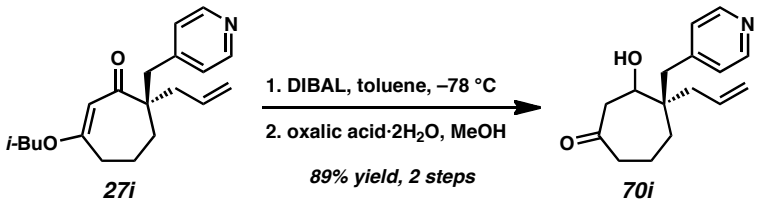
Full characterization data is reported for acylcyclopentenes **53**, cycloheptenone **55a**, and β-hydroxyketone intermediate **70a** (mixture of diastereomers). For all other β-hydroxyketone intermediates (**70b–j, l–o,** mixtures of diastereomers), R_f, IR, and HRMS data are reported and ^{1}H NMR and IR spectra are provided for reference in Figures A2.44–A2.58. For acylcyclopentenes **53a**, the ee value was unchanged from corresponding vinylogous ester **27a**. For all other acylcyclopentenes (**53**), ee values are assumed to be unchanged from the corresponding vinylogous esters (**27**). Representative procedures for General Methods A–E are described below.



27a *55a* *6% yield* *70a* *87% yield*

General Method A: $LiAlH_4$ Hydride Reduction / 10% Aq HCl Hydrolysis

Cycloheptenone 55a and **β-Hydroxyketone 70a.** A 500 mL round-bottom flask with magnetic stir bar was charged with Et_2O (150 mL) and cooled to 0 °C in an ice/water bath. $LiAlH_4$ (806 mg, 21.2 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **27a** (9.13 g, 38.6 mmol, 1.00 equiv) in Et_2O (43 mL) was added dropwise using positive pressure cannulation. The grey suspension was stirred for 40 min and additional $LiAlH_4$ (148 mg, 3.9 mmol, 0.10 equiv) was added in one portion. After an additional 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (110 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 20 mL) and purified using flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-hydroxyketone **70a** (6.09 g, 33.41 mmol, 87% yield, 1.3:1 dr) as a colorless semi-solid and cycloheptenone **55a** (387 mg, 2.36 mmol, 6% yield) as a colorless oil. (For characterization data, see p. 319).

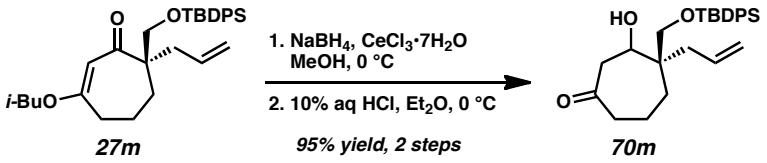


General Method B: DIBAL Reduction / Oxalic Acid Hydrolysis

β-Hydroxyketone 70i. A 25 mL pear-shaped flask was charged with vinylogous ester **27i** (29.4 mg, 0.094 mmol, 1.00 equiv) and toluene (3.0 mL). The solution was cooled to –78 °C using an acetone/CO_2(s) bath. A 1.0 M solution of DIBAL in toluene (112.6 μL, 0.113 mmol, 1.00 equiv) was added dropwise and the solution was stirred for 10 min. MeOH (180 μL), $Na_2SO_4 \cdot 10H_2O$ (1.08 g), and Celite (360 mg) were added. The reaction was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated under reduced pressure. $R_f = 0.28$, broad (1:2 hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask and dissolved in MeOH (4.0 mL). Oxalic acid dihydrate (354.9 mg, 2.82 mmol, 30.0 equiv) was added in one portion. After 1 h of stirring, the reaction was neutralized to pH 7 with 1 M aqueous pH 7 NaH_2PO_4/Na_2HPO_4 buffer (6 mL). The biphasic mixture was stirred vigorously for 10 min and the phases were separated. The aqueous layer was extracted with Et_2O (4 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 4:1→2:1→1:2 hexanes:acetone) to afford β-hydroxyketone **70i** as a mixture of diastereomers (21.6 mg, 0.083 mmol, 89%

yield over 2 steps, 2.8:1 dr) as a clear, colorless residue which solidified upon standing. (For characterization data, see p. 329).

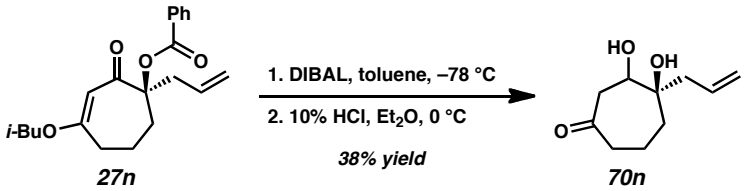


General Method C: Luche Reduction / 10% Aq HCl Hydrolysis

β-Hydroxyketone 70m. A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester **27m** (65.6 mg, 0.134 mmol, 1.00 equiv) and anhydrous MeOH (8.3 mL). The solution was cooled to 0 °C in an ice/water bath. $CeCl_3 \cdot 7H_2O$ (78.2 mg, 0.21 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Addition of $NaBH_4$ (23.8 mg, 0.63 mmol, 4.70 equiv) led to the evolution of gas and a turbid solution that became clear after several minutes. The reaction was stirred at 0 °C. After 15 min, the reaction was diluted with CH_2Cl_2 (20 mL) until turbid, filtered through a Celite plug (3 x 3 cm, CH_2Cl_2), and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered through a Celite plug (3 x 5 cm, CH_2Cl_2), and concentrated under reduced pressure a second time. R_f = 0.33 (10:1 hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask with a magnetic stir bar and dissolved in Et_2O (3.8 mL). The vigorously stirred solution was cooled to 0 °C and aqueous HCl (384 μL, 10% w/w) was added dropwise via syringe. After 30 min, the reaction was allowed to warm to ambient temperature and extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4,

filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 6:1→4:1 hexanes:EtOAc) to afford β-hydroxyketone **70m** as a mixture of diastereomers (55.6 mg, 0.13 mmol, 95% yield over 2 steps, 3.5:1 dr) as a colorless oil. (For characterization data, see p. 332).



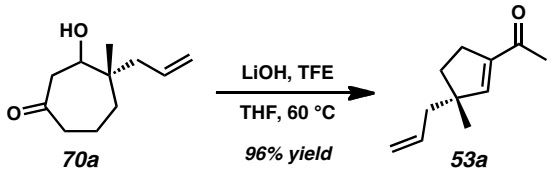
27n *70n*

General Method D: DIBAL Reduction / 10% Aq HCl Hydrolysis

β-Hydroxyketone 70n. A 50 mL pear-shaped flask was charged with vinylogous ester **27n** (100 mg, 0.292 mmol, 1.00 equiv) and toluene (9.5 mL). The solution was cooled to –78 °C using an acetone/CO_2(s) bath. A 1.0 M solution of DIBAL in toluene (963 μL, 0.963 mmol, 1.00 equiv) was added dropwise and the mixture was stirred for 15 min. MeOH (1.0 mL), $Na_2SO_4 \cdot 10\ H_2O$ (6.0 g), and Celite (1.2 g) were added, and the mixture was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated under reduced pressure. $R_f = 0.30$ (2:1 hexanes:EtOAc).

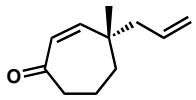
The crude hydroxy isobutyl enol ether was added to a 50 mL pear-shaped flask, dissolved in Et_2O (10 mL), and cooled to 0 °C in an ice/water bath. Aqueous HCl (0.835 mL, 10% w/w) was added dropwise and the biphasic mixture was stirred vigorously at 0 °C. After 40 min or stirring, additional aqueous HCl (0.835 mL, 10% w/w) was added. After 1.5 h, the layers were separated and the aqueous layer was extracted with Et_2O (5 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated

under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→6:1→4:1→2:1→1:1→1:2 hexanes:EtOAc) to afford β-hydroxyketone **70n** as a mixture of diastereomers (20.3 mg, 0.110 mmol, 38% yield over 2 steps) as a clear, colorless oil. (For characterization data, see p. 337).



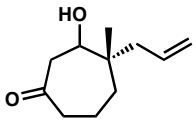
General Method E: β-Hydroxyketone Ring Contraction

Acylcyclopentene 53a. Alcohol **70a** (6.09 g, 33.4 mmol, 1.00 equiv) was dissolved in THF (334 mL) in a 500 mL round-bottom flask. The solution was treated with 2,2,2-trifluoroethanol (3.67 mL, 50.1 mmol, 1.50 equiv) and anhydrous LiOH (1.20 g, 50.1 mmol, 1.50 equiv). The flask was fitted with a condenser, purged with N_2, and heated to 60 °C using an oil bath. After 18 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (150 mL), dried over Na_2SO_4 (30 min of stirring), filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash column chromatography (SiO_2, 5 x 15 cm, 15:1 hexanes:Et_2O) to afford acylcyclopentene **53a** (5.29 g, 32.2 mmol, 96% yield) as a colorless fragrant oil. (For characterization data, see p. 320).



55a

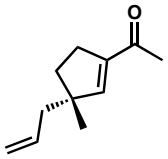
Cycloheptenone 55a. Prepared using General Method A. 387 mg, 2.36 mmol, 6% yield. Flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite). R_f = 0.54 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 12.9, 0.7 Hz, 1H), 5.82 (d, *J* = 12.9 Hz, 1H), 5.75 (dddd, *J* = 17.1, 10.3, 7.8, 7.1 Hz, 1H), 5.10 (dddd, *J* = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.08–5.03 (m, 1H), 2.65–2.52 (m, 2H), 2.19 (app dd, *J* = 13.7, 6.8 Hz, 1H), 2.11 (app dd, *J* = 13.7, 8.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.68–1.63 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 152.5, 133.8, 128.6, 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^{+\bullet}$: 164.1201; found 164.1209; $[\alpha]_D^{21.0}$ –9.55 (*c* 1.07, $CHCl_3$, 88.0% ee).



70a

β-Hydroxyketone 70a ***(Table 2.4, entry 1).*** Prepared using General Method A. 6.09 g, 33.41 mmol, 87% yield, 1.3:1 dr. Flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite). R_f = 0.23 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ **major epimer**: 5.88 (dddd, *J* = 15.1, 9.0, 7.6, 7.6 Hz, 1H), 5.12–5.08 (m, 2H), 3.70 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.86 (dd, *J* = 15.6, 1.7 Hz, 1H), 2.65

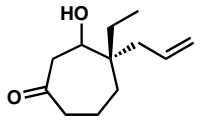
(dd, *J* = 15.6, 7.3 Hz, 1H), 2.54–2.43 (m, 2H), 2.24 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.07 (dd, *J* = 13.4, 7.3 Hz, 1H), 1.99 (dd, *J* = 15.9, 4.4 Hz, 1H), 1.82–1.69 (m, 2H), 1.45–1.41 (m, 1H), 0.96 (s, 3H); **minor epimer:** 5.83 (dddd, *J* = 14.9, 10.3, 7.6, 7.6 Hz, 1H), 5.12–5.06 (m, 2H), 3.68 (dd, *J* = 4.1, 2.4 Hz, 1H) 2.80 (dd, *J* = 15.4, 2.4 Hz, 1H), 2.74 (dd, *J* = 15.4, 8.1 Hz 1H), 2.46–2.38 (m, 2H), 2.18 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.09 (dd, *J* = 12.9, 7.8 Hz, 1H), 1.82–1.65 (m, 3H), 1.50–1.47 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ **major epimer**: 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; **minor epimer**: 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7; IR (Neat Film NaCl) 3436, 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1318, 1246, 1168, 1106, 1069, 999, 913, 840 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1313; found 182.1307; $[\alpha]_D^{22.8}$ –57.10 (*c* 2.56, $CHCl_3$, 88.0% ee).



53a

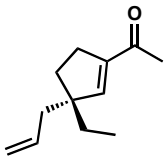
Acylcyclopentene 53a ***(Table 2.4, entry 1).*** Prepared using General Method E. 5.29 g, 32.2 mmol, 96% yield. Flash column chromatography (SiO_2, 5 x 15 cm, 15:1 hexanes:Et_2O). R_f = 0.67 (8:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (app t, *J* = 1.7 Hz, 1H), 5.76 (dddd, *J* = 16.4, 10.7, 7.3, 7.3 Hz, 1H), 5.07–5.03 (m, 2H), 2.59–2.48 (m, 2H), 2.30 (s, 3H), 2.21–2.14 (m, 2H), 1.85 (ddd, *J* = 12.9, 8.3, 6.3 Hz, 1H), 1.64 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993,

914, 862 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{17}O$ $[M+H]^{+\bullet}$: 165.1279; found 165.1281; $[\alpha]_D^{21.4}$ +17.30 (*c* 0.955, $CHCl_3$, 88.0% ee); GC conditions: 80 °C isothermal, GTA column, t_R (min): major = 54.7, minor = 60.2.



70b

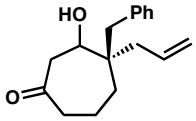
β-Hydroxyketone 70b ***(Table 2.4, entry 2).*** Prepared using General Method A. 111.5 mg, 0.57 mmol, 95% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.36 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.45.1; IR (Neat Film NaCl) 3448, 3073, 2965, 2933, 1832, 1696, 1691, 1673, 1459, 1413, 1381, 1352, 1334, 1323, 1306, 1269, 1252, 1269, 1252, 1172, 1138, 1111, 1084, 1071, 1050, 997, 955, 930, 912, 876, 825, 777, 737 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}O_2$ $[M]^{+\bullet}$: 196.1463; found 196.1480.



53b

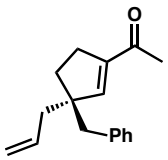
Acylcyclopentene 53b ***(Table 2.4, entry 2).*** Prepared using General Method E. 21.8 mg, 0.12 mmol, 95% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.73 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.80–5.64 (m, 1H), 5.08–5.04 (m, 1H), 5.03–5.00 (m, 1H), 2.55–2.46 (m, 2H), 2.30 (s, 3H), 2.19–2.16 (m, 2H), 1.81–1.68 (m, 2H), 1.52–1.41 (m,

2H), 0.85 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 150.7, 144.6, 134.8, 117.7, 54.0, 43.1, 32.9, 31.3, 30.1, 26.9, 9.1; IR (Neat Film NaCl) 3075, 2962, 2922, 2878, 2855, 1669, 1639, 1617, 1459, 1437, 1372, 1319, 1266, 1207, 1052, 995, 913, 868, 784 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{12}H_{19}O$ $[M+H]^+$: 179.1436; found 179.1401; $[\alpha]_D^{25.0}$ +7.06 (*c* 0.98, $CHCl_3$, 91.6% ee).



70c

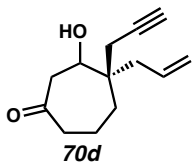
β-Hydroxyketone 70c ***(Table 2.4, entry 3).*** Prepared using General Method A. 109.9 mg, 0.43 mmol, 89% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.11 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.46.1; IR (Neat Film NaCl) 3443, 3072, 3028, 3003, 2930, 2865, 1696, 1692, 1685, 1636, 1601, 1582, 1495, 1453, 1413, 1400, 1352, 1340, 1255, 1182, 1163, 1118, 1058, 1031, 995, 970, 916, 885, 848, 809, 754 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{17}H_{22}O_2$ $[M]^{+\bullet}$: 258.1620; found 258.1642.



53c

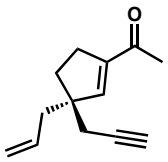
Acylcyclopentene 53c ***(Table 2.4, entry 3).*** Prepared using General Method E. 22.7 mg, 0.094 mmol, 97% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.54 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18

(m, 3H), 7.14–7.08 (m, 2H), 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.78 (dddd, *J* = 16.3, 10.8, 7.7, 7.0 Hz, 1H), 5.13–5.10 (m, 1H), 5.07 (dddd, *J* = 9.1, 2.2, 1.2, 1.2 Hz, 1H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.73 (d, *J* = 13.3 Hz, 1H), 2.43 (dddd, *J* = 16.5, 8.6, 5.7, 1.7 Hz, 1H), 2.27–2.17 (m, 3H), 2.21 (s, 3H), 1.91–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 150.1, 144.9, 138.2, 134.7, 130.4, 128.1, 126.4, 118.3, 54.6, 45.2, 43.3, 33.3, 30.0, 26.9; IR (Neat Film NaCl) 3061 3027, 3002, 2920, 2853, 1668, 1638. 1617, 1495, 1453, 1442, 1371, 1314, 1264, 1197, 1089, 1030, 995, 914, 861, 734 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O$ $[M]^{+\bullet}$: 240.1514; found 240.1530; $[\alpha]_D^{25.0}$ –20.63 (*c* 0.83, $CHCl_3$, 86.3% ee).



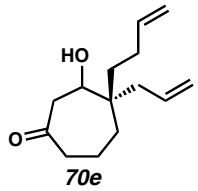
70d

β-Hydroxyketone 70d ***(Table 2.4, entry 4).*** Prepared using General Method A. 117 mg, 0.56 mmol, 98% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.35 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.47.1; IR (Neat Film NaCl) 3434, 3295, 3074, 3002, 2932, 2114, 1690, 1684, 1637, 1447, 1354, 1252, 1166, 1124, 1064, 977, 917, 886, 838 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_2$ $[M]^{+\bullet}$: 206.1307; found 206.1311.



53d

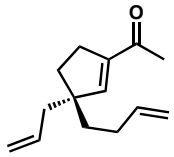
Acylcyclopentene 53d ***(Table 2.4, entry 4).*** Prepared using General Method E. 22.5 mg, 0.12 mmol, 97% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.74 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.73 (dddd, *J* = 16.9, 10.2, 7.4, 7.4 Hz, 1H), 5.13 (dm, *J* = 10.2 Hz, 1H), 5.10–5.07 (m, 1H), 2.66–2.46 (m, 2H), 2.34–2.33 (m, 1H), 2.33–2.32 (m, 1H), 2.32 (s, 3H), 2.32–2.30 (m, 2H), 1.99 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.93–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 197.3, 148.6, 145.2, 133.9, 118.6, 81.4, 70.3, 53.2, 42.4, 33.4, 30.0, 28.5, 26.9; IR (Neat Film NaCl) 3298, 3075, 3001, 2924, 2857, 2116, 1669, 1639, 1617, 1457, 1437, 1372, 1318, 1265, 1222, 1204, 996, 919, 867 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O$ $[M]^{+\bullet}$: 188.1201; found 188.1211; $[\alpha]_D^{25.0}$ –58.65 (*c* 0.71, $CHCl_3$, 88.5% ee).



70e

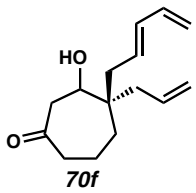
β-Hydroxyketone 70e ***(Table 2.4, entry 5).*** Prepared using General Method A. 116.7 mg, 0.52 mmol, 97% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.48.1; IR (Neat Film NaCl) 3447, 3075, 3001, 2975, 2931, 2866, 1827, 1693, 1639, 1456, 1415, 1352, 1336, 1250, 1169, 1116, 1073, 995,

910, 855, 763, 714 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{28}O_2$ $[M]^{+\bullet}$: 276.2089; found 276.2060.



53e

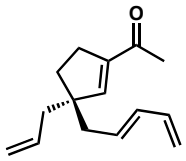
Acylcyclopentene 53e ***(Table 2.4, entry 5).*** Prepared using General Method E. 19.1 mg, 0.093 mmol, 90% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.62 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.79 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.72 (dddd, *J* = 16.8, 9.5, 7.3, 7.3 Hz, 1H), 5.09–5.07 (m, 1H), 5.05–4.97 (m, 2H), 4.94 (dm, *J* = 10.2 Hz, 1H), 2.56–2.49 (m, 2H), 2.30 (s, 3H), 2.23–2.17 (m, 2H), 2.15–1.91 (m, 2H), 1.85–1.70 (m, 2H), 1.58–1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.4, 144.6, 138.8, 134.6, 117.9, 114.6, 53.5, 43.6, 38.1, 33.3, 30.1, 29.2, 26.9; IR (Neat Film NaCl) 3076, 3001, 2976, 2919, 2854, 1670, 1640, 1618, 1437, 1372, 1314, 1265, 1204, 995, 911, 865 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1592; found 205.1588; $[\alpha]_D^{25.0}$ –30.08 (*c* 0.92, $CHCl_3$, 86.9% ee).



70f

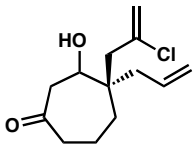
β-Hydroxyketone 70f ***(Table 2.4, entry 6).*** Prepared using General Method A. 117.5 mg, 0.50 mmol, 96% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1

hexanes:EtOAc). R_f = 0.19 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.49.1; IR (Neat Film NaCl) 3448, 3075, 3035, 3007, 2972, 2929, 2865, 1700, 1696, 1691, 1685, 1648, 1637, 1600, 1449, 1415, 1352, 1333, 1245, 1171, 1120, 1068, 1052, 1005, 969, 954, 912, 855, 838, 817, 720 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1698; found 235.1697.



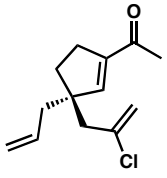
53f

Acylcyclopentene 53f ***(Table 2.4, entry 6).*** Prepared using General Method E. 25.2 mg, 0.12 mmol, 95% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.30 (ddd, *J* = 16.9, 10.2, 10.2 Hz, 1H), 6.08 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.73 (dddd, *J* = 16.4, 11.6, 8.9, 7.5 Hz, 1H), 5.63 (ddd, *J* = 15.0, 7.6, 7.6 Hz, 1H), 5.14–5.09 (m, 2H), 5.06–5.02 (m, 1H), 5.00 (dm, *J* = 10.1 Hz, 1H), 2.54–2.46 (m, 2H), 2.30 (s, 3H), 2.25–2.17 (m, 4H), 1.80–1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.0, 144.8, 137.0, 134.5, 134.3, 130.4, 118.1, 115.9, 54.0, 43.3, 42.0, 33.2, 30.0, 26.9; IR (Neat Film NaCl) 3079, 3006, 2929, 2857, 1735, 1670, 1640, 1617, 1439, 1371, 1318, 1267, 1201, 1175, 1084, 1004, 952, 912 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1592; found 217.1568; $[\alpha]_D^{25.0}$ –32.14 (*c* 1.26, $CHCl_3$, 89.6% ee).



70g

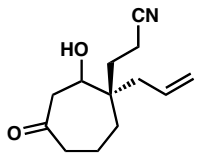
β-Hydroxyketone 70g ***(Table 2.4, entry 7).*** Prepared using General Method A. 114.9 mg, 0.47 mmol, 93% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.50.1; IR (Neat Film NaCl) 3436, 3075, 2931, 2869, 1695, 1627, 1452, 1414, 1352, 1297, 1251, 1222, 1151, 1064, 1021, 997, 974, 915, 887, 839 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{19}O_2Cl$ $[M]^{+\bullet}$: 242.1074; found 242.1063.



53g

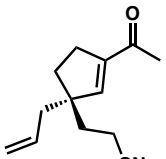
Acylcyclopentene 53g ***(Table 2.4, entry 7).*** Prepared using General Method E. 23.8 mg, 0.11 mmol, 99% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.73 (dddd, *J* = 15.9, 11.1, 7.9, 7.3 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 5.15–5.14 (m, 1H), 5.11–5.10 (m, 1H), 5.08–5.04 (m, 1H), 2.56–2.48 (m, 4H), 2.31 (s, 3H), 2.28–2.25 (m, 2H), 1.93 (ddd, *J* = 13.3, 8.4, 6.6 Hz, 1H), 1.84 (ddd, *J* = 13.3, 8.1, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 149.6, 144.4, 139.4, 134.0, 118.7, 116.4, 53.4, 48.0, 43.4, 33.3, 29.8, 26.9; IR (Neat Film NaCl) 3076, 2946, 2857, 1669, 1629, 1434, 1372, 1320, 1266, 1230, 1206, 1167, 996, 917, 886 cm^{-1}; HRMS (EI+) *m/z*

calc'd for $C_{13}H_{18}OCl$ $[M+H]^+$: 225.1046; found 225.1053; $[\alpha]_D^{25.0}$ +46.29 (*c* 1.06, $CHCl_3$, 85.7% ee).



70h

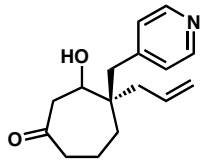
β-Hydroxyketone 70h ***(Table 2.4, entry 8).*** Prepared using General Method A. 72.4 mg, 0.33 mmol, 90% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 4:1→2:1→1:1 hexanes:EtOAc). R_f = 0.40, broad (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.51.1; IR (Neat Film NaCl) 3468, 3075, 2932, 2871, 2247, 1696, 1458, 1437, 1420, 1352, 1319, 1252, 1169, 1122, 1070, 999, 921, 853, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{19}O_2N$ $[M]^{+\bullet}$: 221.1416; found 221.1411.



53h

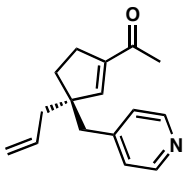
Acylcyclopentene 53h ***(Table 2.4, entry 8).*** Prepared using General Method E. 19.4 mg, 0.095 mmol, 94% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 2:1→3:2→1:1 hexanes:Et_2O). R_f = 0.84, broad (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.70 (dddd, *J* = 16.4, 10.6, 7.4, 7.4 Hz, 1H), 5.15–5.12 (m, 1H), 5.15–5.06 (m, 1H), 2.60–2.52 (m, 2H), 2.37–2.22 (m, 2H), 2.32

(s, 3H), 2.23–2.20 (m, 2H), 1.93–1.82 (m, 3H), 1.73 (ddd, J = 13.6, 8.2, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 147.2, 146.0, 133.3, 120.0, 119.0, 53.2, 43.5, 34.2, 32.7, 30.2, 27.0, 13.1; IR (Neat Film NaCl) 3074, 2923, 2857, 2245, 1667, 1640, 1618, 1423, 1373, 1308, 1264, 1202, 1090, 996, 918, 867 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388; found 204.1385; $[\alpha]_D^{25.0}$ –31.11 (*c* 0.90, $CHCl_3$, 87.4% ee).



70i

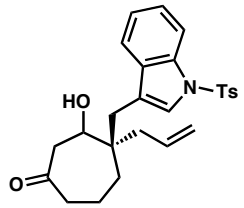
β-Hydroxyketone 70i ***(Table 2.4, entry 9).*** Prepared using General Method B. 21.6 mg, 0.083 mmol, 89% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 4:1→2:1→1:2 hexanes:acetone). R_f = 0.10 (2:1 hexanes:acetone); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.52.1; IR (Neat Film NaCl) 3391, 3201, 3073, 2929, 2865, 1699, 1636, 1603, 1557, 1497, 1456, 1418, 1352, 1332, 1297, 1258, 1222, 1187, 1161, 1113, 1069, 1005, 995, 972, 915, 886, 851, 802, 735 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{22}O_2N$ $[M+H]^+$: 260.1650; found 260.1649.



53i

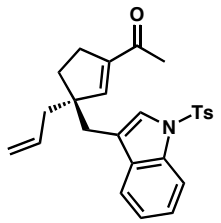
Acylcyclopentene 53i ***(Table 2.4, entry 9).*** Prepared using General Method E. 15.7 mg, 0.065 mmol, 90% yield. Flash column chromatography (SiO_2, 1.5 x 16 cm, 2:1→1:1

hexanes:acetone). R_f = 0.47 (2:1 hexanes:acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br d, *J* = 3.8 Hz, 2H), 7.04 (d, *J* = 5.7 Hz, 2H), 6.40 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.75 (dddd, *J* = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 5.16–5.04 (m, 2H), 2.77 (d, *J* = 13.0 Hz, 1H), 2.71 (d, *J* = 13.0 Hz, 1H), 2.52–2.39 (m, 1H), 2.33–2.35 (m, 1H), 2.28 (s, 3H), 2.24–2.20 (m, 2H), 1.85–1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 149.6, 148.6, 147.3, 145.4, 134.0, 125.7, 118.8, 54.2, 44.4, 43.3, 33.3, 30.0, 27.0; IR (Neat Film NaCl) 3401, 3071, 3025, 2922, 2856, 1668, 1640, 1618, 1600, 1557, 1495, 1441, 1415, 1373, 1318, 1277, 1265, 1220, 1194, 1071, 994, 917, 874, 844, 810, 763 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{19}ON$ $[M]^{+\bullet}$: 176.1467; found 176.1458; $[\alpha]_D^{25.0}$ –8.58 (*c* 0.77, $CHCl_3$, 84.6% ee).



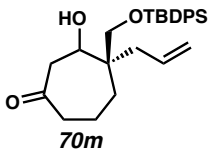
70j

β-Hydroxyketone 70j ***(Table 2.4, entry 10).*** Prepared using General Method A. 300.1 mg, 0.67 mmol, 94% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 4:1→3:1→2:1→1:1 hexanes:EtOAc). R_f = 0.20, 0.26 (two diastereomers) (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.53.1; IR (Neat Film NaCl) 3436, 3068, 2930, 2873, 1693, 1639, 1597, 1494, 1447, 1365, 1402, 1365, 1279, 1211, 1188, 1172, 1133, 1121, 1095, 1063, 1020, 995, 975, 913, 813, 778, 747 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{30}O_4NS$ $[M+H]^+$: 452.1896; found 452.1896.



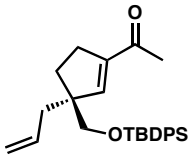
53j

Acylcyclopentene 53j ***(Table 2.4, entry 10).*** Prepared using General Method E. 55.7 mg, 0.10 mmol, 93% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→8:1→6:1→4:1 hexanes:EtOAc). R_f = 0.67 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (br d, *J* = 8.2 Hz, 1H), 7.63 (dm, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.33 (br s, 1H), 7.30 (ddd, *J* = 8.2, 8.2, 1.3 Hz, 1H), 7.21 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.17 (dm, *J* = 8.2 Hz, 2H), 6.35 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.75 (dddd, *J* = 16.9, 10.3, 7.7, 6.9 Hz, 1H), 5.13–5.10 (m, 1H), 5.10–5.04 (m, 1H), 2.82 (s, 3H), 2.44 (dddd, *J* = 14.7, 8.8, 5.9, 1.7 Hz, 1H), 2.33 (br s, 2H), 2.31–2.18 (m, 3H), 2.16 (s, 3H), 1.86 (ddd, *J* = 14.6, 8.6, 6.1 Hz, 1H), 1.79 (ddd, *J* = 14.8, 7.6, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 149.9, 145.1, 144.9, 135.2, 135.1, 134.3, 131.9, 130.0, 126.7, 124.8, 124.7, 123.2, 119.9, 119.4, 118.5, 113.9, 54.5, 43.5, 33.8, 33.4, 30.0, 26.8, 21.7; IR (Neat Film NaCl) 3316, 3129, 3101, 3068, 3001, 2974, 2922, 2855, 1667, 1639, 1618, 1597, 1562, 1493, 1448, 1400, 1372, 1307, 1293, 1277, 1211, 1188, 1174, 1121, 1094, 1020, 978, 916, 853, 813, 747 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{26}H_{27}O_3NS$ $[M]^{+\bullet}$: 433.1712; found 433.1694; $[\alpha]_D^{25.0}$ +0.35 (*c* 1.09, $CHCl_3$, 82.9% ee).



70m

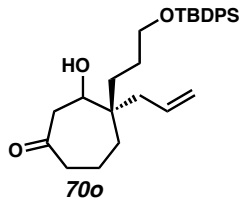
β-Hydroxyketone 70m ***(Table 2.4, entry 11).*** Prepared using General Method C. 55.6 mg, 0.13 mmol, 95% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.22, 0.28 (two diastereomers) (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.54.1; IR (Neat Film NaCl) 3468, 3072, 3050, 2999, 3013, 2931, 2895, 2858, 2248, 1960, 1891, 1823, 1772, 1698, 1638, 1590, 1472, 1462, 1446, 1428, 1391, 1361, 1337, 1260, 1222, 1186, 1172, 1158, 1113, 1088, 1030, 1006, 999, 976, 914, 841, 823, 810, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{27}H_{37}O_3Si$ $[M+H]^+$: 437.2512; found 437.2517.



53m

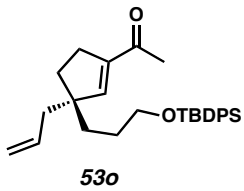
Acylcyclopentene 53m ***(Table 2.4, entry 11).*** Prepared using General Method E. 32.6 mg, 0.078 mmol, 96% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.60 (m, 4H), 7.47–7.34 (m, 6H), 6.50 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.71 (dddd, *J* = 17.0, 10.1, 7.8, 6.9 Hz, 1H), 5.12–5.08 (m, 1H), 5.06–5.02 (m, 1H), 3.57 (d, *J* = 9.8 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 2.54–2.48 (m, 2H), 2.38 (ddd, *J* = 13.8, 6.9, 1.1 Hz, 1H), 2.31–2.25 (m, 1H), 2.29 (s, 3H), 1.81–1.72 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 148.5, 145.7, 135.8, 135.7, 134.5, 133.6, 133.6, 129.9, 129.9, 127.8, 118.0, 69.1, 56.5,

40.4, 30.7, 30.0, 27.0, 26.8, 19.5; IR (Neat Film NaCl) 3072, 3050, 2999, 2956, 2931, 2896, 2857, 1671, 1639, 1618, 1472, 1463, 1427, 1367, 1320, 1266, 1232, 1188, 1112, 998, 936, 915, 864, 824, 740 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{27}H_{34}O_2Si$ $[M]^{+\bullet}$: 433.1712; found 433.1694; $[\alpha]_D^{25.0}$ –17.58 (*c* 0.94, $CHCl_3$, 51.4% ee).



70o

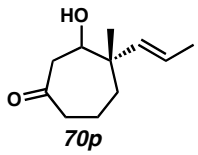
β-Hydroxyketone 70o ***(Table 2.4, entry 12).*** Prepared using General Method C. 110.6 mg, 0.24 mmol, 92% yield over 2 steps. Flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.55.1; IR (Neat Film NaCl) 3436, 3071, 3050, 3013, 2999, 2931, 2896, 2859, 1960, 1891, 1826, 1694, 1638, 1589, 1472, 1461, 1428, 1390, 1360, 1325, 1307, 1251, 1218, 1188, 1168, 1111, 1092, 1007, 998, 973, 934, 914, 823, 798, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{41}O_3Si$ $[M+H]^+$: 465.2825; found 465.2810.



53o

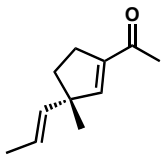
Acylcyclopentene 53o ***(Table 2.4, entry 12).*** Prepared using General Method E. 92.2 mg, 0.21 mmol, 92% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 15:1 hexanes:Et_2O). R_f = 0.64 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71–7.64

(m, 4H), 7.48–7.35 (m, 6H), 6.44 (dd, J = 1.7, 1.7 Hz, 1H), 5.81–5.65 (m, 1H), 5.10–5.07 (m, 1H), 5.05–5.02 (m, 1H), 3.69–3.64 (m, 2H), 2.55–2.49 (m, 2H), 2.31 (s, 3H), 2.20–2.18 (m, 2H), 1.84–1.67 (m, 2H), 1.53–1.48 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.7, 144.4, 135.7, 134.7, 134.0, 129.7, 127.7, 117.8, 64.3, 53.3, 43.5, 34.8, 33.3, 30.0, 28.0, 27.0, 26.8, 19.3; IR (Neat Film NaCl) 3071, 3050, 3013, 2999, 2931, 2897, 2857, 1670, 638, 1618, 1589, 1472, 1461, 1448, 1428, 1388, 1372, 1316, 1263, 1201, 1157, 1111, 1093, 1030, 1008, 998, 937, 915, 865, 823, 803, 741, 726 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{29}O_2Si$ $[M–C_4H_9]^+$: 389.1968; found 389.1958; $[\alpha]_D^{25.0}$ –14.19 (c 0.92, $CHCl_3$, 78.4% ee).



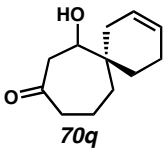
70p

β-Hydroxyketone 70p ***(Table 2.4, entry 13).*** Prepared using General Method A. 429.5 mg, 2.36 mmol, 87% yield. Flash column chromatography (SiO_2, 3 x 20 cm, 9:1→3:1 hexanes:EtOAc). R_f = 0.14 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.56.1; IR (Neat Film NaCl) 3449, 3027, 2963, 2928, 2873, 1694, 1454, 1404, 1350, 1320, 1251, 1170, 1066, 969 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{11}H_{19}O_2$ $[M+H]^+$: 165.1274; found 165.1278.



53p

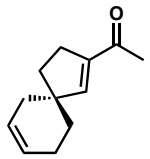
Acylcyclopentene 53p ***(Table 2.4, entry 13).*** Prepared using General Method E. Due to the volatility of acylcyclopentene **53p**, the work-up solvent (Et_2O) was removed using ambient pressure distillation (50→80 °C). 323.8 mg, 1.97 mmol, 93% yield. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 80 g column, linear gradient, 0→30% Et_2O in pentane [33 min]) and solvent was removed using ambient pressure distillation (60 °C). R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.50 (dq, *J* = 15.5, 1.3 Hz, 1H), 5.39 (dq, *J* = 15.6, 6.2 Hz, 1H), 2.58–2.52 (m, 2H), 2.31–2.28 (m, 1H), 2.30 (s, 3H), 1.91 (ddd, *J* = 12.8, 7.4, 7.4 Hz, 1H), 1.74 (ddd, *J* = 12.8, 7.2, 7.2 Hz, 1H), 1.68–1.64 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 151.4, 143.8, 137.5, 122.3, 51.5, 38.1, 29.6, 26.8, 25.4, 18.2; IR (Neat Film NaCl) 3022, 2958, 2859, 1674, 1617, 1451, 1377, 1365, 1310, 1271, 1229, 1165, 967 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}O$ $[M+H]^+$: 165.1279; found 165.1278; $[\alpha]_D^{25.0}$ +89.82 (*c* 1.04, $CHCl_3$, 88.0 % ee).



70q

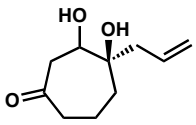
β-Hydroxyketone 70q ***(Table 2.4, entry 14).*** Prepared using General Method A. 29.1 mg, 0.150 mmol, 96% yield. Flash column chromatography (SiO_2, 2 x 20 cm, 9:1→3:1

hexanes:EtOAc). R_f = 0.09 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.57.1; IR (Neat Film NaCl) 3436, 3021, 2922, 2873, 2842, 2697, 1692, 1656, 1436, 1402, 1353, 1318, 1256, 1202, 1184, 1172, 1152, 1093, 1071, 1050, 1000, 981, 970, 949, 932, 876, 850, 834, 798, 750 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^{+\bullet}$: 194.1307; found 194.1315.



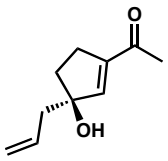
53q

Acylcyclopentene 53q ***(Table 2.4, entry 14).*** Prepared using General Method E. 21.7 mg, 0.123 mmol, 91% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.72 (dm, *J* = 10.0 Hz, 1H), 5.65 (dm, *J* = 10.0 Hz, 1H), 2.59–2.52 (m, 2H), 2.30 (s, 3H), 2.13–2.04 (m, 2H), 2.02–1.98 (m, 2H), 1.77–1.70 (m, 2H), 1.69 (ddd, *J* = 12.8, 6.3, 6.3 Hz, 1H), 1.56 (ddd, *J* = 12.8, 6.5, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 151.4, 143.9, 127.0, 125.5, 48.7, 35.8, 35.8, 32.5, 28.9, 26.8, 23.1; IR (Neat Film NaCl) 3320, 3023, 2918, 2856, 1704, 1669, 1616, 1436, 1371, 1436, 1371, 1316, 1269, 1231, 11945, 1116, 1086, 1045, 1020, 980, 962, 935, 864, 763 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{16}O$ $[M]^{+\bullet}$: 176.1201; found 176.1234; $[\alpha]_D^{25.0}$ –10.42 (*c* 1.08, $CHCl_3$, 78.4% ee).



70n

β-Hydroxyketone 70n ***(Table 2.4, entry 15).*** Prepared using General Method D. 20.3 mg, 0.110 mmol, 38% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→6:1→4:1→2:1→1:1→1:2 hexanes:EtOAc). R_f = 0.19 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.58.1; IR (Neat Film NaCl) 3369, 3077, 3011, 2947, 2924, 1688, 1641, 1469, 1439, 1343, 1268, 1216, 1193, 1128, 1108, 1079, 1052, 1032, 1019, 999, 966, 909, 889, 808, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{15}O_2$ $[M–OH]^+$: 167.1067; found 167.1066.

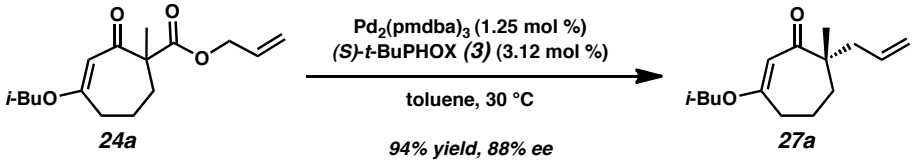


53n

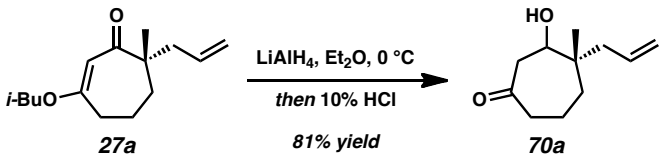
Acylcyclopentene 53n ***(Table 2.4, entry 15).*** Prepared using General Method E. 12.2 mg, 0.073 mmol, 67% yield. Flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→4:1→2:1→1:1 hexanes:EtOAc); R_f = 0.44 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (app t, *J* = 1.9 Hz, 1H), 5.91–5.77 (dddd, *J* = 16.5, 10.7, 7.4, 7.4 Hz, 1H), 5.23–5.15 (m, 2H), 2.67 (dddd, *J* = 17.0, 8.9, 4.1, 1.7 Hz, 1H), 2.50–2.40 (m, 3H), 2.33 (s, 3H), 2.14 (ddd, *J* = 13.7, 8.5, 4.1 Hz, 1H), 2.03 (br s, 1H), 1.91 (ddd, *J* = 13.7, 9.0, 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 145.9, 145.5, 132.9, 119.8, 85.2, 44.9, 37.4, 29.1, 27.0; IR (Neat Film NaCl) 3400, 3077, 3004, 2961, 2929, 2856, 1841, 1668, 1622, 1428, 1372, 1295, 1267, 1228, 1205, 1173, 1070, 1057, 1016, 998,

966, 935, 917, 862, 831, 776 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{13}O$ $[M–OH]^+$: 149.0961; found 149.0967; $[\alpha]_D^{25.0}$ –22.45 (*c* 1.22, $CHCl_3$, 57.1% ee).

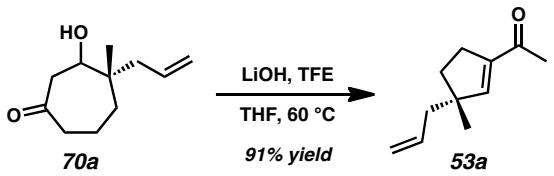
2.7.2.9 LARGE SCALE SYNTHESIS OF ACYLCYCLOPENTENE 53a



Vinylogous Ester 27a. $Pd_2(pmdba)_3$ (733.1 mg, 0.67 mmol, 0.0125) and (*S*)-*t*-BuPHOX (647.0 mg, 1.67 mmol, 0.0312 equiv) were placed in a 500 mL round-bottom flask. The flask was evacuated/backfilled with N_2 (3 cycles, 10 min evacuation per cycle). Toluene (222 mL, sparged with N_2 for 1 h immediately before use) was added and the black suspension was immersed in an oil bath preheated to 30 °C. After 30 min of stirring, β-ketoester **24a** (15.0 g, 53.5 mmol, 1.0 equiv) in toluene (46 mL, sparged with N_2 immediately before use) was added using positive pressure cannulation. The dark orange catalyst solution turned olive green immediately after the addition of β-ketoester **24a**. The solution was stirred at 30 °C for 32 h, allowed to cool to ambient temperature, filtered through a silica gel plug (2 x 5.5 cm SiO_2, Et_2O), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 8 x 12 cm, 19:1 hexanes:EtOAc, dry-loaded using SiO_2) to afford vinylogous ester **27a** (11.83 g, 50.1 mmol, 94% yield, 88% ee) as a pale yellow oil. (For characterization data, see p. 287).

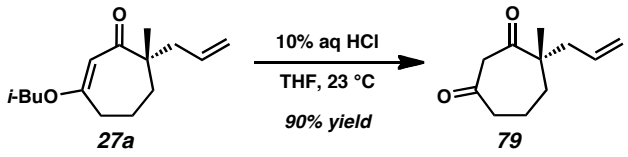


β-Hydroxyketone 70a. A 500 mL round-bottom flask with magnetic stir bar was charged with Et_2O (150 mL) and cooled to 0 °C. $LiAlH_4$ (1.04 g, 0.0275 mol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **27a** (11.83 g, 50 mmol, 1.0 equiv) in Et_2O (50 and 25 mL for quantitative transfer) was added dropwise using positive pressure cannulation. The grey suspension was stirred for 60 min after which $LiAlH_4$ (190 mg, 5.0 mmol, 0.1 equiv) was added in one portion. After an additional 10 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (143 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 10 h. The reaction was diluted with Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was azeotroped with toluene (50 mL) and purified using flash column chromatography (SiO_2, 8 x 13 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-hydroxyketone **70a** (7.25 g, 39.8 mmol, 81% yield) as a colorless semi-solid. (For characterization data, see p. 319).



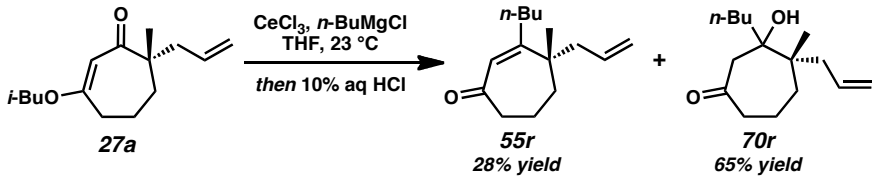
Acylcyclopentene 53a. Alcohol **70a** (7.25 g, 39.8 mmol, 1.0 equiv) was dissolved in THF (400 mL) in a 1 L round-bottom flask. The solution was treated with 2,2,2-trifluoroethanol (5.99 g, 4.36 mL, 59.7 mmol, 1.5 equiv) and LiOH (1.43 g, 59.7 mmol, 1.5 equiv). The flask was fitted with a reflux condenser, purged with N_2, and heated to 60 °C using an oil bath. After 18 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (200 mL), stirred with Na_2SO_4 for 30 min, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash column chromatography (SiO_2, 8 x 12 cm, 15:1→9:1 pentane:Et_2O) to afford acylcyclopentene **53a** (5.93 g, 36.1 mmol, 91% yield) as a colorless fragrant oil. (For characterization data, see p. 320).

2.7.2.10 INITIAL SYNTHETIC STUDIES ON THE ORGANOMETALLIC ADDITION/REARRANGEMENT OF 27a



Cyclic Dione 79. A 20 mL scintillation vial equipped with a stir bar was charged with vinylogous ester **27a** (144.6 mg, 0.61 mmol, 1.00 equiv), THF (1 mL), and aqueous HCl (1 mL, 10% w/w, 2.87 mmol, 4.69 equiv). After 4.5 h of vigorous stirring, the solution

was diluted with H_2O (5 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (70 mL) were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→10% EtOAc in hexanes) to afford cyclic dione **79** (99.4 mg, 0.55 mmol, 90% yield) as a pale yellow oil; R_f = 0.48 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, J = 14.0 Hz, 1H), 5.12–5.04 (m, 2H), 3.72 (d, J = 14.0 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H), 2.48 (t, J = 6.6 Hz, 2H), 2.40 (dddd, J = 13.9, 7.1, 1.2, 1.2 Hz, 1H), 2.22 (dddd, J = 13.9, 7.7, 1.1, 1.1 Hz, 1H), 2.02–1.75 (m, 4H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 203.7, 133.1, 119.1, 57.6, 50.9, 43.5, 42.9, 36.7, 21.9, 19.8; IR (Neat Film NaCl) 3076, 2972, 2935, 2871, 1719, 1695, 1639, 1463, 1417, 1378, 1337, 1210, 1160, 1112, 1059, 1026, 921 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O_2$ $[M]^{+\bullet}$: 180.1150; found 180.1165; $[\alpha]_D^{25.0}$ –19.38 (*c* 1.00, $CHCl_3$, 88.0% ee).

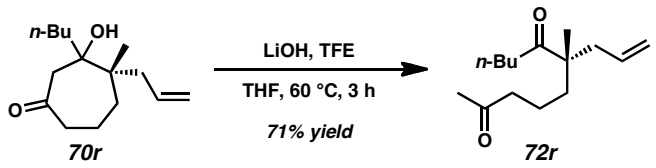


Cycloheptenone 55r and β-Hydroxyketone 70r. $CeCl_3 \cdot 7H_2O$ (419 mg, 1.13 mmol, 2.55 equiv) in a 100 mL round-bottom flask was immersed in a preheated oil bath at 150 °C and placed under vacuum for 4 h while stirring. The flask was cooled to ambient temperature, backfilled with N_2, and charged with THF (4 mL). After 15 h of stirring, additional THF (4 mL) and *n*-butylmagnesium chloride solution (1.2 mL, 1.86 M in THF, 2.23 mmol, 5.02 equiv) were added to the flask. The resulting slurry was stirred for 4.25

h before vinylogous ester **27a** (105 mg, 0.444 mmol, 1.00 equiv) dissolved in THF (1 mL) was added using positive pressure cannulation followed by two THF rinses (2 x 0.5 mL). After 45 min of stirring, the reaction was quenched by addition of 10% w/w HCl (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 25 g loading cartridge, 12 g column, multi-step gradient, hold 0% [1 min]→ramp to 10% [5 min]→hold 10% [31 min]→100% EtOAc in hexanes [10 min]) to afford cycloheptenone **55r** (28 mg, 0.13 mmol, 28% yield) and β-hydroxyketone **70r** (69 mg, 0.29 mmol, 65% yield) as pale yellow oils.

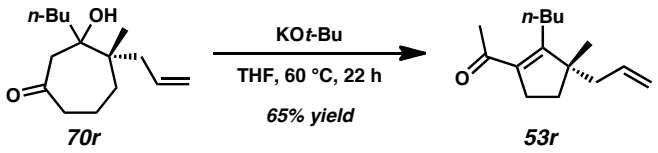
Cycloheptenone 55r. R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.63 (dddd, *J* = 16.9, 10.3, 7.9, 6.7 Hz, 1H), 5.10–4.98 (m, 2H), 2.61–2.54 (m, 2H), 2.37 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.18–2.03 (m, 3H), 1.85–1.72 (m, 3H), 1.66–1.56 (m, 1H), 1.53–1.43 (m, 2H), 1.37 (app. septuplet, *J* = 7.3 Hz, 2H), 1.15 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 163.0, 134.2, 128.7, 118.1, 45.7, 45.3, 44.4, 38.8, 34.0, 32.4, 25.7, 23.0, 17.6, 14.1; IR (Neat Film NaCl) 3076, 2957, 2933, 2872, 1652, 1611, 1467, 1414, 1379, 1342, 1263, 1218, 1178, 1109, 1072, 996, 962, 914, 841, 780, 713 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found 221.1905; $[\alpha]_D^{25.0}$ –33.17 (*c* 1.17, $CHCl_3$, 88.0% ee).

β-Hydroxyketone 70r. R_f = 0.48 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.76.1 (Neat Film NaCl) 3502, 3073, 2956, 2871, 1695, 1638, 1468, 1404, 1380, 1341, 1286, 1181, 1125, 1052, 1028, 998, 913, 868, 796, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006; found 239.2013.



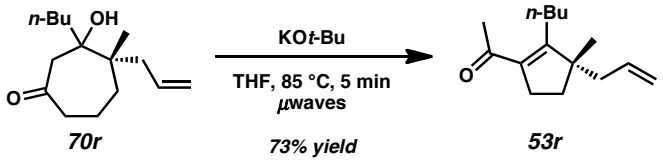
Linear Dione 72r. A 50 mL round-bottom flask equipped with a magnetic stir and fitted with a water condenser was charged with β-hydroxyketone **70r** (56.9 mg, 0.24 mmol, 1.00 equiv), THF (3 mL), TFE (60 μL, 0.83 mmol, 3.50 equiv), and LiOH (17.3 mg, 0.72 mmol, 3.03 equiv). The flask was backfilled with argon and lowered into a preheated oil bath (60 °C). After 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 21 cm, 10%→20%→30% EtOAc in hexanes) to afford linear dione **72r** (40.1 mg, 0.17 mmol, 71% yield) as a pale yellow oil; R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68–5.57 (m, 1H), 5.06–4.98 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.31 (dddd, J = 14.0, 7.3, 1.2, 1.2 Hz, 1H), 2.18 (dddd, *J* = 14.0, 7.7, 1.2, 1.2 Hz, 1H), 2.11 (s, 3H), 1.63–1.34 (m, 6H), 1.33–1.24 (m, 2H), 1.10 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 208.6, 133.9, 118.1, 50.9, 44.0, 42.6, 37.4, 37.4, 30.1, 25.9, 22.6, 21.1, 18.7, 14.1; IR (Neat Film NaCl) 3076, 2958, 2933, 2873, 1718, 1701, 1639,

1465, 1409, 1378, 1360, 1256, 1230, 1174, 1142, 1120, 1029, 994, 916, 766, 728 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006; found 239.2005; $[\alpha]_D^{25.0}$ +5.57 (*c* 1.17, $CHCl_3$, 88.0% ee).



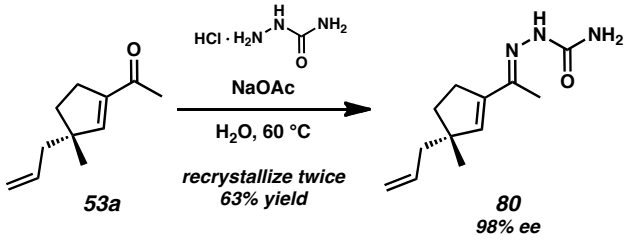
Acylcyclopentene 53r. A 25 mL round-bottom flask equipped with a stir bar and fitted with a water condenser was charged with β-hydroxyketone **70r** (91.5 mg, 0.38 mmol, 1.00 equiv), THF (4 mL), and KO*t*-Bu (66.5 mg, 0.59 mmol, 1.55 equiv). The flask was lowered into a preheated oil bath (60 °C) and stirred overnight. Additional THF (4 mL) was added after 19 h of heating. After an additional 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na_2SO_4, filtered through a silica gel plug, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 27 cm, 100% pentane→2%→5%→10% Et_2O in pentane) to afford acylcyclopentene **53r** (55.1 mg, 0.25 mmol, 65% yield) as a pale yellow oil; R_f = 0.81 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.65 (m, 1H), 5.08–5.00 (m, 2H), 2.60–2.49 (m, 2H), 2.45–2.37 (m, 1H), 2.24–2.17 (m, 4H), 2.15–2.10 (m, 2H), 1.85 (ddd, *J* = 12.8, 7.7, 6.2 Hz, 1H), 1.60–1.51 (m, 1H), 1.47–1.34 (m, 4H), 1.06 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 164.2, 135.0, 134.7, 117.6, 52.6, 43.8, 35.0, 32.1, 31.5, 30.4, 27.6, 24.7, 23.8, 14.0; IR (Neat film NaCl) 3075, 3002, 2957, 2930, 2870, 2859, 1677, 1653, 1639, 1602, 1456, 1432, 1373, 1355, 1311, 1275, 1258, 1188, 1141, 1089, 995, 959, 913, 848, 801, 726 cm^{-1};

HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found 221.1900; $[\alpha]_D^{25.0}$ –1.44 (*c* 1.35, $CHCl_3$, 88.0% ee).



Acylcyclopentene 53r. KO*t*-Bu (32 mg, 0.283 mmol, 1.62 equiv), THF (1.75 mL), and β-hydroxyketone mmol, 1.00 equiv) were added to a 0.5–2.0 mL microwave vial with a magnetic spin vane. The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 °C, sensitivity: normal). After 5 min of irradiation, the crimp cap was removed and Na_2SO_4 was added to the vial. The contents were filtered through a silica gel plug with Et_2O, concentrated under reduced pressure, and purified by flash column chromatography (5% Et_2O in pentane) to yield acylcyclopentene **53r** (31 mg, 0.14 mmol, 73% yield) as a pale yellow oil.

2.7.2.11 PREPARATION OF ACYLCYCLOPENTENE DERIVATIVES

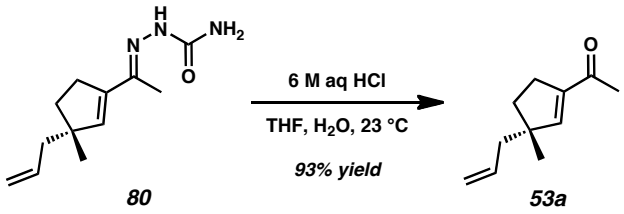


Semicarbazone 80. A 15 mL round-bottom flask was charged with sodium acetate (150 mg, 1.83 mmol, 1.20 equiv), semicarbazide hydrochloride (204 mg, 1.83 mmol, 1.20 equiv), and a magnetic stir bar. Purified water (1.7 mL) was added and the mixture was

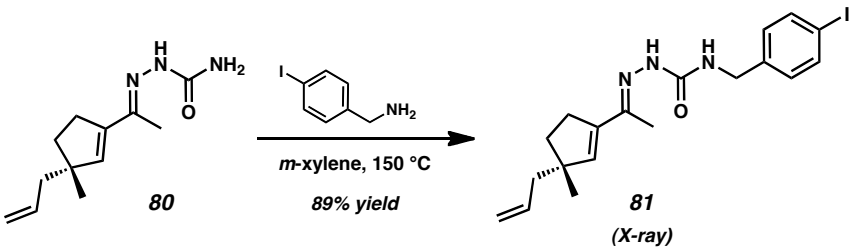
stirred until all the solids had dissolved. Acylcyclopentene **53a** (250 mg, 1.52 mmol, 1.00 equiv) was added neat and the mixture was heated to 60 °C for 4 h. The slurry was allowed to cool to ambient temperature while stirring and was then vacuum filtered (water aspirator). The white solid was dried under reduced pressure to afford semicarbazone **15** (311 mg, 1.40 mmol, 92% yield). The ee of the semicarbazone at this point was found to be 91% (measured by hydrolysis to ketone **53a,** GC conditions: 80 °C isothermal for 90 min, G-TA column, t_R (min): acylcyclopentene **53a** = 54.98).

The semicarbazone **80** (300 mg, 1.36 mmol) was transferred to a round-bottom flask, the solids were suspended in toluene-hexanes (50:50), and the mixture was heated to 90 °C while stirring. After a few minutes of stirring, the solids had dissolved completely to afford a clear, colorless solution. Heating was discontinued, and the stirring mixture was allowed to cool to ambient temperature while still immersed in the oil bath. After 10 h had elapsed, the slurry was vacuum filtered to afford **80** (246 mg, 1.11 mmol, 82% yield, 63% overall yield after recrystallizing twice). The ee at this point was found to be 94.5% (measured by hydrolysis to ketone **53a**). A second recrystallization following the above procedure employing **80** (241 mg, 1.09 mmol) afforded **80** (201 mg, 0.91 mmol, 83% yield). The ee at this point was found to be 97.9% (measured by hydrolysis to ketone **53a**); R_f = 0.30 (9:1 $CHCl_3$-MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 6.06 (br s, 1H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.76 (dddd, *J* = 16.7, 9.3, 7.4, 7.4 Hz, 1H), 5.47 (br s, 1H), 5.06–4.98 (m, 2H), 2.67–2.49 (m, 2H), 2.15–2.12 (m, 2H), 1.98 (s, 3H), 1.82 (ddd, *J* = 12.8, 8.2, 6.9 Hz, 1H), 1.62 (ddd, *J* = 12.8, 8.5, 6.4 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 145.0, 141.7, 141.2, 135.6, 117.2, 49.2, 45.9, 36.2, 30.8, 26.3, 12.8; IR (Neat Film NaCl) 3473, 3266,

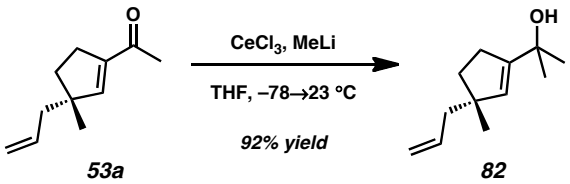
3189, 2946, 2858, 1698, 1579, 1478, 1437, 1377, 1349, 1321, 1130, 1109, 993, 910, 845, 768 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{20}N_3O$ $[M+H]^+$: 222.1606; found 222.1610; $[\alpha]_D^{22.6}$ +39.80 (*c* 0.84, $CHCl_3$, 97.9% ee); mp = 145–146 °C (1:1 toluene-hexanes).



Acylcyclopentene 53a. A solution of semicarbazone **80** (191.8 mg, 0.867 mmol, 1.00 equiv) in THF (1.92 mL) was treated with aqueous HCl (3.84 mL, 6.0 M, in H_2O) was added. The resulting biphasic mixture was stirred vigorously at ambient temperature for 30 h. The reaction was diluted with Et_2O (10 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The residue was filtered through a short silica gel plug (1 x 10 cm SiO_2, 4:1 hexanes:Et_2O) to afford acylcyclopentene **53a** (132.6 mg, 0.81 mmol, 93% yield); $[\alpha]_D^{22.6}$ +39.80 (*c* 0.84, $CHCl_3$, 97.9% ee). (For characterization data, see p. 320).

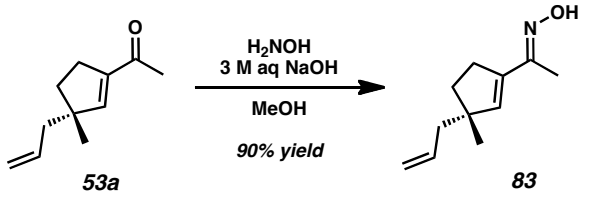


Iodoarene 81. To a solution of semicarbazone **80** (50 mg, 0.23 mmol, 1.00 equiv) in *m*-xylene (2.2 mL) was added 4-iodo-benzylamine (63 mg, 0.27 mmol, 1.17 equiv). The resulting pale yellow solution was immersed in an oil bath and heated to 150 °C. After 9 h of stirring at 150 °C, the reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a pale yellow solid. The crude solid was purified by flash column chromatography (1.0 x 15 cm SiO_2, 9:1→7:3 hexanes:EtOAc) to afford iodoarene **81** (88 mg, 0.20 mmol, 89% yield) as a white solid. X-ray quality crystals were obtained by slow vapor diffusion of pentane into a chloroform solution of **81**; R_f = 0.52 (9:1 $CHCl_3$-MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.66–7.64 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.50 (t, *J* = 6.1 Hz, 1H), 5.86 (app t, *J* = 1.5 Hz, 1H), 5.76 (dddd, *J* = 16.9, 9.0, 7.6, 7.6 Hz, 1H), 5.04–5.01 (m, 2H), 4.46 (d, *J* = 6.3 Hz, 2H), 2.60–2.49 (m, 2H), 2.18–2.10 (m, 2H); 1.95 (s, 3H), 1.82 (ddd, *J* = 12.9, 8.5, 6.3 Hz, 1H), 1.62 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 144.5, 141.5, 141.4, 139.2, 137.8, 135.6, 129.4, 117.2, 92.6, 49.3, 45.9, 43.2, 36.2, 30.9, 26.3, 12.5; IR (Neat Film NaCl) 3411, 3194, 3075, 2946, 2920, 2863, 1677, 1528, 1486, 1401, 1323, 1259, 1142, 1114, 1057, 1000, 913, 845 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}N_3OI$ $[M+H]^+$: 438.1043; found 438.1036; $[\alpha]_D^{22.2}$ +31.43 (*c* 0.36, $CHCl_3$, 91.0% ee); mp = 123–124 °C ($CHCl_3$-*n*-pentane).



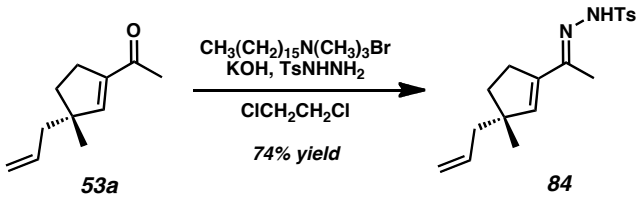
Alcohol 82. $CeCl_3$ (187 mg, 0.759 mmol, 2.50 equiv) was weighed out in a glove box and placed in a 25 mL round-bottom flask. The flask was sealed with a septum and removed from the glove box. THF (3 mL) was added to the flask, the suspension was cooled to –78 °C using an acetone/CO_2(s) bath, and MeLi (326 μL, 0.912 mmol, 2.80 M in DME, 3.00 equiv) was added in a dropwise manner. The resulting pale brown suspension was stirred at –78 °C for 30 min. Acylcyclopentene **53a** (50.0 mg, 0.304 mmol, 1.00 equiv) was added neat to the reaction in a dropwise manner. After 30 min of stirring at –78 °C, the reaction was quenched by dropwise addition of sat. aqueous NH_4Cl (1.0 mL), the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction was diluted with Et_2O (10 mL) and H_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 5 g loading cartridge, 12 g column, multi-step gradient, 5% [5 min]→10% Et_2O in pentane) to afford alcohol **82** (50.4 mg, 0.280 mmol, 92% yield) as a pale yellow oil; R_f = 0.31 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 14.7, 11.8, 9.3, 7.4 Hz, 1H), 5.34 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.04–5.00 (m, 1H), 5.00–4.97 (m, 1H), 2.45–2.29 (m, 2H), 2.18–2.00 (m, 2H), 1.81 (ddd, *J* = 12.7, 8.3, 6.0 Hz, 1H), 1.60 (ddd, *J* = 12.7, 8.5, 6.1 Hz, 1H), 1.44 (br s, 1H), 1.34 (s, 6H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 149.7, 136.21, 131.6, 116.7, 70.9, 48.2, 46.2, 36.9, 30.9, 29.3, 29.3, 26.5; IR (Neat Film NaCl) 3370, 3077, 2973, 2943, 2859, 1637, 1454, 1412, 1367, 1328, 1254, 1212, 1162, 1137, 997, 960, 940, 910, 853, 806 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{19}$ $[M\text{-}OH]^+$: 163.1481; found 163.1482; $[\alpha]_D^{25.0}$ +5.34 (*c* 1.16, $CHCl_3$, 88.0 % ee).



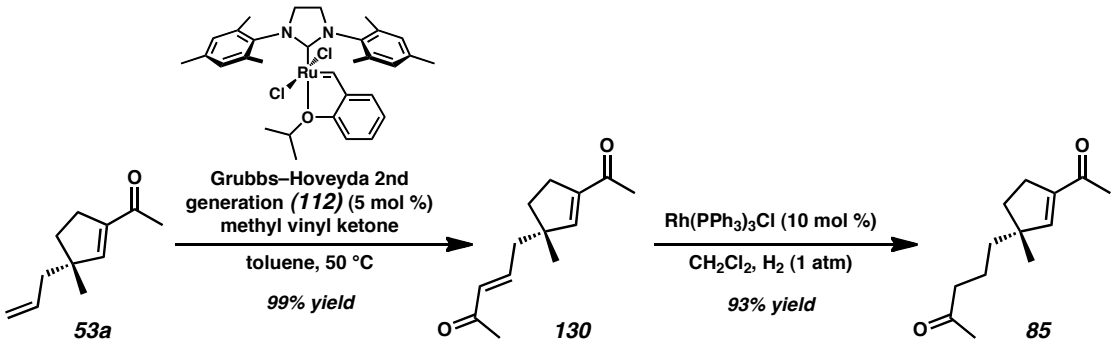
Oxime 83. A 1 dram vial with magnetic stir bar was charged with acylcyclopentene **53a** (40.0 mg, 0.24 mmol, 1.00 equiv), MeOH (0.24 mL), 50% wt aqueous hydroxylamine (47 μL, 0.76 mmol, 3.13 equiv), and 3 M aqueous NaOH (125 μL, 0.376 mmol, 0.51 equiv). After 9 d, the reaction was diluted with Et_2O (10 mL) and H_2O (2 mL) and stirred vigorously for several minutes. The layers were separated and the aqueous layer was extracted with Et_2O (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered through a cotton plug, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 1.5 x 20 cm, 20:1→ 15:1 hexanes:EtOAc) to afford oxime **83** (39.3 mg, 0.21 mmol, 90% yield) as a clear oil; R_f = 0.52 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 5.90 (br t, *J* = 1.5 Hz, 1H), 5.85–5.66 (m, 1H), 5.02 (m, 2H), 2.70–2.45 (m, 2H), 2.14 (m, 2H), 2.05 (s, 3H), 1.85 (ddd, *J* = 12.9, 8.1, 6.6 Hz, 1H), 1.65 (ddd, *J* = 12.8, 8.3, 6.3 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.8, 139.1, 135.6, 117.2, 48.9, 45.9, 36.3,

30.6, 26.2, 11.3; IR (Neat Film NaCl) 3272, 3233, 3075, 3003, 2952, 2925, 2864, 1639, 1455, 1437, 1414, 1379, 1322, 1280, 1103, 1010, 995, 913, 850, 828, 756, 715 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}NO$ $[M–C_3H_5]^+$: 138.0919; found 138.0960; $[\alpha]_D^{25.0}$ +21.34 (*c* 1.57, $CHCl_3$, 88.0% ee).



Tosylhydrazone 84. A 25 mL flask with magnetic stir bar was charged with acylcyclopentene **53a** (40.0 mg, 0.24 mmol, 1.00 equiv), 1,2-dichloroethane (2.7 mL), cetyltrimethylammonium bromide (26.6 mg, 0.073 mmol, 0.30 equiv), KOH (136.7 mg, 2.44 mmol, 10.0 equiv), and $TsHNNH_2$ (271.9 mg, 1.46 mmol, 6.00 equiv), forming a thick white suspension. After 43 h, the reaction was quenched by the addition of sat. aqueous NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 3 x 25 cm, 4:1→3:1 hexanes:EtOAc) to afford tosylhydrazone **84** (196.7 mg, 0.94 mmol, 74% yield) as a clear oil; R_f = 0.41 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.54 (br s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.81–5.62 (m, 1H), 5.06–4.92 (m, 2H), 2.58–2.48 (m, 2H), 2.43 (s, 3H), 2.19–2.00 (m, 2H), 1.89 (s, 3H), 1.85–1.71 (m, 1H), 1.71–1.50 (m, 1H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 144.1, 142.4, 141.6, 135.5, 135.4, 129.5, 128.3, 117.2, 49.3, 45.8, 36.2, 30.7, 26.1, 21.7, 12.9; IR (Neat

Film NaCl) 3217, 3072, 2953, 2924, 2864, 1706, 1639, 1618, 1598, 1495, 1454, 1401, 1337, 1307, 1292, 1212, 1185, 1168, 1094, 1059, 1029, 996, 914, 870, 850, 830, 813, 706 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}O_2N_2S$ $[M–C_3H_5]^+$: 291.1167; found 291.1181; $[\_]_D^{25.0}$ +34.25 (*c* 1.05, $CHCl_3$, 88.0% ee).

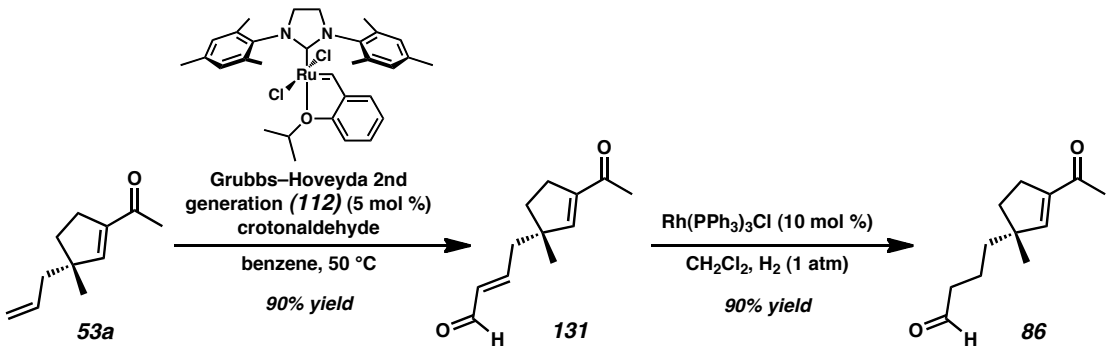


Bis-enone 130. To an oven-dried reaction tube with magnetic stir bar was added acylcyclopentene **53a** (50 mg, 0.304 mmol, 1.00 equiv). The headspace was purged with N_2 and dry degassed toluene (2.0 mL, sparged with N_2 for 1 h immediately before use) was added, followed by methyl vinyl ketone (124 μL, 1.53 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd generation catalyst (9.5 mg, 15.2 μmol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. A reflux condenser was attached and the reaction was inserted into a 50 °C heating block. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. The solution was filtered through a short silica gel plug (2 x 4 cm, Et_2O). The filtrate was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→2:1→1:1 hexanes:EtOAc) to afford bis-enone **130** (62.3 mg, 0.30 mmol, 99% yield) as a brown liquid; R_f = 0.31 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (ddd, *J* = 15.5, 7.6, 7.6 Hz, 1H),

6.42 (s, 1H), 6.10 (d, J = 15.8 Hz, 1H), 2.68–2.40 (m, 2H), 2.33 (dd, J = 7.6, 0.9 Hz, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 1.84 (ddd, J = 14.7, 8.2, 6.6 Hz, 1H), 1.70 (ddd, J = 13.1, 8.4, 6.1 Hz, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 197.1, 150.2, 144.3, 143.8, 133.8, 50.1, 43.7, 36.2, 29.8, 27.3, 26.8, 25.7; IR (Neat Film NaCl) 3584, 3318, 2956, 2866, 1697, 1669, 1626, 1454, 1429, 1365, 1308, 1254, 1182, 1098, 1021, 982, 937, 867 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{18}O_2$ $[M]^{+\bullet}$: 206.1307; found 206.1303; $[\alpha]_D^{25.0}$ +47.61 (c 1.02, $CHCl_3$, 88.0% ee).

Mono-enone 85. An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and glass T-joint with 14/20 adapter was charged with bis-enone **130** (50.0 mg, 0.24 mmol, 1.00 equiv) and evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH_2Cl_2 (2.5 mL) and $Rh(PPh_3)_3Cl$ (22.4 mg, 0.024 mmol, 10 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H_2 balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H_2 (3 cycles, 2 min evacuation per cycle). After 10 h of stirring, the brown reaction mixture was filtered through a short silica gel plug (2 x 4 cm, Et_2O) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→2:1 hexanes:Et_2O) to afford enone **85** (46.8 mg, 0.23 mmol, 93% yield) as an orange liquid; R_f = 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (app t, J = 1.7 Hz, 1H), 2.65–2.46 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 2.27 (s, 3H), 2.11 (s, 3H), 1.88–1.72 (m, 1H), 1.71–1.46 (m, 3H), 1.46–1.29 (m, 2H), 1.08 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 208.8, 197.5, 152.0, 143.6, 50.0, 44.2, 40.4, 36.1, 30.1, 29.7, 26.8, 25.6, 19.4; IR (Neat Film NaCl) 2998, 2953, 2866, 1716, 1667, 1616, 1456, 1427, 1367, 1308, 1270, 1225, 1190, 1170, 1103, 1058, 1021, 841, 871, 726 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O_2$ $[M]^{+\bullet}$: 208.1463; found 208.1460; $[\alpha]_D^{25.0}$ +25.55 (*c* 1.46, $CHCl_3$, 88.0% ee).

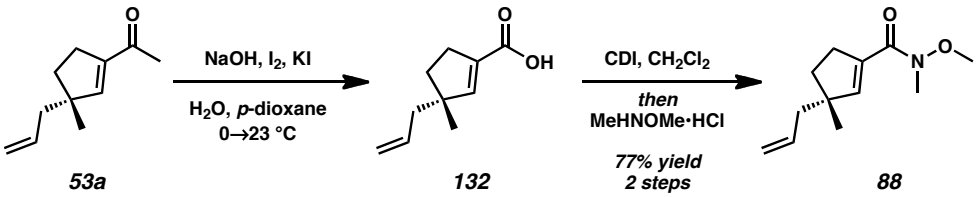


Bis-enone 131. To a 2-neck round-bottomed flask with magnetic stir bar and attached reflux condenser was added acylcyclopentene **53a** (100 mg, 0.608 mmol, 1.00 equiv). The flask was evacuated/backfilled with N_2 (3 cycles, 30 s evacuation per cycle). Dry degassed benzene (8.0 mL, sparged with N_2 for 1 h immediately before use) was added, followed by crotonaldehyde (251 μL, 3.06 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd generation catalyst (19.0 mg, 30.4 μmol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. The flask was immersed in a 50 °C oil bath. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. Several drops of ethyl vinyl ether were added and the reaction mixture was stirred for 5 min. The mixture was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO_2, 2 x 25 cm,

10:1→4:1→2:1 hexanes:EtOAc) to afford bis-enone **131** (105.4 mg, 0.55 mmol, 90% yield) as a brown oil; R_f = 0.38 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.8 Hz, 1H), 6.76 (app dt, *J* = 15.4, 7.6 Hz, 1H), 6.42 (app t, *J* = 1.8 Hz, 1H), 6.13 (app ddt, *J* = 15.5, 7.8, 1.3 Hz, 1H), 2.68–2.50 (m, 2H), 2.45 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.28 (s, 3H), 1.85 (ddd, *J* = 13.1, 8.4, 6.5 Hz, 1H), 1.72 (ddd, *J* = 13.1, 8.5, 6.0 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 193.5, 154.0, 149.7, 144.5, 135.6, 50.1, 43.9, 36.1, 29.8, 26.8, 25.8; IR (Neat Film NaCl) 3359, 3317, 3041, 2957, 2928, 2867, 2820, 2743, 2708, 1691, 1668, 1636, 1618, 1456, 1431, 1378, 1369, 1341, 1308, 1269, 1203, 1162, 1149, 1109, 1093, 1036, 1013, 978, 936, 893, 868 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{17}O_2$ $[M+H]^+$: 193.1229; found 193.1224; $[\alpha]_D^{25.0}$ +46.07 (*c* 1.13, $CHCl_3$, 88.0% ee).

Mono-enone 86. An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and a glass T-joint with 14/20 adapter was charged with and bis-enone **131** (42.8 mg, 0.22 mmol, 1.00 equiv) and evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH_2Cl_2 (2.5 mL) and $Rh(PPh_3)_3Cl$ (10.3 mg, 0.011 mmol, 5 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H_2 balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H_2 (five cycles, 2 min evacuation per cycle). After 20 h of stirring, an additional portion of $Rh(PPh_3)_3Cl$ (10.3 mg, 0.011 mmol, 5 mol %) in CH_2Cl_2 (0.5 mL) was added to the reaction using positive pressure cannulation. After 1.5 h of stirring, the reaction

was diluted with Et_2O, filtered through a short silica gel plug (2 x 4 cm, Et_2O), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1 hexanes:Et_2O) to afford enone **86** (39.2 mg, 0.20 mmol, 90% yield) as an pale colorless oil; R_f = 0.48 (2:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 6.44 (app t, *J* = 1.7 Hz, 1H), 2.59–2.48 (m, 2H), 2.43 (td, *J* = 7.1, 1.4 Hz, 2H), 2.28 (s, 3H), 1.88–1.73 (m, 1H), 1.73–1.51 (m, 3H), 1.51–1.33 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 197.5, 151.7, 143.8, 50.0, 44.5, 40.4, 36.1, 29.8, 26.8, 25.6, 17.8; IR (Neat Film NaCl) 3427, 3314, 3042, 2951, 2865, 2721, 1723, 1665, 1616, 1457, 1411, 1378, 1367, 1340, 1308, 1269, 1193, 1156, 1105, 1060, 1034, 1020, 970, 942, 867, 801 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^{+\bullet}$: 194.1307; found 194.1321; $[\alpha]_D^{25.0}$ +32.50 (*c* 0.69, $CHCl_3$, 88.0% ee).

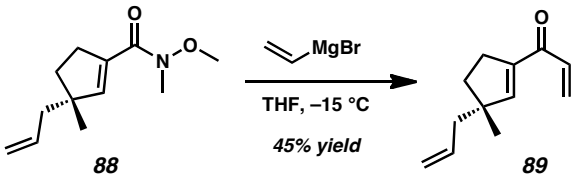


Carboxylic acid 132. A 50 mL round-bottom flask with magnetic stir bar was charged with acylcyclopentene **53a** (200 mg, 1.22 mmol, 1.00 equiv) and *p*-dioxane (10 mL). The solution was cooled to 0 °C and 5 M aqueous NaOH (10 mL) was added dropwise. The white suspension was stirred for 5 min at 0 °C. A dark brown solution of I_2 (1.37 g, 5.40 mmol, 4.40 equiv) and KI (2.09 g, 12.59 mmol, 10.50 equiv) in purified H_2O (10 mL) was added to the reaction dropwise, causing the reaction to become a yellow suspension. After 6.5 h of stirring at 0 °C, an additional portion of I_2 (343 mg, 1.35

mmol, 1.11 equiv) in *p*-dioxane (2 mL) was added to the reaction. After 30 min of stirring at 0 °C, the reaction was acidified to pH 2 using 2 M aqueous HCl. The reaction was extracted with Et_2O (3 x 30 mL) until the organic layer was clear. The combined organic phases were washed with sat. aqueous $K_2S_2O_3$ (2 x 10 mL), H_2O (2 x 10 mL), and brine (2 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow semi-solid. The residue was taken up in EtOAc, filtered through a silica gel plug (3 x 3 cm, EtOAc), and concentrated to give carboxylic acid **132** as a pale yellow oil which was used directly in the next step; R_f = 0.35, broad (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (app t, *J* = 1.9 Hz, 1H), 5.89–5.62 (m, 1H), 5.11–4.99 (m, 2H), 2.68–2.47 (m, 2H), 2.26–2.09 (m, 2H), 1.91 (ddd, *J* = 13.0, 8.2, 7.0 Hz, 1H), 1.69 (ddd, *J* = 13.0, 8.2, 6.2 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.3, 134.8, 133.9, 117.8, 49.8, 45.2, 36.3, 30.3, 25.5; IR (Neat Film NaCl) 3076, 3004, 2956, 2926, 2865, 2610, 1687, 1634, 1454, 1424, 1374, 1348, 1306, 1280, 1216, 1180, 1083, 995, 915, 745, 720 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_9O_2$ $[M–C_3H_5]^+$: 125.0603; found 125.0629; $[\alpha]_D^{25.0}$ +1.43 (*c* 0.80, $CHCl_3$, 88.0% ee).

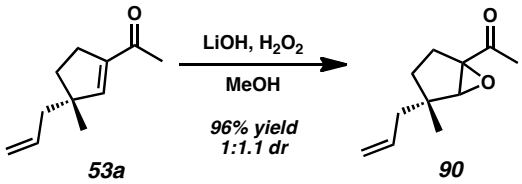
Amide 88. A 50 mL flask with magnetic stir bar was charged with carboxylic acid **132** (202.7 mg, 1.22 mmol, 1.00 equiv) and anhydrous CH_2Cl_2 (4.0 mL). To the vigorously stirred reaction was added 1,1'-carbonyldiimidazole (217 mg, 1.34 mmol, 1.10 equiv) in a portionwise manner. After 15 min, anhydrous *N*,*O*-dimethylhydroxylamine hydrochloride (143 mg, 1.46 mmol, 1.20 equiv) was added portionwise. The reaction became turbid after several min. After 21 h, an additional portion of *N*,*O*-

dimethylhydroxylamine hydrochloride (14.3 mg, 0.146 mmol, 0.12 equiv) was added. At 23.5 h, the reaction was transferred to a separatory funnel, washed with 0.25 M HCl (2 x 2 mL), sat. aqueous $NaHCO_3$, and brine. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 4:1→3:1 hexanes:EtOAc) to afford amide **88** as a clear oil (196.7 mg, 0.94 mmol, 77% yield over 2 steps); R_f = 0.41 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (app t, *J* = 1.9 Hz, 1H), 5.87–5.68 (m, 1H), 5.09–4.97 (m, 2H), 3.63 (s, 3H), 3.23 (s, 3H), 2.77–2.55 (m, 2H), 2.21–2.11 (m, 2H), 1.83 (ddd, *J* = 12.8, 8.3, 6.4 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.4, 6.0 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 147.0, 135.4, 135.3, 117.4, 61.2, 49.4, 45.4, 35.9, 33.3, 32.9, 25.6; IR (Neat Film NaCl) 3584, 3401, 3078, 2954, 2930, 2864, 1641, 1609, 1454, 1441, 1414, 1378, 1329, 1198, 1177, 1152, 1105, 1043, 997, 969, 914, 812, 723 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}NO_2$ $[M+H]^+$: 210.1494; found 210.1498; $[\alpha]_D^{25.0}$ +1.41 (*c* 0.98, $CHCl_3$, 88.0% ee).



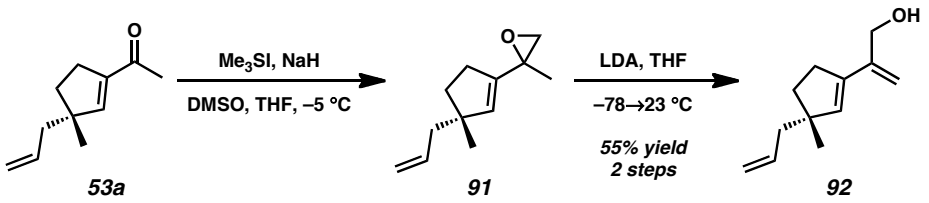
Divinylketone 89. A 25 mL round-bottomed flask with magnetic stir bar was charged with amide **88** (97.0 mg, 0.46 mmol, 1.00 equiv), evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle), dissolved in THF (3.0 mL), and cooled to –15 °C using an ethylene glycol/CO_2(s) bath. The yellow solution became cloudy. Vinylmagnesium bromide solution (1.38 mL, 1.0 M in THF, 1.38 mmol, 3.00 equiv) was added dropwise.

The solution was maintained at –15 °C for 20 min before the flask was allowed to warm to ambient temperature. The reaction was quenched by addition into sat. aqueous NH_4Cl (2.0 mL) using positive pressure cannulation. The mixture was extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 0%→1%→2%→3% Et_2O in hexanes) to afford divinylketone **89** (36.2 mg, 0.21 mmol, 45% yield) as a pale yellow liquid; R_f = 0.68 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.53 (app t, *J* = 1.7 Hz, 1H), 6.28 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.85–5.65 (m, 1H), 5.69 (dd, *J* = 10.5, 1.9 Hz, 1H), 5.11–4.99 (m, 2H), 2.76–2.50 (m, 2H), 2.29–2.09 (m, 2H), 1.87 (ddd, *J* = 12.9, 8.2, 6.8 Hz, 1H), 1.67 (ddd, *J* = 12.9, 8.3, 6.3 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 152.1, 143.7, 134.8, 132.6, 127.7, 117.8, 50.3, 45.3, 35.8, 30.1, 25.5; IR (Neat Film NaCl) 3584, 3400, 3078, 2955, 2927, 2866, 1622, 1606, 1453, 1440, 1408, 1374, 1348, 1308, 1255, 1204, 1169, 1059, 981, 956, 915, 783 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{11}O$ $[M–C_3H_5]^+$: 135.0846; found 135.0810; $[\alpha]_D^{25.0}$ +0.84 (*c* 0.81, $CHCl_3$, 88.0% ee).



Epoxide 90. A solution of acylcyclopentene **53a** (100 mg, 0.609 mmol, 1.00 equiv) in MeOH (6.1 mL) in a 25 mL round-bottom flask was treated with LiOH (7.3 mg, 0.30 mmol, 0.50 equiv) in one portion. Aqueous H_2O_2 (75.0 μL, 83.3 mg, 2.00 equiv, 50% in H_2O) was added dropwise. After 12 h of stirring at ambient temperature additional

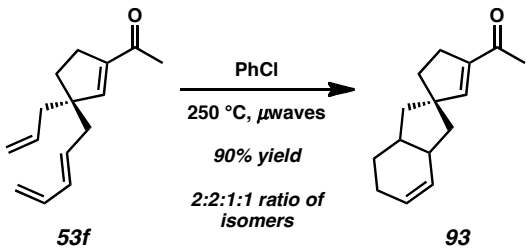
aqueous H_2O_2 (75.0 μL, 83.3 mg, 2.00 equiv, 50% in H_2O) was added. The reaction was stirred for an additional 8 h, diluted with CH_2Cl_2 (10 mL), sat. aqueous $NaHCO_3$ (1.0 mL), and water (1.0 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Mg_2SO_4, filtered, and concentrated carefully under reduced pressure. The crude product was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 12 g loading cartridge, 25 g column, linear gradient, 5%→30% Et_2O in pentane [15 min]) to afford epoxide **90** (106 mg, 0.588 mmol, 96% yield) as a colorless fragrant oil and as a 1.1:1 mixture of diastereomers; R_f = 0.54 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.68 (m, 2H), 5.14–5.01 (m, 4H), 3.32 (s, 1H), 3.30 (s, 1H), 2.35–2.21 (m, 4H), 2.07 (s, 3H), 2.07 (s, 3H), 2.05–1.99 (m, 2H), 1.96–1.85 (m, 2H), 1.54–1.49 (m, 1H), 1.33–1.29 (m, 2H), 1.20–1.16 (m, 1H), 1.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 205.6, 134.7, 133.6, 118.4, 117.8, 70.3, 70.2, 69.4, 69.3, 42.7, 42.7, 42.4, 42.3, 41.3, 31.9, 31.4, 25.0, 24.8, 24.1, 21.7, 20.5; IR (Neat Film NaCl) 3072, 3002, 2958, 2878, 1706, 1642, 1459, 1444, 1419, 1397, 1360, 1325, 1286, 1261, 1115, 922, 856, 831 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}$ $[M+H]^+$: 181.1223; found 181.1226; $[\alpha]_D^{25.0}$ –6.94 (*c* 1.40, $CHCl_3$, 88.0 % ee).



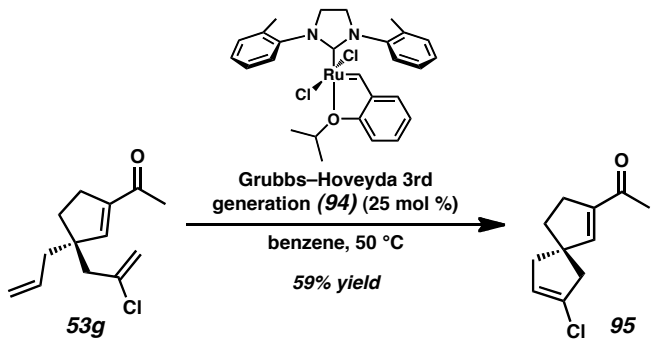
Allylic alcohol 92. NaH (36.5 mg, 0.91 mmol, 3.0 equiv, 60% w/w in mineral oil) was suspended in DMSO (1.2 mL) in a 25 mL round-bottom flask. After 20 min of stirring at ambient temperature, THF (3.7 mL) was added and the resulting mixture was cooled to –5 °C using a water/NaCl/ice bath. Me_3SI (192.3 mg, 0.95 mmol, 3.1 equiv) was dissolved in DMSO (1.2 mL) and added dropwise to the stirred reaction. After an additional 5 min of stirring, acylcyclopentene **53a** (50 mg, 0.30 mmol, 1.0 equiv) was added neat dropwise. After 1.5 h of stirring at –5 °C, the reaction was diluted with Et_2O (15 mL) and quenched by pouring the reaction over 10 g of ice. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to give the volatile crude epoxide **91** as a colorless oil; R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.92.1; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.92.3; IR (Neat Film NaCl) 3072, 3037, 2953, 2923, 2864, 1637, 1451, 1437, 1385, 1370, 1338, 1259, 1140, 1105, 1066, 994, 910, 856, 846, 806, 730 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{12}H_{19}O$ $[M+H]^+$: 179.1435; found 179.1430.

To a solution of diisopropylamine (0.11 mL, 0.76 mmol, 2.5 equiv) in THF (2.0 mL) in a 10 mL round-bottom flask at 0 °C was added *n*-BuLi (370 µL, 0.76 mmol, 2.05 M in cyclohexane, 2.5 equiv) dropwise over 10 min. After 15 min of stirring, the

reaction was cooled to –78 °C using an acetone/CO_2(s) bath and crude epoxide **91** in THF (1.0 mL) was added dropwise using positive pressure cannulation. The cooling bath was allowed to warm to ambient temperature and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (10 mL) and quenched by addition of a 50:50 (v/v) mixture of sat. aqueous NH_4Cl and water (2.0 mL each). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to afford a pale yellow oil. The residue was purified by flash column chromatography (SiO_2, 1 x 22 cm, 20% Et_2O in pentane) to afford allylic alcohol **92** (29.9 mg, 0.17 mmol, 55% yield over 2 steps) as a colorless oil; R_f = 0.25 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82–5.72 (m, 1H), 5.60 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.22 (app q, *J* = 1.4 Hz, 1H), 5.05–5.04 (m, 1H), 5.04–5.01 (m, 1H), 5.01–4.99 (m, 1H), 4.33 (br s, 2H), 2.58–2.45 (m, 2H), 2.17–2.08 (m, 2H), 1.82 (ddd, *J* = 12.7, 8.8, 5.9 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.8, 5.8 Hz, 1H), 1.51 (br s, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 139.1, 136.0, 135.9, 116.9, 111.9, 64.3, 49.3, 46.2, 35.9, 32.0, 26.4; IR (Neat Film NaCl) 3325, 3071, 3032, 2948, 2859, 1639, 1600, 1451, 1437, 1414, 1370, 1320, 1226, 1194, 1078, 1029, 994, 910, 848 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}$ $[M–OH]^+$: 161.1325; found 161.1324; $[\alpha]_D^{25.0}$ +17.59 (c 1.38, $CHCl_3$, 88.0% ee).

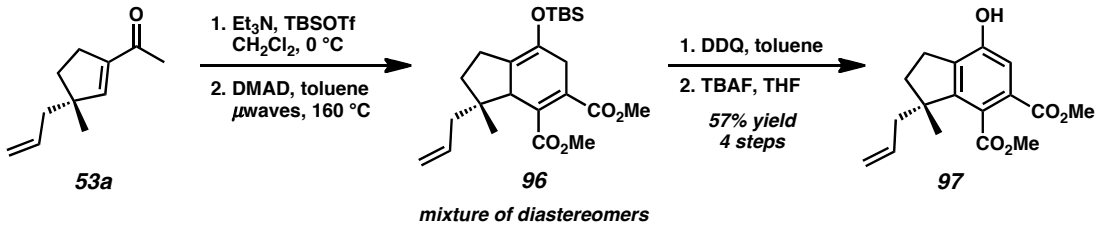


Cyclohexene 93. Acylcyclopentene **53f** (25.2 mg, 0.12 mmol, 1.00 equiv) was added to a 2.0–5.0 mL microwave vial with magnetic stir bar and sealed with a septum-fitted crimp cap. Chlorobenzene (5 mL) was added via syringe. The clear, colorless solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 250 °C, sensitivity: low). After 2 h of irradiation, the vial was uncapped and the solvent was removed under reduced pressure. The yellow residue was purified by flash column chromatography (SiO_2, 1.5 x 15 cm, 15:1 hexanes:Et_2O) to afford cyclohexene **93** as a yellow oil (22.5 mg, 0.104 mmol, 90% yield); R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of four diastereomers (2:2:1:1), see Figure A2.94.1; ^{13}C NMR (125 MHz, $CDCl_3$) mixture of four diastereomers, see Figure A2.94.3; IR (Neat Film NaCl) 3014, 2921, 2855, 1666, 1611, 1448, 1437, 1369, 1339, 1303, 1268, 1190, 1093, 1075, 1051, 1037, 1024, 935, 868, 798, 733, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{20}O$ $[M]^{+\bullet}$: 216.1514; found 216.1518; $[\alpha]_D^{25.0}$ –15.57 (*c* 1.01, $CHCl_3$, 88.0% ee).



Spirocycle 95. A 2-neck flask fitted with rubber septum and reflux condenser under N_2 was charged with Grubbs–Hoveyda 3rd generation catalyst (2.2 mg, 0.035 mmol, 6.1 mol %). Dry degassed benzene (4 mL, sparged with N_2 for 1 h immediately before use) was added to give a pale green solution. The flask was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Acylcyclopentene **53g** (14.2 mg, 0.063 mmol, 1.0 equiv) in dry, degassed benzene (4 mL) under N_2 was added to the catalyst solution using positive pressure cannulation. The flask was rinsed with benzene (2 mL) and washes were added into the catalyst solution. The reaction was immersed in a preheated 50 °C oil bath and stirred for 44 h. An additional portion of Grubbs–Hoveyda 3rd generation catalyst (4.4 mg, 0.070 mmol, 12.2 mol %) in degassed benzene (2 mL) was added into the reaction using positive pressure cannulation. After stirring for an additional 15 h, a third portion of Grubbs–Hoveyda 3rd generation catalyst (2.2 mg, 0.035 mmol, 6.1 mol %) in degassed benzene (2 mL) was added into the reaction using positive pressure cannulation. After 31 h, the reaction was treated with several drops of ethyl vinyl ether and allowed to cool to ambient temperature. The solution was diluted with Et_2O (15 mL) and filtered through a short silica gel plug (2 x 10 cm, Et_2O). The orange filtrate was purified by flash column chromatography (SiO_2, 2 x 25 cm, 1%→3%→5%→6.5% Et_2O in hexanes) to give volatile spirocycle **95** (7.3 mg, 0.0376 mmol, 59% yield); R_f = 0.49

(4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (app t, *J* = 1.7 Hz, 1H), 5.64 (app p, *J* = 2.2 Hz, 1H), 2.66 (ddd, *J* = 16.2, 4.5, 2.1 Hz, 1H), 2.62–2.53 (m, 3H), 2.51 (ddd, *J* = 16.2, 4.6, 2.4 Hz, 1H), 2.43 (ddd, *J* = 16.3, 4.6, 2.4 Hz, 1H), 2.31 (s, 3H), 2.09–1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 150.2, 144.2, 130.7, 125.2, 56.2, 49.7, 44.3, 39.4, 29.6, 26.8; IR (Neat Film NaCl) 2929, 2845, 1726, 1668, 1616, 1436, 1370, 1340, 1314, 1276, 1193, 1079, 1052, 990, 966, 936, 905, 866, 822, 804 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{13}OCl$ $[M]^{+\bullet}$: 196.0655; found 196.0655; $[\alpha]_D^{25.0}$ –19.80 (*c* 0.53, $CHCl_3$, 88.0% ee).



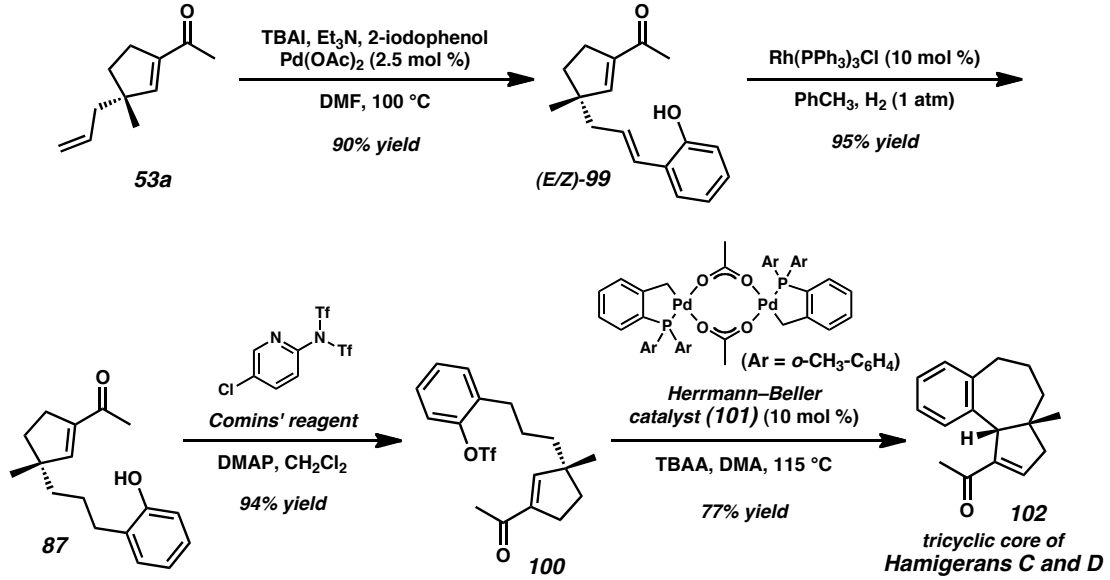
Phenol 97. A 15 mL flask with magnetic stir bar was charged with acylcyclopentene **53a** (50 mg, 0.274 mmol, 1.00 equiv) and anhydrous CH_2Cl_2 (3.0 mL). The flask was cooled to 0 °C and Et_3N (152.8 μL, 1.096 mmol, 4.00 equiv) was added, followed by dropwise addition of TBSOTf (125.8 μL, 0.548 mmol, 2.00 equiv). The reaction became a pale yellow solution. After 1 h of stirring at 0 °C, the reaction was quenched by the addition of sat. aqueous $NaHCO_3$ and slowly allowed to warm to ambient temperature. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a silica gel plug (2 x 3 cm, 5:1 H:Et_2O) and concentrated under reduced pressure to give crude silyl enol ether as a pale yellow oil. R_f = 0.79 (10:1 hexanes:EtOAc).

The silyl enol ether was added to a 2.0–5.0 mL microwave vial with magnetic stir bar and sealed with a septum-fitted crimp cap. Toluene (5 mL) was added, followed by dimethyl acetylenedicarboxylate (101 μL, 0.822 mmol, 3.00 equiv). The clear, colorless solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 160 °C, sensitivity: low). After 2.5 h of irradiation, the vial was uncapped and solvent was removed under reduced pressure. The yellow residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 15:1→10:1→4:1→2:1 hexanes:EtOAc) to afford siloxydiene **96** as a mixture of diastereomers. R_f = 0.31 (10:1 hexanes:EtOAc).

A 20 mL scintillation vial with magnetic stir bar was charged with siloxydiene **96** and toluene (3.0 mL). DDQ (63.5 mg, 0.280 mmol, 1.02 equiv) was added portionwise. Upon complete addition, the solution became a turbid red suspension. After 2 h, the reaction was diluted with CH_2Cl_2 and filtered through a Celite plug (2 x 3 cm, CH_2Cl_2). The clear yellow solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 20:1→15:1→10:1→4:1→2:1 hexanes:EtOAc) to afford the intermediate silyl aryl ether. R_f = 0.31 (10:1 hexanes:EtOAc).

A 20 mL scintillation vial with magnetic stir bar was charged with silyl aryl ether. The vial was evacuated, and backfilled with N_2. Anhydrous THF (3 mL) was added and a TBAF solution (300 μL, 1.0 M in THF) was added dropwise, giving a bright red solution. After 10 min, the reaction was quenched by the addition of sat. aqueous NH_4Cl (600 μL) and H_2O (600 μL). The mixture was stirred vigorously for 20 min and extracted with Et_2O (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography (SiO_2, 2 x 25 cm, 5:1→4:1 hexanes:EtOAc) to afford phenol **97** as a pale yellow oil (52.6 mg, 0.173 mmol, 57% yield over 4 steps); R_f = 0.11 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 5.89 (br s, *J* = 1.9 Hz, 1H), 5.66 (dddd, *J* = 17.3, 10.2, 7.9, 7.9 Hz, 1H), 5.09–4.91 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.47–2.26 (m, 2H), 2.24–2.08 (ddd, *J* = 12.0, 7.0, 7.0 Hz, 1H), 1.85–1.70 (ddd, *J* = 12.7, 7.6, 7.6 Hz, 1H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 166.7, 152.5, 150.0, 135.8, 135.3, 128.3, 124.0, 117.7, 115.4, 52.7, 52.5, 49.4, 44.1, 38.3, 26.1, 25.6; IR (Neat Film NaCl) 3401, 3075, 2953, 2871, 1723, 1639, 1588, 1435, 1418, 1376, 1330, 1311, 1258, 1192, 1175, 1142, 1047, 995, 964, 916, 884, 857, 794, 769, 738, 719 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_5$ $[M]^{+\bullet}$: 304.1311; found 304.1317; $[\alpha]_D^{25.0}$ –45.63 (*c* 0.91, $CHCl_3$, 88.0% ee).



Phenol 87. DMF (1.52 mL) was sparged with N_2 in a 25 mL Schlenk flask for 1 h. Et_3N (0.849 mL, 6.09 mmol, 5.0 equiv), TBAI (450 mg, 1.22 mmol, 1.0 equiv) and 2-

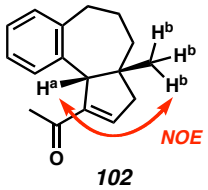
iodophenol (282.2 mg, 1.28 mmol, 1.05 equiv) were added, followed by $Pd(OAc)_2$ (6.84 mg, 0.030 mmol, 2.5 mol %). The flask was carefully evacuated/backfilled with N_2 (3 cycles, 1 min evacuation per cycle) followed by addition of acylcyclopentene **53a** (200 mg, 1.22 mmol, 1.0 equiv). The suspension was immersed in an oil bath at 100 °C. The reaction turned orange within 15 min of stirring. After 5 h of stirring, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (10 mL), and poured into aqueous HCl (10 mL, 1.0 M). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 40 g column, linear gradient, 5%→30% EtOAc in hexanes [25 min]) to afford styrenyl phenol **99** as a mixture of olefin isomers (283.0 mg, 1.10 mmol, 90% yield) as a colorless oil. R_f = 0.17 (4:1 hexanes:EtOAc).

$Rh(PPh_3)_3Cl$ (22.2 mg, 0.024 mmol, 0.10 equiv) was weighed out in a glove box and added to a long reaction tube with magnetic stir bar. Styrenyl phenol **99** (61.5 mg, 0.240 mmol, 1.0 equiv) was dissolved in toluene (4.8 mL) and added to the reaction tube using positive pressure cannulation. H_2 was bubbled through the suspension for 5 min and the reaction tube was fitted with a balloon containing H_2 (1 atm). The reaction was stirred for an additional 6 h at which point TLC analysis indicated complete conversion of the starting material. The resulting clear orange reaction mixture was adsorbed onto a 12 g Isco loading cartridge and purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 24 g column, linear

gradient, 5%→50% Et_2O in hexanes [40 min]) to afford phenol **87** (58.9 mg, 0.228 mmol, 95% yield) as a pale yellow oil; R_f = 0.18 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.04 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.46 (app t, *J* = 1.7 Hz, 1H), 4.82 (bs, 1H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.56–2.50 (m, 2H), 2.29 (s, 3H), 1.87–1.75 (m, 1H), 1.71–1.42 (m, 5H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 153.6, 152.8, 143.4, 130.4, 128.4, 127.3, 120.9, 115.3, 50.1, 40.8, 36.2, 30.8, 29.7, 26.8, 25.8, 25.5; IR (Neat Film NaCl) 3344, 3054, 3039, 2951, 2863, 1651, 1610, 1592, 1507, 1455, 1377, 1365, 1313, 1272, 1238, 1179, 1155, 1127, 1106, 1042, 907, 853, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1693; found 259.1691; $[\alpha]_D^{25.0}$ +28.73 (c 0.74, $CHCl_3$, 88.0% ee).

Triflate 100. To a solution of phenol **87** (104.2 mg, 0.40 mmol, 1.00 equiv) in CH_2Cl_2 (8.0 mL) in a 20 mL vial was added DMAP (97.8 mg, 0.80 mmol, 2.0 equiv) in one portion, followed by *N*,*N*-Bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (172.8 mg, 0.44 mmol, 1.1 equiv). After 15 min of stirring at ambient temperature, TLC revealed full conversion of phenol **87**. The reaction mixture was adsorbed onto a 12 g Isco loading cartridge and purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 40 g column, linear gradient, 5→20% EtOAc in hexanes [25 min]) to afford triflate **100** (146.2 mg, 0.374 mmol, 94% yield) as a clear, colorless oil; R_f = 0.44. (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2H), 7.28 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.24 (dm, *J* = 7.8 Hz, 1H), 6.44 (app t, *J* = 1.8 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.61–2.46 (m, 2H), 2.29 (s, 3H),

1.80 (ddd, J = 13.0, 8.7, 6.5 Hz, 1H), 1.66 (ddd, J = 11.8, 8.0, 5.2 Hz, 1H), 1.64–1.45 (m, 3H), 1.50 (ddd, J = 11.4, 7.5, 5.1 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 152.0, 148.1, 143.7, 135.1, 131.3, 128.5, 128.0, 121.5, 118.7 (q, J = 320 Hz, 1C), 50.0, 40.7, 36.1, 30.8, 29.8, 26.8, 25.8, 25.7; IR (Neat Film NaCl) 3032, 2958, 2868, 1671, 1617, 1486, 1454, 1420, 1365, 1303, 1251, 1217, 1140, 1100, 1073, 893, 814, 767 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{22}F_3O_4S$ $[M+H]^+$: 391.1188; found 391.1193; $[\alpha]_D^{25.0}$ +22.00 (c 1.31, $CHCl_3$, 88.0% ee).

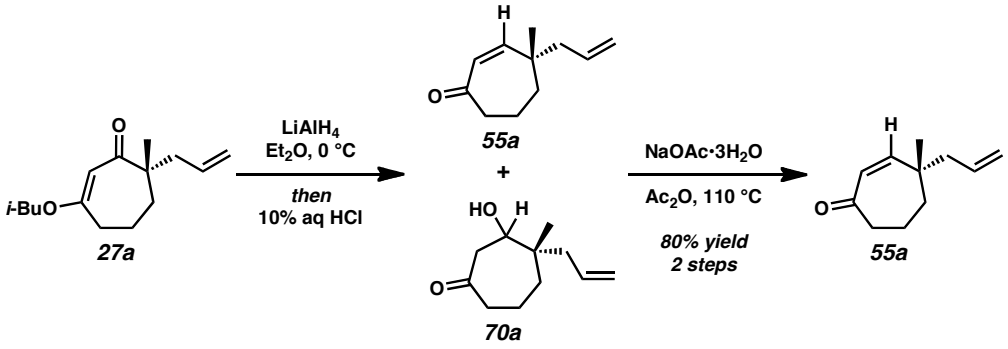


102

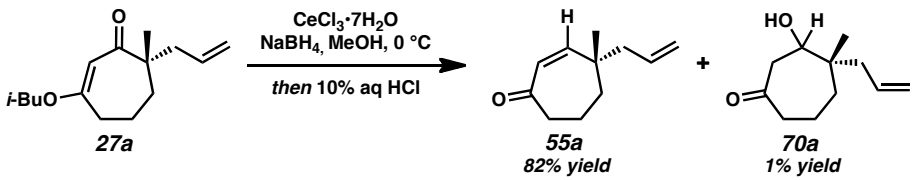
Acylcyclopentene 102. To a solution of triflate **100** (30.0 mg, 0.077 mmol, 1.0 equiv) in dry DMA (1.54 mL) in a 4 dram vial was added TBAA (57.9 mg, 0.19 mmol, 2.5 equiv, stored and weighed out in a glove box). The resulting clear, colorless solution was degassed by bubbling Ar though the solution for 1 h. Herrmann's catalyst[57] (7.2 mg, 7.7 μmol, 0.10 equiv) was placed in a reaction tube which was subsequently evacuated/backfilled with Ar (3 cycles, 1 min evacuation per cycle). The solution containing triflate **100** was added to the catalyst using positive pressure cannulation. The resulting pale green-yellow solution was immersed in an oil bath at ambient temperature and heated to 115 °C. After 2 h of stirring, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (10 mL), and poured into aqueous HCl (1.0 M, 5.0 mL). The phases were separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organics were washed with brine (5.0 mL), dried over $MgSO_4$, filtered,

and concentrated under reduced pressure. The crude product was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 2.5 g loading cartridge, 4 g column, multi-step gradient, hold 5% [10 min]→hold 10% [4 min]→hold 20% [3 min]→ hold 60% EtOAc in hexanes [3 min]) to afford acylcyclopentene **102** (14.3 mg, 0.0595 mmol, 77% yield, 62% yield over 4 steps) as a pale yellow solid. The relative stereochemistry was assigned based on strong NOE interaction between H^a and H^b; R_f = 0.46 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.06 (m, 3H), 6.95 (app t, *J* = 2.4 Hz, 1H), 6.63 (bd, *J* = 6.2 Hz, 1H), 3.86 (s, 1H), 2.92–2.84 (m, 1H), 2.66 (app dd, *J* = 13.5, 7.9 Hz, 1H), 2.41 (s, 3H), 2.32–2.18 (m, 2H) 1.84 (app ddt, *J* = 13.5, 7.7, 5.6 Hz, 1H), 1.58–1.43 (m, 1H), 1.30 (ddd, *J* = 14.0, 5.1, 2.3 Hz, 1H), 1.18 (s, 3H), 0.85 (app dt, *J* = 13.5, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 146.2, 144.6, 139.6, 139.2, 128.5, 126.7, 126.2, 125.0, 55.5, 48.4, 43.9, 34.1, 30.6, 26.9, 25.9, 21.4; IR (Neat Film NaCl) 3062, 3012, 2933, 2893, 2859, 1659, 1617, 1476, 1456, 1446, 1370, 1278, 1266, 1244, 1199, 1123, 997, 935, 794, 757, 752, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587; found 241.1591; $[\alpha]_D^{25.0}$ +3.88 (*c* 1.43, $CHCl_3$, 88.0% ee).

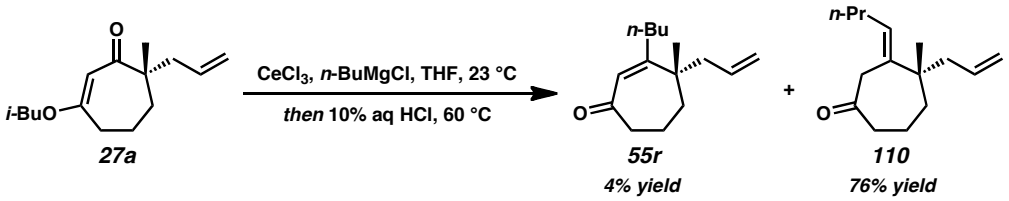
2.1.1.12 REVISED APPROACH TO THE REDUCTION/REARRANGEMENT AND ORGANOMETALLIC ADDITION/REARRANGEMENT OF 27a



Cycloheptenone 55a. A round-bottom flask charged with vinylogous ester **27a** (367.0 mg, 1.55 mmol, 1.00 equiv) and THF (5 mL, 0.3 M) was cooled in a 0 °C ice/water bath and $LiAlH_4$ (34.0 mg, 0.90 mmol, 0.58 equiv) was added. After 25 min of stirring, the reaction was quenched at 0 °C with the addition of aqueous HCl (10 mL, 10% w/w) and transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the resulting crude oil was added Ac_2O (3.8 mL) and $NaOAc{\cdot}3H_2O$ (1.28 g, 9.43 mmol, 6.08 equiv) and the mixture was lowered into a preheated oil bath (110 °C). After 15 h of heating, the reaction was allowed to cool to ambient temperature and quenched with K_2CO_3 (5.59 g, 40.5 mmol) and water (10 mL). After an addition 30 min of stirring, the solution was transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 16 cm, 20:1 hexanes:EtOAc) to afford cycloheptenone **55a** (203.9 mg, 1.24 mmol, 80% yield) as a pale yellow oil. (For characterization data, see p. 319).

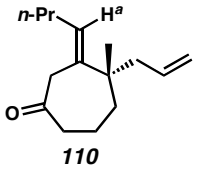


Cycloheptenone 55a and β-Hydroxyketone 70a. A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester **27a** (186.8 mg, 0.79 mmol, 1.00 equiv) and anhydrous MeOH (14 mL). The solution was cooled to 0 °C (water/ice bath). $CeCl_3 \cdot 7H_2O$ (294.5 mg, 0.79 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Portionwise addition of $NaBH_4$ (89.7 mg, 2.37 mmol, 3.00 equiv) at 0 °C led to the evolution of gas and a turbid solution that became clearer after several minutes. TLC analysis indicated that no starting material remained after 2 min. Consequently, the reaction was quenched by dropwise addition of aqueous HCl (2 mL, 10% w/w) at 0 °C. After an additional 10 min of stirring, the reaction was diluted with CH_2Cl_2 (60 mL) and H_2O (2 mL). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 x 5 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (2 x 5 mL) and brine (2 x 5 mL), dried over Na_2SO_4, filtered, and evaporated to give a pale yellow oil. The crude mixture was purified using flash chromatography (SiO_2, 2 x 25 cm, 20:1→15:1→3:1 hexanes:EtOAc) to afford volatile enone **55a** (106.9 mg, 0.645 mmol, 82% yield) as a pale yellow oil and β-hydroxyketone **70a** as a mixture of diastereomers (1.4 mg, 0.0077 mmol, 1% yield, 3.5:1 dr) as a colorless oil. (For characterization data of **55a** and **70a**, see p. 319–320).



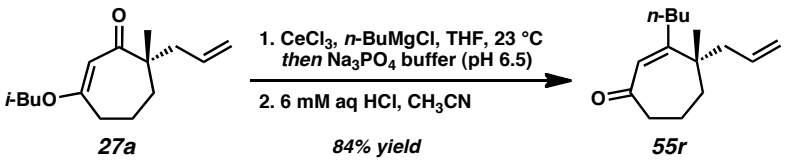
Cycloheptenone 55r and Cycloheptenone Isomer 110. An oven dried 15 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (130.4 mg, 0.53 mmol, 2.49 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (5.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium chloride (340 μL, 1.89 M in THF, 0.64 mmol, 3.03 equiv) was added and the mixture turned pale yellow. After 45 min of stirring, neat vinylogous ester **27a** (50.2 mg, 0.21 mmol, 1.00 equiv) was added to the flask. The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with aqueous HCl (1 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 17 h, the yellow suspension was removed from the bath, cooled to ambient temperature, and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 1 x 27 cm, 100% hexanes→2%→10% EtOAc in hexanes) to afford moderately contaminated cycloheptenone **55r** and pure alkene isomer **110** (35.4 mg, 0.16 mmol, 76% yield) as an orange oil. Additional purification by flash chromatography (SiO_2, 1 x 27 cm, 100% hexanes→2%→5% EtOAc in hexanes)

furnished cycloheptenone **55r** (1.7 mg at 95% purity, 0.0076 mmol, 4% yield) as a yellow oil. (For characterization data of **55r**, see p. 342).



110

Cycloheptenone Isomer 110. R_f = 0.76 (30% EtOAc in hexanes); The relative alkene stereochemistry was assigned based on NOE interactions of H^a proton; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dddd, J = 16.9, 10.6, 7.9, 6.6 Hz, 1H), 5.43 (t, J = 7.1 Hz, 1H), 5.03–4.97 (m, 2H), 3.20 (d, J = 14.6 Hz, 1H), 3.13 (d, J = 14.6 Hz, 1H), 2.47–2.38 (m, 1H), 2.36–2.26 (m, 2H), 2.15–1.95 (m, 3H), 1.82–1.69 (m, 2H), 1.66–1.58 (m, 1H), 1.58–1.50 (m, 1H), 1.40–1.32 (m, 2H), 1.07 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 136.2, 135.1, 130.0, 117.2, 44.8, 43.3, 43.3, 41.8, 41.1, 30.2, 25.0, 22.9, 19.6, 13.9; IR (Neat Film NaCl) 3074, 3042, 2959, 2929, 2871, 1706, 1638, 1457, 1436, 1378, 1351, 1302, 1262, 1231, 1163, 1098, 1069, 996, 953, 912, 805, 776, 729 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 220.1827; found 220.1780; $[\alpha]_D^{25.0}$ –10.92 (*c* 0.76, $CHCl_3$, 88.0% ee).



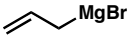
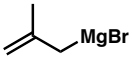
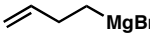
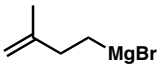
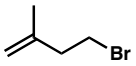
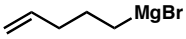
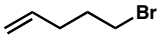
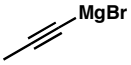
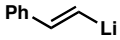
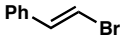
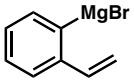
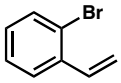
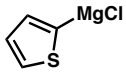
27a ***84% yield*** ***55r***

Cycloheptenone 55r. A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride

(260.8 mg, 1.06 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (8.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium bromide (680 μL, 1.87 M in THF, 1.27 mmol, 3.00 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester **27a** (100.0 mg, 0.42 mmol, 1.00 equiv) was added neat from a Hamilton syringe and the needle was rinsed with a small portion of THF (2 mL; total THF added = 10.5 mL, 0.04 M). The color of the slurry initially transitioned to yellow with the vinylogous ester addition before turning back to grey. TLC analysis indicated that no starting material remained after 15 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (8 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (1.0 mL), and 6 mM aqueous HCl (1.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55r** (82.4 mg, 0.35 mmol, 84% yield) as a pale yellow oil. (For characterization data of **55r**, see p. 342).

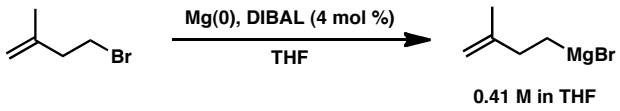
2.1.1.13 GRIGNARD AND ORGANOLITHIUM REAGENTS

Table 2.7. Sources of Grignard and organolithium reagents.[a]

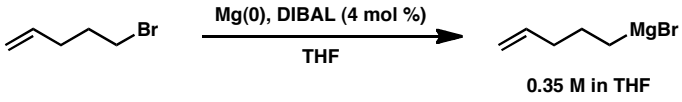
entry	reagent	molarity (M)	obtained from
1		0.86 M in Et_2O	Sigma-Aldrich
2		0.39 M in THF	Sigma-Aldrich
3		0.44 M in THF	Sigma-Aldrich
4		0.41 M in THF	
5		0.35 M in THF	
6		0.25 M in THF	Sigma-Aldrich
7		n/a[b]	
8		0.40 M in THF	
9		n/a[b]	
10		0.44 M in THF	

[a] *Titrated using method of Love (see ref. 49).* [b] *Not titrated.*

Grignard and Organolithium Reagents. Reagents were purchased from Sigma-Aldrich or prepared according to procedures listed below. Reagents were titrated according to the method of Love.[49]

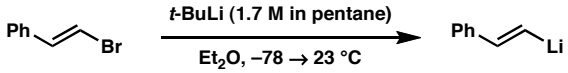


(3-Methylbut-3-enyl)magnesium bromide ***(Table 2.7, entry 4).*** A 250 mL Schlenk bomb (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (2.04 g, 83.79 mmol, 2.50 equiv) was added. After three argon backfilling cycles, the flask was charged with THF (50 mL, 0.7 M) and neat DIBAL[61] (150 μL, 1.29 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min, and 4-bromo-2-methylbut-1-ene[62] (5.00 g, 33.57 mmol, 1.00 equiv) was added via syringe with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction color became amber over time. After 30 min, an aliquot was removed and titrated following the procedure of Love (0.41 M in THF).[49] See p. 392 for use of this reagent.

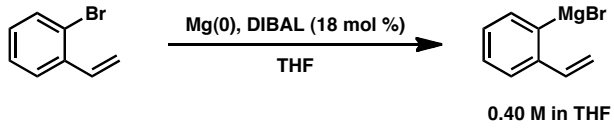


Pent-4-enylmagnesium bromide ***(Table 2.7, entry 5).*** A 250 mL Schlenk bomb (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (614.4 mg, 25.27 mmol, 2.53 equiv) was added. After three argon backfilling cycles, the flask was charged

with THF (20 mL, 0.5 M) and neat DIBAL[59] (50 μL, 0.43 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min and 5-bromopent-1-ene (1.18 mL, 9.98 mmol, 1.00 equiv) was added via a syringe, with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction color became amber over time. After 30 min, an aliquot was removed and titrated following the procedure of Love (0.35 M in THF).[49] See p. 381 and p. 393 for use of this reagent.

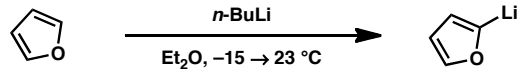


(*E*)-Styryllithium ***(Table 2.7, entry 7).*** See p. 394 for the synthesis and use of this reagent.

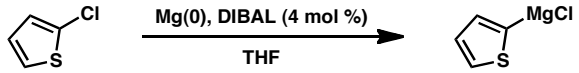


(2-Vinylphenyl)magnesium bromide ***(Table 2.7, entry 8).*** A 250 mL Schlenk round-bottom flask (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (491.3 mg, 20.21 mmol, 2.53 equiv) was added. After three argon backfilling cycles, the flask was charged with THF (16 mL, 0.5 M) and neat DIBAL[59] (170 μL, 1.46 mmol, 18 mol %) and stirring was initiated. The stirring was stopped after 10 min and *o*-

bromostyrene (1.00 mL, 7.98 mmol, 1.00 equiv) was added with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction became amber over time. After 2 h, a small portion of the reaction was removed and titrated following the procedure of Love.[49] See p. 396 for use of this reagent.



Furan-2-yllithium ***(Table 2.7, entry 9).*** Prepared following a procedure similar to Sauers and Hagedorn.[63] See p. 398 for the synthesis and use of this reagent.



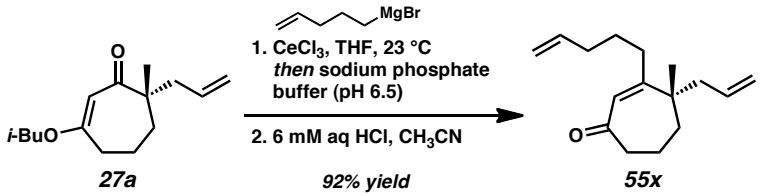
0.44 M in THF

Thiophen-2-ylmagnesium chloride ***(Table 2.7, entry 10).*** A two-neck 50 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum on one neck and a water condenser on the other neck, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (635.0 mg, 26.12 mmol, 2.60 equiv) was added. After two argon backfilling cycles, the flask was charged with THF (20 mL) and neat DIBAL[59] (50 μL, 0.43 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min and 2-chlorothiophene (930 μL, 10.04 mmol, 1.00 equiv) was added via a syringe, with the needle in the solution directly above the magnesium. The mixture

was heated to reflux. A small piece of I_2 (size of a spatula tip) dissolved in THF (1 mL) was cannula-transferred into the mixture after 12 h and 13.5 h. The flask was allowed to cool to room temperature (23 °C). After 15 h, an aliquot was removed and titrated following the procedure of Love (0.44 M in THF).[49] See p. 382 and p. 400 for use this reagent.

2.1.1.14 CARBONYL TRANSPOSITION TO γ-QUATERNARY CYCLOHEPTENONES

Representative procedures for General Methods F–H are described below.

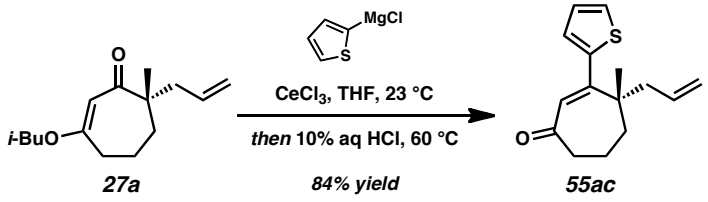


General Method F:

Organometallic Addition / Na_3PO_4 Buffer Quench / Dilute HCl Workup

Cycloheptenone 55x. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of pent-4-enylmagnesium bromide (8.6 mL, 0.35 M in THF, 3.01 mmol, 3.01 equiv) was added and the mixture turned grey. After 30 min of stirring,

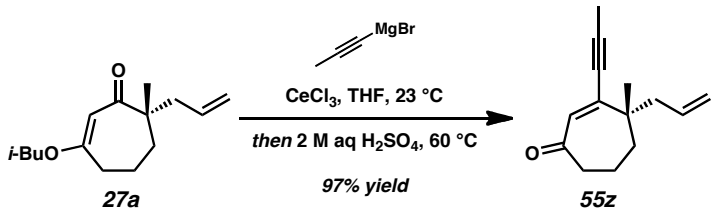
vinylogous ester **27a** (236.3 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and aqueous HCl (2.0 mL, 6 mM) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→1%→2%→5% EtOAc in hexanes) to afford cycloheptenone **55x** (214.2 mg, 0.92 mmol, 92% yield) as a clear colorless oil.



General Method G: Organometallic Addition / Aq HCl Quench

Cycloheptenone 55ab. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box,

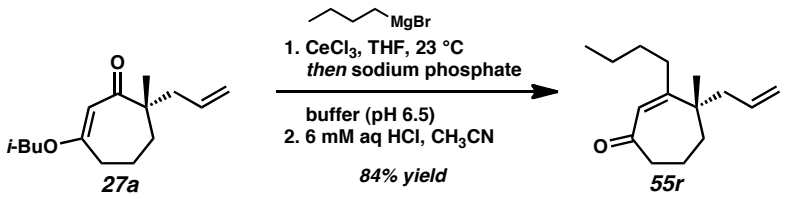
and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of thiophen-2-ylmagnesium chloride (6.8 mL, 0.44 M in THF, 2.99 mmol, 2.99 equiv) was added and the mixture turned dark grey. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 25 min. After an additional 5 min of stirring, the reaction was quenched with aqueous HCl (5 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 20 h, additional aqueous HCl (5 mL, 10% w/w) was added. After 26 h, the yellow solution was removed from the bath, cooled to ambient temperature, treated with sat. aqueous $NaHCO_3$ solution (25 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (150 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55ac** (206.1 mg, 0.84 mmol, 84% yield) as a yellow/orange oil.



General Method H: Organometallic Addition / Aq H_2SO_4 Quench

Cycloheptenone 55z. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of prop-1-ynylmagnesium bromide (12 mL, 0.25 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned yellow. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with 2 M H_2SO_4 (5 mL) and lowered into a preheated oil bath (60 °C). A white precipitate formed within several minutes. After 12 h, the yellow suspension was removed from the bath, cooled to ambient temperature, treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (175 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was

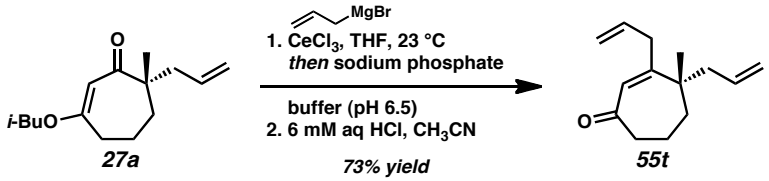
purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55z** (195.4 mg, 0.97 mmol, 97% yield) as a yellow oil.



Cycloheptenone 55r ***(Table 2.5, entry 1).*** Prepared using General Method F. A 50 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (260.8 mg, 1.06 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (8.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium bromide (680 μL, 1.87 M in THF, 1.27 mmol, 3.00 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester **27a** (100.0 mg, 0.42 mmol, 1.00 equiv) was added neat from a Hamilton syringe and the needle was rinsed with a small portion of THF (2 mL; total THF added = 10.5 mL, 0.04 M). The color of the slurry initially transitioned to yellow with the vinylogous ester addition before turning back to grey.

TLC analysis indicated that no starting material remained after 15 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (8

mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (1.0 mL), and 6 mM aqueous HCl (1.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55r** (82.4 mg, 0.35 mmol, 84% yield) as a pale yellow oil. (For characterization data, see p. 342).

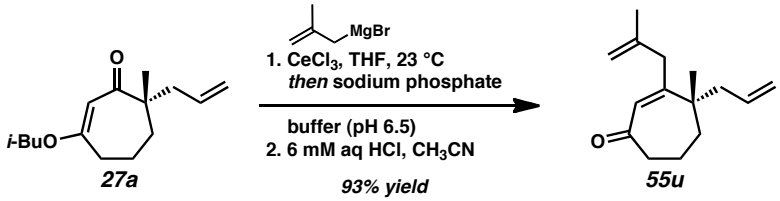


Cycloheptenone 55t ***(Table 2.5, entry 2).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.3 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove

box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of allylmagnesium bromide (3.49 mL, 0.86 M in Et_2O, 3.00 mmol, 3.00 equiv) was added and the mixture turned initially orange, then red over time. After 30 min of stirring, vinylogous ester **27a** (236.6 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The mixture faded back to orange with the addition.

TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (250 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55t** (148.6 mg, 0.73 mmol, 73% yield) as a pale yellow oil; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.75 (dddd, *J* = 16.9, 10.1, 6.8, 6.8 Hz, 1H), 5.64 (dddd, *J* = 17.0, 10.3, 7.8, 6.8 Hz, 1H), 5.14–5.00 (m,

4H), 2.96–2.84 (m, 2H), 2.62–2.54 (m, 2H), 2.38 (dddd, J = 14.2, 6.8, 1.3, 1.3 Hz, 1H), 2.10 (dddd, J = 14.2, 7.8, 1.1, 1.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.67–1.57 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 160.3, 136.0, 134.0, 130.0, 118.3, 117.9, 45.5, 45.2, 44.4, 38.8, 38.5, 25.7, 17.6; IR (Neat Film NaCl) 3077, 2976, 2939, 2872, 1654, 1612, 1458, 1412, 1380. 1342, 1290, 1250, 1217, 1177, 1106, 996, 916 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1587; found 205.1587; $[\alpha]_D^{25.0}$ –34.64 (*c* 1.55, $CHCl_3$, 88% ee).

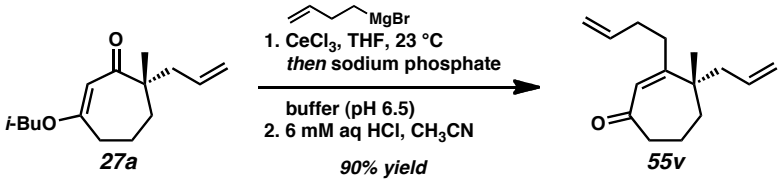


Cycloheptenone 55u ***(Table 2.5, entry 3).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (2-methylallyl)magnesium bromide (7.7 mL, 0.39 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned initially yellow and eventually orange with time. After 30 min of stirring, vinylogous ester **27a** (236.2 mg,

1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

TLC analysis indicated that no starting material remained after 5 min. After an additional 15 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55u** (202.9 mg, 0.93 mmol, 93% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.65 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.09–5.01 (m, 2H), 4.94–4.91 (m, 1H), 4.78 (dd, *J* = 1.9, 0.9 Hz, 1H), 2.85 (q, *J* = 16.2 Hz, 2H), 2.63–2.55 (m, 2H), 2.37 (dddd, *J* = 14.1, 6.8, 1.3, 1.3 Hz, 1H), 2.10 (dddd, *J* = 14.2, 7.8, 1.1, 1.1 Hz, 1H), 1.85–1.75 (m, 3H), 1.68 (s, 3H), 1.66–1.59 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 159.1, 142.8, 134.0, 129.5, 118.3, 115.2, 45.4, 45.0, 44.4, 42.7, 38.8, 25.6, 22.2, 17.6; IR (Neat Film NaCl) 3075, 2970, 2939, 2872, 1661, 1652, 1612, 1455, 1376, 1342, 1309, 1249, 1218,

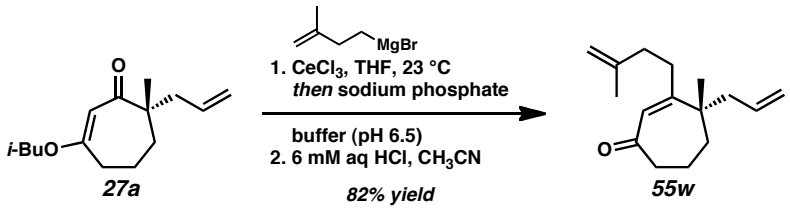
996, 914, 893 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1740; $[\alpha]_D^{25.0}$ –35.09 (*c* 0.95, $CHCl_3$, 88% ee).



Cycloheptenone 55v ***(Table 2.5, entry 4).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting white mixture was stirred, a solution of but-3-enylmagnesium bromide (6.82 mL, 0.44 M in THF, 3.00 mmol, 3.00 equiv) was added, generating a thick grey slurry. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

After 20 min, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL)

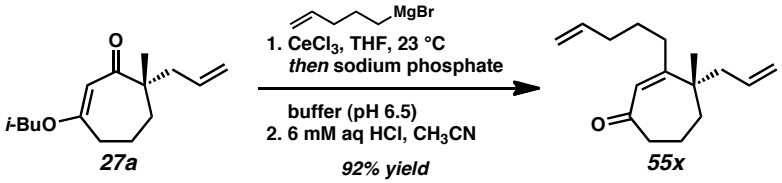
were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (80 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5%→10% EtOAc in hexanes) to afford cycloheptenone **55v** (196.6 mg, 0.90 mmol, 90% yield) as a yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.86–5.77 (m, 1H), 5.63 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.08–4.96 (m, 4H), 2.59–2.54 (m, 2H), 2.36 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.28–2.17 (m, 4H), 2.08 (dddd, *J* = 14.1, 7.9, 2.1, 1.0 Hz, 1H), 1.83–1.73 (m, 3H), 1.65–1.57 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 161.6, 137.7, 134.0, 128.9, 118.2, 115.4, 45.7, 45.2, 44.3, 38.7, 34.0, 33.4, 25.7, 17.6; IR (Neat Film NaCl) 3076, 2975, 2938, 2872, 1652, 1611, 1465, 1452, 1415, 1379, 1342, 1263, 1218, 1177, 1109, 1069, 996, 914, 877, 841, 764, 714 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1742; $[\alpha]_D^{25.0}$ –34.11 (*c* 1.21, $CHCl_3$, 88% ee).



Cycloheptenone 55w ***(Table 2.5, entry 5).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (3-methylbut-3-enyl)magnesium bromide (7.3 mL, 0.41 M in THF, 2.99 mmol, 2.99 equiv) was added and the mixture turned yellow. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

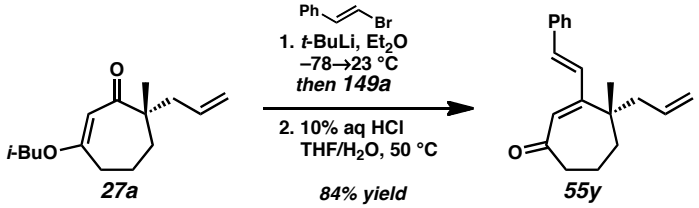
TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under

reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55w** (191.1 mg, 0.82 mmol, 82% yield) as a clear colorless oil; R_f = 0.69 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.64 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.09–4.99 (m, 2H), 4.77–4.73 (m, 1H), 4.72–4.69 (m, 1H), 2.59–2.56 (m, 2H), 2.38 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.31–2.14 (m, 4H), 2.10 (dddd, *J* = 14.1, 7.8, 1.1, 1.1 Hz, 1H), 1.83–1.75 (m, 3H), 1.75–1.74 (m, 3H), 1.66–1.57 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 162.1, 145.1, 134.0, 129.0, 118.3, 110.6, 45.8, 45.3, 44.3, 38.8, 38.3, 32.5, 25.7, 22.7, 17.6; IR (Neat Film NaCl) 3075, 2968, 2938, 2873, 1652, 1611, 1455, 1415, 1377, 1342, 1262, 1218, 1181, 1109, 1069, 996, 915, 887 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900; found 233.1896; $[\alpha]_D^{25.0}$ –32.57 (*c* 1.32, $CHCl_3$, 88% ee).



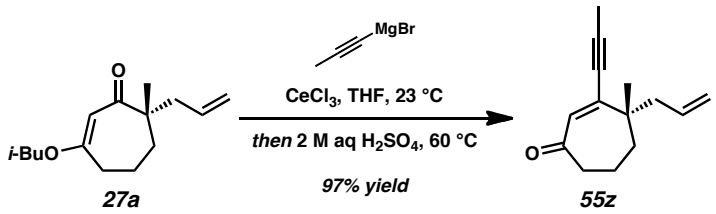
Cycloheptenone 55x ***(Table 2.5, entry 6).*** Prepared using General Method F. See procedure described above. R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.79 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.67–5.57 (m, 1H),

5.07–4.96 (m, 4H), 2.60–2.53 (m, 2H), 2.35 (dddd, J = 14.1, 6.7, 2.5, 1.2 Hz, 1H), 2.20–2.04 (m, 5H), 1.83–1.73 (m, 3H), 1.66–1.53 (m, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 162.6, 138.2, 134.1, 128.8, 118.2, 115.3, 45.7, 45.2, 44.3, 38.7, 33.8, 33.5, 29.3, 25.7, 17.6; IR (Neat Film NaCl) 3076, 2975, 2937, 2870, 1652, 1611, 1456, 1415, 1380, 1343, 1257, 1218, 1179, 1110, 1071, 994, 913 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900; found 233.1900; $[\alpha]_D^{25.0}$ –34.96 (*c* 1.46, $CHCl_3$, 88% ee).

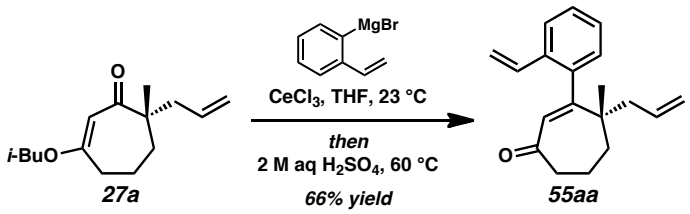


Cycloheptenone 55y ***(Table 2.5, entry 7).*** Prepared using General Method G. A flame-dried round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was connected to a Schlenk manifold. The flask was charged with (*E*)-β-bromostyrene (1.5 mL, 11.69 mmol, 1.98 equiv) and Et_2O (13 mL) and lowered into a dry ice/acetone bath (–78 °C). After dropwise addition of *t*-butyllithium (13.5 mL, 1.7 M in pentane, 22.95 mmol, 3.88 equiv), the solution was stirred for 2 h (at –78 °C), warmed to room temperature (30 min stir at 23 °C), and placed back into the dry ice/acetone bath. Vinylogous ester **27a** (1.40 g, 5.92 mmol, 1.00 equiv) was transferred to the round-bottom flask by two Et_2O rinses (2 x 3 mL, total Et_2O added = 19 mL, 0.3 M). The flask was stirred at –78 °C for 25 min before being transferred to an ice/water bath (0 °C).

TLC analysis indicated that no starting material remained after 2 h. Consequently, the reaction was quenched with 10% w/w aqueous HCl (10 mL). After 20 min of stirring, the mixture was transferred to a separatory funnel where the aqueous phase was extracted three times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A round-bottom flask was charged with the crude oil, THF (20 mL), and 10% w/w aqueous HCl (0.5 mL) and lowered into a preheated oil bath (50 °C). After 2 h, the reaction allowed to cool to room temperature, concentrated under reduced pressure, diluted with water (10 mL) and Et_2O (20 mL), and transferred to a separatory funnel where the aqueous layer was extracted twice with Et_2O (2 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 23 cm, 20:1→ 15:1→10:1 hexanes:EtOAc) to afford cycloheptenone **55y** (1.33 g, 4.99 mmol, 84% yield) as a yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 6.90 (s, 2H), 6.30 (s, 1H), 5.67 (dddd, *J* = 16.8, 10.3, 8.1, 6.5 Hz, 1H), 5.09–5.02 (m, 2H), 2.71–2.57 (m, 2H), 2.46 (dddd, *J* = 14.1, 6.5, 1.3, 1.3 Hz, 1H), 2.14 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.92–1.79 (m, 3H), 1.72–1.64 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 158.5, 136.7, 133.9, 133.3, 129.2, 128.9, 128.5, 127.1, 127.1, 118.4, 46.2, 44.5, 44.4, 38.7, 26.8, 17.6; IR (Neat Film NaCl) 3075, 3059, 3002, 2966, 2936, 2869, 1640, 1581, 1573, 1495, 1449, 1414, 1379. 1343, 1303, 12.77, 1250, 1217, 1178, 1109, 1082, 1028, 996, 963, 916, 839, 799, 752, 718 cm^{-1}; HRMS (MM: ESI-APCI+) *m*/*z* calc'd for $C_{19}H_{23}O$ $[M+H]^+$: 267.1743; found 267.1755; $[\alpha]_D^{25.0}$ –44.99 (*c* 0.81, $CHCl_3$, 88% ee).



Cycloheptenone 55z ***(Table 2.5, entry 8).*** Prepared using General Method H. See procedure described above. R_f = 0.65 (30% EtoAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.70 (dddd, *J* = 16.8, 10.5, 8.2, 6.6 Hz, 1H), 5.10–5.01 (m, 2H), 2.65–2.49 (m, 3H), 2.16 (dddd, *J* = 13.8, 8.2, 1.0, 1.0 Hz, 1H), 2.01 (s, 3H), 1.83–1.75 (m, 3H), 1.66–1.59 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 145.6, 135.0, 134.3, 118.3, 92.9, 80.7, 46.5, 45.4, 44.6, 37.3, 27.0, 17.6, 4.7; IR (Neat Film NaCl) 3076, 2969, 2937, 2219, 1652, 1580, 1455, 1415, 1377, 1346, 1255, 1225, 1184, 1110, 998, 916, 893, 866, 813, 784, 716 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430; found 203.1428; $[\alpha]_D^{25.0}$ –49.25 (*c* 1.21, $CHCl_3$, 88% ee).

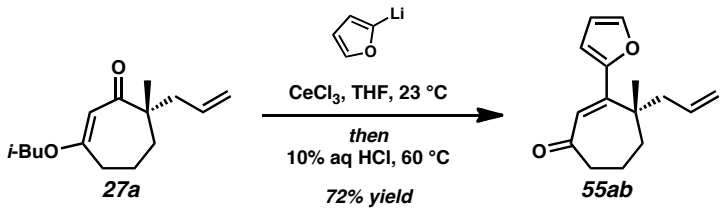


Cycloheptenone 55aa ***(Table 2.5, entry 9).*** Prepared using General Method H. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (4 cycles, 1 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride

(616.4 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (2-vinylphenyl)magnesium bromide (7.5 mL, 0.40 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned yellow and green over time. After 30 min of stirring, vinylogous ester **27a** (236.3 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The reaction color returned to yellow with addition of vinylogous ester **27a**.

TLC analysis indicated that no starting material remained after 40 min. After an additional 30 min of stirring, the reaction was quenched with 2 M H_2SO_4 (5 mL) and lowered into a preheated oil bath (60 °C). A grey precipitate formed within several minutes. After 26 h, the yellow suspension was removed from the bath, cooled to room temperature (23 °C), treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (175 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified first by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) and then by flash chromatography using a Teledyne Isco CombiFlash R*f* system (SiO_2, 12 g loading cartridge, 40 g column, multi-step gradient, hold 0% [2 min]→ramp to 85% [17 min]→hold 85% CH_2Cl_2 in hexanes [2.5 min]→ramp to 100% [3 min]→hold 100% CH_2Cl_2 [5 min]) to afford cycloheptenone **55aa** (176.7 mg, 0.66 mmol, 66% yield) as a pale yellow oil; R_f = 0.74 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$)

and ^{13}C NMR (125 MHz, $CDCl_3$) mixture of two atropisomers isomers (1.9 : 1 ratio), see Figure A1.307 for ^{1}H NMR (in $CDCl_3$) and Figure A1.308 for variable temperature ^{1}H NMR data (in DMSO-d_6 at 25, 50, 75, and 100 °C); IR (Neat Film NaCl) 3060, 3007, 2973, 2936, 2936, 1669, 1626, 1604, 1594, 1476, 1464, 1443, 1413, 1379, 1356, 1338, 1307, 1281, 1251, 1214, 1177, 1136, 1109, 1095, 1057, 1020, 996, 915, 864, 818, 769, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{23}O$ $[M+H]^+$: 267.1743; found 267.1751.



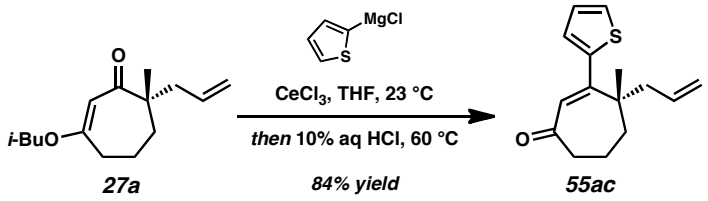
Cycloheptenone 55ab ***(Table 2.5, entry 10).*** Prepared using General Method G. A 100 and a 25 mL round-bottom flask each equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold were flame-dried three times, backfilling with argon after each drying cycle. The hot 100 mL flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold.

Once cool, the 25 mL flask was charged with furan (230 μL, 3.16 mmol, 1.05 equiv) and Et_2O (3 mL, 1 M) and lowered into an ethylene glycol/dry ice bath (–15 °C). To the cooled solution was added *n*-BuLi (1.42 mL, 2.12 M in hexanes, 3.01 mmol, 1.00

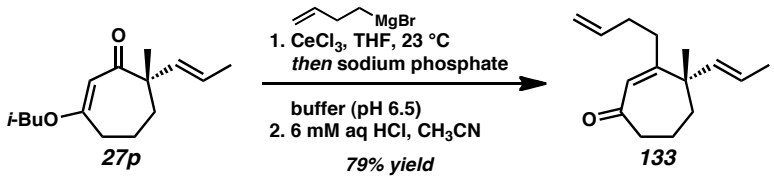
equiv) dropwise and the flask was warmed to room temperature (23 °C). The reaction became cloudy and white with time. After 1 h, a portion of THF (13 mL) was added to the 100 mL flask before the contents of the 25 mL flask were cannula-transferred to the 100 mL flask. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the 100 mL flask from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

After 35 min, the reaction was quenched with 10% w/w aqueous HCl (5 mL) and lowered into a preheated oil bath (60 °C). After 17 h, the solution was removed from the bath, cooled to room temperature (23 °C), treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (250 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55ab** (164.7 mg, 0.72 mmol, 72% yield) as a yellow oil; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.56 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.43 (s, 1H), 6.41 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.65 (dddd, *J* = 16.9, 10.2, 8.1, 6.6 Hz, 1H), 5.01 (dddd, *J* = 10.2, 2.0, 0.9, 0.9 Hz, 1H), 4.97 (dddd, *J* = 16.9, 2.3, 1.4, 1.4 Hz, 1H), 2.71–2.60 (m, 3H), 2.24 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.97–1.81 (m, 3H), 1.72–1.64 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 155.3, 149.2, 142.9, 134.3, 129.3, 118.1, 111.4, 111.2, 45.9, 44.7, 44.3, 39.8, 26.3, 17.4; IR (Neat Film NaCl) 3118, 3075, 2941, 2871, 1661, 1652, 1645, 1581, 1557, 1455, 1415, 1380, 1341, 1258, 1215, 1173, 1152, 1106, 1080, 1029, 997, 956, 917, 898, 886, 858, 812, 742 cm^{-1};

HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1374; $[\alpha]_D^{25.0}$ –26.90 (*c* 1.18, $CHCl_3$, 88% ee).



Cycloheptenone 55ac ***(Table 2.5, entry 11).*** Prepared using General Method G. See procedure described above. R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.00–6.95 (m, 2H), 6.17 (s, 1H), 5.69 (dddd, *J* = 16.7, 10.2, 8.1, 6.4 Hz, 1H), 5.06 (dddd, *J* = 10.2, 2.0, 1.0, 1.0 Hz, 1H), 5.01 (ddd, *J* = 16.9, 3.4, 1.5 Hz, 1H), 2.74–2.59 (m, 2H), 2.50 (dddd, *J* = 14.1, 6.4, 1.4, 1.4 Hz, 1H), 2.12 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.96–1.84 (m, 3H), 1.77–1.68 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 154.6, 143.8, 134.0, 133.7, 127.0, 126.7, 125.5, 118.5, 45.6, 45.1, 44.2, 38.8, 26.4, 17.7; IR (Neat Film NaCl) 3103, 3075, 2964, 2938, 2871, 1671, 1655, 1590, 1519, 1454, 1438, 1415, 1378, 1341, 1251, 1234, 1218, 1178, 1134, 1107, 1077, 1045, 996, 917, 849, 836, 761, 708 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{19}OS$ $[M+H]^+$: 247.1151; found 247.1152; $[\alpha]_D^{25.0}$ –3.65 (*c* 1.31, $CHCl_3$, 88% ee).

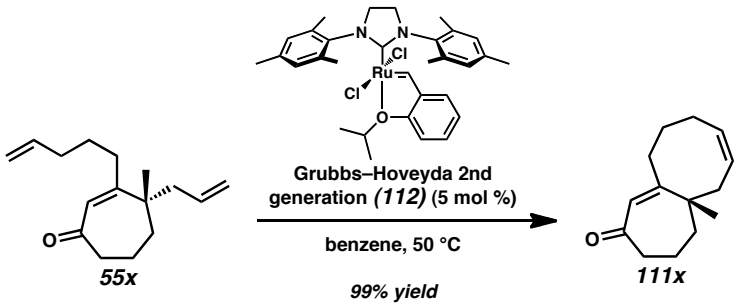


Cycloheptenone 133. Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (4 cycles, 1 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (591.6 mg, 2.40 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (12 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of but-3-enylmagnesium bromide (6.55 mL, 0.44 M in THF, 2.88 mmol, 3.00 equiv) was added and the mixture turned pale yellow. After 40 min of stirring, vinylogous ester **27p** (226.9 mg, 0.96 mmol, 1.00 equiv) was cannula-transferred to the slurry from a 20 mL scintillation vial using several THF rinses (3 x 4 mL; total THF added = 24 mL, 0.04 M).

TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A

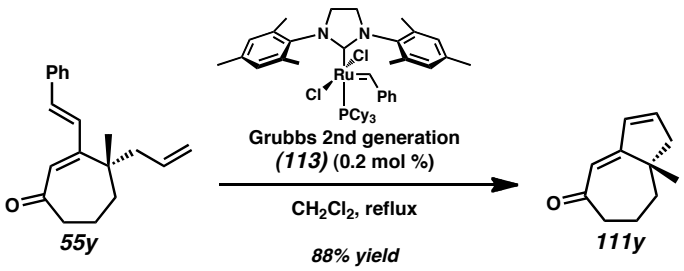
stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **133** (165.0 mg, 0.76 mmol, 79% yield) as a pale yellow oil; R_f = 0.74 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.83–5.74 (m, 1H), 5.43–5.32 (m, 2H), 5.02 (dm, *J* = 17.2 Hz, 1H), 4.97 (dm, *J* = 10.2 Hz, 1H), 2.66–2.50 (m, 2H), 2.27–2.12 (m, 4H), 1.84–1.71 (m, 4H), 1.69 (dd, *J* = 4.8, 0.7 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 161.7, 137.8, 137.2, 129.3, 124.4, 115.2, 48.6, 44.1, 41.3, 34.8, 34.1, 26.0, 18.2, 18.0; IR (Neat Film NaCl) 3077, 2962, 2937, 2874, 2856, 1650, 1614, 1451, 1414, 1378, 1342, 1273, 1251, 1224, 1198, 1126, 1069, 974, 911 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1741; $[\alpha]_D^{20.0}$ +123.43 (*c* 1.10, $CHCl_3$, 88% ee).

2.1.1.15 PREPARATION OF POLYCYCLIC CYCLOHEPTENONE DERIVATIVES BY RING-CLOSING METATHESIS



General Method I: Ring-Closing Metathesis

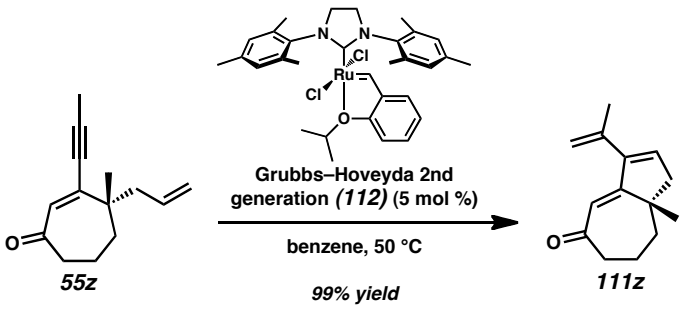
Enone 111x. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55x** (50.0 mg, 0.22 mmol, 1.00 equiv) and backfilled with argon twice. Benzene (1 h argon sparge before use, 43 mL, 0.005 M) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (6.7 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C). The reaction was removed from the oil bath after 30 min, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified twice by flash chromatography (SiO_2, both columns 2 x 28 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111x** (43.5 mg, 0.21 mmol, 99% yield) as a yellow oil.



Enone 111y ***(Table 2.6, entry 1).*** A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55y** (452.8 mg, 1.70 mmol, 1.00 equiv) and dichloromethane (60 mL, 0.03 M) and the resulting solution was sparged with Ar. After 30 min of degassing, Grubbs 2nd generation catalyst (3.4 mg, 0.0040 mmol, 0.2 mol %) was added to the flask. The solution color turned pale red with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

The flask was removed from oil bath after 1 h, cooled to room temperature (23 °C), and charged with DMSO (50 μL) and silica gel (70 mg). The resulting mixture was concentrated the reaction under reduced pressure and purified by flash chromatography (SiO_2, 2 x 17 cm, 15:1 hexanes:EtOAc) to afford cycloheptenone **111y** (242.9 mg, 1.50 mmol, 88% yield) as a yellow oil; R_f = 0.52 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35–6.32 (m, 1H), 6.14 (dddd, *J* = 5.6, 2.5, 1.7, 0.7 Hz, 1H), 5.87 (app s, 1H), 2.70 (dddt, *J* = 15.1, 6.4, 3.5, 0.9 Hz, 1H), 2.59–2.51 (m, 2H), 2.41 (ddd, *J* = 17.9, 2.9, 1.6 Hz, 1H), 2.11–2.02 (m, 1H), 2.00–1.82 (m, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 169.2, 142.7, 134.4, 121.7, 51.6, 46.7, 45.1, 37.9, 29.7, 21.2; IR (Neat Film NaCl) 3056, 2930, 2867, 2841, 1651, 1615, 1580, 1449, 1372, 1352, 1293, 1261, 1211, 1190, 1159, 1080, 968, 951, 862, 844, 801, 811, 723 cm^{-1}; HRMS (MM:

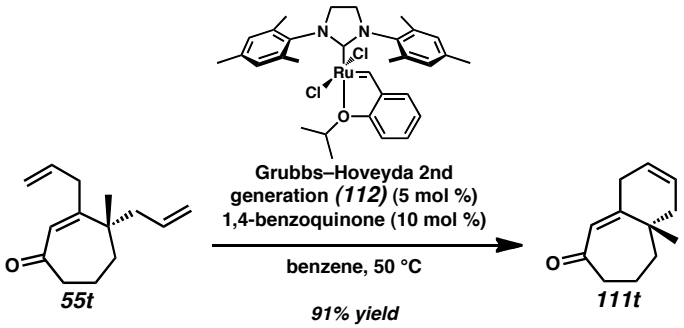
ESI–APCI+) *m/z* calc'd for $C_{11}H_{15}O$ $[M+H]^+$: 163.1117; found 163.1120; $[\alpha]_D^{26.0}$ –48.88 (*c* 1.83, $CHCl_3$, 88% ee).



Enone 111z ***(Table 2.6, entry 2)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55z** (50.0 mg, 0.25 mmol, 1.00 equiv) and backfilled with argon. Benzene (1 h argon sparge before use, 39 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (7.8 mg, 0.012 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 49 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 3 h. Consequently, the reaction was removed from oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28.5 cm, 100% hexanes→2%→5% EtOAc in

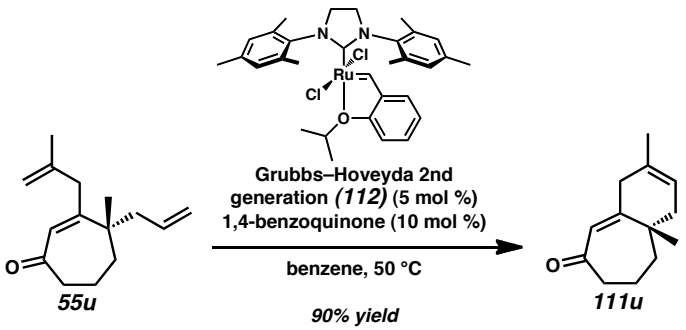
hexanes) to afford cycloheptenone **111z** (50 mg, 0.25 mmol, 99% yield) as a yellow oil; R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (t, *J* = 2.8 Hz, 1H), 6.02 (s, 1H), 5.13–5.11 (m, 1H), 4.97 (s, 1H), 2.76 (ddd, *J* = 14.7, 6.7, 4.7 Hz, 1H), 2.56 (ddd, *J* = 14.7, 9.8, 5.1 Hz, 1H), 2.48 (dd, *J* = 17.8, 2.0 Hz, 1H), 2.33 (dd, *J* = 17.8, 3.1 Hz, 1H), 2.09–1.99 (m, 1H), 1.94 (dd, *J* = 9.9, 4.0 Hz, 2H), 1.91–1.89 (m, 3H), 1.89–1.83 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 167.2, 146.8, 138.4, 137.5, 122.0, 115.9, 49.5, 48.3, 45.0, 38.2, 28.4, 23.1, 20.9; IR (Neat Film NaCl) 3084, 3052, 2918, 2868, 2845, 1652, 1607, 1450, 1374, 1352, 1311, 1290, 1259, 1210, 1190, 1164, 1117, 1082, 1004, 982, 944, 898, 881, 848, 811, 771, 746 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430; found 203.11428; $[\alpha]_D^{25.0}$ –55.41 (*c* 1.61, $CHCl_3$, 88% ee).



Enone 111t ***(Table 2.6, entry 3)***. Prepared using General Method I. A 250 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, cycloheptenone **55t** (174.6 mg, 0.85 mmol, 1.00 equiv) was cannula-transferred from a 20 mL scintillation vial to the 250 mL flask using several benzene rinses (1.5 h argon sparge before use, 5 x 4 mL).

Additional benzene (141 mL) was added to the flask followed by 1,4-benzoquinone (9.2 mg, 0.085 mmol, 10 mol %) and Grubbs–Hoveyda 2nd generation catalyst (26.8 mg, 0.043 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 171 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

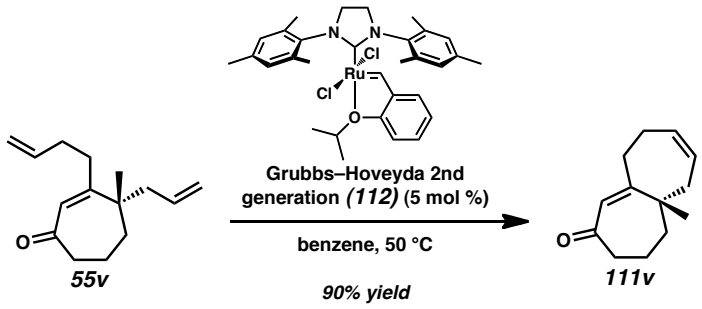
The reaction was removed from oil bath after 2.5 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (2 mL). The reaction color turned dark green with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 25 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111t** (47.7 mg, 0.27 mmol, 91% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (d, *J* = 2.1 Hz, 1H), 5.46–5.41 (m, 1H), 5.34 (ddddd, *J* = 9.9, 4.4, 2.8, 2.8, 1.0 Hz, 1H), 2.72 (dm, *J* = 20.2 Hz, 1H), 2.44–2.33 (m, 2H), 2.27 (dm, *J* = 20.2 Hz, 1H), 1.97 (dm, *J* = 17.6 Hz, 1H), 1.44 (ddd, *J* = 17.5, 5.2, 0.9 Hz, 1H), 1.33–1.19 (m, 4H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.2, 156.0, 127.2, 125.1, 125.0, 44.3, 41.8, 41.4, 41.2, 36.3, 26.1, 17.6; IR (Neat Film NaCl) 3274, 3029, 2933, 2833, 1720, 1650, 1619, 1452, 1420, 1381, 1345, 1306, 1264, 1239, 1219, 1185, 1125, 1105, 1082, 1004, 976, 952, 938, 924, 892, 884, 871, 836, 775, 733 cm^{-1}; HRMS (MM: ESI–APCI+) *m*/*z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1277; $[\alpha]_D^{25.0}$ –49.94 (*c* 0.86, $CHCl_3$, 88% ee).



Enone 111u ***(Table 2.6, entry 4)***. Prepared using General Method I. A three-neck 100 mL round-bottom flask equipped with a magnetic stir bar and fitted with rubber septa and a water condenser was connected to a Schlenk manifold (through the condenser). The flask was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55u** (50.0 mg, 0.23 mmol, 1.00 equiv), benzene (1 h argon sparge before use, 46 mL, 0.005 M), 1,4-benzoquinone (2.5 mg, 0.023 mmol, 10 mol %), and Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

The reaction was removed from oil bath after 1 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1.5 mL). The reaction color turned dark green with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111u** (39.0 mg, 0.21 mmol, 90% yield) as a yellow oil; R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, *J* = 2.0 Hz, 1H), 5.38–5.34 (m, 1H), 3.06 (dm, *J* = 19.7 Hz, 1H), 2.63–2.49 (m, 3H), 2.28 (dm, *J* = 17.2 Hz, 1H), 1.85 (dd, *J* = 17.2, 5.3 Hz, 1H), 1.81–1.75 (m, 2H), 1.74–1.65 (m, 2H),

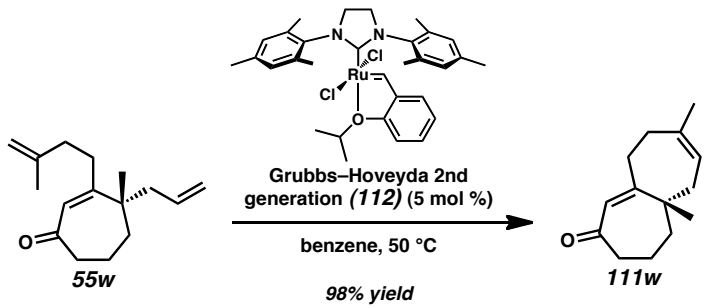
1.68 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 159.4, 131.8, 126.3, 119.5, 44.3, 41.6, 41.5, 41.3, 41.3, 26.6, 22.5, 17.6; IR (Neat Film NaCl) 3273, 3017, 2963, 2930, 1720, 1656, 1651, 1645, 1619, 1616, 1450, 1418, 1378, 1363, 1345, 1268, 1239, 1220, 1191, 1151, 1134, 1104, 1072, 1038, 989, 972, 962, 944, 931, 897, 877, 854, 827, 784, 732 cm^{-1}; HRMS (MM: ESI–APCI+) *m*/*z* calc'd for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430; found 191.1436; $[\alpha]_D^{25.0}$ +9.09 (*c* 0.86, $CHCl_3$, 88% ee).



Enone 111v ***(Table 2.6, entry 5)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55v** (50.0 mg, 0.23 mmol, 1.00 equiv), Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %), benzene (1 h argon sparge before use, 46 mL, 0.005 M). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 15 min. Consequently, the reaction was removed from the oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction color turned amber with the ethyl

vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 27.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111v** (39.4 mg, 0.21 mmol, 90% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.65–5.58 (m, 1H), 5.54–5.49 (m, 1H), 2.81–2.74 (m, 1H), 2.66–2.59 (m, 2H), 2.56–2.46 (m, 2H), 2.24–2.13 (m, 2H), 2.07 (ddd, *J* = 14.1, 11.1, 3.1 Hz, 1H), 1.93 (ddddd, *J* = 14.1, 11.0, 9.3, 4.8, 2.9 Hz, 1H), 1.85–1.79 (m, 1H), 1.76 (dd, *J* = 14.9, 7.9 Hz, 1H), 1.66 (ddd, *J* = 14.0, 6.9, 2.8 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 165.3, 129.9, 129.7, 126.2, 47.8, 43.9, 40.7, 40.3, 34.5, 32.2, 27.8, 19.6; IR (Neat Film NaCl) 3287, 3017, 2930, 2833, 1652, 1616, 1481, 1450, 1380, 1352, 1342, 1291, 1279, 1262, 1243, 1224, 1204, 1184, 1162, 1084, 1075, 1047, 1021, 984, 963, 921, 896, 877, 846, 834, 788, 755 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430; found 191.1430; $[\alpha]_D^{25.0}$ –92.01 (*c* 0.82, $CHCl_3$, 88% ee).

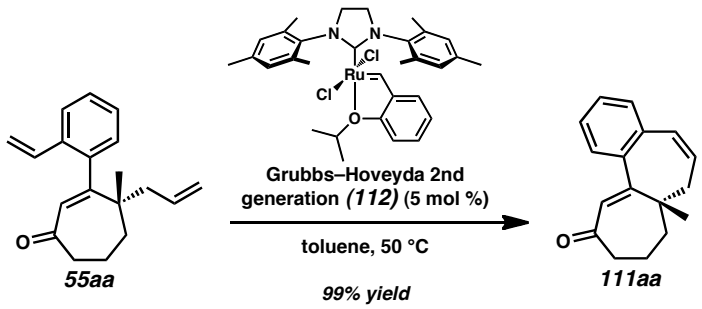


Enone 111w ***(Table 2.6, entry 6)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was

flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55w** (50.0 mg, 0.22 mmol, 1.00 equiv) and backfilled with argon. Benzene (1 h argon sparge before use, 33 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (6.7 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 43 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 30 min. After an additional 10 min of stirring, the reaction was removed from the oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction color turned dark brown with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111w** (43.2 mg, 0.21 mmol, 98% yield) as a clear colorless oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.41–5.34 (m, 1H), 2.79 (td, *J* = 12.3, 5.3 Hz, 1H), 2.66–2.55 (m, 2H), 2.54–2.42 (m, 2H), 2.19 (ddd, *J* = 12.5, 6.0, 3.3 Hz, 1H), 2.14–2.02 (m, 2H), 1.98–1.88 (m, 1H), 1.85–1.76 (m, 1H), 1.71–1.63 (m, 2H), 1.62 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 165.8, 136.9, 129.5, 120.7, 47.7, 43.9, 40.6, 40.2, 36.9, 34.3, 27.5, 25.3, 19.7; IR (Neat Film NaCl) 3300, 3014, 2928, 2828, 1657, 1617, 1480, 1450, 1379, 1353, 1342, 1292, 1259, 1216, 1171, 1131, 1106, 1082, 1050, 1009, 982, 962, 916, 897, 874, 833, 814, 795, 765 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z*

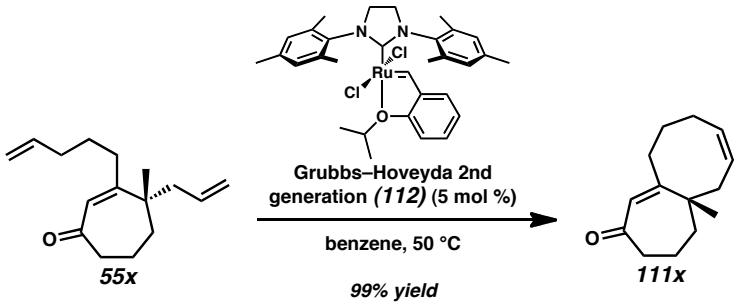
calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$: 205.1587; found 205.1582; $[\alpha]_D^{25.0}$ –73.66 (*c* 0.95, $CHCl_3$, 88% ee).



Enone 111aa ***(Table 2.6, entry 7)***. Prepared using General Method I. A three-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, cycloheptenone **55aa** (65.8 mg, 0.25 mmol, 1.00 equiv) was cannula-transferred from a 20 mL scintillation vial to the 100 mL flask using several toluene rinses (1.5 h argon sparge before use, 5 x 4 mL). Additional toluene (20 mL) was added to the flask followed by Grubbs–Hoveyda 2nd generation catalyst (7.7 mg, 0.012 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more toluene (9 mL; total toluene added = 49 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

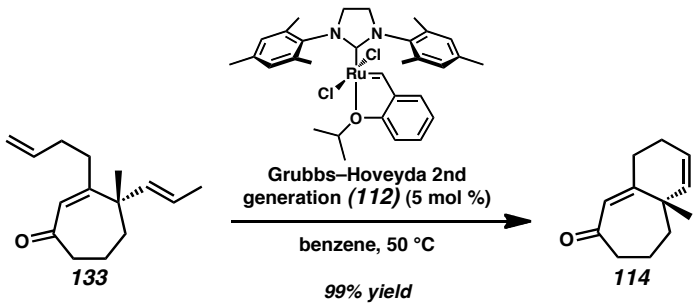
The reaction was removed from the oil bath after 6.5 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (0.5 mL). The reaction color turned dark brown with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with EtOAc and concentrated under reduced pressure. The

crude oil was purified by flash chromatography (SiO_2, 2 x 24.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111aa** (56.7 mg, 0.23 mmol, 96% yield) as a yellow oil; R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 7.22–7.19 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.53 (dm, *J* = 11.1 Hz, 1H), 6.03 (dt, *J* = 11.2, 6.0 Hz, 1H), 5.82 (s, 1H), 2.71–2.60 (m, 2H), 2.30 (ddd, *J* = 15.6, 5.8, 0.8 Hz, 1H), 2.21 (ddd, *J* = 15.6, 6.3, 1.8 Hz, 1H), 2.15 (ddd, *J* = 13.9, 7.5, 4.5 Hz, 1H), 2.01–1.85 (m, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 162.5, 142.5, 135.5, 132.0, 130.8, 130.0, 128.8, 128.8, 127.9, 127.3, 50.6, 44.2, 42.4, 40.1, 27.8, 19.3; IR (Neat Film NaCl) 3057, 3017, 2933, 2870, 1718, 1665, 1601, 1481, 1445, 1417, 1383, 1354, 1340, 1286, 1258, 1228, 1180, 1125, 996, 984, 936, 890, 828, 780, 757 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{17}H_{19}O$ $[M+H]^+$: 239.1430; found 239.1432; $[\alpha]_D^{20.0}$ –86.75 (*c* 0.70, $CHCl_3$, 88% ee).



Enone 185w ***(Table 2.6, entry 8)***. Prepared using General Method I. See procedure described above. R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.70 (m, 1H), 5.65 (tdt, *J* = 10.4, 6.4, 1.3 Hz, 1H), 2.68–2.55 (m, 2H), 2.54–2.44 (m, 1H), 2.30–2.24 (m, 2H), 2.24–2.15 (m, 1H), 2.13–2.04 (m, 1H), 1.94–1.69 (m, 7H), 1.52–1.41 (m, 1H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 165.6, 132.2,

131.9, 128.5, 49.0, 44.2, 39.8, 39.5, 35.5, 31.1, 27.0, 26.5, 17.8; IR (Neat Film NaCl) 3018, 2928, 2859, 1645, 1608, 1468, 1448, 1411, 1380, 1343, 1327, 1279, 1253, 1214, 1178, 1131, 1102, 1088, 1051, 1015, 987, 965, 937, 920, 899, 880, 845, 796, 777, 747 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1587; found 205.1587; $[\alpha]_D^{25.0}$ –141.99 (*c* 1.01, $CHCl_3$, 88% ee).

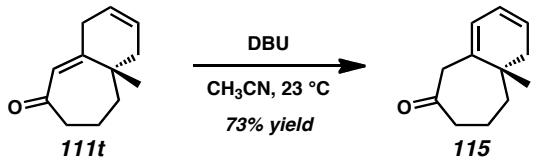


Enone 114. Prepared using General Method I. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **133** (50.0 mg, 0.23 mmol, 1.00 equiv) and backfilled with argon twice. Benzene (1 h argon sparge before use, 44 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %). The flask was rinsed with more benzene (2 mL; total benzene added = 46 mL, 0.005 M) and lowered into a preheated oil bath (50 °C). The solution color turned pale green with addition of catalyst and amber over time.

The reaction was removed from the oil bath after 50 min, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (0.5 mL). The reaction was

filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified twice by flash chromatography (SiO_2, both columns 2 x 27.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **114** (35.8 mg, 0.23 mmol, 89% yield, 70% yield from vinylogous ester **27p**) as a pale yellow oil; R_f = 0.62 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.72–5.67 (m, 1H), 5.28 (dd, *J* = 9.7, 2.4 Hz, 1H), 2.71–2.64 (m, 1H), 2.62–2.54 (m, 1H), 2.53–2.46 (m, 1H), 2.31–2.11 (m, 3H), 1.92–1.74 (m, 3H), 1.70 (ddd, *J* = 14.0, 6.6, 2.4 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 161.3, 137.8, 126.9, 125.3, 44.6, 43.6, 40.6, 33.8, 28.1, 27.7, 18.6; IR (Neat Film NaCl) 3019, 2934, 2866, 2845, 1665, 1653, 1621, 1450, 1414, 1350, 1309, 1281, 1258, 1217, 1181, 1171, 1132, 1087, 1074, 1024, 1013, 973, 938, 902, 881, 865, 783, 767, 716 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1274; $[\alpha]_D^{20.0}$ –188.35 (*c* 0.72, $CHCl_3$, 88% ee).

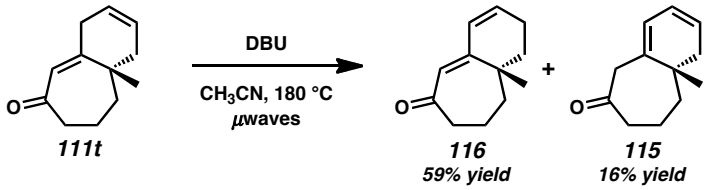
2.1.1.16 PREPARATION OF POLYCYCLIC CYCLOHEPTENONE DERIVATIVES BY OTHER METHODS



111t *115*

Diene 115. A 20 mL scintillation vial containing enone **111t** (31.5 mg, 0.18 mmol, 1.00 equiv) was equipped with a stir bar and sealed with a screw cap containing a teflon septum. The vial was connected to a Schlenk manifold and backfilled with argon three

times. Acetonitrile (1.8 mL, 0.1 M) was added to the vial followed by DBU (30 μL, 0.20 mmol, 1.12 equiv). The solution was stirred at room temperature (23 °C) until no starting material remained by TLC analysis (4 h). The reaction was passed through a short silica gel plug, rinsed with water, dried over $MgSO_4$, filtered through another short silica gel plug, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 1 x 28.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford diene **115** (23.1 mg, 0.13 mmol, 73% yield) as a pale yellow oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 9.0, 5.3, 1.7 Hz, 1H), 5.79–5.73 (m, 2H), 3.27 (d, *J* = 16.3 Hz, 1H), 2.93 (d, *J* = 16.3 Hz, 1H), 2.73 (ddd, *J* = 12.4, 10.0, 4.7 Hz, 1H), 2.33–2.23 (m, 2H), 2.08–2.00 (m, 1H), 1.89–1.67 (m, 3H), 1.49–1.41 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 138.6, 125.4, 123.9, 123.6, 49.5, 42.7, 37.6, 37.5, 36.5, 24.1, 20.9; IR (Neat Film NaCl) 3039, 2929, 2865, 2817, 1708, 1645, 1587, 1453, 1424, 1403, 1371, 1356, 1319, 1286, 1263, 1235, 1211, 1143, 1105, 1082, 1039, 987, 969, 940, 925, 851, 817, 761, 704 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{12}H_{16}O$ [M+·]$^+$: 176.1201; found 176.1219; $[\alpha]_D^{25.0}$ –205.54 (*c* 0.71, $CHCl_3$, 88% ee).

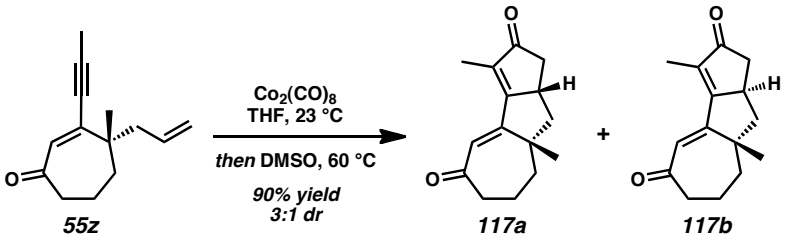


Diene 115 and Diene 116. A 2.0–5.0 mL μwave vial fitted with a stir bar and sealed with a screw cap containing a teflon septum was flame-dried three times, backfilling with

argon after each drying cycle. Once cool, diene **111t** (66.7 mg, 0.38 mmol, 1.00 equiv) was cannula-transferred to the vial with several acetonitrile rinses (4 x 1 mL, 0.09 M) and the flask was charged with DBU (66 μL, 0.44 mmol, 1.17 equiv). The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 180 °C, sensitivity: normal). After 5 h of irradiation, the crimp cap was removed and the reaction was filtered through a silica gel plug. The resulting solution was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2 x 29 cm, 100% hexanes→10%→30%→50%→80% CH_2Cl_2 in hexanes) to yield diene **116** (39.5 mg, 0.22 mmol, 59% yield) as a yellow oil and diene **115 (**10.4 mg, 0.059 mmol, 16% yield) as a pale yellow oil.

Diene 115: Characterization data is identical to that described above.

Diene 116: R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13–6.07 (m, 1H), 6.02 (dd, *J* = 9.9, 2.8 Hz, 1H), 5.76 (s, 1H), 2.75 (dddt, *J* = 15.6, 6.6, 5.0, 0.9 Hz, 1H), 2.52 (ddd, *J* = 15.4, 9.5, 5.6 Hz, 1H), 2.38–2.27 (m, 1H), 2.19 (dtt, *J* = 19.3, 5.6, 1.3 Hz, 1H), 2.05–1.93 (m, 1H), 1.87–1.77 (m, 2H), 1.74–1.62 (m, 2H), 1.44 (ddt, *J* = 13.2, 5.4, 1.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 156.2, 135.1, 131.4, 129.1, 44.6, 42.2, 38.9, 37.6, 23.1, 22.9, 18.8; IR (Neat Film NaCl) 3026, 2967, 2922, 2868, 2849, 1650, 1621, 1583, 1449, 1428, 1383, 1353, 1338, 1284, 1244, 1225, 1207, 1173, 1163, 1130, 1114, 1090, 1077, 1023, 978, 954, 935, 911, 881, 866, 840, 777, 727 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1278; $[\alpha]_D^{25.0}$ –298.04 (*c* 1.24, $CHCl_3$, 88% ee).



Enones 117a and 117b. A 20 mL scintillation vial containing cycloheptenone **55z** (185.6 mg, 0.92 mmol, 1.00 equiv) was equipped with a stir bar and sealed with a screw cap containing a teflon septum. The vial was connected to a Schlenk manifold and backfilled with argon three times. The vial was charged with THF (5.0 mL, 0.2 M) and dicobalt octacarbonyl (388.5 mg, 1.14 mmol, 1.24 equiv), generating a dark brown solution. After 12 h of stirring at room temperature (23 °C), DMSO (380 μL, 5.35 mmol, 5.83 equiv) was added and the vial was lowered into a preheated oil bath (60 °C). Reaction turned dark red over time. The vial was removed from the oil bath after 14 h and cooled to room temperature. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 25 g loading cartridge, 40 g column, multi-step gradient, hold 0% [5 min]→ramp to 5% [5 min]→hold 5% [50 min]→ramp to 10% [5 min]→hold 10% [15 min]→ramp to 15% [1 min]→hold 15% [7 min]→ramp to 20% [1 min]→hold 20% EtOAc in hexanes [27 min]) to afford a 3:1 diastereomeric mixture of cycloheptenones **117a**:**117b** (190.2 mg, 0.83 mmol, 90% yield). Analytically pure samples of **117a** and **117b** could be obtained using the above column conditions.

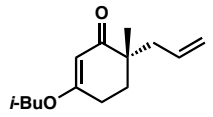
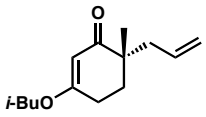
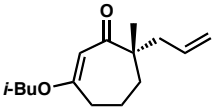
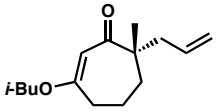
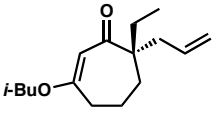
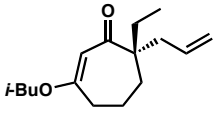
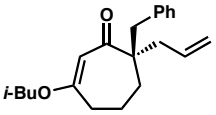
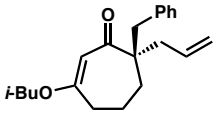
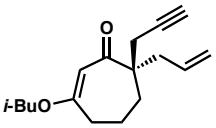
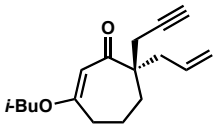
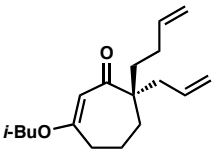
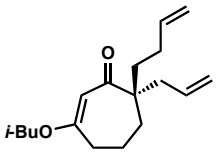
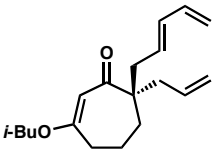
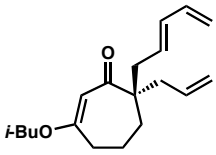
Major diastereomer (117a): yellow oil that solidified upon cooling; R_f = 0.32 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 3.21–3.12 (m, 1H),

2.81–2.75 (m, 1H), 2.75 (dd, *J* = 17.8, 6.3 Hz, 1H), 2.62 (ddd, *J* = 14.0, 11.4, 4.6 Hz, 1H), 2.19–2.09 (m, 1H), 2.11 (dd, *J* = 17.8, 3.7 Hz, 1H), 2.01 (dd, *J* = 11.6, 6.9 Hz, 1H), 1.99–1.90 (m, 2H), 1.89 (d, *J* = 2.6 Hz, 3H), 1.88–1.81 (m, 1H), 1.32 (s, 3H), 1.28 (t, *J* = 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 204.8, 172.4, 155.0, 135.6, 128.8, 50.9, 47.2, 45.6, 42.3, 40.5, 39.5, 26.8, 20.9, 9.0; For NOESY correlation data, see Figure A1.351; IR (Neat Film NaCl) 2945, 2917, 2867, 1701, 1662, 1446, 1375, 1332, 1304, 1258, 1219, 1196, 1148, 1099, 1054, 978, 945, 895, 869, 852, 830, 802, 706 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1381; $[\alpha]_D^{20.0}$ +150.77 (*c* 1.01, $CHCl_3$, 88% ee).

Minor diastereomer (117b): orange oil that solidified upon cooling; R_f = 0.25 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, 1H), 3.09–2.98 (m, 1H), 2.70 (dd, *J* = 18.1, 6.4 Hz, 1H), 2.71–2.64 (m, 1H), 2.63–2.56 (m, 1H), 2.16 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.11 (dd, *J* = 18.1, 3.3 Hz, 1H), 2.12–1.96 (m, 2H), 1.95–1.87 (m, 2H), 1.87 (d, *J* = 2.5 Hz, 3H), 1.28 (dd, *J* = 12.4, 11.6 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 206.4, 173.0, 154.6, 133.7, 127.4, 48.9, 48.3, 42.4, 42.3, 41.3, 37.5, 31.9, 22.2, 8.5; For NOESY correlation data, see Figure A1.355; IR (Neat Film NaCl) 2928, 2867, 1703, 1668, 1453, 1410, 1377, 1305, 1285, 1236, 1208, 1157, 1094, 1054, 996, 949, 891, 874, 859, 791, 720 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1372; $[\alpha]_D^{20.0}$ –407.06 (*c* 1.65, $CHCl_3$, 88% ee).

2.1.1.17 DETERMINATION OF ENANTIOMERIC EXCESS

Table 2.8. Methods for the determination of enantiomeric excess (Chiral HPLC and SFC).

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 **22a**	 **22a**	HPLC Chiralcel OD-H 5% IPA in hexane isocratic, 1.0 mL/min	5.80	6.53	86
2	 **27a**	 **27a**	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	6.30	7.26	88
3	 **27b**	 **27b**	HPLC Chiralcel AD 0.25% IPA in hexane isocratic, 1.0 mL/min	18.08	16.23	92
4	 **27c**	 **27c**	HPLC Chiralcel OD-H 0.5% IPA in hexane isocratic, 1.0 mL/min	15.70	13.96	86
5	 **27d**	 **27d**	HPLC Chiralcel OD-H 0.5% IPA in hexane isocratic, 1.0 mL/min	12.35	13.43	89
6	 **27e**	 **27e**	HPLC Chiralcel AD 0.8% IPA in hexane isocratic, 2.0 mL/min	5.03	6.06	87
7	 **27f**	 **27f**	SFC Chiralcel AD-H 5% IPA in hexane isocratic, 2.5 mL/min	6.99	6.31	90

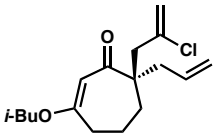
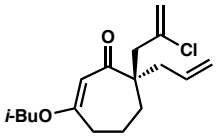
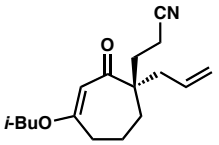
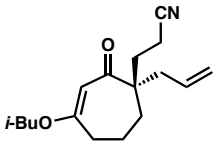
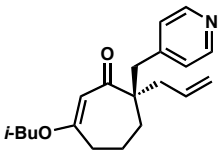
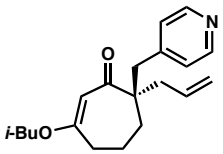
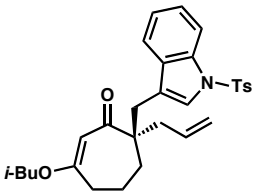
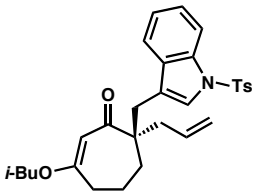
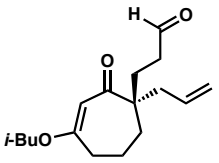
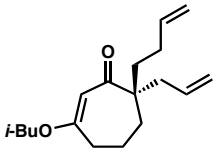
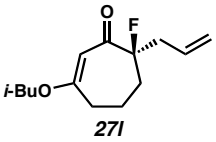
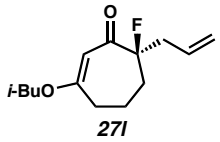
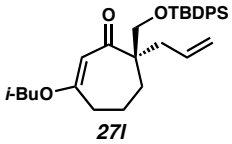
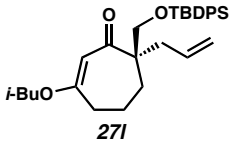
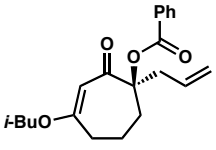
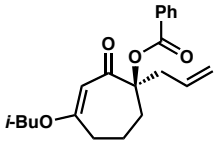
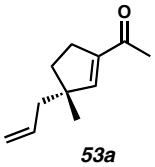
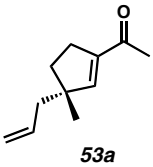
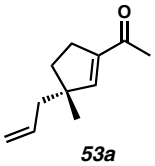
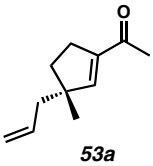
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
8	 ***27g***	 ***27g***	HPLC Chiralcel OD-H 0.1% IPA in hexane isocratic, 1.0 mL/min	27.22	24.19	86
9	 ***27h***	 ***27h***	HPLC Chiralcel OD-H 5% IPA in hexane isocratic, 1.0 mL/min	10.67	14.66	87
10	 ***27i***	 ***27i***	HPLC Chiralcel AD 5% EtOH in hexane isocratic, 1.0 mL/min	13.22	15.13	85
11	 ***27j***	 ***27j***	HPLC Chiralcel AD 5% EtOH in hexane isocratic, 1.0 mL/min	11.11	16.64	83
12	 ***27k***	 ***27e***	HPLC Chiralcel AD 0.8% IPA in hexane isocratic, 2.0 mL/min	4.39	5.17	80
13	 ***27l***	 ***27l***	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	8.80	8.05	91
14	 ***27l***	 ***27l***	HPLC Chiralcel OD-H 0.2% IPA in hexane isocratic, 1.0 mL/min	21.74	25.53	58
15	 ***27n***	 ***27n***	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	18.28	22.01	57

Table 2.9. Methods for the determination of enantiomeric excess (Chiral GC).

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 ***53a***	 ***53a***	GC G-TA 80 °C isotherm	54.98	61.35	88
2	 ***53a***	 ***53a***	GC G-TA 80 °C isotherm	54.74	60.24	98

2.2 NOTES AND REFERENCES

(1) For a review discussing our strategy of using natural product structures to drive the development of enantioselective catalysis, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(2) For examples of asymmetric palladium-catalyzed allylic alkylation reactions of carbocyclic ketone enolates developed by our group, see: (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, Jr., J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 14199–14223.

(3) For examples of asymmetric palladium-catalyzed allylic alkylation reactions of heterocyclic ketone enolates (such as those derived from dioxanones and lactams) developed by our group, see: (a) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130–133.

(4) For examples of asymmetric palladium-catalyzed protonation reactions of cyclic ketone enolates, see: (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042.

(5) For an example of an asymmetric palladium-catalyzed conjugate addition/enolate alkylation cascade reaction of cyclic ketone enolates, see: Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2010**, *2*, 192–196.

(6) For studies on the computational and experimental studies on the mechanism of palladium-catalyzed asymmetric alkylation using the PHOX ligand scaffold, see: (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877. (b) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840–6843. (c) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060.

(7) For examples of the asymmetric alkylation of cyclic ketone, vinylogous ester, or vinylogous thioester-derived enolates in the context of natural product synthesis, see: (a) Dichroanone: McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (b) Elatol: White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (c) Cyanthiwigin F: Enquist, Jr., J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (d) Carissone: Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (e) Cassiol: Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295. (f) Elatol, Laurencenone C, α-Chamigrene, and the Proposed Structure of Laurencenone B: White, D. E.; Stewart, I. C.; Seashore-Ludlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668–4686. (g) Hamigeran B: Mukherjee, H. McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 825–827. (h) Liphagal: Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B.

M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818. (i) Cyanthiwigins B, F, and G: Enquist, Jr., J. A.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 9957–9969.

(8) For our initial communication on the addition of organometallic reagents to chiral vinylogous esters to form γ-quaternary cycloheptenones, see: Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56–59.

(9) For our initial communication on the palladium catalyzed asymmetric alkylation and ring contraction studies in the synthesis of γ-quaternary acylcyclopentenes, see: Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756–2760.

(10) Concurrent with our efforts, palladium–catalyzed asymmetric allylic alkylations reactions of unstabilized enolates for the synthesis of enantioenriched α-quaternary cyclic ketones, vinylogous esters, and vinylogous thioesters were reported by Trost. See: (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480–4481. (b) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174–184. (c) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.—Eur. J.* **2005**, *11*, 951–959. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (e) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112.

(11) 1,3-Cycloheptanedione (catalog #515981) and 3-isobutoxy-2-cyclohepten-1-one (catalog #T271322) are commercially available from Sigma-Aldrich. The price of 1,3-cycloheptanedione is $40,000/mol. Adopted from Aldrich August 28th, 2011.

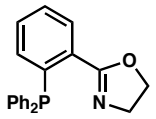
(12) (a) Ragan, J. A.; Makowski, T. W.; am Ende, D. J.; Clifford, P. J.; Young, G. R.; Conrad, A. K.; Eisenbeis, S. A. *Org. Process Res. Dev.* **1998**, *2*, 379–381. (b) Ragan, J. A.; Murry, J. A.; Castaldi, M. J.; Conrad, A. K.; Jones, B. P.; Li, B.; Makowski, T. W.; McDermott, R.; Sitter, B. J.; White, T. D.; Young, G. R. *Org. Process. Res. Dev.* **2001**, *5*, 498–507. (c) Do, N.; McDermott, R. E.; Ragan, J. A. *Org. Synth.* **2008**, *85*, 138–146.

(13) (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, 65, 253–266. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

(14) $Pd_2(pmdba)_3$ is preferable to $Pd_2(dba)_3$ in this reaction for ease of separation of pmdba from the reaction products during purification. pmdba = 4,4'-methoxydibenzylideneacetone.

(15) Our group has made improvements to the synthetic route toward PHOX ligands and developed procedures for large-scale synthesis. See: (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

(16) Racemic products were obtained using $Pd(PPh_3)_4$ (5 mol %) or achiral PHOX ligand **128** (6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in toluene at 30 °C.



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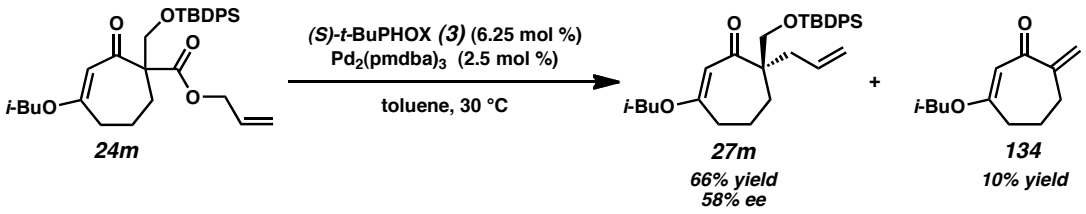
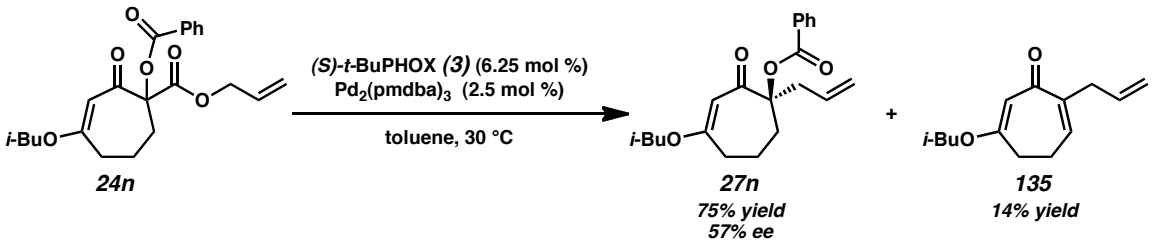
(17) For a preparation of electron-deficient PHOX ligand **8** ((*S*)-$(CF_3)_3$-*t*-BuPHOX), see: (a) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett*. **2010**, *51*, 5550–5554. (b) Also see ref. 7b and 7f.

(18) The reaction with silyl-protected alcohol **24m** afforded alkylation product **27m** and exocyclic enone **134** in 10% yield. A related silyl-protected alcohol substrate did not display this type of elimination during an asymmetric decarboxylative alkylation reaction on a six-membered ring β-ketoester substrate. See ref. 2b.



(19) The reaction with benzoate ester **24n** afforded alkylation product **27n** and endocyclic enone **135** in 14% yield.



(20) Stork, G.; Danheiser, R. L. *J. Org. Chem*. **1973**, *38*, 1775–1776.

(21) 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 ref. 12c.

(22) For selected examples of the two-carbon ring contraction of seven-membered carbocycles, see: (a) Frankel, J. J.; Julia, S.; Richard-Neuville, C. *Bull. Soc.*

Chim. Fr. **1968**, 4870–4875. (b) Jun, C.-H.; Moon, C. W.; Lim, S.-G.; Lee, H. *Org. Lett.* **2002**, *4*, 1595–1597.

(23) Notably, **70a** and related β-hydroxyketones appear to undergo minimal decomposition after several months of storage at room temperature by TLC and ^{1}H NMR analysis, and immediate conversion to acylcyclopentenes **53a** is not necessary to achieve high yields.

(24) 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. See: Rinderhagen, H.; Mattay, J. *Chem.—Eur. J.* **2004**, *10*, 851–874.

(25) For an example of a photochemical two-carbon ring contraction of a macrocycle, see: Yang, Z.; Li, Y.; Pattenden, G. *Tetrahedron* **2010**, *66*, 6546–6549.

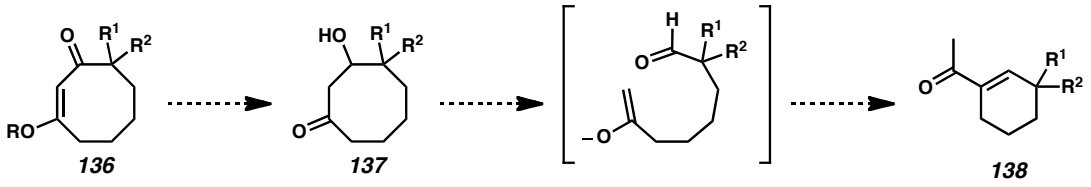
(26) For examples of ring contractions of medium-sized ring heterocycles, see: (a) Nasveschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3264–3267. (b) Nasveschuk, C. G.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 612–617. (c) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240–254. (d) Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin A. K. *Org. Lett.* **2010**, *12*, 240–243. (e) Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924–5926. (f) Volchkov, I.; Park, S.; Lee, D. *Org. Lett.* **2011**, *13*, 3530–3533. (g) Dubinina, G. G.; Chain, W. J. *Tetrahedron Lett.* **2011**, *52*, 939–942.

(27) For a discussion of the properties of fluorinated alcohols and their use, see: Begue, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29.

(28) A lithium alkoxide species is presumably generated in situ based on the following pK_a values: (H_2O = 15.7, TFE = 12.5, HFIP = 9.3 [water]; H_2O = 31.2, TFE = 23.5, HFIP = 18.2 [DMSO]); Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(29) No reaction was observed with the following bases (with or without TFE additive): DBU, TMG, Na_2CO_3, $BaCO_3$, and CaH_2. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

(30) The two-carbon ring contraction strategy can potentially be extended to β-hydroxyketones of other medium sized rings to provide other useful cyclic enone products. These possibilities are the subject of current investigations.

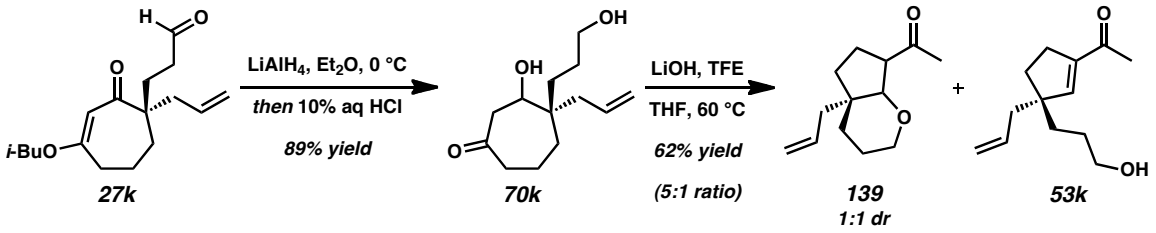


(31) Fluorinated lithium alkoxides were recently used to promote Horner–Wadsworth–Emmons olefinations of sensitive substrates, demonstrating their mild reactivity. See: Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281–4283.

(32) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(33) Although we had success in preparing silyloxy acylcyclopentene **53p** from vinylogous ester **27p**, we wondered whether it would be possible to perform a ring contraction on aldehyde **27k**. Under our standard conditions, the intermediate ketodiol **70k** can be obtained in 89% yield, however the subsequent

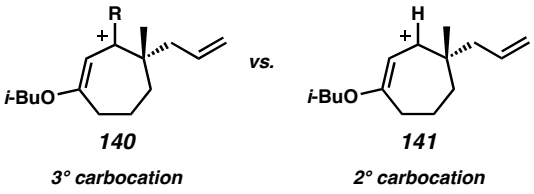
ring contraction proceeded in 62% yield to afford a complex mixture of pyran diastereomers **139** and uncyclized acylcyclopentene **53k**.



(34) Analytically pure samples of dione **79** can be obtained from vinylogous ester **27a** by treatment with acid. See Experimental Section (Section 2.7.2.10) for details.

(35) The addition of cerium chloride to reactions with organolithium or Grignard reagents has been shown to increase reactivity and reduce side reactions with vinylogous ester systems, see: Crimmins, M. T.; Dedopoulou, D. *Synth. Commun.* **1992**, *22*, 1953–1958.

(36) The increase in enone formation with the organometallic addition relative to the hydride reduction is likely due to the higher stability of the tertiary carbocation (**140**) compared to the secondary carbocation (**141**) formed along the reduction pathway.



(37) CCDC 686849 (**81**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The data can also be viewed in Appendix 3.

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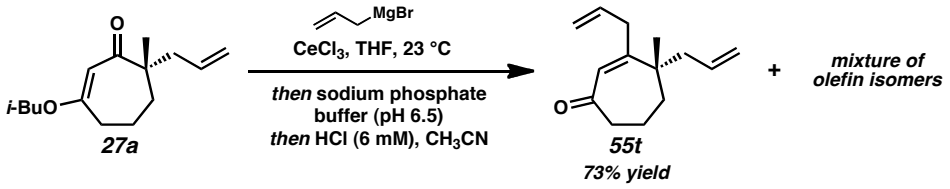
(40) Another application of the ring contraction methodology toward daucane sesquiterpenes is presented in Chapter 3.

(41) Hong, A. Y.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9674–9678.

(42) Preferential β-hydroxyketone formation is observed when the acidification of the intermediate isobutyl enol ether is performed in diethyl ether instead of methanol. See Table 2.4.

(43) Attempts to purify the crude enol ether were challenging due to decomposition to enone **55r** and β-hydroxyketone **70r**.

(44) The yield of cycloheptenone **55t** is lower than many related enones due to the formation of several side products presumed to be non-conjugated alkene isomers.



(45) Synthesis of the simple β-vinyl substituted enone proved challenging due to the formation of a complex product mixture.

(46) Quenching the alkynyl nucleophile addition with hydrochloric acid provided a complex mixture of products, most notably one with an equivalent of HCl added into the molecule. This issue was resolved by instead using sulfuric acid.

(47) Cycloheptenone **55aa** is formed as a 1.9:1 mixture of atropisomers whose isomeric peaks coalesce in a variable temperature ^{1}H NMR study. See Figure A2.108.4.

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