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The intramolecular Morita–Baylis–Hillman-type alkylation reaction

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Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

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ABSTRACT

From the initial development of a homologous Morita–Baylis–Hillman reaction utilizing epoxides as electrophiles, the method was expanded to enable the exclusively organocatalyzed intramolecular allylation of enones and to develop the intramolecular MBH-type alkylation of activated alkenes. We successfully utilized both enones and unsaturated thioesters as the activated alkene component. This work, carried out using stoichiometric amounts of the trialkylphosphine, gave an array of functionalized five- and six-membered carbocycles in high yields. With the cycloalkylation of enones and thioesters, conditions that allowed the use of substoichometric amounts of the phosphine catalyst were developed. As a result both five- and six-membered rings can be formed efficiently with little to no loss in yield upon comparison to yields obtained when stoichiometric amounts of trialkylphosphines were employed. We isolated, for the first time, an MBH-type intermediate exhibiting unprecedented trans geometry of the phosphonium salt and acyl group.

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1. Introduction

Discovering new high yielding and selective reactions is vital for the advancement of synthetic organic chemistry. Reactions that generate new carbon–carbon bonds and maximize molecular complexity with a minimum of operations are fundamental for the construction of organic molecular frameworks. The Morita–Baylis–Hillman reaction (MBH),[1,2] originating from both German[1] and Japanese[2] patents, is an organocatalytic reaction involving the coupling of electron deficient alkenes with sp^2 hybridized carbon electrophiles under the catalytic influence of a nucleophilic species, providing a convenient method for the synthesis of α-functionalized activated alkenes. Over the last two decades, the intermolecular Morita–Baylis–Hillman (MBH) reaction has seen tremendous development of all three components and now encompasses a wide range of activated alkenes, electrophiles, and nucleophilic catalysts.[3] Over the last few years its scope has been further extended through the development of asymmetric versions of the reaction.[3f,g] While the intermolecular MBH reaction has been well-studied, the intramolecular MBH has not received as much attention due in part to its variable efficiency.[4]

Furthermore, the MBH reaction has long been limited to reactions of highly reactive sp^2 hybridized electrophiles, such as aldehydes, α-keto esters, 1,2-diketones, and aldimine[3f,5] derivatives, α-bromo methyl enoates,[6] allylic acetates under Pd catalysis,[7a] arenes,[7b] enones,[7c] and vinyl sulfones,[7d] whereas less reactive sp^2 hybridized electrophiles, such as allyl halides and sp^3 hybridized electrophiles, such as epoxides and alkyl halides have been overlooked and underutilized as the electrophilic partner in the Morita–Baylis–Hillman coupling.

2. Stoichiometric intramolecular MBH-type cycloalkylations

2.1. Epoxides: homologous MBH-type reaction[8]

Nucleophilic epoxide-opening reactions play a key role in the construction of both carbon–carbon and carbon–oxygen bonds, essential components of organic synthesis. Reactions of epoxides with enolates generate a chain extended homologous aldol product.[9] A number of examples illustrate effective epoxide opening resulting in skeletal enhancement under either Lewis acidic or base-catalyzed reaction conditions.[10]

In the presence of nucleophilic catalysts, epoxides have demonstrated variable stability and reactivity. An early communication reported that epoxides failed to yield recognizable products in the tertiary amine-catalyzed intermolecular MBH reaction with acrylates,[11] whereas α,β-epoxy aldehydes, on the other hand, underwent efficient DABCO catalyzed coupling giving a traditional MBH aldol adduct.[12] To date, there have been no reports of

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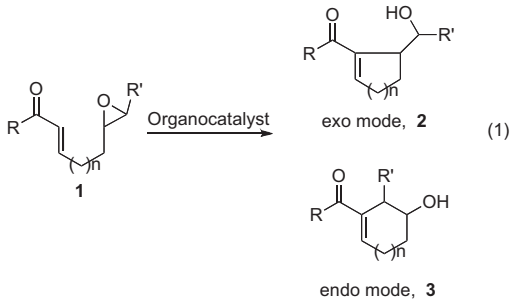
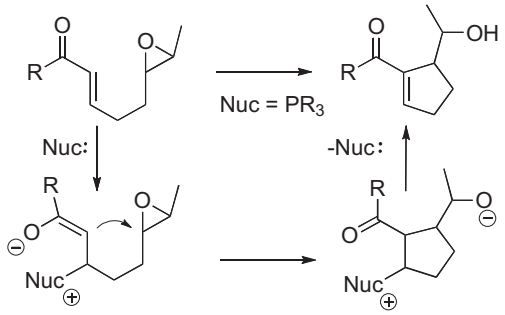
attempted phosphine catalyzed MBH-type reactions with epoxides. Under tributylphosphine catalysis, epoxides have been shown to react with deoxygenation (160 °C),[13] or react with the phosphine resulting in ring opening under mild conditions (room temperature to refluxing *t*-BuOH).[14] In addition, epoxides react with acetate generated by reaction of Ac_2O with Bu_3P in refluxing toluene, thus illustrating the stability of epoxides in the presence of a trialkylphosphine when competing processes are possible.[15] These examples demonstrate that the reactivity of epoxides in the presence of trialkylphosphines or tertiary amines is highly dependent on the reaction environment. With this in mind we sought to use epoxides as an electrophile in our initial research toward expanding the scope of the Morita–Baylis–Hillman reaction.

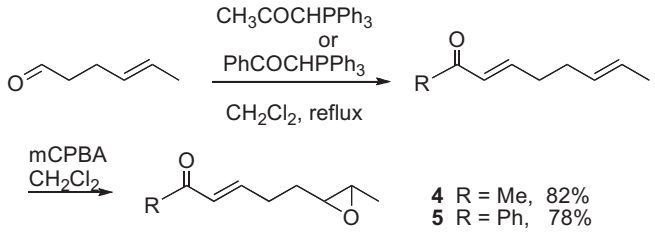


It was envisaged that organocatalyzed reaction of epoxy enone **1** would be expected to generate either alcohol **2** from *exo* opening of the epoxide or alcohol **3** from the *endo* mode of opening (Eq. 1) via a traditional MBH organocatalyzed mechanism (Scheme 1), thus in either way giving a homologous MBH type product.



Scheme 1.

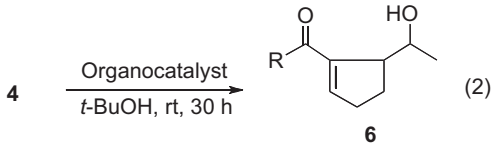
Substitution on the epoxide or the tether was expected to bias, which cyclization mode would operate. Initial studies were conducted with epoxy enones **4** and **5** that were prepared as described in Scheme 2.[16]



Scheme 2.

During our initial optimization studies it was found that amine nucleophiles, such as DABCO, quinuclidine,[17] DBU, and DMAP, which are commonly employed in the traditional Morita–Baylis–Hillman coupling, were ineffective at promoting the cyclization of either epoxy enone **4** or **5**. However, it was found that tertiary phosphines, which are also widely employed nucleophiles in the traditional Morita–Baylis–Hillman reaction, gave more promising results. Treatment of epoxide **4** with 1 equiv of PBu_3 in *t*-BuOH at room temperature led to the isolation of 25% of cyclic enone **6** in addition to a significant amount of unrecognizable materials (Eq. 2). None of the *endo* epoxide opening adduct was observed. Further refinement, paying particular attention to both solvent concentration and equivalents of trialkylphosphine, led to conditions for efficient epoxide opening (Table 1, Eq. 2), constituting the first reported reaction of an sp^3 hybridized electrophile with a zwitterionic enolate in an intramolecular MBH-type reaction. The results showed that PMe_3 was a more effective organocatalyst than Bu_3P. At higher concentrations (Table 1, entries 1–3), loss of material and generation of unrecognizable products was observed with both trialkylphosphines.[18] However, at lower concentrations, while no improvement was seen with Bu_3P, Me_3P was found to be an effective organocatalysts at a 0.025 M reaction concentration, giving rise to 67% of the desired cyclized adduct (entry 8). Further attempts at optimization, such as the use of higher temperatures, was not found to be advantageous to the reaction outcome.

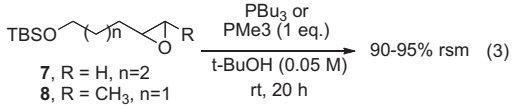
Table 1
Optimization of Morita-Baylis-Hillman-type epoxide opening reactions



Entry	Concentration (M)	PR_3	Yield (%)
1	2.0	PBu_3	0[a]
2	0.50	PMe_3	0[a]
3	0.50	PBu_3	25
4	0.25	PBu_3	<10[b]
5	0.20	PMe_3	38
6	0.10	PMe_3	44
7	0.10	PBu_3	<10[b]
8	0.025	PMe_3	67

[a] Complicated mixture of products was observed by ^1H NMR.
[b] Inseparable mixture of products, yield estimated from ^1H NMR.

To ensure that direct reaction of the phosphine with the epoxide was not a competing or interfering process, control reactions were carried out. Reaction of epoxides **7** or **8** with 1 equiv of either PBu_3 or PMe_3 in *t*-BuOH (0.05 M) at room temperature for 20 h resulted in the recovery of 90–95% of the epoxide (Eq. 3).



These results strongly suggest that the traditional MBH organocatalyzed mechanism[3] described in Scheme 1 is operative and the trialkylphosphine acts as a nucleophile adding to the enone and not the epoxide. Conjugate addition of PMe_3 to the enone gives rise to a zwitterionic enolate, which subsequently adds to the epoxide giving the corresponding zwitterionic alkoxide. Subsequent alkoxide induced elimination of Me_3P gives rise to the observed cyclic enone homoaldol adduct. A number of epoxy enones underwent effective cyclization giving new homologous MBH adducts resulting from opening of the epoxide by the zwitterionic enolate (Table 2). Enones with terminal unsubstituted epoxides, **10** and **13**, gave almost equimolar mixtures of the *endo* and *exo* modes of opening due to minimal steric bias. The products of a 5-*exo* mode of opening, alcohols **12** or **15**, respectively, should be expected to be favored kinetically. However, with the unsubstituted epoxide terminus, the 6-*endo* mode of cyclization apparently competes favorably giving rise to alcohols **11** or **14**.

Table 2
Homologous Morita–Baylis–Hillman type epoxide-opening reactions[a]

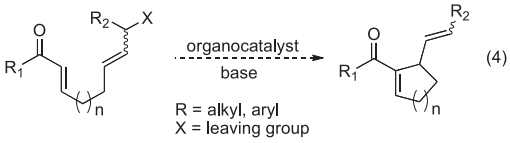
Entry	Epoxide	Equiv PMe_3	Time (h)	Product(s)			Yield (%)
1	**4** R=Me	1.0	30	**6**			67
2	**5** R=Ph	1.0	30	**9**			66
3	**10** R=Me	1.0	18	**11**	1.7:1	**12**	65
4	**13** R=Ph	1.0	18	**14**	1.7:1	**15**	73
5	**16** R=Me	1.0	72	**17**			60
6	**18** R=Ph	1.0	72	**19**			50
7	**20** R=Me	1.0	18	**21**			76
8	**22** R=Ph	1.0	18	**23**			70
9	**24** R=Me	10.0	7 days	**25**			43
10	**26** R=Ph	10.0	72	**27**			92

[a] Reactions were conducted at a concentration of 0.025 M in *tert*-butanol at room temperature.

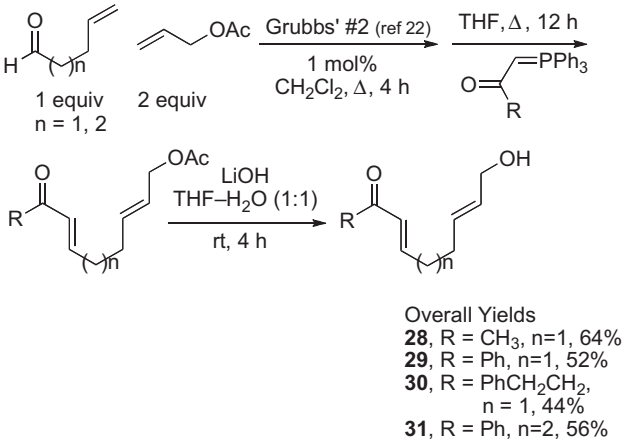
Reaction at the unsubstituted epoxide terminus giving *endo* selectivity is competitive in the absence of any other overriding steric factors evident in the examples in entries 5–10, Table 2. While reaction of the unsubstituted epoxides **10** or **13** (entries 3 and 4, Table 2) exhibited marginal regioselectivity in the epoxide opening, the examples in entries 5–10 were highly selective. Introduction of geminal substituents adjacent to the epoxide (entries 7 and 8) did not have a detrimental effect on the cyclization, and ring opening via the 6-*endo* mode was preferred due to significant steric interactions generated between the geminal dimethyl groups and the enolate as shown with transition state models **20x** and **20n** (Fig. 1). Reaction of the gamma-disubstituted enone was expected to be slow if reactive at all. Substitution adjacent to the site of nucleophilic addition of Me_3P should make the addition difficult and thus decrease the zwitterion concentration. Reaction of methyl ketone **24** was extremely slow, requiring 7 days and 10 equiv of phosphine for complete consumption of starting material and a moderate 43% yield of product. The corresponding phenyl ketone **26** was consumed during the course of 72 h to give **27** in high yield, although 10 equiv of phosphine were also required. When the reaction of enone **24** was conducted at higher concentration (0.1 M) with 10 equiv of PMe_3 for 30 h, enone **25** was still generated in only 44% yield. As expected, opening to form the five-membered ring via the *exo* mode was preferred over the *endo* mode generating the cyclohexenol. In homologous cases where 6-*exo* adducts were expected to form we were unable to promote the desired cyclizations under our conditions.

2.2. Allyl halides as electrophiles[19]

With the successful development of the first homologous intramolecular MBH-type reaction utilizing epoxides we turned our attention to other underutilized electrophiles, particularly allylic halides, which we deemed potentially reactive under our conditions. In the case of sp^2 hybridized electrophiles there is some precedence for the use of allylic electrophiles in the Morita–Baylis–Hillman reaction. Basavaiah demonstrated the use of ethyl 2-bromomethyl acrylate in an intermolecular allylation to generate 1,4-pentadienes[6] and the Krische group cleverly blended organomediated and transition metal-catalyzed reactions in an enone *cyclo*-allylation reaction using primary allylic acetates.[7a] Consequently, we established an initial goal of utilizing allylic electrophiles in an entirely organomediated intramolecular MBH-type reaction (Eq. 4).



Preliminary studies evaluated the effectiveness of different leaving groups and organocatalysts. Primary allylic alcohols **28**–**31** were readily prepared in good overall yield beginning from 4-pentenal (Scheme 3). It was necessary to use the allylic acetate rather than the allylic alcohol to ensure high yields in the alkene cross-metathesis reaction.



Scheme 3. Synthesis of allylic alcohols **28**–**31**.

Our early efforts then focused on the reactions of allylic mesylates and tosylates.[20] As with the homologous MBH reaction, amine nucleophiles were found to be ineffective organocatalysts for the reaction. None of the expected cyclization adduct was seen with either tosylate **32** or mesylate **33** in solvents, such as THF, 1,4-dioxane, acetone, EtOAc, $CHCl_3$, CH_3CN, MeOH, EtOH, *t*-BuOH, and amyl-OH at temperatures from ambient to 63 °C. Accordingly, various tertiary phosphines, such as Bu_3P, Cy_3P, Ph_3P, and Me_3P,[7b,21] were investigated and it was found that Bu_3P provided the cyclization adduct **35** in moderate yield from either tosylate **32** or mesylate **33** (Eq. 5).

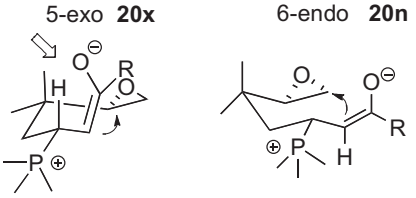
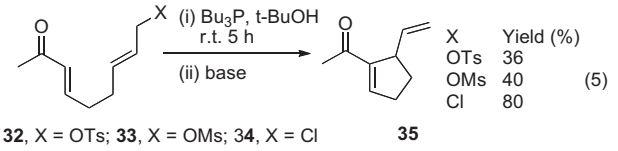


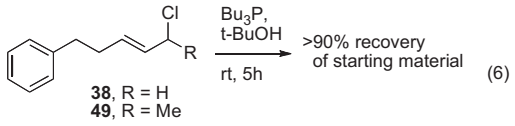
Fig. 1. Modes of Epoxide opening.



Optimal yields were obtained using mesylate **33** at ambient temperature, providing cyclic enone **35** in 40% yield within 5 h. In the traditional MBH reaction and presumably with our homologous MBH reaction utilizing epoxides, in the key carbon–carbon bond-forming step, an alkoxide anion is generated, which, either directly or indirectly, leads to product formation via α-deprotonation and expulsion of the phosphine catalyst.[3] However, in the case of an allylic halide the subsequent counterion is only weakly basic and therefore ineffective at promoting elimination of the phosphine catalyst from the product via α-deprotonation. It was reasoned that this might account for the low yields. Noting that a stronger base might facilitate the process, a variety of bases were screened including Et_3N, EtN^iPr_2, DBU, NaH, KH, NaOMe, *t*-BuOK, NaOH, and KOH but, in spite of these additional attempts at optimization, we were unable to improve on this initial result.

At this point we turned our attention to changing the leaving group to chloride. It was discovered that, upon treatment with 1 equiv of Bu_3P in *t*-BuOH (0.5 M) and similar screening of bases, chloride **34** gave an 80% isolated yield of the desired cyclization adduct **35** when KOH was used as the base under phase transfer conditions with $BnEt_3NCl$ (entry 1, Table 3).

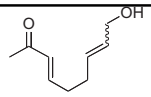
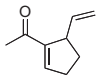
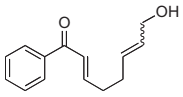
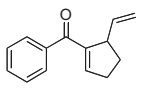
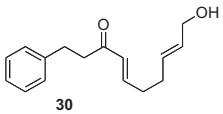
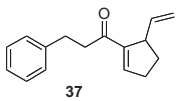
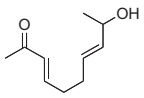
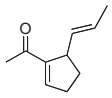
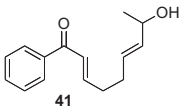
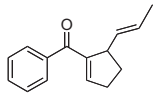
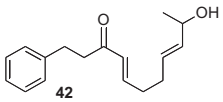
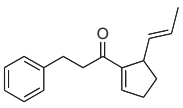
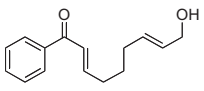
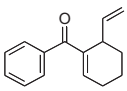
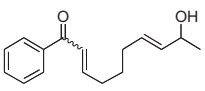
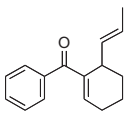
To gain insight into the mechanism, two reactions were performed using primary and secondary allylic chlorides **38** and **39**, respectively. Treated with 1 equiv of Bu_3P in *t*-BuOH for 5 h under the same conditions as the cyclization reactions, 90% of each allylic chloride was recovered. This discounted the possibility of an initial direct S_N2 attack of the phosphine at the allylic chloride moiety to give a phosphonium salt, which could also serve as a leaving group (Eq. 6).



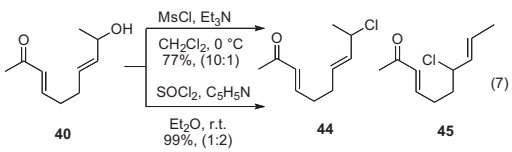
To further probe the scope of this transformation we tested the tolerance of the organomediated cyclization to structural alterations at both the enone and allyl moieties. Both aryl enones and sterically more encumbered alkyl enones readily underwent the Morita–Baylis–Hillman-type cyclization (entries 2 and 3; Table 3). Given these results we set out to evaluate the tolerance of the cyclization toward substitution at the allylic leaving group. Consequently, a series of secondary alcohols **40**–**43** was synthesized.

Conversion of alcohol **40** to the desired allylic chloride **44** using methanesulfonyl chloride resulted in a regioisomeric mixture (10:1) in favor of chloride isomer **44** (Eq. 7). Changing the chlorinating agent to $SOCl_2$ unfortunately gave a 1:2 ratio in favor of regioisomer **45**. Remarkably however, subjecting either regioisomeric mixture of allylic chlorides to the optimized cyclization conditions gave the desired cyclization product **46** (entry 4, Table 3) in an excellent 78% yield under equivalent reaction conditions. From a practical standpoint, preparation of the chloride using $SOCl_2$ became the method of choice. It was pleasing to find that secondary allylic alcohols of aromatic or aliphatic enones also cyclized without reduction in yield (entries 5 and 6). It is possible that the allylic isomers are interconverting under the reaction conditions or that both S_N2' and S_N2 mechanisms are operative.

Table 3
Organomediated cyclizations

Entry	Allylic alcohol[a]	Product	Yield[b] (%)
1	 **28** 9:1 E:Z	 **35**	80
2	 **29** 9:1 E:Z	 **36**	82
3	 **30**	 **37**	84
4	 **40**	 **46** >10:1 E:Z	78
5	 **41**	 **47** >10:1 E:Z	94
6	 **42**	 **48**	74
7	 **31**	 **49**	75[c]
8	 **43** 4:1 E:Z	 **50** >10:1 E:Z	80[c]

[a] Alcohols were converted to a regioisomeric mixture of allylic chlorides and used without further purification.
[b] Isolated yields after purification by silica gel chromatography.
[c] Me_3P was used.

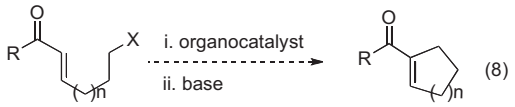


We turned our attention to the generation of six-membered rings in the cyclization event. Thus, subjecting alcohols **31** and **43** (entries 7 and 8, Table 3) to the optimized cyclization conditions (PMe_3, *t*-BuOH, CH_2Cl_2, KOH, $BnEt_3NCl$) gave enones **49** and **50** also in excellent yield.

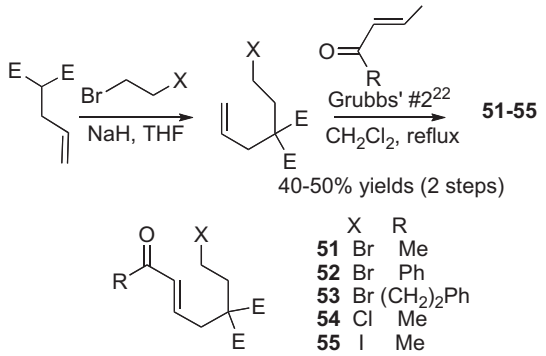
2.3. Alkyl halides as electrophiles[23]

In view of our success with sp^2 hybridized allylic electrophiles we chose to investigate the feasibility of extending our methodology to the related, yet unprecedented, cycloalkylation reaction

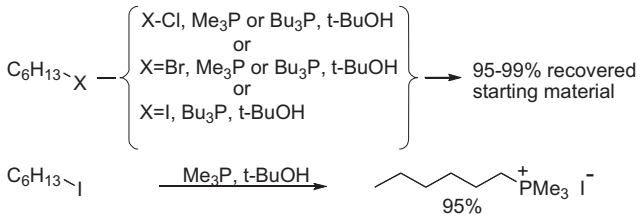
using an sp^3 hybridized electrophile to facilitate the formation of five- and six-membered enone cycloalkylation products, thus constituting a direct intramolecular α-alkylation of enones (Eq. 8).



To assess its viability, initial studies were performed using enones bearing different halide leaving groups. These were readily prepared from diethyl allylmalonate (Scheme 4) via alkylation with 1,2-dibromoethane or 1-bromo-2-chloroethane to give the substituted malonate, followed by cross-metathesis with the appropriate enone, using Grubbs second generation catalyst,[22] to furnish the desired cycloalkylation precursors **51**–**55** in good overall yields.



Scheme 4. Synthesis of alkyl halides **51**–**55**.

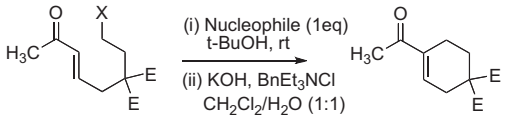


Scheme 5.

As we had previously observed with epoxides and allylic halides, amine nucleophiles were found to be ineffective at promoting the cycloalkylation of **51** in various solvents at temperatures from ambient to 63 °C. However, with the MBH-type allylation reaction, tertiary phosphine organocatalysts were found to be very effective at promoting the desired cyclization. Initial optimization studies revealed that treatment of bromide **51** with Bu_3P in 0.5 M *t*-BuOH at room temperature for 2 h followed by addition of KOH under phase transfer conditions afforded the cycloalkylation product **56** in excellent yield (entry 3, Table 4). In light of the transient nature of the putative MBH zwitterionic intermediate, this result is truly remarkable since sp^3 hybridized electrophiles are typically far less reactive than the sp^2 hybridized electrophiles used in traditional MBH reactions.

Following the initial cycloalkylation result, we set out to investigate the efficiency of the electrophilic partner. Reaction of chloride **54** with Bu_3P or Me_3P resulted in low recoveries of both starting material and cyclized enone (entries 1 and 2, Table 4). Evidently, the chloride is too weak of a leaving group to undergo facile displacement by the transiently formed zwitterionic enolate, thus giving rise to low yields of enone **56**. For the reaction of iodide **55** with Bu_3P, the cycloalkylation product was obtained in a slightly

Table 4
Optimization of cycloalkylation



51, X = Br; **54**, X = Cl; **55**, X = I **56**

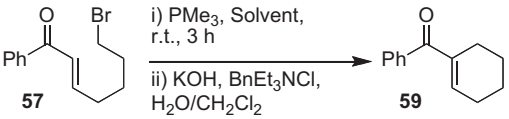
Entry	X	Nucleophile	Time (h)	Yield[a] (%)
1	Cl	Bu_3P	72	12[b]
2	Cl	Me_3P	72	46[c]
3	Br	Bu_3P	3	99
4	Br	Me_3P	5	98
5	I	Bu_3P	87	87
6	I	Me_3P	24	—[d]

[a] Isolated yields after purification by silica gel chromatography.
[b] Excess Bu_3P (3 equiv) added over 3 days; 18% recovery of chloride.
[c] Excess Me_3P (4 equiv) added over 3 days; 10% recovery of chloride.
[d] Decomposition of enone.

diminished yield when compared to reaction of the bromide (entry 5, Table 4). Use of Me_3P led to the disappearance of starting material, but no recognizable products were isolated after treatment with base. These results clearly illustrate the delicate balance of reactivity between the nucleophile and electrophilic centers in the molecule.

Further optimization studies (Tables 5 and 6) with **57** and **58** (for synthesis: see Scheme 6) confirmed *t*-BuOH as the most efficient solvent medium. Although acetone was also found to be an equally good solvent, results were more variable over a larger number of substrates and reaction runs. Reasonable yields were achieved in most solvents after 3 h, even under neat conditions (Table 5) and only in 2,2,2-trifluoro ethanol did the reaction fail to form product, with only starting material recovered after 3 h. Additionally, Me_3P and Bu_3P were confirmed as the catalysts of choice for the reaction (Table 6). As expected, Ph_3P was found to be completely inert under our reaction conditions, probably owing to its comparatively weak nucleophilic character, while $P(CH_2OH)_3$ resulted in a white uncharacterizable precipitate, which did not break down in the presence of base. We hypothesized that the alcohol probably plays a role in binding to the substrate to give a very stable complex or addition product. Some evidence for this was provide by the fact that $P(CH_2CH_2CH_2OH)_3$, where the oxygen is less accessible for intramolecular binding to the substrate once the catalyst has added, proved to be an efficient catalyst.

Table 5
Further optimization studies: solvents

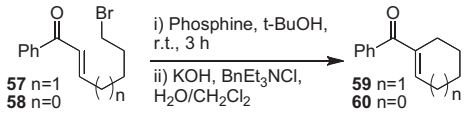


57 **59**

Entry	Solvent	Yield (%)
1	Neat	76
2	Hexane	77
3	Benzene	79
4	DCM	71
5	Acetonitrile	72
6	THF	80
7	Acetone	98
8	DMF	91
9	CF_3CH_2OH	0
10	*t*-BuOH	99

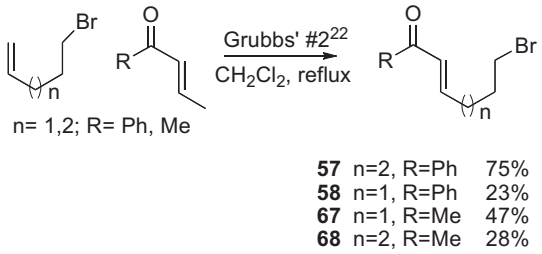
To discount the possibility that the phosphine reacted initially with the halide to generate a phosphonium salt, hexyl bromide, and chloride, where treated with 1 equiv of either Bu_3P or Me_3P in

Table 6
Further optimization studies: phosphines



Entry	Phosphine	*n*	Yield (%)
1	PMe_3	1	100
2	PBu_3	1	92
3	PPh_3	1	No reaction
4	$P(CH_2OH)_3$	0	—[a]
5	$P(CH_2CH_2CH_2OH)_3$	1	85

[a] Formed precipitate stable to base.



Scheme 6. Synthesis of alkyl halides **57**, **58**, **67**, and **68**.

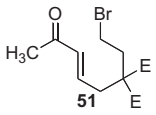
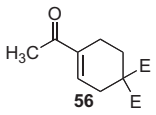
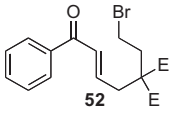
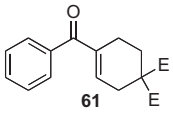
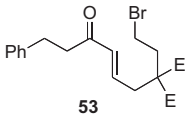
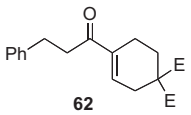
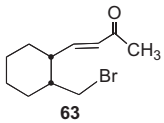
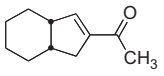
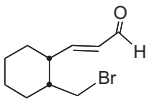
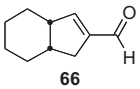
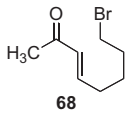
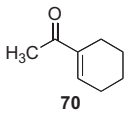
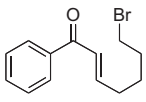
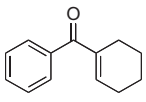
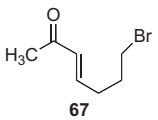
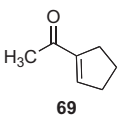
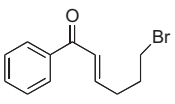
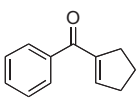
t-BuOH at room temperature for 5 h, resulting in quantitative recovery of the starting material (Scheme 5). Treatment of hexyl iodide with Bu_3P in *t*-BuOH also resulted in the quantitative recovery of the iodide. However, upon reaction of hexyl iodide with Me_3P in *t*-BuOH, the corresponding phosphonium salt, hexyl trimethylphosphonium iodide, was generated in 95% yield. This explains the differing cycloalkylation results in Table 4, entries 5 and 6 with alkyl iodides and their reaction with Bu_3P or Me_3P.

Having established that the phosphonium salt was not a likely intermediate using our optimized conditions we further probed the generality of the enone cycloalkylation. Remarkably, increasing the enone steric bulk had little consequence on the isolated yield of the six-membered ring cycloalkylation adducts (Table 7, entries 1–3). Even reactions of aryl enones were equally successful under these same reaction conditions.

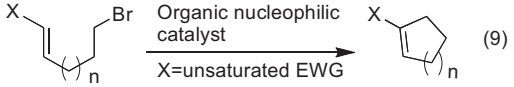
Driven by these results and building upon previous success, we directed our attention to the cyclic analogues **63** and **64**. As expected, treatment of enone **63** with 1 equiv of Bu_3P in 0.5 M *t*-BuOH at room temperature for 2 h followed by addition of KOH under phase transfer conditions afforded the *cis*-fused bicycle **65** in good yield. This cyclization protocol also cleanly provided bicyclic enal **66** in similarly high yield from enal **64**.

To further demonstrate the scope of this cyclization reaction we modified the tether leaving it unsubstituted to ascertain the extent to which steric compression in the transition state is necessary. Additional enones for the synthesis of five- and six-membered carbocycles were readily prepared via a cross-metathesis reaction starting with 5-bromo-1-pentene and 6-bromo-1-hexene to form the cycloalkylation precursors, in moderate to good yields (Scheme 6). Subjecting these compounds to the optimized cyclization conditions also gave the five- and six-membered cycloalkylation adducts in excellent yields (Table 7, entries 6–9).

Table 7
MBH-type cycloalkylation reactions

Entry	Alkyl Bromide	Product	Yield (%)
1	 **51**	 **56**	99
2	 **52**	 **61**	90
3	 **53**	 **62**	79
4	 **63**	 **65**	90
5	 **64**	 **66**	83
6	 **68**	 **70**	80
7	 **57**	 **59**	99
8	 **67**	 **69**	81
9	 **58**	 **60**	95

vinyl nitriles, vinyl sulfones, allenic esters, and acrolein (Eq. 9).[3] Recently the list of viable activated alkenes has been expanded to include thiol esters.[24]

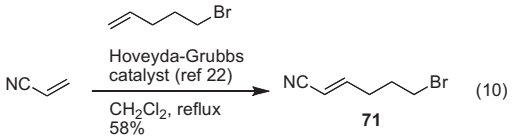


(9)

2.4. Investigation of alternative activated alkenes in the MBH-type alkylation reaction

2.4.1. Nitriles, esters, and acylpyrroles. Activated alkenes now utilized in the Morita–Baylis–Hillman reaction include acrylates,

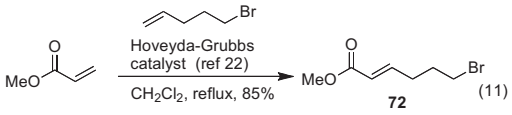
Consequently we sought to examine the tolerance of various alternative activated alkenes in the intramolecular MBH-type alkylation reaction. Accordingly, vinyl nitrile **71** was prepared via cross-metathesis of acrylonitrile with 5-bromo-1-pentene in 58% yield (Eq. 10).



(10)

Using the reaction conditions that were successful in the MBH-type alkylation reactions of enones, treatment of nitrile **71** with either Me_3P or Bu_3P in *t*-BuOH followed by base under phase transfer conditions failed to provide the desired product, with mainly starting material recovered. Hoping to promote cyclization by using a better leaving group, bromide **71** was converted to the corresponding iodide in 88% yield using NaI in acetone. However, after 24 h no reaction was observed from the addition of tributylphosphine to the iodide in *t*-BuOH.

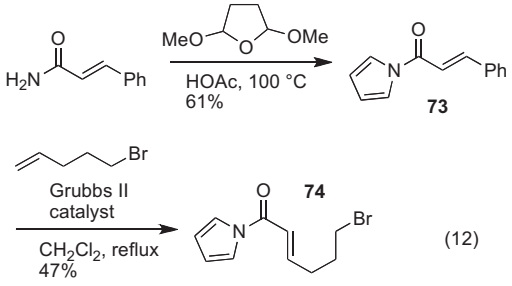
Given the apparent inertness of vinyl nitriles to our reaction conditions we turned to the use of oxoesters as alternative alkenes in the MBH-type alkylation.[4f] Hence, cross-metathesis of methyl acrylate with 5-bromo-1-pentene using Hoveyda–Grubbs catalyst provided ester **72** in 85% yield (Eq. 11).



(11)

Under the MBH-type alkylation conditions in the presence of Bu_3P, as with the unsaturated nitrile, no reaction was observed with the unsaturated oxoester and only starting material was recovered. Employing Me_3P, Bu_3P or Cy_3P as the nucleophile also failed to promote the expected cyclization. Again, employment of the more activated iodide analogue did not improve the reactivity.

Given that the intrinsic reactivity of α,β-unsaturated esters is lower than that of α,β-unsaturated ketones it was hoped a more reactive analogue might provide more promising results. α,β-Unsaturated *N*-acylpyrroles, incorporating the *N*-acylpyrrole ester equivalent, are known to exhibit reactivity similar to enones,[25a,b] consequently they were investigated as an alternative activated alkene in the Morita–Baylis–Hillman-type alkylation reaction. *N*-acylpyrrole **74** was synthesized in two steps starting from readily available cinnamamide. Cinnamamide in acetic acid was treated with 2,5-dimethoxytetrahydrofuran and heated to 100 °C for 24 h providing pyrrole **73** in 61% yield.[25c] Cross-metathesis with 5-bromo-1-pentene using Grubbs second generation catalyst[22] afforded *N*-acylpyrrole **74** in 47% yield (Eq. 12).

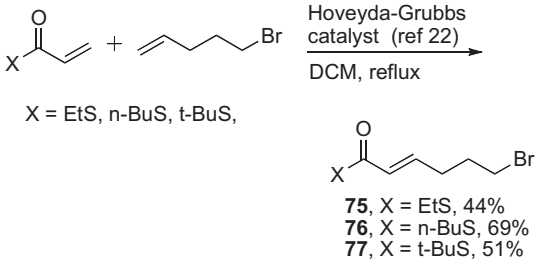


(12)

Treatment of *N*-acylpyrrole **74** with either Bu_3P or Me_3P in *t*-BuOH followed by addition of base under phase transfer conditions provided none of the desired cyclized products.

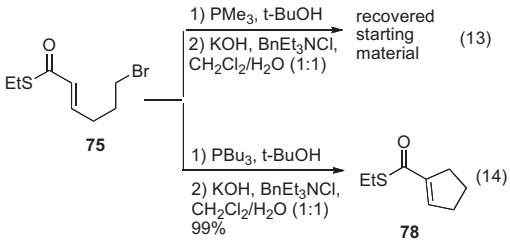
2.4.2. Thioesters[26]. Thioesters seemed an intriguing target for use in the Morita–Baylis–Hillman-type alkylation reaction due to their stability and ease in handling.[27] Keck employed thioesters containing enolizable aldehydes in the intramolecular Morita–Baylis–Hillman reaction.[4f] Treatment of unsaturated thiol esters with a catalytic amount of Me_3P provided efficient cyclization, giving rise to both cyclohexene and cyclopentene derivatives in good yields. In addition, Krische examined thiol esters with vinyl sulfones as the electrophilic partner.[28] Using catalytic amounts of Bu_3P, five- and six-membered ring cross-Michael cycloisomerization products were obtained in excellent yields.

A series of unsaturated thioesters were synthesized, in the same manner as for the oxoesters, via cross-metathesis of acrylates with 5-bromo-1-pentene (Scheme 7).



Scheme 7.

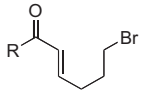
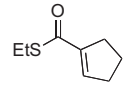
Reaction of unsaturated thioester **75** with 1 equiv of Me_3P in *t*-BuOH followed by the addition of KOH and $BnEt_3NCl$ in DCM/H_2O (1:1) provided none of the desired product (Eq. 13). However, recognizing the variability in effectiveness of trialkylphosphine catalysts with different substrates from our earlier work on the MBH-type alkylation of enones, the MBH-type alkylation of thioester **75** was attempted using Bu_3P. Treatment of thioester **75** in *t*-BuOH with Bu_3P followed by addition of base under phase transfer conditions provided 99% of the desired cyclized enone **78** (Eq. 14).



(13)
(14)

Building on these promising initial results, the impact of steric bulk on the thioester alkyl group was investigated. Treatment of *n*-butyl thioester **77** with Bu_3P in *t*-BuOH followed by addition of KOH and $BnEt_3NCl$ in DCM/H_2O (1:1) afforded the desired product, **79**, in 95% yield (Table 8, entry 2). Unfortunately treatment of *tert*-butyl thioester **77** with Bu_3P in *t*-BuOH followed by addition of base under phase transfer conditions provided none of the desired product, leaving only starting material. It was speculated the steric hindrance of the more bulky *tert*-butyl thioester group might be slowing down nucleophilic addition to the unsaturated thioester thus minimizing the concentration of zwitterion available for cyclization. With this in mind, thioester **77** in *t*-BuOH was treated with Me_3P followed by addition of base under phase transfer conditions giving 60% of the desired product **80** (Table 8, entry 3).

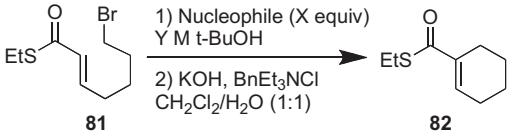
Table 8
Impact of thioester steric bulk on product yield

Entry	Thiol ester		Product	Yield (%)
				
1	**75**	R=EtS	**78**	99
2	**76**	R=*n*-BuS	**79**	95
3	**77**	R=*t*-BuS	**80**	60[a]

[a] Me_3P was used.

To further expand the reaction scope, precursors to generate six-membered rings were synthesized. Treatment of thioester **81** in *t*-BuOH with 1 equiv of Bu_3P followed by the addition of KOH and $BnEt_3NCl$ in DCM/*t*-BuOH (1:1) did not afford the desired product (Table 9, entry 1). More concentrated conditions were found not to be of benefit (entry 5). Likewise treatment of thioester **81** with 2 equiv of Bu_3P failed to provide the desired product leaving mainly starting material along with some decomposition (entry 3). However, treatment of thioester **81** in *t*-BuOH with Me_3P followed by the addition of base under phase transfer conditions yielded 21% of the desired product (entry 2). Increasing the concentration of the reaction from 0.5 M to 1 M provided only a slight increase in the yield of the desired product (entry 6). Lastly, addition of 2 equiv of Me_3P following the same procedure gave 47% of the desired product **82** as well as some decomposition of starting material (entry 4).

Table 9
Optimization of reaction conditions for six-membered ring formation



81 **82**

Entry	Nucleophile	X	Y	Yield (%)
1	PBu_3	1	0.5	0
2	PMe_3	1	0.5	21
3	PBu_3	2	0.5	0
4	PMe_3	2	0.5	47
5	PBu_3	1	1	0
6	PMe_3	1	1	29

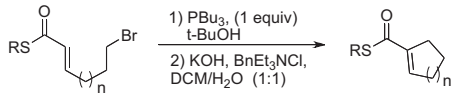
Speculating that by exploiting Thorpe–Ingold assistance, the formation of six-membered rings might be made more efficient, enones substituted on the tether were synthesized. Treatment of **83** with Bu_3P in *t*-BuOH followed by the addition of KOH under phase transfer conditions, afforded six-membered ring **84** in 92% yield (Table 10, entry 5). As expected, and building on this excellent result, reaction of thioesters **85** and **87** with Bu_3P in *t*-BuOH followed by the addition of base under phase transfer conditions provided the products, **86** and **88**, in 91% and 82% yield, respectively (Table 10).

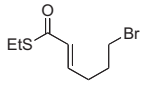
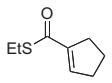
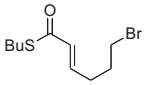
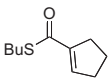
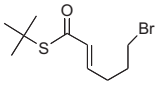
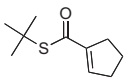
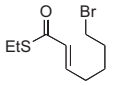
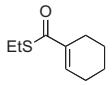
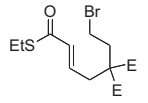
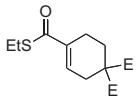
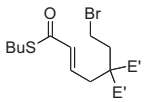
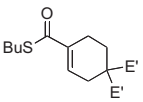
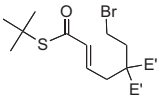
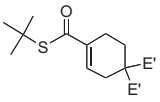
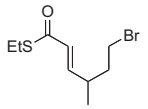
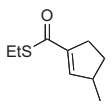
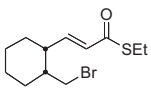
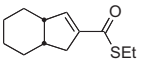
For unsaturated thioester **89**, regardless of whether Bu_3P or Me_3P were used, none of the desired cyclic enone was isolated. Speculating that the substitution at the gamma position might be hindering addition of the nucleophile to the activated alkene, excess phosphine was used, however neither five nor 10 equiv of either phosphine promoted the desired process. Hoping to use a more rigid conformation to assist in the cyclization of substituted enoates, a *cis*-fused bicycle was targeted where substitution at the γ-position was still present. Treatment of thioester **91** with Bu_3P in *t*-BuOH followed by addition of KOH and $BnEt_3NCl$ in DCM/H_2O (1:1), afforded *cis*-fused bicycle **92** in 85% yield (Table 10, entry 9).

3. Catalytic intramolecular cycloalkylation[29]

Organocatalyzed reactions[30] have broad applications and have been used extensively in the Mannich, Wittig,[31] Aldol,[32] and Michael[33] reactions and have more recently been applied to the Stetter,[34] Sonagashira,[35] Ullmann,[36] and aza-Henry reactions.[37] In the past few years there has been significant progress in realizing more effective catalysis of the organocatalyzed Morita–Baylis–Hillman (MBH) reaction. While the MBH reaction has drawn increasing attention in the past 15 years and has seen tremendous refinement of conditions, trialkylphosphines[38] as catalysts have not been as widely employed as tertiary amines. Having

Table 10
Morita–Baylis–Hillman-type alkylation of unsaturated thioesters



Entry	Thiol ester		Product		Yield (%)
1		**75**		**78**	99
2		**76**		**79**	95
3		**77**		**80**	60[a]
4		**81**		**82**	47[b]
5[c]		**83**		**84**	92
6[d]		**85**		**86**	91
7[d]		**87**		**88**	82
8		**89**		**90**	0
9		**91**		**92**	85

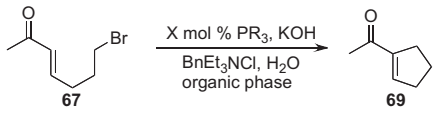
[a] 1 equiv of Me_3P.
[b] 2 equiv of Me_3P.
[c] E=CO_2Et.
[d] E'=CO_2Me.

provided the first examples of the intramolecular Morita–Baylis–Hillman-type reaction employing an alkyl halide as the electrophile,[23] we set out to augment the synthetic utility and increase the efficiency of the reaction by employing catalytic amounts of the nucleophilic organomediator.

To assess the feasibility of the proposed transformation and the compatibility of the reagents, a trialkylphosphine mediated intramolecular cycloaddition of bromo enone **67** (Table 7) was attempted. Upon exposure of 1 mmol of enone **67** in 2 mL of *t*-BuOH/DCM (1:1) and 5 mL of a 0.2 M solution of KOH, to 27 mg (0.1 mmol) of $BnEt_3NCl$ and a stoichiometric amount of Bu_3P, the desired product, enone **69**, was obtained with no reduction in yield when compared to the stoichiometric reaction involving the sequential addition of reagents. This result suggested all the reagents required for the stepwise process were compatible with each other and thus that use of a catalytic amount of trialkylphosphine should be feasible.

Accordingly, enone **67**, in a solution of 0.5 M *t*-BuOH/DCM (1:1), 1 equiv of 0.2 M aqueous KOH, and 0.1 equiv of $BnEt_3NCl$, was treated with 20 mol % of Me_3P. However, only starting material was recovered and we speculated that the volatility of Me_3P might be a problem. Upon exchanging the catalyst with the less volatile Bu_3P the desired product was obtained in 84% yield (Table 11, entry 2). Building on this initial result we set out to further optimize the reaction conditions and investigate the role of the components involved in the reaction. In the absence of methylene chloride the reaction was very slow and after 5 days had not gone to completion, producing only 56% of the desired product (Table 11, entry 3). The reaction was also run using various amounts of Bu_3P in order to determine the optimal percent loading of the catalyst. Upon treatment of enone **67** with 10 mol % of Bu_3P under the standard conditions a reduced yield of 65% of the desired product was obtained in comparison to the 84% yield when 20 mol % of the catalyst was used (Table 11, entry 2 vs entry 4). With these results in hand it was necessary to discount the possibility of base catalyzed enolate formation followed by alkylation as a means of forming cyclic enone, **69**. Reaction of bromide **67** with aqueous KOH and $BnEt_3NCl$ in 0.5 M *t*-BuOH/DCM (1:1) in the absence of PR_3 gave 95% yield of starting material suggesting the reaction was not simply base catalyzed but required the use of an organocatalyst (Table 11, entry 5). With these optimized reaction conditions, application to more a diverse set of substrates was performed (Table 12).

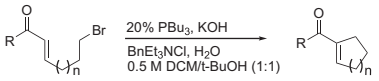
Table 11
Optimization of Catalytic MBH-type cycloalkylation reactions

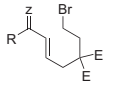
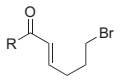
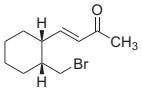
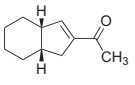


Entry	PR_3	X mol %	Organic phase	Yield (%)
1	PMe_3	20	DCM/*t*-BuOH	0
2	PBu_3	20	DCM/*t*-BuOH	84
3	PBu_3	20	*t*-BuOH	56
4	PBu_3	10	DCM/*t*-BuOH	65
5	—	—	DCM/*t*-BuOH	95 (r.s.m.)

Five-membered rings were readily formed in yields equal to those reported using stoichiometric amounts of trialkylphosphine.[23] Unfortunately, upon increasing the anticipated ring size by one carbon, difficulties were encountered in the cyclization under the previously optimized conditions with a couple of exceptions. Highly activated, electron deficient enone **95** and phenyl enone **52** readily cyclized with the latter owing to the ease of cyclization to Thorpe–Ingold assistance provided by substitution on the tether. However, without the substitution on the tether, phenyl enone **57** initially failed to cyclize in spite of the stability of the enolate formed upon conjugate addition of the phosphine nucleophile. Further optimization was needed in order to effect cyclization of the less activated enones that form six-membered rings. Having optimized the catalyst loading, demonstrated the necessity of the methylene chloride and investigated the role of the base, we focused our attention on the concentration of the organic phase. Accordingly phenyl enone **57** was treated with 20 mol % of Bu_3P, KOH, and $BnEt_3NCl$ under more concentrated 5 M conditions in the organic phase, resulting in 33% recovery of product **59**. The concentration was subsequently decreased to 3 M and eventually 1 M, which yielded 45% of the desired product (Table 12, entry 4). Further dilution decreased the yield to where little or no product was formed. Having established

Table 12
Catalytic MBH-type cycloalkylation reactions

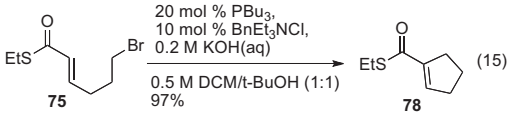


Entry	Bromide		Enone	Time (h)	Yield (%)
1[a]		**51** R = CH_3 **52** R = Ph E = CO_2Et	**56** **61**	5 2	43 91
3		**68** R = CH_3	**70**	—	0
4[a]		**57** R = Ph	**59**	5	45
5[a]		**93** R = naphth	**94**	5	94
6		**95** R = p-$NO_2C_6H_4$	**96**	0.1	97
7		**67** R = CH_3	**69**	3	84
8		**58** R = Ph	**60**	3	88
9		**97** R = naphth	**98**	2	97
10		**99** R = p-$NO_2C_6H_4$	**100**	0.1	99
11		**63**	**65** 	5	90

[a] For entries 1,4, and 5 a 1.0 M solution of *tert*-butyl alcohol/methylene chloride (1:1) was employed for the catalytic reaction.

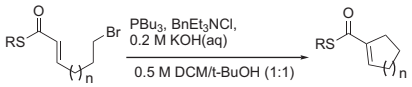
a newly optimized procedure for formation of six-membered rings, bromides **51** and **93** were submitted to the new conditions giving 43% and 94% of the desired products, respectively (Table 12, entries 1 and 5).

For the homologous intramolecular Morita–Baylis–Hillman-type reaction, in which epoxides were employed as the electrophilic group, an initial study revealed that the use of substoichiometric amounts of trialkylphosphine required reaction times of the order of days to achieve acceptable yields. Consequently, further development of a catalytic version of the reaction was abandoned. However, having shown that unsaturated thioesters work well in the stoichiometric Morita–Baylis–Hillman-type alkylation reaction, we viewed them as ideal substrates for screening in the catalytic version of the MBH-type cycloalkylation.[26] Thioester **76** was subjected to the optimized conditions used for alkyl enones. Thus, thioester **75** with 10 mol % $BnEt_3NCl$ and 0.2 M KOH(aq) solution, in 0.5 M DCM/*t*-BuOH was treated with 20 mol % Bu_3P, and as expected, thioester **78** was obtained in 97% yield (Eq. 15).



The generality of thioesters in the catalytic reaction was explored as summarized in Table 13. Upon treatment of thioester **76** with 20 mol % Bu_3P, the desired product **79** was isolated with no reduction in yield (Table 13, entry 2). The bulky thioester **77** was not investigated in the catalytic reaction due to the fact that the reaction failed to provide products when stoichiometric Bu_3P was employed (cf. Table 10, entry 3) and the use of Me_3P in the catalytic reaction proved futile due to its volatility. Formation of six-membered ring adducts preceded with ease in the catalytic reaction. Thioesters **83**, **85**, and **87** all furnished the cyclized product in 90%, 83%, and 79% yield, respectively, exhibiting only a slight reduction of yield (cf. Table 10, entries 5, 6, and 7). Lastly, thioester **91** failed to form products when treated with 20 mol % of Bu_3P in a 0.5 M organic solution. However, when thioester **91** was subjected to reaction with 20 mol % of Bu_3P in 1.0 M CH_2Cl_2 cyclization proceeded to give 85% yield of the desired product **92** (Table 13, entry 4).

Table 13
Catalytic MBH-type alkylation of unsaturated thioesters

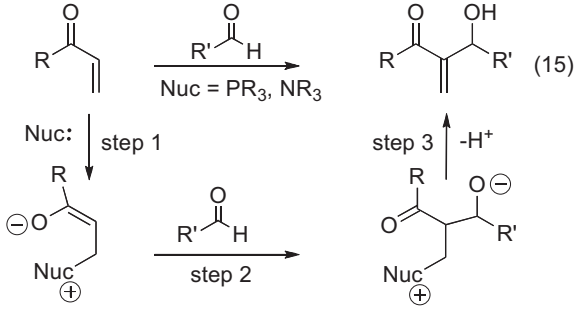


Entry	Thiol Ester	Product	Yield (%)
1	**75**, R = Et	**78**	97
2	**76**, R = Bu	**79**	96
3	**77**, R = t-Bu	**80**	–
4	**91**	**92**	85[a]
5[b]	**83**, R = Et	**84**	90
6[b]	**85**, R = Bu	**86**	83
7[b]	**87**, R = t-Bu	**88**	79
8	**81**	**82**	–

[a] Under catalytic conditions a 1.0 M organic phase was used. Reaction times varied from 1 h to 16 h.
[b] **83**, **84** E = CO_2Et; **85**, **86**, **87**, **88**, E = CO_2Me.

4. Mechanistic study: isolation of the zwitterionic intermediate[39]

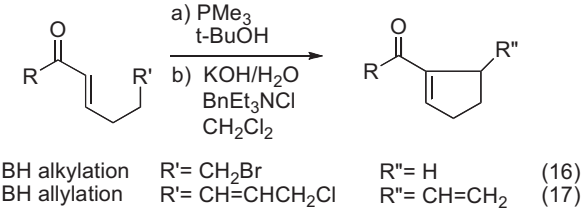
The generally accepted mechanism of the Morita–Baylis–Hilman reaction[1,2] involves three steps (Scheme 8, Eq. 15); nucleophilic addition to the enone, reaction of the aldehyde with the resulting zwitterionic intermediate, and base promoted elimination. An electrostatic interaction between the positive center and the enolate oxygen was proposed to stabilize the zwitterionic intermediate formed in step 1 and has been considered a key component necessary for success in the MBH reaction.[3] However, no intermediates in the MBH reactions had been isolated and characterized at the time of our investigation.[40] Shi and co-workers proposed that an interaction between an alcohol on a chiral phosphine {(*R*)-2′-diphenylphosphanyl-[1,1′] binaphthalenyl-2-ol} and the *Z*(*O*)-zwitterionic enolate oxygen was responsible for enantioselectivity in an asymmetric aza-Baylis–Hillman reaction.[41]



Scheme 8.

The rate determining step has long been considered to be the aldehyde addition step,[3] however work by the McQuade group suggests that the elimination step is rate determining.[42] McQuade found the MBH reaction, under aprotic, protic, polar and non-polar conditions, to be second order in aldehydes and therefore proposed a hemiacetal intermediate, which assists the proton transfer step. Aggarwal had similar findings in that the RDS is step 3, the proton transfer step. However, his data suggests that in the absence of protic solvents, while the initial RDS is the proton transfer step, once there is a build up of enough product the RDS reverts back to the previously conceived one, the aldehyde addition step.[43]

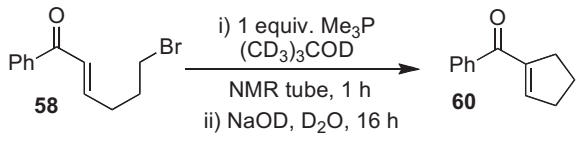
When aldehydes are used as the electrophilic partner in the MBH reaction a phosphonium alkoxide is generated in step 2, which involves the zwitterionic enolate adding to the aldehyde in an aldol fashion (Scheme 8). However, in the key C–C bond-forming step in either the MBH alkylation or allylation the resulting phosphonium counterion is a weakly basic halide ion, therefore a second discrete step involving the addition of a stronger base was required to promote formation of the product (Scheme 9).



Scheme 9.

To gain a greater insight into the mechanism of the MBH-type alkylation reaction we set out to investigate the nature of the two-stage cycloalkylation process. Upon reaction of bromide **51** with either Bu_3P or Me_3P, the starting material is completely consumed as evidenced by TLC analysis. Direct treatment of the resulting mixture with base under phase transfer conditions generates cycloalkylation product **56**. Under identical conditions, reaction of bromide **51** with only 0.5 equiv of Me_3P gave rise to 44% of enone **56** and 51% recovery of starting material.

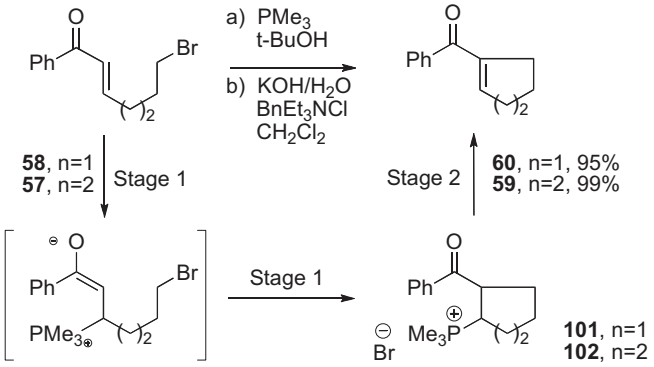
To probe the identity of the intermediate material, enone **58** (Scheme 10) was treated with 1 equiv of Me_3P in $(CD_3)_3COD$ in an NMR tube. During the course of the reaction (1 h), ^1H NMR spectral analysis, taken at 5 min intervals, revealed that the signal for the methylene protons on the carbon bearing the bromide gradually disappeared suggesting that cyclization was occurring. Once the bromomethylene proton signal was completely gone, the solution in the NMR tube was treated with NaOD in D_2O. Enone **60** was observed to slowly form (16 h) as determined by the gradual appearance of the signal for the alkene hydrogen of the newly forming enone during this time period. This information strongly suggested that cyclization had occurred prior to the addition of base, which serves only to promote elimination to the enone analogous to step 3 in the general mechanism.



Scheme 10.

Therefore in the MBH-type alkylation and presumably the allylation, three steps are also involved in the mechanism as in the traditional MBH reaction, however they are evident as two distinct and separate stages. The first stage encompassing the first 2 steps of

the general mechanism, the addition of the nucleophile to the activated alkene followed by the cyclization step to form the beta-phosphonoketone (Scheme 11) and the second stage, involving base promoted elimination to give the product.



Scheme 11.

With two distinct stages present, it opened the possibility for isolation and characterization of a reaction intermediate before addition of base. Accordingly, we attempted to isolate the phosphonium salt from an MBH-type alkylation and determine its structure by X-ray crystallography. The stereochemical information obtained from the crystal structure and related transition state analyses was viewed to potentially have important mechanistic implications for the MBH reaction.

For a typical MBH-type alkylation, treatment of enone **58** with Me_3P followed by addition of base under phase transfer conditions (100 mol % KOH, 10 mol % $BnClEt_3N$, DCM/H_2O 0.1 M) yielded 95% of cycloalkenone **60** in a one-pot, two stage process (Scheme 11). Upon addition of 1 equiv of Me_3P to enone **58** in *t*-BuOH a precipitate forms in 3 h. Filtration yields 98% of a solid whose ^1H NMR spectrum suggested that it was phosphonium salt **101**, an assumed intermediate in the process,[3,44] Recrystallization of the solid from cyclohexane/CH_2Cl_2 under argon yielded X-ray quality crystals. Attempts to obtain X-ray quality crystals of the intermediate formed from addition of Me_3P to enone **57** were also made. However, keto-phosphonium salt **102**, although isolable as a white solid, did not form crystals suitable for X-ray analysis.

The structural representation for keto-phosphonium salt **101** is illustrated in Fig. 2. A striking characteristic of the intermediate evident in the crystal structure is that the ring substituents are in the trans orientation. To determine whether the keto-phosphonium salt **101** was formed under kinetic or thermodynamic conditions, enone **58** was treated with 1 equiv of PMe_3 in $(CD_3)_3COD$ (0.17 M) for 5 min. A lower concentration was used to ensure that the intermediate remained in solution. Intermediate **101** that precipitated during the reaction conducted at higher concentration was identical to the intermediate that was isolated from the solution, with

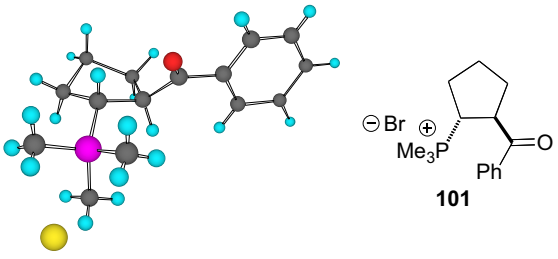


Fig. 2. Structural representation for phosphonium salt **101**. Br is disordered with a half water molecule; Br(2) and the water are removed for clarity.

analysis by 500 MHz ^1H NMR spectroscopy revealing that no deuterium was incorporated either α to the ketone or phosphonium salt. This strongly suggested that the intermediate isolated is the kinetic product. Furthermore, analysis of the resulting enone showed no deuterium incorporation at the alkene β-position.

The stereochemistry of the *trans*-disubstituted phosphonium ketone **101** can be correlated with potential transition state conformations leading to its formation. Consideration of both chair-like and boat-like conformations and the *Z*(*O*)- and *E*(*O*)-enolates, provides four viable transition states that lead to the trans stereochemistry (Fig. 3; **A**–**D**). Steric interactions present in the boat-like conformations (**B**, **D**) should result in a higher transition state energy. Either of the chair-like conformations could be considered likely transition states. However, it is remarkable that none of the four conformations exhibit any obvious electrostatic interaction between the positively charged phosphorus and the negatively charged enolate oxygen, an attractive force that has been the cornerstone of the traditional MBH explanation.

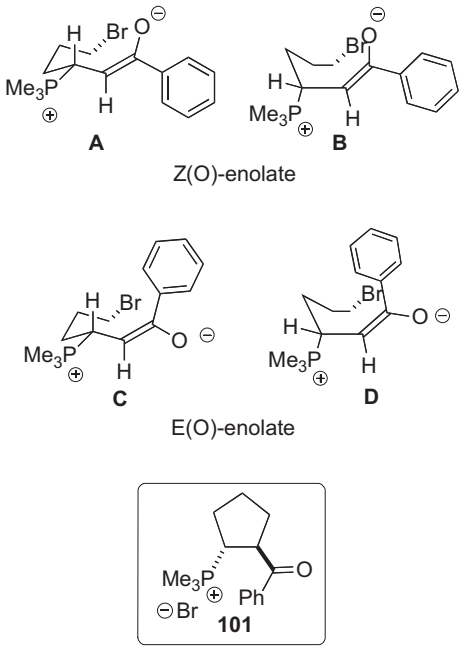


Fig. 3. Transition states leading to trans-disubstituted phosphonium ketone, 101.

With the *E*(*O*)-enolates, electrostatic interaction is sterically prohibited, whereas reactions proceeding through the *Z*(*O*)-enolate could develop electrostatic interactions, but these transition states would lead to the cis-disubstituted intermediate, that is, not observed (Fig. 4; **E**, **F**). Electrostatic interactions in ketophosphonium salts were recently described as a control element in a regioselective intramolecular aldol cyclization.[45]

The generally accepted explanation regarding the putative intermediate in the traditional MBH reaction takes advantage of an electrostatic interaction between the positively charged phosphorus and the enolate oxygen as a necessary stabilizing interaction that drives the C–C bond-forming step.[3] However, any intermediate exhibiting this type of electrostatic interaction will necessarily lead to the *cis*-disubstituted phosphonium ketone (Fig. 4, **E** and **F**). Our results, in which the trans-disubstituted intermediate salt has been isolated from the MBH-type alkylation under kinetically controlled conditions, suggest that this electrostatic interaction, while typically an electronically favorable interaction, is not the overriding electronic influence defining the stereochemical outcome of the cyclization. We don't rule out the existence of electrostatically stabilized *Z*-enolates, only that they

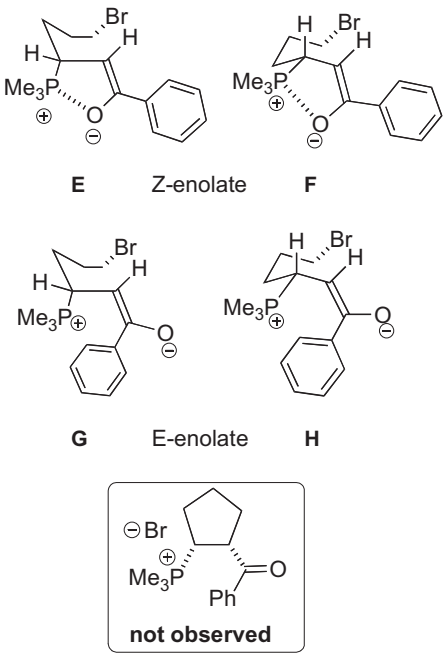


Fig. 4. Transition states leading to a cis-disubstituted phosphonium ketone.

are not the dominant species in the alkylation transition state These results obtained in the MBH-type alkylation suggest that the oxygen–phosphorus electrostatic interaction in the transition state, long considered to be a key component in the traditional MBH reaction, is not a requirement for successful MBH-like alkylation.

5. Summary

From the initial development of a homologous MBH, utilizing epoxides as electrophiles, we were able to expand and adapt the methodology to enable the exclusively organocatalyzed intramolecular allylation of enones and to develop the first intramolecular MBH-type alkylation of activated alkenes. We successfully utilized both enones and unsaturated thioesters as the activated alkene component. This work, carried out using stoichiometric amounts of the trialkylphosphine, gave an array of functionalized five- and six-membered carbocycles in high yields. In the case of six-membered rings steric assistance from the Thorpe–Ingold effect is often required to ensure an efficient reaction. With the more reactive systems, particularly the cycloalkylation of enones and thioesters, we saw the opportunity to further enhance the methodology by developing conditions that allowed the use of substoichometric amounts of the phosphine catalyst in the reaction. As a result both five- and six-membered rings can be formed efficiently with little to no loss in yield upon comparison to yields obtained when stoichiometric amounts of trialkylphosphines are employed. Finally we were able to isolate for the first time an MBH-type intermediate exhibiting unprecedented trans geometry of the phosphonium salt and acyl group. The lack of the previously accepted electrostatic stabilization of the zwitterionic intermediate in this alkylation provides new insight into the MBH mechanism.

6. Experimental

6.1. General

All oxygen- or moisture-sensitive reactions were carried out in oven-dried glassware under a positive pressure of argon. Sensitive liquids and solutions were transferred by oven-dried glass syringes, or canula and were introduced through rubber septa through, which a positive pressure of argon was maintained. Concentration of solutions was accomplished using a Buchi rotary evaporator with a water aspirator followed by removal of residual solvents on a vacuum line held at 0.1–1 Torr. Unless otherwise noted, all reagents and solvents were used without additional purification. Exceptions include: Et_2O (ether) and THF were distilled from sodium-benzophenone ketyl under argon; pyridine, methylene chloride, triethylamine, and *t*-BuOH were distilled from CaH_2 under argon atmosphere. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} glass plates. Visualization on TLC achieved by use of UV light (254 nm) or exposure to basic potassium permanganate solution, acidic anisaldehyde, or 5% phosphomolybdic acid in ethanol stain followed by heating. Flash column chromatography was carried out using Merck 60, 230–400 mesh ASTM silica gel. Additional purification was achieved through use of a CombiFlash Graduate Medium Pressure LC unit. Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was recorded on a Varian Fourier Transform 500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform or in ppm relative to the singlet at 7.15 ppm for benzene. The following abbreviations are used to describe peak patterns where appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants, *J*, are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on a Varian Fourier Transform 300 (75 MHz) and was fully decoupled by broadband decoupling. Chemical shifts are reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.0 ppm or for benzene-d_6 at 128.0 ppm. Infrared (IR) spectra were recorded as thin films on sodium chloride plates using a Perkin–Elmer FTIR Paragon 1000 Fourier Transform spectrometer with frequencies given in reciprocal centimeters (cm^{-1}). Mass spectra were obtained on a Jeol model JMS600H mass spectrometer using either fast atom bombardment (FAB^+) or electron impact (EI) (70 eV). Elemental analyses were performed by Atlantic Microlab Inc. in Northcross, GA.

All compounds isolated and characterized were colorless oils.

Compounds **7**,[46] **35**, **36**, **49**,[7a] **70**,[47a] **69**,[47b] **59**, **60**,[47c] **71**,[48] **72**,[49] **73**,[50] **80**,[51] and **82**[52] have been previously reported.

6.2. Typical cross-metathesis procedure

To a solution of methyl vinyl ketone (2.8 g, 40 mmol), 1,2-epoxy-5-hexene (3.9 g, 40 mmol) and methylene chloride (120 mL) was added 849 mg of Grubbs second generation catalyst (1 mmol). The reaction mixture was then refluxed under argon for 18 h. Upon completion of the reaction, the methylene chloride was removed in vacuo and the mixture was passed through a short plug of silica gel with 50% ethyl acetate in hexanes. Subsequent column chromatography using 50% ethyl acetate in hexanes provided a brown oil. A distillation under reduced pressure (0.1 mmHg) at 150 °C (bath temperature) afforded 3.25 g (58%) of epoxide **10** as a colorless oil.

6.3. Typical epoxidation procedure

To a solution of nona-3,7-dien-2-one (2.7 g, 19.5 mmol) in methylene chloride (65 mL) was added MCPBA (4.8 g, 19.5 mmol). The reaction mixture continued to stir at room temperature for 12 h. Upon completion of the reaction, the mixture was diluted with methylene chloride, washed with a solution of saturated sodium bisulfite and then with 1 M sodium hydroxide, dried over $MgSO_4$, and filtered through a short pad of Celite. Subsequent purification by column chromatography using 25% ethyl acetate in hexanes provided 2.46 g (82%) of epoxide **4** as a colorless oil.

6.4. Typical epoxide-opening procedure

To a solution containing epoxide **20** (100 mg, 0.59 mmol) in 24 mL of *tert*-butanol was added trimethylphosphine (0.05 mL, 0.59 mmol). The reaction mixture continued to stir at room temperature under an argon atmosphere for 18 h. Subsequent removal of a majority of the *tert*-butanol in vacuo and purification by column chromatography, using 25% ethyl acetate in methylene chloride, yielded 76 mg (76%) of cyclohexenone alcohol **21** as a viscous colorless oil.

6.4.1. Nona-3,7-dien-2-one. 1-Triphenyl-phosphoranylidene-2-propanone (9.7 g, 30.5 mmol) was added to a solution of 4-hexenal[53] (3.0 g, 30.5 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was refluxed under argon for 16 h. Upon completion of the reaction, the CH_2Cl_2 was removed in vacuo. The crude material was washed with pentane and filtered through a short pad of Celite. Purification by column chromatography using 9% ethyl acetate in hexanes afforded 3.16 g (75%) of nona-3,7-dien-2-one as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (dt, J=16.1, 6.6 Hz, 1H), 6.08 (dt, J=16.1, 1.5 Hz, 1H), 5.37–5.52 (m, 2H), 2.28 (ddt, J=6.6, 1.5, 7.3 Hz, 2H), 2.24 (s, 3H), 2.16 (ddt, J=6.6, 1.5, 7.3 Hz, 2H), 1.65 (dt, J=5.1, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.1, 147.4, 131.1, 129.2, 125.8, 32.0, 30.7, 26.4, 17.5. IR (NaCl, cm^{-1}): 3024, 2919, 2854, 1698, 1678, 1627, 1436, 1360, 1253, 968. HRMS (CI^+) calcd for $C_9H_{15}O$: 139.11230, Found: 139.11197. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.91; H, 10.29.

*6.4.2. Epoxide **4**.* Epoxide **4** was prepared by the typical epoxidation procedure using nona-3,7-dien-2-one (82% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.81 (dt, J=16.1, 6.6 Hz, 1H), 6.11 (dt, J=16.1, 1.5 Hz, 1H), 2.78 (dq, J=2.2, 5.1 Hz, 1H), 2.66 (ddd, J=6.6, 4.4, 2.2 Hz, 1H), 2.31–2.45 (m, 2H), 2.25 (s, 3H), 1.78 (dddd, J=13.2, 8.8, 7.3, 4.4 Hz, 1H), 1.58–1.66 (m, 1H), 1.30 (d, J=5.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.7, 146.4, 131.1, 58.1, 54.0, 30.0, 28.4, 26.3, 17.0. IR (NaCl, cm^{-1}): 2982, 2927, 1697, 1674, 1627, 1434, 1362, 1255, 981. HRMS (CI^+) calcd for $C_9H_{15}O_2$: 155.1072, Found: 155.1064. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.16.

6.4.3. 1-Phenyl-octa-2,6-dien-1-one[54]. Phenylcarbonylmethylene-triphenylphosphorane[55] (9.7 g, 30.5 mmol) was added to a solution of 4-hexenal (5.0 g, 50.9 mmol) in THF (200 mL). The reaction mixture was refluxed under argon for 16 h. Upon completion of the reaction, the THF was removed in vacuo. The crude material was washed with pentane and filtered through a short pad of Celite. Purification by column chromatography using 6% ethyl acetate in hexanes afforded 7.3 g (72%) of 1-phenyl-octa-2,6-dien-1-one as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89–7.94 (m, 2H, Ar H), 7.52–7.58 (m, 1H, Ar H), 7.43–7.49 (m, 2H, Ar H), 7.04 (dt, J=15.4, 6.8 Hz, 1H), 6.87 (dt, J=15.4, 1.5 Hz, 1H), 5.40–5.55 (m, 2H), 2.38 (ddd, J=6.8, 1.5, 7.3 Hz, 1H), 2.22 (dt, J=7.3, 7.3 Hz, 2H), 1.66 (dd, J=6.1, 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.1, 148.6, 137.5, 132.1, 129.3, 128.1, 128.0, 125.6, 32.3, 30.8, 17.5. IR (NaCl, cm^{-1}): 3058, 3025, 2917, 2853, 1668, 1651, 1621, 1598, 1579, 1447, 1350, 1284, 1227, 1179, 1019, 1002, 967. HRMS (EI^+) calcd for $C_{14}H_{16}O$: 200.12012, Found: 200.11996. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.10.

*6.4.4. Epoxide **5**.* Epoxide **5** was prepared by the typical epoxidation procedure with 1-phenyl-octa-2,6-dien-1-one (78% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91–7.95 (m, 2H, Ar H), 7.53–7.59 (m, 1H, Ar H), 7.44–7.50 (m, 2H, Ar H), 7.06 (dt, J=15.4, 6.6 Hz, 1H), 6.93 (dt, J=15.4, 1.5 Hz, 1H), 2.80 (dq, J=2.2, 5.1 Hz, 1H), 2.70 (ddd, J=6.6, 4.4, 2.2 Hz, 1H), 2.41–2.55 (m, 2H), 1.83 (dddd, J=13.2, 8.8, 7.3, 5.1 Hz, 1H), 1.66–1.75 (m, 1H), 1.30 (d, J=5.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.7, 147.6, 137.3, 132.2, 128.0, 128.0, 125.8, 58.2, 54.0, 30.1, 28.7, 17.0. IR (NaCl, cm^{-1}): 3058, 2982, 2926, 1668, 1651, 1621, 1597, 1578, 1447, 1380, 1345, 1287, 1225, 1180, 1020, 983. HRMS (EI^+) calcd for $C_{14}H_{16}O_2$: 216.11503, Found: 216.11500. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.51; H, 7.33.

*6.4.5. Alcohol **6**.* (>20:1, determined by 500 MHz ^{1}H NMR spectroscopy) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.97 (dd, J=4.4, 2.9 Hz, 1H), 3.94 (dq, J=2.9, 6.6 Hz, 1H), 3.20–3.27 (m, 1H), 2.53–2.62 (m, 1H), 2.48 (ABdddd, J_{AB}=19.8 Hz, J=9.5, 5.1, 2.9, 1.5 Hz, 1H), 2.38 (s, 3H), 2.14 (dddd, J=13.2, 9.5, 9.5, 6.6 Hz, 1H), 1.71 (ddt, J=13.2, 9.5, 5.1 Hz, 1H), 1.01 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.9, 149.8, 145.6, 68.9, 51.1, 32.3, 26.9, 26.0, 18.9. IR (NaCl, cm^{-1}): 3418, 3057, 2969, 2929, 2839, 1660, 1651, 1614, 1455, 1428, 1372, 1290, 1205, 1128, 1077, 1056, 1000, 975. HRMS (CI^+) calcd for $C_9H_{15}O_2$: 155.1072, Found: 155.1066. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.39; H, 9.12.

*6.4.6. Alcohol **9**.* (>20:1, determined by 500 MHz ^{1}H NMR spectroscopy) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73–7.77 (m, 2H, Ar H), 7.52–7.58 (m, 1H Ar H), 7.42–7.48 (m, 2H, Ar H), 6.66 (dd, J=4.4, 2.9 Hz, 1H), 4.08 (dq, J=2.9, 6.6 Hz, 1H), 3.38–3.45 (m, 1H), 2.48–2.67 (m, 2H), 2.20 (dddd, J=13.9, 9.5, 9.5, 5.9 Hz, 1H), 1.85 (ddt, J=13.9, 9.5, 5.9 Hz, 1H), 1.12 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.0, 150.8, 144.2, 138.7, 132.1, 129.0, 128.1, 68.7, 52.4, 32.7, 25.5, 19.4. IR (NaCl, cm^{-1}): 3418, 3060, 2968, 1714, 1634, 1574, 1446, 1352, 1289, 1178, 1130, 1077, 1001, 976. HRMS (CI^+) calcd for $C_{14}H_{17}O_2$: 217.12286, Found: 217.12297. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.55; H, 7.36.

*6.4.7. Epoxide **10**.* Epoxide **10** was prepared by the typical cross-metathesis procedure using 1,2-epoxy-5-hexene and methyl vinyl ketone (58% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.82 (dt, J=16.1, 6.6 Hz, 1H), 6.12 (dt, J=16.1, 1.5 Hz, 1H), 2.95 (ddt, J=7.3, 2.9, 4.4 Hz, 1H), 2.78 (dd, J=5.1, 4.4 Hz, 1H), 2.50 (dd, J=5.1, 2.9 Hz, 1H), 2.34–2.47 (m, 2H), 2.25 (s, 3H), 1.81 (dddd, J=13.2, 8.1, 6.6, 4.4 Hz, 1H), 1.60–1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5, 146.2, 131.0, 50.7, 46.1, 30.3, 28.2, 26.1. IR (NaCl, cm^{-1}): 2994, 2925, 1697, 1674, 1627, 1431, 1362, 1255, 1201, 981. HRMS (CI^+) calcd for $C_8H_{13}O_2$: 141.09156, Found: 141.09158. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.36; H, 8.75.

*6.4.8. Alcohol **11***[56]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.89 (ddd, J=5.9, 4.4, 2.2 Hz, 1H), 4.04 (dddd, J=8.1, 8.1, 5.1, 2.9 Hz, 1H), 2.62 (ABddd, J_{AB}=17.6 Hz, J=6.6, 2.9, 1.5 Hz, 1H), 2.49 (ABm, J_{AB}=19.8 Hz, 1H), 2.32 (partly obscured ABm, J_{AB}=19.8 Hz, 1H), 2.29 (s, 3H), 2.19 (ABddd, J_{AB}=17.6 Hz, J=6.6, 4.4, 2.2 Hz, 1H), 1.83 (ddddd, J=13.2, 5.9, 5.9, 2.9, 1.5 Hz, 1H), 1.61–1.73 (m, 1H).

*6.4.9. Alcohol **12**.* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.92 (ddd, J=4.4, 2.9, 2.9 Hz, 1H), 3.61 (ABd, J_{AB}=11.0 Hz, J=4.4 Hz, 1H), 3.53 (ABd, J_{AB}=11.0 Hz, J=8.0 Hz, 1H), 3.14 (ddddd, J=8.0, 7.3, 5.9, 4.4, 2.2 Hz), 2.44–2.62 (m, 2H), 2.38 (s, 3H), 2.16 (dddd, J=13.2, 9.5, 9.5, 5.9 Hz, 1H), 1.61 (ddt, J=13.2, 8.8, 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.1, 148.9, 147.6, 66.3, 47.2, 32.0, 27.3, 26.9. IR (NaCl, cm^{-1}): 3421, 2928, 1703, 1662, 1612, 1430, 1373, 1297, 1256, 1080, 1034. HRMS (CI^+) calcd for $C_8H_{13}O_2$: 141.09156, Found: 141.09165. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.36; H, 8.82.

*6.4.10. Epoxide **13**.* Epoxide **13** was prepared by the typical cross-metathesis procedure using 1,2-epoxy-5-hexene and 1-phenylbut-2-en-1-one[57] (55% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91–7.95 (m, 2H, Ar H), 7.53–7.59 (m, 1H, Ar H), 7.44–7.50 (m, 2H, Ar H), 7.07 (dt, J=15.4, 6.6 Hz, 1H), 6.94 (dt, J=15.4, 1.5 Hz, 1H), 2.98 (ddt, J=6.6, 2.2, 4.4 Hz, 1H), 2.79 (dd, J=4.4, 4.4 Hz, 1H), 2.44–2.57 (obscured m, 2H), 2.53 (obscured dd, J=4.4, 2.2 Hz, 1H), 1.86 (dddd, J=13.9, 8.8, 6.6, 4.4 Hz, 1H), 1.67–1.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.0, 147.6, 137.4, 132.3, 128.1, 128.1, 126.0, 51.0, 46.5,

30.7, 28.8. IR (NaCl, cm^{-1}): 3055, 2990, 2923, 1668, 1651, 1621, 1597, 1578, 1447, 1352, 1288, 1224, 1180, 1002, 916. HRMS (CI^+) calcd for $C_{13}H_{15}O_2$: 203.10721, Found: 203.10713. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.91; H, 6.95.

6.4.11. Alcohol ***14***. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.65 (m, 2H, Ar H), 7.46–7.53 (m, 1H, Ar H), 7.39–7.44 (m, 2H, Ar H), 6.58 (ddd, J=5.6, 4.1, 1.5 Hz, 1H), 4.14 (dddd, J=8.5, 8.5, 4.9, 3.2 Hz, 1H), 2.83 (ABddd, J_{AB}=15.8 Hz, J=4.9, 2.9, 1.5 Hz, 1H), 2.50 (ABdddd, J_{AB}=19.8 Hz, J=8.1, 6.1, 4.1, 2.4 Hz, 1H), 2.29–2.44 (m, 2H), 1.87–1.95 (m, 1H), 1.69–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.6, 143.2, 138.3, 135.9, 131.3, 129.0, 127.9, 65.9, 32.7, 29.2, 23.9. IR (NaCl, cm^{-1}): 3418, 3058, 2928, 1634, 1575, 1446, 1267, 1127, 1067, 1000, 958. HRMS (FAB^+) calcd for $C_{13}H_{14}O_2Na$: 225.0892, Found: 225.0897. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.53; H, 6.93.

6.4.12. Alcohol ***15***. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.71–7.76 (m, 2H, Ar H), 7.52–7.58 (m, 1H, Ar H), 7.42–7.48 (m, 2H, Ar H), 6.63–6.67 (m, 1H), 3.75 (ABd, J_{AB}=10.7 Hz, J=4.1 Hz, 1H), 3.70 (ABd, J_{AB}=10.7 Hz, J=7.6 Hz, 1H), 3.29–3.38 (m, 1H), 2.50–2.68 (m, 2H), 2.25 (dddd, J=13.2, 9.0, 9.0, 6.4 Hz, 1H), 1.77 (ddt, J=13.2, 9.0, 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.2, 150.6, 145.8, 138.7, 132.2, 129.1, 128.2, 66.1, 48.3, 32.5, 27.4. IR (NaCl, cm^{-1}): 3417, 3059, 2929, 1643, 1634, 1598, 1576, 1446, 1431, 1351, 1316, 1285, 1179, 1158, 1130, 1075, 1055, 1028, 975. HRMS (CI^+) calcd for $C_{13}H_{15}O_2$: 203.10721, Found: 203.10735. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.05; H, 6.86.

6.4.13. 2-But-3-enyl-2-methyl-oxirane[58]. This was prepared by the typical epoxidation procedure using 2-methyl-1,5-hexadiene (73% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ5.82 (ddt, J=16.8, 10.3, 6.6 Hz, 1H), 5.04 (ddt, J=16.8, 1.5, 1.5 Hz, 1H), 4.97 (dd, J=10.3, 1.5 Hz, 1H), 2.62 (AB, J_{AB}=5.1 Hz, 1H), 2.58 (AB, J_{AB}=5.1 Hz, 1H), 2.13–2.20 (m, 2H), 1.71 (ddd, J=13.9, 8.8, 6.6 Hz, 1H), 1.60 (ddd, J=13.9, 8.8, 7.3 Hz, 1H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.5, 114.3, 56.0, 53.2, 35.5, 29.0, 20.5. IR (NaCl, cm^{-1}): 3076, 3040, 2980, 2928, 2858, 1642, 1489, 1450, 1390, 1262, 1108, 1068, 995, 911. HRMS (CI^+) calcd for $C_7H_{13}O$: 113.09665, Found: 113.09706.

6.4.14. Epoxide ***16***. Epoxide **16** was prepared by the typical cross-metathesis procedure using 2-but-3-enyl-2-methyl-oxirane and methyl vinyl ketone (62% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.79 (dt, J=16.1, 6.6 Hz, 1H), 6.09 (dt, J=16.1, 1.5 Hz, 1H), 2.63 (AB, J_{AB}=4.4 Hz, 1H), 2.60 (AB, J_{AB}=4.4 Hz, 1H), 2.33 (ddt, J=7.3, 1.5, 7.3 Hz, 2H), 2.24 (s, 3H), 1.75 (ABt, J_{AB}=13.9 Hz, J=7.3 Hz, 1H), 1.72 (ABt, J_{AB}=13.9 Hz, J=7.3 Hz, 1H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.0, 146.4, 130.6, 55.2, 52.5, 34.1, 27.2, 25.9, 20.0. IR (NaCl, cm^{-1}): 3039, 2928, 1697, 1674, 1627, 1430, 1391, 1362, 1255, 1190, 981. HRMS (CI^+) calcd for $C_9H_{15}O_2$: 155.10721, Found: 155.10757. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.24.

6.4.15. Alcohol ***17***. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.93 (ddd, J=6.3, 3.4, 1.7 Hz, 1H), 2.46–2.57 (m, 1H), 2.40 (ABm, J_{AB}=18.1 Hz, 1H), 2.24–2.37 (obscured m, 2H), 2.31 (s, 3H), 1.72 (dddd, J=13.2, 6.1, 4.1, 1.7 Hz, 1H), 1.54 (ddd, J=13.2, 8.8, 6.1 Hz, 1H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.9, 139.9, 137.4, 68.2, 37.1, 33.7, 29.2, 25.2, 23.9. IR (NaCl, cm^{-1}): 3418, 3051, 2966, 2929, 1667, 1651, 1644, 1634, 1428, 1385, 1250, 1204, 1104, 1078, 1022, 959. HRMS (EI^+) calcd for $C_9H_{14}O_2$: 154.09938, Found: 154.09941. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.93; H, 9.05.

6.4.16. Epoxide ***18***. Epoxide **18** was prepared by the typical cross-metathesis procedure using 2-but-3-enyl-2-methyl-oxirane and 1-phenylbut-2-en-1-one (48% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90–7.95 (m, 2H, Ar H), 7.53–7.59 (m, 1H, Ar H), 7.44–7.50 (m, 2H, Ar H), 7.05 (dt, J=15.4, 6.6 Hz, 1H), 6.91 (dt, J=15.4, 1.5 Hz, 1H), 2.66 (AB, J_{AB}=5.1 Hz, 1H), 2.62 (AB, J_{AB}=5.1 Hz, 1H), 2.40–2.47 (m, 2H), 1.77–1.84 (m, 2H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.9, 148.0, 137.3, 132.2, 128.1, 128.0, 125.7, 55.8, 53.2, 34.6, 27.9, 20.5. IR (NaCl, cm^{-1}): 3039, 2928, 1668, 1651, 1622, 1598, 1578, 1448, 1390, 1336, 1288, 1222, 1180, 1072, 1002. HRMS (CI^+) calcd for $C_{14}H_{17}O_2$: 217.12286, Found: 217.12279. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.65; H, 7.48.

6.4.17. Alcohol ***19***. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.65 (m, 2H, Ar H), 7.47–7.52 (m, 1H, Ar H), 7.39–7.44 (m, 2H, Ar H), 6.59–6.63 (m, 1H), 2.46–2.61 (m, 3H), 2.28–2.37 (m, 1H), 1.73–1.81 (m, 1H), 1.59–1.67 (m, 1H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.6, 142.7, 138.5, 136.4, 131.4, 129.1, 128.0, 68.4, 38.1, 34.0, 29.2, 24.0. IR (NaCl, cm^{-1}): 3435, 3057, 2964, 2927, 1637, 1597, 1577, 1446, 1421, 1374, 1277, 1254, 1141, 1107, 1027, 1001, 972. HRMS (CI^+) calcd for $C_{14}H_{17}O_2$: 217.12286, Found: 217.12301. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.58; H, 7.32.

6.4.18. Epoxide ***20***. Epoxide **20** was prepared by the typical cross-metathesis procedure using 2-(1,1-dimethyl-but-3-enyl)-oxirane[59] and methyl vinyl ketone (64% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.85 (dt, J=16.1, 8.1 Hz, 1H), 6.10 (d, J=16.1 Hz, 1H), 2.78 (dd, J=4.4, 2.9 Hz, 1H), 2.66 (dd, J=4.4, 4.4 Hz, 1H), 2.61 (dd, J=4.4, 2.9 Hz, 1H), 2.19–2.29 (obscured m, 2H), 2.25 (obscured s, 3H), 0.93 (s, 3H), 0.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.9, 143.2, 132.9, 58.1, 42.7, 42.3, 33.4, 26.0, 22.0. IR (NaCl, cm^{-1}): 3053, 3002, 2965, 2932, 2876, 1697, 1673, 1627, 1473, 1430, 1405, 1364, 1255, 1188, 983, 914. HRMS (CI^+) calcd for $C_{10}H_{17}O_2$: 169.12286, Found: 169.12258. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.59.

6.4.19. Alcohol ***21***. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.80–6.85 (m, 1H), 3.60 (dd, J=5.1, 5.1 Hz, 1H), 2.57 (dm, J=2.2 Hz, 1H), 2.23–2.32 (obscured m, 2H), 2.30 (s, 3H), 2.05 (dm, J=2.2 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.8, 139.5, 136.1, 73.0, 37.6, 33.1, 29.5, 25.8, 25.1, 22.5. IR (NaCl, cm^{-1}): 3444, 3050, 2956, 1667, 1651, 1470, 1422, 1392, 1354, 1329, 1255, 1199, 1176, 1133, 1056, 1012, 981. HRMS (CI^+) calcd for $C_{10}H_{17}O_2$: 169.12286, Found: 169.12257. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.50.

6.4.20. Epoxide ***22***. Epoxide **22** was prepared by the typical cross-metathesis procedure using 2-(1,1-dimethyl-but-3-enyl)-oxirane and 1-phenylbut-2-en-1-one (52% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.91–7.96 (m, 2H, Ar H), 7.53–7.59 (m, 1H, Ar H), 7.44–7.50 (m, 2H, Ar H), 7.09 (dt, J=15.4, 8.1 Hz, 1H), 6.91 (dt, J=15.4, 1.5 Hz, 1H), 2.82 (dd, J=4.4, 2.9 Hz, 1H), 2.67 (dd, J=4.4, 4.4 Hz, 1H), 2.64 (dd, J=4.4, 2.9 Hz, 1H), 2.37 (ABdd, J_{AB}=13.9 Hz, J=8.1, 1.5 Hz, 1H), 2.31 (ABdd, J_{AB}=13.9 Hz, J=8.1, 1.5 Hz, 1H), 0.96 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.1, 145.2, 137.6, 132.5, 128.4, 128.3, 58.8, 43.7, 43.1, 34.2, 22.9, 22.9, 22.4. IR (NaCl, cm^{-1}): 3057, 2965, 2931, 2874, 1668, 1651, 1621, 1598, 1579, 1471, 1448, 1404, 1365, 1348, 1280, 1222, 1180, 1158, 1072, 1011, 983, 914. HRMS (ESI^+) calcd for $C_{15}H_{18}O_2Na$: 253.12045, Found: 253.12025. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.05; H, 7.92.

6.4.21. Alcohol ***23***. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60–7.65 (m, 2H, Ar H), 7.48–7.56 (m, 1H, Ar H), 7.39–7.44 (m, 2H, Ar H), 6.51 (ddd, J=3.7, 2.2, 1.5 Hz, 1H), 3.70 (dd, J=5.9, 5.1 Hz, 1H), 2.78 (ABdt, J_{AB}=18.3 Hz, J=2.2, 5.1 Hz, 1H), 2.46 (ABddd, J_{AB}=18.3 Hz, J=5.9, 3.7, 2.2 Hz, 1H), 2.29 (ABdt, J_{AB}=19.8 Hz, J=2.2, 3.7 Hz, 1H), 2.07 (ABdt, J_{AB}=19.8 Hz, J=2.2, 4.4 Hz, 1H), 1.00 (s, 3H), 0.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.4, 142.5, 138.3, 135.1, 131.3, 129.0, 127.9, 73.0, 37.8, 33.2, 30.4, 25.9, 22.5. IR (NaCl, cm^{-1}): 3458, 3058, 2957, 1633, 1597, 1577, 1471, 1446, 1422, 1383, 1268, 1200, 1178, 1116, 1057, 982. HRMS (ESI^+) calcd for $C_{15}H_{18}O_2Na$: 253.12045,

Found: 253.12053. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.95; H, 7.86.

*6.4.22. Epoxide **24**.* Epoxide **24** was prepared by the typical epoxidation procedure with 5,5-dimethyl-octa-3,7-dien-2-one[60] (70% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.82 (d, J=16.1 Hz, 1H), 6.06 (d, J=16.1 Hz, 1H), 2.88 (dddd, J=6.9, 5.1, 4.8, 2.6 Hz, 1H), 2.74 (dd, J=5.1, 5.1 Hz, 1H), 2.41 (dd, J=5.1, 2.6 Hz, 1H), 2.27 (s, 3H), 1.66 (ABd, J_{AB}=14.3 Hz, J=4.8 Hz, 1H), 1.55 (ABd, J_{AB}=14.3 Hz, J=6.9 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 155.8, 127.5, 48.9, 46.5, 44.8, 36.5, 27.1, 26.7, 26.48. IR (NaCl, cm^{-1}): 3045, 2965, 2928, 2874, 1698, 1623, 1469, 1426, 1387, 1363, 1301, 1257, 1182, 1134, 986. HRMS (CI^+) calcd for $C_{10}H_{17}O_2$: 169.1229, Found: 169.1223. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.66.

*6.4.23. Alcohol **25**.* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.63 (d, J=1.5 Hz, 1H), 3.57 (ABd, J_{AB}=11.0 Hz, J=3.3 Hz, 1H), 3.51 (ABd, J_{AB}=11.0 Hz, J=8.8 Hz, 1H), 3.17 (ddddd, J=8.8, 8.8, 7.7, 3.3, 1.5 Hz, 1H), 2.37 (s, 3H), 1.98 (dd, J=13.2, 8.8 Hz, 1H), 1.34 (dd, J=13.2, 7.7 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.0, 158.2, 144.5, 66.6, 47.1, 44.2, 42.3, 28.4, 27.5, 26.9. IR (NaCl, cm^{-1}): 3428, 3038, 2956, 2866, 1651, 1614, 1464, 1362, 1301, 1201, 1132, 1040, 965. HRMS (CI^+) calcd for $C_{10}H_{17}O_2$: 169.12286, Found: 169.12279. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.45.

6.4.24. 4,4-Dimethyl-1-phenyl-hepta-2,6-dien-1-one. Sodium hydride (60% in mineral oil, 800 mg, 20 mmol) was added to 60 mL of ethanol and stirred at room temperature for 15 min. This was followed by the addition of acetophenone (2.4 g, 20 mmol) and 2,2-dimethyl-4-pentenal (2.5 g, 20 mmol). The reaction mixture then was allowed to stir at room temperature for 5 h. Upon completion of the aldol reaction, the ethanol was removed in vacuo. The crude mixture was diluted with ethyl acetate, washed with water, dried over $MgSO_4$, and filtered through a short pad of Celite. Purification by column chromatography using 6% ethyl acetate in hexanes provided 3.5 g (81%) of 4,4-dimethyl-1-phenyl-hepta-2,6-dien-1-one as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90–7.95 (m, 2H, aromatic H), 7.53–7.59 (m, 1H, aromatic H), 7.44–7.50 (m, 2H, aromatic H), 7.02 (d, J=15.7 Hz, 1H), 6.76 (d, J=15.7 Hz, 1H), 5.75 (ddt, J=16.7, 10.2, 7.3 Hz, 1H), 5.07 (dm, J=10.2 Hz, 1H), 5.05 (dm, J=16.7 Hz, 1H), 2.18 (d, J=7.3 Hz, 2H), 1.13 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.1, 158.0, 138.0, 134.2, 132.4, 128.4, 128.3, 122.1, 117.7, 46.4, 37.0, 26.1. IR (NaCl, cm^{-1}): 3075, 3004, 2963, 2928, 2871, 1673, 1651, 1620, 1598, 1580, 1464, 1448, 1385, 1365, 1329, 1298, 1283, 1221, 1180, 1090, 1035, 1019, 993, 916. HRMS (EI^+) calcd for $C_{15}H_{18}O$: 214.13577, Found: 214.13550. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.84; H, 8.60.

*6.4.25. Epoxide **26**.* Epoxide **26** was prepared by the typical epoxidation procedure with 4,4-dimethyl-1-phenyl-hepta-2,6-dien-1-one (76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91–7.96 (m, 2H, Ar H), 7.54–7.60 (m, 1H, Ar H), 7.45–7.51 (m, 2H, Ar H), 7.07 (d, J=15.7 Hz, 1H), 6.86 (d, J=15.7 Hz, 1H), 2.92 (dddd, J=7.0, 5.1, 4.8, 2.6 Hz, 1H), 2.75 (dd, J=4.8, 4.8 Hz, 1H), 2.44 (dd, J=4.8, 2.6 Hz, 1H), 1.71 (ABd, J_{AB}=14.3 Hz, J=5.1 Hz, 1H), 1.62 (ABd, J_{AB}=14.3 Hz, J=7.0 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.7, 157.0, 137.7, 132.4, 128.3, 128.3, 122.2, 48.9, 46.4, 44.7, 36.8, 26.8, 26.2. IR (NaCl, cm^{-1}): 3054, 2963, 2927, 2872, 1732, 1670, 1650, 1619, 1597, 1578, 1464, 1447, 1426, 1410, 1386, 1366, 1297, 1223, 1180, 1158, 1132, 1091, 1036, 1019, 991, 953. HRMS (FAB^+) calcd for $C_{15}H_{18}O_2Na$: 253.12045, Found: 253.12044. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.27; H, 7.85.

*6.4.26. Alcohol **27**.* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.75 (m, 2H, Ar H), 7.53–7.58 (m, 1H, Ar H), 7.43–7.48 (m, 2H, Ar H), 6.39 (d, J=1.5 Hz, 1H), 3.74 (ABd, J_{AB}=11.0 Hz, J=4.4 Hz, 1H), 3.70 (ABd, J_{AB}=11.0 Hz, J=8.1 Hz, 1H), 3.37–3.44 (m, 1H), 2.07 (dd, J=13.2, 8.1 Hz, 1H), 1.55 (dd, J=13.2, 7.3 Hz, 1H), 1.20 (s, 3H), 1.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.4, 159.4, 142.1, 138.6, 132.0, 128.9, 128.0, 66.9, 47.9, 44.8, 42.0, 28.4, 27.6. IR (NaCl, cm^{-1}): 3418, 3059, 2954, 2863, 1644, 1576, 1446, 1384, 1295, 1212, 1177, 1113, 1044, 1027, 960. HRMS (FAB^+) calcd for $C_{15}H_{18}O_2Na$: 253.12045, Found: 253.12052. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.98; H, 7.96.

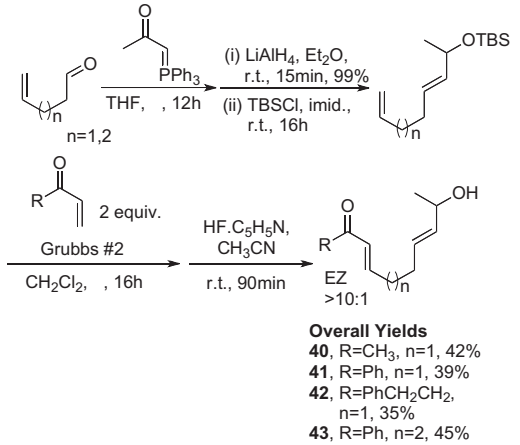
6.5. Typical procedure for MBH *cyclo*-allylation

To $SOCl_2$ (2 equiv) in Et_2O (0.1 M) at ambient temperature was added dropwise over 5 min a 0.1 M Et_2O solution of the alcohol with pyridine (2 equiv). After stirring for 20 min, the Et_2O layer was washed with saturated $NaHCO_3$(aq), dried over Na_2SO_4 and concentrated in vacuo to provide the crude allylic chloride, which was used without further purification. PBu_3 (100 mol %) was then added to a 0.5 M solution of the allylic chloride in *tert*-butyl alcohol and the mixture was allowed to stir at room temperature until complete consumption of starting material (TLC), at which point CH_2Cl_2/water (1:1) was added to the mixture followed by addition of KOH (200 mol %) and $BnEt_3NCl$ (10 mol %) and stirred until complete (2 h).

6.5.1. Cross-metathesis. To a mixture of 4-pentenal (1.68 g, 20 mmol) and allyl acetate (4.00 g, 40 mmol) in CH_2Cl_2 (100 mL, 0.2 M) was added Grubbs' #2[22] catalyst (125 mg, 0.2 mmol, 1 mol %). The mixture was heated at reflux for 4 h and the solvent removed in vacuo. The resulting aldehyde could be used without further purification in the Wittig olefination reaction or purified by flash chromatography. Yield after purification, (2.8 g, 90%).

6.5.2. Wittig olefination. A mixture of the aldehyde (1.56 g, 10 mmol) and methyl-(triphenylphosphoranylidene)-2-propanone (3.18 g, 10 mmol) in THF (50 mL, 0.2 M) was heated at reflux for 12 h. The solvent was removed in vacuo and the residue purified by filtration through a plug of silica gel before flash chromatography. Yield after purification, (1.86 g, 95%).

6.5.3. Acetate hydrolysis. To the acetate (1.57 g, 8 mmol) in the THF/H_2O (1:1) (40 mL, 0.2 M) at ambient temperature was added $LiOH\cdot H_2O$ (336 mg, 8 mmol). After stirring for 4 h, the mixture was diluted with Et_2O, and added to saturated brine. The mixture was extracted with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided the alcohol **28** (924 mg, 75%).



Overall Yields
40, R=CH_3, n=1, 42%
41, R=Ph, n=1, 39%
42, R=$PhCH_2CH_2$, n=1, 35%
43, R=Ph, n=2, 45%

6.5.4. Wittig olefination. A mixture of 4-pentenal (1.68 g, 20 mmol) and methyl (triphenylphosphoranylidene)-2-propanone (6.36 g, 20 mmol) in THF (100 mL, 0.2 M) was heated at reflux for 12 h. The

solvent was removed in vacuo and the residue purified by filtration through a plug of silica gel. The resulting olefin could be used without further purification in reduction reaction or further purified by flash chromatography. Yield of enone after purification (2.41 g, 97%).

6.5.5. Reduction. To a suspension of $LiAlH_4$ (474 mg, 12.5 mmol) in Et_2O (50 mL) at room temperature was added the enone (3.1 g, 25 mmol) in Et_2O (10 mL). After stirring for 15 min, the excess $LiAlH_4$ was quenched with H_2O–NaOH(aq)–H_2O following the procedure of Fieser.[61] The mixture was filtered through Celite®, dried over Na_2SO_4 and concentrated in vacuo. The resulting alcohol could be used without further purification in the TBS protection reaction or purified by flash chromatography. Yield of alcohol after purification (3.15 g, 99%).

6.5.6. TBS ether protection. To the alcohol (3.15 g, 25 mmol) in CH_2Cl_2 (50 mL, 0.5 M) at room temperature was added imidazole (1.87 g, 27.5 mmol) and TBSCl (3.77 g, 25 mmol). The mixture was stirred for 16 h and water added. The layers were separated, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The TBS ether was purified by flash chromatography to provide (5.59 g, 93%).

6.5.7. Cross-metathesis. To a mixture of the TBS ether (5.52 g, 23 mmol) and methyl vinyl ketone (3.22 g, 46 mmol) in CH_2Cl_2 (115 mL, 0.2 M) was added Grubbs' #2[22] catalyst (195 mg, 0.23 mmol, 1 mol %). The mixture was heated at reflux for 16 h and the solvent removed in vacuo. The resulting enone could be purified by filtration through a plug of silica gel and used without further purification or alternatively could be further purified by flash chromatography. Yield after purification (3.89 g, 60%).

6.5.8. TBS deprotection. To the TBS ether (2.82 g, 10 mmol) in CH_3CN (20 mL, 0.5 M) at ambient temperature was added HF·Py complex (70% HF) (2 equiv) and the mixture stirred until complete (TLC analysis) (~90 min). The mixture was diluted with Et_2O and added to saturated aqueous $NaHCO_3$. It was extracted with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. The alcohol was purified by flash chromatography to provide (1.34 g, 80%).

6.5.9. Cyclization reactions. To $SOCl_2$ (0.15 mL, 2 mmol) in Et_2O (10 mL) at ambient temperature was added dropwise over 5 min a 0.1 M Et_2O solution of the alcohol **28** (154 mg, 1 mmol) and pyridine (0.16 mL, 2 mmol). After stirring for 20 min, the Et_2O layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo to provide the allylic chloride, which was used without further purification. Tributylphosphine (0.25 mL, 1 mmol) was then added to a 0.5 M solution of the allylic chloride (1 mmol) in *t*-BuOH (2 mL) and the mixture was allowed to stir at ambient temperature until complete consumption of starting material (TLC analysis) (~5 h), at which point methylene chloride/water (1:1) was added to the mixture followed by addition of potassium hydroxide (112 mg, 200 mol %) and $BnEt_3NCl$ (22 mg, 10 mol %) and stirred until complete (2 h). The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined CH_2Cl_2 extracted were dried over Na_2SO_4 and concentrated in vacuo. Purification of the cyclization adduct **35** was achieved by flash chromatography. Yield (109 mg, 80%).

*6.5.10. Alcohol **28**.* This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; 9:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): 6.78 (dt, *J*=16.1, 6.6 Hz, 1H), 6.09 (d, *J*=16.1 Hz, 1H), 5.70–5.68 (m, 2H), 4.11 (dm, *J*=3.2 Hz, 2H), 2.33 (dt, *J*=6.6, 6.6 Hz, 2H), 2.24 (partly obscured s, 3H, CH_3) 2.26–2.23 (partly obscured m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 147.5, 131.2, 130.2, 129.0, 62.7, 31.6, 30.3, 26.5. HRMS (CI) calcd for $C_9H_{14}O_2$ $(M+H)^+$, 155.1072; Found 155.1074. FTIR (film): 3418, 2924, 1673, 1626, 1362, 1257, 973 cm^{-1}. Anal. Calcd For $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.47; H, 9.01.

*6.5.11. Alcohol **29**.* This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; 9:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.91 (m, 2H, Ar H), 7.57–7.53 (m, 1H, Ar H), 7.48–7.44 (m, 2H, Ar H), 7.04 (dt, *J*=15.4, 6.8 Hz, 1H), 6.90 (d, *J*=15.4 Hz, 1H), 5.73–5.71 (m, 2H), 4.11 (dm, *J*=3.7 Hz, 2H), 2.42 (dt, *J*=6.8, 6.8 Hz, 2H), 2.30 (dt, *J*=6.8, 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 148.8, 137.5, 137.5, 132.5, 130.3, 130.2, 128.3126.0, 62.9, 32.0, 30.5. HRMS (FAB) calcd for $C_{14}H_{16}O_2$ $(M+Na)^+$, 239.1048; Found 239.1036. FTIR (film): 3412, 2924, 1668, 1620, 1597, 1578, 1448, 1288, 1228, 972 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.85; H, 7.49.

*6.5.12. Alcohol **30**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.26 (m, 2H, Ar H), 7.20–7.17 (m, 3H, Ar H), 6.80 (dt, *J*=15.9, 6.8 Hz, 1H), 6.12 (dm, *J*=15.9 Hz, 1H), 5.69–5.66 (m, 2H), 4.10 (dd, *J*=3.2, 0.5 Hz, 2H), 2.94 (t, *J*=6.9 Hz, 2H), 2.87 (td, *J*=6.9, 1.7 Hz, 2H), 2.30 (dt, *J*=6.8, 6.8 Hz, 2H), 2.24–2.20 (dt, *J*=6.8, 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5, 146.4, 141.1, 130.7, 130.5, 130.2, 128.4, 128.3, 126.0, 63.3, 41.6, 31.8, 30.5, 30.0. HRMS (FAB)calcd for $C_{16}H_{20}O_2$ $(M+Na)^+$, 267.1361; Found 267.1362. FTIR (film): 2418, 3027, 2627, 2855, 1694, 1668, 1627, 1496, 1454, 1367, 1095, 973 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.95; H, 8.33.

*6.5.13. Alcohol **31**.* This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; 10:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.91 (m, 2H, Ar H), 7.57–7.54 (m, 1H, Ar H), 7.48–7.45 (m, 2H, Ar H), 7.06 (dt, *J*=15.4, 7.1 Hz, 1H), 6.89 (dt, *J*=15.4, 1.2 Hz, 1H COCH), 5.73–5.65 (m, 2H), 4.11 (dm, *J*=4.4 Hz, 2H), 2.34 (dt, *J*=7.1, 7.1 Hz, 2H), 2.14 (dt, *J*=7.1, 7.1 Hz, 2H), 1.64 (tt, *J*=7.1, 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 149.5, 137.6, 132.5, 131.4, 129.8, 128.4, 128.3, 125.8, 63.1, 32.0, 31.4, 27.3. HRMS (EI) calcd for $C_{15}H_{18}O_2$ $(M)^+$, 230.1307; Found 230.1312. FTIR (film): 3412, 2929, 2858, 1668, 1619, 1448, 1290, 1226, 970, 695 cm^{-1}.

*6.5.14. Cyclopentene **37**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.26 (m, 2H, Ar H), 7.19–7.17 (m, 3H, Ar H), 6.75–6.73 (br s, 1H), 5.83 (ddd, *J*=17.3, 10.3, 7.3 Hz, 1H), 5.01 (dm, *J*=17.1 Hz, 1H), 4.96 (dm, *J*=10.3 Hz, 1H), 3.65–3.61 (m, 1H), 3.03–2.89 (m, 4H), 2.57 (ddddd, *J*=18.6, 8.1, 8.1, 2.4, 2.4 Hz, 1H), 2.45 (ddddd, *J*=18.6, 9.0, 3.7, 3.7, 1.0 Hz, 1H), 2.15 (dddd, *J*=12.9, 9.0, 8.8, 8.8 Hz, 1H), 1.82 (dddd, *J*=12.9, 12.8, 3.7, 3.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 147.0, 143.9, 141.4, 139.9, 128.4, 128.3, 126.0, 113.5, 47.0, 41.1, 32.0, 30.3, 30.2. HRMS (EI) calcd for $C_{16}H_{18}O$ $(M+H)^+$, 226.1358; Found 226.1355. FTIR (film): 2930, 1668, 1453, 911 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.60; H, 8.33.

*6.5.15. Alcohol **40**.* ^{1}H NMR (500 MHz, CDCl3): δ 6.78 (dt, *J*=15.9, 6.8 Hz, 1H), 6.08 (d, *J*=15.9 Hz, 1H), 5.63 (dt, *J*=15.6, 6.8 Hz, 1H), 5.57 (dd, *J*=15.6, 6.3 Hz, 1H), 4.27 (dq, *J*=6.3, 6.3 Hz, 1H), 2.32 (dt, *J*=6.8, 6.8 Hz, 2H), 2.24 (s, 3H), 2.22 (dt, *J*=6.8, 6.8 Hz, 2H), 1.25 (d, *J*=6.3 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 198.6, 147.4, 135.4, 131.2, 127.9, 67.9, 31.6, 30.2, 26.5, 23.2. HRMS (CI) calcd for C10H16O2 $(M+H)^+$, 169.1229; Found 169.1230. FTIR (film): 3410, 2970, 1673, 1626, 1366, 1255, 973 cm^{-1}.

*6.5.16. Alcohol **41**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.91 (m, 2H, Ar H), 7.57–7.54 (m, 1H, Ar H), 7.48–7.45 (m, 2H, Ar H), 7.02 (dt, *J*=15.4, 6.8 Hz, 1H), 6.89 (dm, *J*=15.4 Hz, 1H), 5.66 (dt, *J*=15.4,

6.8 Hz, 1H), 5.60 (dd, *J*=15.4, 6.6 Hz, 1H), 4.28 (dq, *J*=6.6, 6.6 Hz, 1H), 2.42 (dt, *J*=6.8, 6.8 Hz, 2H), 2.27 (dt, *J*=6.8, 6.8 Hz, 2H), 1.26 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 148.7, 137.6, 135.4, 132.5, 128.5, 128.4, 128.3, 126.1, 68.3, 32.1, 30.5, 23.3. HRMS (CI) calcd for $C_{15}H_{18}O_2$ $(M+H)^+$, 231.1385; Found 231.1384. FTIR (film): 3412, 2969, 2927, 1668, 1619, 1448, 1288, 971 cm^{-1}.

6.5.17. Alcohol ***42***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.26 (m, 2H, Ar H), 7.20–7.17 (m, 3H, Ar H), 6.79 (dt, *J*=15.9, 7.1 Hz, 1H), 6.10 (d, *J*=15.9 Hz, 1H), 5.62 (dt, *J*=15.6, 7.1 Hz, 1H), 5.56 (dd, *J*=15.6, 6.4 Hz, 1H), 4.27 (dq, *J*=6.4, 6.4 Hz, 1H), 2.94 (t, *J*=7.5 Hz, 2H), 2.87 (t, *J*=7.5 Hz, 2H), 2.29 (dt, *J*=7.1, 7.1 Hz, 2H), 2.19 (dt, *J*=7.1, 7.1 Hz, 2H), 1.25 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 146.4, 141.2, 135.4, 130.5, 128.5, 128.4, 128.3, 126.0, 68.5, 41.6, 31.9, 30.4, 30.0, 23.4. HRMS (EI) calcd for $C_{17}H_{22}O_2$ $(M)^+$, 258.1620; Found 258.1618. FTIR (film): 3422, 3027, 2969, 2927, 1670, 1628, 1453, 1367, 1063, 974 cm^{-1}.

6.5.18. Alcohol ***43***. This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; 4:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.91 (m, 2H, Ar H), 7.57–7.54 (m, 1H, Ar H), 7.48–7.45 (m, 2H, Ar H), 7.04 (dt, *J*=15.4, 7.1 Hz, 1H), 6.89 (dm, *J*=15.4 Hz, 1H), 5.66–5.50 (m, 2H), 4.28 (dq, *J*=6.4 Hz, 1H), 2.33 (dt, *J*=7.1, 7.1 Hz, 2H), 2.12 (dt, *J*=7.1, 7.1 Hz, 2H), 1.63 (tt, *J*=7.1, 7.1 Hz, 2H), 1.27 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 149.3, 137.3, 134.9, 132.2, 128.7, 128.0, 127.3, 125.7, 67.8, 31.7, 31.1, 27.1, 23.1. HRMS (CI) calcd for $C_{16}H_{20}O_2$ $(M+H)^+$, 245.1542; Found 245.1545. FTIR (film): 3429, 2969, 2928, 1668, 1620, 1448, 1288, 971, 695 cm^{-1}.

6.5.19. Cyclopentene ***46***. This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; >10:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74–6.72 (br s, 1H), 5.48–5.39 (m, 2H), 3.58–3.55 (m, 1H), 2.56 (ddddd, *J*=18.4, 8.3, 8.3, 2.2, 2.2 Hz, 1H), 2.44 (ddddd, *J*=18.4, 8.4, 3.7, 3.2, 1.0 Hz, 1H), 2.29 (s, 3H), 2.12 (dddd, *J*=12.9, 9.0, 9.0, 9.0 Hz, 1H), 1.78–1.76 (m, 1H), 1.63 (d, *J*=4.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 148.0, 144.3, 132.5, 124.1, 45.8, 31.9, 31.0, 27.2, 17.8. HRMS (CI) calcd for $C_{10}H_{14}O$ $(M+H)^+$, 151.1123; Found 151.1121. FTIR (film): 2934, 1668, 1612, 1367, 963 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.68; H, 9.46.

6.5.20. Cyclopentene ***47***. This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; >10:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78–7.75 (m, 2H, Ar H), 7.53–7.50 (m, 1H, Ar H), 7.44–7.41 (m, 2H, Ar H), 6.47–6.45 (br s, 1H), 5.56–5.45 (m, 2H), 3.84–3.78 (m, 1H), 2.66 (ddddd, *J*=19.3, 8.3, 5.9, 2.4, 2.4 Hz, 1H), 2.48 (ddddd, *J*=19.3, 9.0, 5.6, 2.7, 2.7 Hz, 1H), 2.24 (dddd, *J*=14.9, 9.0, 5.9, 5.9 Hz, 1H), 1.82 (dddd, *J*=14.9, 8.3, 5.6, 5.6 Hz, 1H), 1.63 (d, *J*=5.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 146.6, 145.5, 138.8, 132.4, 131.9, 128.9, 128.1, 124.9, 47.5, 32.6, 30.7, 17.9. HRMS (CI) calcd for $C_{15}H_{16}O$ $(M+H)^+$, 213.1280; Found 213.1276. FTIR (film): 2934, 1645, 1598, 1447, 960 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.63; H, 7.66.

6.5.21. Cyclopentene ***48***. This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; >10:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.25 (m, 2H, Ar H), 7.20–7.16 (m, 3H, Ar H), 6.71–6.70 (br s, 1H), 5.47–5.38 (m, 2H), 3.60–3.54 (m, 1H), 3.00–2.88 (m, 4H), 2.56 (ddddd, *J*=18.6, 8.3, 8.3, 2.4, 2.4 Hz, 1H), 2.42 (ddddd, *J*=18.6, 9.3, 3.9, 3.9, 1.0 Hz, 1H), 2.11 (dddd, *J*=12.9, 9.0, 7.8, 7.8, Hz), 1.76 (dddd, *J*=12.9, 8.3, 3.9, 3.9 Hz, 1H), 1.63 (d, *J*=4.9, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 147.6, 143.4, 141.5, 132.6, 128.4, 125.9, 124.2, 46.1, 41.1, 32.0, 30.9, 30.2, 17.9. HRMS (EI) calcd for $C_{17}H_{20}O$ $(M+H)^+$, 240.1514; Found 240.1512. FTIR (film): 2933, 1670, 1607, 1453, 963 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.57; H, 8.64.

6.5.22. Cyclohexene ***50***. This compound was isolated as a mixture of alkene geometrical isomers (*E*/*Z*; 10:1). Spectral data for the major isomer is reported. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H, Ar H), 7.51–7.48 (m, 1H, Ar H), 7.43–7.40 (m, 2H, Ar H), 6.50 (t, *J*=3.7 Hz, 1H,), 5.48–5.37 (m, 2H), 3.62–3.57 (m, 1H), 2.34–2.27 (m, 1H), 2.20–2.11 (m, 1H), 1.75–1.60 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 142.5, 140.9, 138.7, 133.0, 131.5, 129.3, 127.9, 125.7, 35.4, 28.2, 26.0, 17.8. HRMS (EI) calcd for $C_{16}H_{18}O$ $(M+H)^+$, 226.1358; Found 226.1353. FTIR (film): 2933, 2856, 1650, 1578, 1446, 1264, 967, 720 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.50; H, 7.63.

6.6. Typical alkylation procedure

Tributylphosphine (100 mol %) was added to a 0.5 M solution of the halide in *tert*-butyl alcohol, and the mixture was allowed to stir at ambient temperature until complete consumption of starting material (TLC), at which point methylene chloride/water (1:1) (dilute to 0.1 M) was added to the mixture followed by addition of potassium hydroxide (100 mol %) and $BnEt_3NCl$ (10%). Stirring was continued until the reaction was complete (TLC analysis).

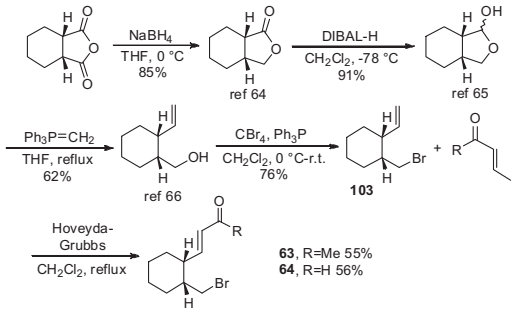
6.7. Synthesis of 51–55 general procedure

6.7.1. Alkylation. A solution of diethyl allylmalonate (9.9 mL, 0.05 mol) in dry THF (14 mL) was added dropwise at room temperature to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 2.40 g, 0.06 mol) in dry THF (14 mL) over a period of 30 min. The mixture was stirred for 1 h at room temperature, and a solution of 1,2-dibromoethane (5.2 mL, 0.06 mol) in dry THF (14 mL) was added dropwise over 30 min following the procedure of Kuehne et al.[62] The mixture was stirred for 15 h at room temperature and then poured into water. The mixture was extracted with ether and washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield the alkylated malonate as a yellow oil. Excess 1,2-dibromoethane and unreacted diethyl allylmalonate were removed by Kugelrohr distillation to yield the bromoester as a colorless oil (14.76 g, 96%).

6.7.2. Cross-metathesis. A flame-dried round-bottom flask equipped with reflux condenser was charged with alkylated malonate (2.14 g, 7 mmol), 3-penten-2-one (2.1 mL, 7 mmol), and dichloromethane (35 mL). Grubbs second generation catalyst22 (219 mg, 0.35 mmol) was subsequently added as a solid, producing a light brown/green solution, which was refluxed for 12 h. The mixture was then plugged through a pad of silica gel and concentrated in vacuo. Purification of the residue via distillation under reduced pressure at 125 °C afforded the desired ester in 48% yield.

6.7.3. Iodination. A mixture containing excess sodium iodide (30 mg, 0.2 mmol) in acetone (0.8 mL) and 2-(2-chloro-ethyl)-2-(4-oxo-pent-2-enyl)-malonic acid diethyl ester, **54**, (50 mg, 0.16 mmol) was stirred under reflux for 24 h. The mixture was extracted with dichloromethane, washed with water, $NaHSO_3$, brine, and then dried with Na_2SO_4. The solvent was removed under reduced pressure affording ester **55** as a thick oil (0.045 g, 71%).

6.8. Synthesis of compounds 63–64 general procedure



6.8.1. Sodium borohydride reduction. To a suspension of sodium borohydride (1.19 g, 30.8 mmol) in THF (0.8 mL) at 0 °C was added *cis*-1-2-cyclohexane dicarboxylic anhydride (5.0 g, 30.8 mmol) and THF (30 mL) following the procedure of Fujiwara.[63] The mixture was stirred for 2 h followed by addition of HCl (6 M, 12 mL) and dilution with water (70 mL). Subsequent extraction with diethyl ether, drying with sodium sulfate, and concentration in vacuo afforded the lactone (3.65 g, 85%).

6.8.2. DIBAL-H reduction. To a solution of hexahydro-isobenzofuran-1-one (3.65 g, 26.1 mmol) in dichloromethane (131 mL) at −78 °C was added DIBAL (31.3 mL, 31.3 mmol). After stirring for 2.5 h at −78 °C the mixture was quenched with methanol (0.188 mL), diluted with ether, and ground sodium sulfate decahydrate (8.41 g) was added following the procedure of Hamilton.[64] The mixture was allowed to slowly warm to room temperature and stirred overnight. The resulting suspension was plugged through a pad of Celite® and the filtrate was concentrated in vacuo yielding 2-hydroxymethyl-cyclohexanecarbaldehyde (3.38 g, 91%).

6.8.3. Wittig olefination. A solution of methyltriphenylphosphonium bromide (30.36 g, 85 mmol) in THF (85 mL) in a heat dried round-bottom flask was cooled to 0 °C. Then while stirring, *n*-butyllithium (53 mL, 1.6 M in hexane) was added slowly and the reaction mixture was allowed to warm to room temperature and stir for 0.5 h. Lactol was added to the reaction mixture slowly and refluxed for an additional 2 h following the procedure of Cho.[65] Upon completion, the reaction mixture was quenched with water and extracted with ethyl acetate. The concentrated residue was then plugged through a pad of silica gel, concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 5:1) to yield the desired alkene (2.26 g, 95%).

6.8.4. Bromination. A solution of alcohol (0.11 g, 0.79 mmol) and carbon tetrabromide (0.33 g, 1 mmol) in dichloromethane was cooled to 0 °C. Then, triphenylphosphine (0.29 g, 1.1 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was stirred for 5 h and the solvent was removed in vacuo. The bromo alkene was purified by column chromatography, eluting with hexane/ethyl acetate (5:1). The bromide was obtained as a clear oil (12 mg, 76%).

6.8.5. Cross-metathesis. A flame-dried round-bottom flask equipped with reflux condenser was charged with the bromide (1.21 g, 6 mmol), crotonaldehyde (0.49 mL, 6 mmol), and dichloromethane (30 mL). Hoveyda–Grubbs catalyst[22] (188 mg, 0.3 mmol) was subsequently added as a solid, producing a light brown/green solution, which was refluxed for 12 h. The mixture was then plugged through a pad of silica gel and concentrated in vacuo. Yield after column chromatography (1.33 g, 56%).

6.9. Synthesis of compounds 57, 58, 67 and 68: general procedure

A flame-dried round-bottom flask equipped with reflux condenser was charged with 5-bromo-1-pentene (1.04 g, 7 mmol), 3-penten-2-one (2.1 mL, 7 mmol), and dichloromethane (35 mL). Grubbs second generation catalyst[22] (219 mg, 0.35 mmol) was subsequently added as a solid, producing a light brown/green solution that was refluxed for 12 h. The mixture was then plugged through a pad of silica gel and concentrated in vacuo. Purification of the residue via distillation under reduced pressure at 125 °C afforded the desired ester in 75% yield.

6.10. Cyclization reactions general procedure

A flame-dried round-bottom flask was charged with 2-(2-bromo-ethyl)-2-(4-oxo-pent-2-enyl)-malonic acid diethyl ester, **51**, (49 mg, 0.14 mmol) and *tert*-butanol (0.28 mL). Tributylphosphine (0.04 mL, 0.14 mmol) was then added to the mixture and stirred until all starting material was consumed (TLC analysis). At this time, dichloromethane (0.07 mL), water (0.07 mL), potassium hydroxide (8 mg, 0.14 mmol), and benzyltriethylammonium chloride (3 mg, 0.014 mmol) were added to the mixture that was allowed to stir until product was formed (TLC analysis). The mixture was extracted with DCM, washed with water, dried with sodium sulfate, plugged through a pad of silica gel, and concentrated in vacuo affording the cyclized product **56** (0.037 g, 99%).

6.10.1. Control reaction. A flame-dried round-bottom flask was charged with 1-iodohexane (0.15 mL g, 1 mmol) and *tert*-butanol (2 mL). Trimethylphosphine (0.09 mL, 1 mmol) was then added to reaction mixture, which was stirred until all starting material was consumed by TLC analysis. At this time a solid precipitate was formed and the reaction mixture was concentrated in vacuo affording the phosphonium salt (151 mg, 94%).

*6.10.2. Bromide **51**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (td, 1H, J=7.93, 15.87 Hz), 6.12 (br d, 1H, J=15.87 Hz), 4.22 (q, 4H, J=7.1 Hz) 3.36 (t, 2H, J=8.1 Hz), 2.80 (dd, 2H, J=1.2, 7.6 Hz) 2.46 (t, 2H, J=8.1 Hz), 2.24 (s, 3H, CH_3), 1.27 (t, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 169.5, 140.7, 134.6, 61.9, 57.2, 36.7, 36.5, 27.0, 26.5, 13.9. HRMS (FAB^+) calcd for $C_{14}H_{21}O_5BrNa$ (M+Na): 371.0470, Found: 371.0467. FTIR (neat): 2981, 2938, 1701, 1677, 1630, 1446, 1366, 1300, 1253, 1194, 1176 cm^{-1}. Anal. Calcd for $C_{14}H_{21}O_5Br$: C, 48.15; H, 6.06. Found: C, 48.18; H, 6.16.

*6.10.3. Bromide **52**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J=7.9 Hz, 2H, Ar H), 7.57 (t, J=7.4 Hz, 1H, Ar H), 7.47 (t, J=7.9 Hz, 2H, Ar H) 6.94 (d, J=15.2 Hz, 1H), 6.85 (td, J=7.4, 15.2 Hz, 1H) 4.23 (q, J=7.4 Hz, 4H), 3.40 (t, J=7.9, Hz, 2H), 2.92 (d, J=7.4 Hz, 2H) 2.50 (t, J=7.9 Hz, 2H) 1.27 (t, J=7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.8, 169.6, 141.9, 137.3, 132.9, 129.6, 128.5, 128.4, 62.9, 57.4, 36.8, 36.7, 26.6, 14.0. HRMS (FAB^+) calcd for $C_{19}H_{23}O_5NaBr$ (M+Na): 433.0626, Found: 433.0644. FTIR (neat): 2980, 2937, 1730, 1674, 1624, 1447 cm^{-1}. Anal. Calcd for $C_{19}H_{23}O_5Br$: C, 55.49; H, 6.99. Found: C, 55.39; H, 6.95.

*6.10.4. Bromide **53**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 2H, Ar), 7.20 (m, 3H, Ar), 6.64 (td, J=7.6, 15.6 Hz, 1H), 6.15 (d, J=15.6 Hz, 1H), 4.21 (q, J=7.1 Hz, 4H), 3.35 (t, J=8.0 Hz, 2H), 2.92 (m, 2H), 2.85 (m, 2H), 2.78 (dd, J=1.2, 7.6 Hz, 2H), 2.43 (t, J=8.0 Hz, 2H), 1.25 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 169.9, 141.2, 140.2, 133.9, 128.8, 128.6, 126.4, 62.2, 57.5, 42.1, 37.0, 36.8, 30.1, 26.8, 14.3. HRMS (FAB^+) calcd for $C_{21}H_{27}O_5NaBr$ (M+Na): 461.0940, Found:

461.0945. FTIR (neat): 2980, 1729, 1445, 1260 cm^{-1}. Anal. Calcd for $C_{21}H_{27}O_5Br$: C, 57.41; H, 6.19. Found: C, 57.03; H, 6.28.

6.10.5. Chloride ***54***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.64 (td, J=7.6, 15.9 Hz, 1H), 6.12 (br d, J=15.9 Hz, 1H), 4.22 (q, J=7.3 Hz, 4H), 3.54 (t, J=7.6 Hz, 2H), 2.82 (dd, J=1.5, 7.6 Hz, 2H) 2.38 (t, J=7.6 Hz, 2H), 2.24 (s, 3H), 1.27 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 169.6, 140.7, 134.5, 61.8, 56.2, 39.4, 36.4, 36.2, 26.8, 13.8. HRMS (FAB^+) calcd for $C_{14}H_{21}O_5NaCl$ (M+Na): 327.0980, Found: 327.0975. FTIR (neat): 2982, 2908, 1731, 1700, 1678, 1632, 1446, 1254, 1180 cm^{-1}. Anal. Calcd for $C_{14}H_{21}O_5Cl$: C, 55.17; H, 6.95. Found: C, 54.94; H, 7.01.

6.10.6. Iodide ***55***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.63 (dt, J=7.6, 15.6 Hz, 1H), 6.11 (d, J=15.6 Hz, 1H), 4.22 (q, J=7.2, 4H), 3.10 (m, 2H), 2.77 (dd, J=1.0, 7.6 Hz, 2H), 2.48 (m, 2H), 2.23 (s, 3H), 1.26 (t, J=7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 169.2, 140.6, 134.3, 61.7, 58.6, 31.2, 36.0, 26.8, 13.8, −3.3. HRMS (FAB^+) calcd for $C_{14}H_{21}O_5INa$ (M+Na): 419.03312, Found: 419.0335. FTIR (neat): 2980, 1729, 1676, 1253, 1188 cm^{-1}. Anal. Calcd for $C_{14}H_{21}O_5I$: C, 42.44; H, 5.35. Found: C, 42.41; H, 5.44.

6.10.7. Enone ***56***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.84 (tt, J=2.2, 3.9 Hz, 1H), 4.187 (ABq, J=7.3, 7.3 Hz, 2H), 4.182 (ABq, J=7.3, 7.3 Hz, 2H) 2.78 (td, J=2.2, 3.9 Hz, 2H), 2.29 (m, 2H) 2.28 (s, 3H), 2.16 (t, J=6.4, Hz, 2H), 1.24 (t, J=7.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 170.9, 138.2, 137.1, 61.5, 52.4, 31.3, 26.9, 25.1, 20.1, 13.9. HRMS (FAB^+) calcd for $C_{14}H_{20}O_5Na$ (M+Na): 291.1211, Found: 291.1208. FTIR (neat): 2980, 1731, 1668, 1258, 1175, 1068, 1021 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.50; H, 7.65.

6.10.8. Bromide ***57***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (m, 1H, Ar H), 7.56 (m, 2H, Ar H), 7.47 (m, 2H, Ar H), 7.04 (td, J=6.8, 15.6 Hz, 1H), 6.90 (td, J=1.2, 15.6 Hz, 1H), 3.44 (t, J=6.6 Hz, 2H), 2.37 (ddt, J=1.2, 6.8, 7.3 Hz, 2H), 1.94 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 148.7, 137.8, 132.6, 128.6, 128.4, 126.2, 33.3, 32.1, 31.7, 26.6. HRMS (FAB^+) calcd for $C_{13}H_{15}OBrNa$ (M+Na): 289.0204, Found: 289.0204. FTIR (neat): 2936, 1670, 1621, 1598, 1447, 1346, 1283, 693 cm^{-1}. Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.89; H, 5.66.

6.10.9. Bromide ***58***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (m, 2H, Ar H), 7.57 (m, 1H, Ar H), 7.48 (m, 2H, Ar H), 7.02 (td, J=6.6, 15.4 Hz, 1H), 6.96 (d, J=15.4 Hz, 1H), 3.46 (t, J=6.6 Hz, 2H), 2.51 (td, J=6.6, 7.3 Hz, 2H), 2.10 (tt, J=6.6, 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 147.0, 132.7, 128.5, 128.4, 128.1, 126.8, 32.6, 30.9, 30.8. HRMS (FAB^+) calcd for $C_{12}H_{13}OBrNa$ (M+Na): 275.0048, Found: 275.0048. FTIR (neat): 2935, 1670, 1622, 1447, 1288, 1220, 972, 693 cm^{-1}. Anal. Calcd for $C_{12}H_{13}OBr$: C, 56.94; H, 5.18. Found: C, 56.69; H, 5.11.

6.10.10. Enone ***61***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (m, 2H, aromatic), 7.53 (m, 1H, aromatic), 7.41 (m, 2H, aromatic), 6.53 (br s, 1H), 4.24 (q, J=7.1 Hz, 4H), 2.79 (m, 2H), 2.50 (m, 2H), 2.27 (t, J=6.4 Hz, 2H), 1.27 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 171.0, 139.8, 138.1, 137.2, 131.6, 129.2, 128.1, 61.6, 52.6, 31.4, 27.2, 21.2, 14.0. HRMS (FAB^+) calcd for $C_{19}H_{22}O_5Na$ (M+Na): 353.1358, Found: 353.1365. FTIR (neat): 1729, 1245, 708 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.06; H, 6.55.

6.10.11. Enone ***62***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (m, 3H, aromatic), 7.18 (m, 2H, aromatic), 6.82 (tt, 1H, J=1.9, 3.9 Hz), 4.187 (ABq, J=7.1, 7.1 Hz, 2H), 4.182 (ABq, J=7.1, 7.1 Hz, 2H), 2.96 (m, 2H), 2.91 (m, 2H), 2.75 (td, J=2.2, 3.9 Hz, 2H), 2.31 (dtt, J=1.9, 2.2, 6.4 Hz, 2H), 2.15 (t, J=6.4 Hz, 2H), 1.24 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 171.0, 141.4, 137.8, 136.2, 128.4, 128.4, 126.0, 61.6, 52.5, 39.0, 31.3, 30.3, 27.1, 20.4, 14.0. HRMS (FAB^+) calcd for $C_{21}H_{26}O_5Na$ (M+Na): 381.1693, Found: 381.1678. FTIR (neat): 2981, 1731, 1668, 1252 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.44; H, 7.21.

6.10.12. Bromide ***103***. ^1H NMR (500 MHz, $CDCl_3$): δ 5.92 (ddd, J=8.1, 10.3, 16.1 Hz, 1H), 5.14 (dd, J=2.2, 16.1 Hz, 1H), 5.09 (dd, J=2.2, 10.3 Hz, 1H), 3.26 (ABd, J=7.3, 10.2 Hz, 1H), 3.23 (ABd, J=7.3, 9.5 Hz, 1H), 2.60 (dddd, J=3.7, 4.4, 4.4, 8.1 Hz, 1H), 1.89 (ddddd, J=3.8, 3.8, 7.3, 7.3, 11.1 Hz, 1H), 1.72–1.31 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1, 116.4, 42.5, 41.8, 37.5, 30.8, 27.1, 25.0, 21.8. FTIR (neat): 3073, 3002, 2927, 2855, 1636, 1448, 1234, 918 cm^{-1}. Anal. Calcd for $C_9H_{15}Br$: C, 53.22; H, 7.44. Found: C, 52.82; H, 7.73.

6.10.13. Bromide ***63***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.90 (dd, J=9.0, 15.9 Hz, 1H), 6.23 (dd, J=0.7, 15.9 Hz, 1H), 3.25 (dd, J=7.1, 10.3 Hz, 1H) 3.14 (dd, J=8.1, 10.3 Hz, 1H), 2.80 (dddd, J=4.2, 4.4, 4.4, 9.0 Hz, 1H) 2.26 (s, 3H), 2.01 (ddddd, J=4.0, 4.2, 7.1, 8.1, 11.8 Hz, 1H), 1.76–1.37 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 146.2, 132.1, 42.5, 40.3, 36.5, 30.2, 27.5, 27.3, 24.7, 21.7. HRMS (FAB^+) calcd for $C_{11}H_{17}ONaBr$ (M+Na): 267.0352, Found: 267.0360. FTIR (neat): 2929, 2857, 1696, 1674, 1622, 1450, 1254 cm^{-1}. Anal. Calcd for $C_{11}H_{17}OBr$: C, 53.89; H, 5.64. Found: C, 53.76; H, 5.95.

6.10.14. Bromide ***64***. ^1H NMR (500 MHz, $CDCl_3$): δ 9.54 (d, J=7.8 Hz, 1H), 6.93 (dd, J=8.6, 15.6 Hz, 1H), 6.25 (ddd, J=1.0, 7.8, 15.6 Hz, 1H), 3.28 (dd, J=7.1, 10.2 Hz, 1H), 3.14 (dd, J=8.1, 10.2, 1H), 2.96 (dddd, J=4.2, 4.4, 4.4, 8.6 Hz, 1H), 2.06 (ddddd, J=4.0, 4.2, 7.1, 8.1, 12.0 Hz, 1H) 1.79–1.65 (m, 4H), 1.54 (m, 2H), 1.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 156.8, 133.9, 42.2, 40.4, 36.0, 29.6, 27.1, 24.4, 21.5. HRMS (FAB^+) calcd for $C_{10}H_{15}ONaBr$ (M+Na): 253.0204, Found: 253.0216. FTIR (neat): 2930, 2857, 1689, 1450, 1137, 1117, 978 cm^{-1}. Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.97; H, 6.54. Found: C, 51.75; H, 6.41.

6.10.15. Hexyltrimethyl-phosphonium iodide. ^1H NMR (500 MHz, $CDCl_3$): δ 2.48 (m, 2H), 2.21 (d, J=13.9 Hz, 9H), 1.58 (m, 2H), 1.52 (m, 2H), 1.33 (m, 4H), 0.89 (t, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 29.9, 24.0, 23.3, 22.0, 21.3, 13.7, 9.6, 8.8. HRMS (FAB^+) calcd for $C_9H_{22}PNa$ (M+Na): 161.1462, Found: 161.1459. FTIR (neat): 2959, 1298, 985, 776 cm^{-1}. Anal. Calcd for $C_9H_{22}PI$: C, 37.51; H, 7.70. Found: C, 37.40; H, 7.79.

6.10.16. Enone ***65***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.67 (br s, 1H), 2.78 (m, 1H), 2.49 (tdd, J=2.0, 8.6, 16.9 Hz, 1H), 2.30 (s, 3H), 2.28 (m, 1H), 1.67 (dddd, J=6.6, 6.6, 6.6, 13.0 Hz, 1H), 1.55–1.00 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 149.4, 145.2, 45.3, 37.5, 35.4, 27.6, 27.5, 26.3, 23.3, 22.9. FTIR (neat): 2925, 2852, 1666, 1604, 1449, 1371 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.82; H, 9.81.

6.10.17. Enone ***66***. ^1H NMR (500 MHz, $CDCl_3$): δ 9.76 (s, 1H); 6.82 (br s, 1H); 2.82 (m, 1H); 2.48 (br dd, J=6.8, 15.5 Hz, 1H); 2.34 (dddt, J=6.6, 6.6, 6.6, 6.8 Hz, 1H); 2.26 (br dd, J=5.3, 15.5 Hz, 1H); 1.71 (dddd, J=5.8, 5.8, 5.8, 11.6 Hz, 1H); 1.56–1.24 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 158.0, 146.9, 45.2, 37.7, 33.3, 27.6, 27.3, 23.3, 22.8. HRMS (FAB^+) calcd For $C_{10}H_{14}ONa$ (M+Na): 150.1042, Found: 150.1045. FTIR (neat): 2926, 2853, 1678, 1449 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.78; H, 9.34.

6.10.18. Bromide ***68***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (m, 1H, Ar H), 7.56 (m, 2H, Ar H), 7.47 (m, 2H, Ar H), 7.04 (td, J=6.8, 15.6 Hz, 1H), 6.90 (td, J=1.2, 15.6 Hz, 1H), 3.44 (t, J=6.6 Hz, 2H), 2.37 (ddt, J=1.2, 6.8, 7.3 Hz, 2H), 1.94 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 148.7, 137.8, 132.6, 128.6, 128.4, 126.2, 33.3, 32.1, 31.7, 26.6. HRMS (FAB^+) calcd for $C_{13}H_{15}OBrNa$ (M+Na): 289.0204, Found: 289.0204. FTIR (neat): 2936, 1670, 1621, 1598, 1447, 1346,

1283, 693 cm^{-1}. Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.89; H, 5.66.

6.10.19. Bromide ***67***. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (m, 2H, Ar H), 7.57 (m, 1H, Ar H), 7.48 (m, 2H, Ar H), 7.02 (td, *J*=6.6, 15.4 Hz, 1H), 6.96 (d, *J*=15.4 Hz, 1H), 3.46 (t, *J*=6.6 Hz, 2H), 2.51 (td, *J*=6.6, 7.3 Hz, 2H), 2.10 (tt, *J*=6.6, 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 147.0, 132.7, 128.5, 128.4, 128.1, 126.8, 32.6, 30.9, 30.8. HRMS (FAB^+) calcd for $C_{12}H_{13}OBrNa$ (M+Na): 275.0048, Found: 275.0048. FTIR (neat): 2935, 1670, 1622, 1447, 1288, 1220, 972, 693 cm^{-1}. Anal. Calcd for $C_{12}H_{13}OBr$: C, 56.94; H, 5.18. Found: C, 56.69; H, 5.11.

6.11. For thioester cyclization procedure, see procedure for the alkylation of enones above

6.11.1. Thioester ***75***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.83 (td, *J*=7.0, 15.5 Hz, 1H), 6.16 (td, *J*=1.3, 15.5 Hz, 1H), 3.41 (t, *J*=6.6 Hz, 2H), 2.95 (q, *J*=7.5 Hz, 2H), 2.38 (ddt, *J*=1.3, 7.0, 7.0 Hz, 2H), 2.03 (tt, *J*=6.6, 7.0 Hz, 2H), 1.28 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 142.4, 129.5, 32.4, 30.6, 30.2, 23.0, 14.6. HRMS (FAB^+) calcd for $C_8H_{13}BrOSNa$ (M+Na): 259.9766, Found: 258.9768. FTIR (neat): 2965, 2960, 2872, 1667, 1633, 1436, 1265, 1026, 970 cm^{-1}. Anal. Calcd for $C_8H_{13}OBrS$: C, 40.52; H, 5.53. Found: C, 40.13; H, 5.53.

6.11.2. Thioester ***76***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.83 (td, *J*=7.1, 15.45 Hz, 1H), 6.16 (td, *J*=1.3, 5.45 Hz, 1H), 3.41 (t, *J*=6.7 Hz, 2H), 2.95 (t, *J*=7.3 Hz, 2H), 2.37 (ddt, *J*=1.3, 7.1, 7.1 Hz, 2H), 2.03 (tt, *J*=6.7, 7.1 Hz, 2H), 1.59 (tt, *J*=7.3, 7.3 Hz, 2H), 1.41 (qt, *J*=7.3, 7.3 Hz, 2H), 0.92 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.4, 142.2, 129.5, 32.3, 31.4, 30.6, 30.1, 28.2, 21.7, 13.4. HRMS (FAB^+) calcd for $C_{10}H_{17}OBrNa$ (M+Na): 287.00813, Found: 287.00812. FTIR (neat): 2959, 2930, 2872, 1671, 1632 cm^{-1}. Anal. Calcd for $C_{10}H_{17}OBr$: C, 45.29; H, 6.46. Found: C, 45.57; H, 6.57.

6.11.3. Thioester ***77***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.75 (td, *J*=7.1, 15.5 Hz, 1H), 6.06 (td, *J*=1.3, 15.5 Hz, 1H), 3.41 (t, *J*=6.6 Hz, 2H), 2.34 (tdd, *J*=1.3, 7.1, 7.1 Hz, 2H), 2.01 (tt, *J*=6.6, 7.1 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 141.4, 130.3, 47.9, 32.5, 30.7, 30.2, 29.8. HRMS (FAB^+) calcd for C10H17OBrSNa (M+Na): 287.00825, Found: 287.00812. FTIR (neat): 2962, 1667, 1630, 1454, 1363, 968 cm^{-1}. Anal. Calcd for $C_{10}H_{17}OBrS$: C, 45.29; H, 6.46. Found: C, 45.54; H, 6.50.

6.11.4. Cyclopentene ***78***. Treatment of bromide **76** (237 mg, 1 mmol), with tributylphosphine (0.23 mL, 1 mmol) in *t*-BuOH (2 mL) followed by addition of KOH (56 mg, 1 mmol) and $BnEt_3NCl$ (23 mg, 0.1 mmol) in DCM/H_2O (10 mL, 1:1) yielded enone **5** in 99% yield (155 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 6.79 (tt, *J*=2.2, 2.4 Hz, 1H), 2.93 (q, *J*=7.4 Hz, 2H), 2.62 (dtt, *J*=2.2, 2.3, 7.6 Hz, 2H), 2.51 (tdt, *J*=2.3, 2.4, 7.6 Hz, 2H), 1.96 (tt, *J*=7.6, 7.6 Hz, 2H), 1.27 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.9, 144.0, 141.4, 33.2, 31.0, 22.8, 22.7, 13.4. HRMS (CI^+) calcd for $C_8H_{13}OS$ (M+H): 157.06899, Found: 157.06872. FTIR (neat): 2957, 2871, 1655, 1459, 1154 cm^{-1}. Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74. Found: C, 61.03; H, 7.65.

6.11.5. Cyclopentene ***79***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (tt, *J*=2.1, 2.3 Hz, 1H), 2.93 (t, *J*=7.4 Hz, 2H), 2.62 (dtt, *J*=2.1, 2.2, 7.6 Hz, 2H) 2.51 (tdt, *J*=2.2, 2.3, 7.6 Hz, 2H), 1.96 (tt, *J*=7.6, 7.6 Hz, 2H) 1.58 (m, 2H), 1.41 (tq, *J*=7.4, 7.4, Hz, 2H), 0.94 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 144.1, 141.5, 33.4, 31.7, 31.2, 28.1, 22.9, 22.0, 13.6. HRMS (CI^+) calcd for $C_{10}H_{17}OS$ (M+): 185.0999, Found: 185.1000. FTIR (neat): 2958, 2930, 1655, 1613, 1156 cm^{-1}. Anal. Calcd for $C_{10}H_{17}OS$: C, 65.17; H, 8.75. Found: C, 64.82; H, 8.87.

6.11.6. Bromide ***81***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (td, *J*=6.9, 15.4 Hz, 1H), 6.12 (td, *J*=1.5, 15.4 Hz, 1H), 3.41 (t, *J*=6.6 Hz, 2H), 2.95 (q, *J*=7.3 Hz, 2H), 2.23 (dtd, *J*=1.5, 7.1, 7.1 Hz, 2H), 1.89 (tt, *J*=6.6, 7.1 Hz, 2H), 1.64 (tt, *J*=7.1, 7.1 Hz, 2H), 1.28 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 143.9, 129.0, 33.0, 31.9, 31.0, 26.3, 22.9, 14.7. HRMS (FAB^+) calcd for $C_9H_{15}OBrSNa$ (M+Na): 272.9927, Found: 272.9925. FTIR (neat): 2930, 1670, 1632, 1451, 1265, 969 cm^{-1}. Anal. Calcd for $C_9H_{15}OBrS$: C, 43.03; H, 6.02. Found: C, 43.36; H, 5.98.

6.11.7. Bromide ***83***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.70 (td, *J*=7.8, 15.4 Hz, 1H), 6.15 (td, *J*=1.2, 15.4 Hz, 1H), 4.23 (ABq, *J*=7.1, 7.1 Hz, 2H), 4.22 (ABq, *J*=7.1, 7.1 Hz, 2H), 3.36 (t, *J*=8.2 Hz, 2H), 2.94 (q, *J*=7.4 Hz, 2H) 2.77 (dd, *J*=1.2, 7.8 Hz, 2H), 2.45 (t, *J*=8.2 Hz, 2H), 1.28 (t, *J*=7.4 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.3, 169.5, 137.5, 132.2, 61.9, 57.2, 36.7, 36.2, 26.6, 23.1, 14.6, 13.9. HRMS (FAB^+) calcd for $C_{15}H_{23}O_5BrSNa$ (M+Na): 417.0340, Found: 417.0347. FTIR (neat): 2980, 2934, 1730, 1671, 1633, 1443, 1261 cm^{-1}. Anal. Calcd for $C_{15}H_{23}O_5BrS$: C, 45.57; H, 5.86. Found: C, 45.47; H, 5.95.

6.11.8. Cyclohexene ***84***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.89 (tt, *J*=1.8, 3.98 Hz, 1H), 4.192, (ABq, *J*=7.1, 7.1 Hz, 1H), 4.190 (ABq, *J*=7.1, 7.1 Hz, 1H), 2.91 (q, *J*=7.4 Hz, 2H), 2.76 (td, *J*=2.4, 3.98 Hz, 2H), 2.39 (dtt, *J*=1.8, 2.4, 6.4 Hz, 2H), 2.18 (t, *J*=6.4 Hz, 2H), 1.26 (t, *J*=7.4 Hz, 3H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 170.7, 137.0, 134.2, 61.5, 52.4, 30.9, 27.0, 22.9, 21.2, 14.7, 13.9. HRMS (CI^+) calcd for $C_{15}H_{23}O_5S$ (M+H): 315.1262, Found: 315.1266. FTIR (neat): 2957, 2930, 2871, 1655, 1156 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O5S$: C, 57.30; H, 7.05. Found: C, 57.34; H, 7.07.

6.11.9. Bromide ***85***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.67 (td, *J*=7.6, 15.3 Hz, 1H), 6.15 (bd, *J*=15.3 Hz, 1H), 3.76 (s, 6H), 3.35 (t, *J*=8.2 Hz, 2H), 2.94 (t, *J*=7.3 Hz, 2H), 2.78 (dd, *J*=1.1, 7.6 Hz, 2H), 2.46 (t, *J*=8.2 Hz, 2H), 1.58 (tt, *J*=7.3, 7.3 Hz, 2H), 1.40 (qt, *J*=7.3, 7.3 Hz, 2H), 0.92 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.2, 169.9, 137.0, 132.2, 57.3, 52.8, 36.6, 36.2, 31.4, 28.4, 26.5, 21.8, 13.5. HRMS (FAB^+) calcd for $C_{15}H_{23}O_5BrSNa$ (M+Na): 417.03409. Found: 417.03472. FTIR (neat): 2956, 1734, 1670, 1437, 1264 cm^{-1}. Anal. Calcd for $C_{15}H_{23}O_5BrS$: C, 45.57; H, 5.86. Found: C, 45.57; H, 6.17.

6.11.10. Cyclohexene ***86***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.91 (tt, *J*=1.5, 3.98 Hz, 1H), 3.73, (s, 6H), 2.90 (t, *J*=7.3 Hz, 2H), 2.78 (td, *J*=2.2, 3.98 Hz, 2H), 2.38 (dtt, *J*=1.5, 2.2, 6.4 Hz, 2H), 2.19 (t, *J*=6.4 Hz, 2H), 1.56 (tt, *J*=7.3, 7.4 Hz, 2H), 1.39 (tq, *J*=7.4, 7.4 Hz, 2H), 0.92 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 171.2, 137.2, 134.0, 52.8, 82.5, 31.6, 31.1, 28.3, 27.2, 22.0, 21.3, 13.6. HRMS (CI^+) calcd for $C_{15}H_{23}O_5S$ (M+H): 315.12677, Found: 315.12662. FTIR (neat): 2955, 2872, 1736, 1651, 1257 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.16; H, 7.20.

6.11.11. Bromide ***87***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.59 (td, *J*=7.6, 15.3 Hz, 1H), 6.06 (td, *J*=1.2, 15.3 Hz, 1H), 3.76 (s, 6H), 3.35 (t, *J*=8.1 Hz, 2H), 2.76 (dd, *J*=1.2, 7.6 Hz, 2H), 2.45 (t, *J*=8.1 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 170.0, 136.0, 133.0, 57.3, 52.9, 48.2, 36.6, 36.1, 29.7, 26.6. HRMS (FAB^+) calcd for $C_{15}H_{23}O_5BrSNa$ (M+Na): 417.03471, Found: 417.02472. FTIR (neat): 2956, 1734, 1667, 1631, 1435, 1264 cm^{-1}. Anal. Calcd for $C_{15}H_{23}O_5BrS$: C, 45.57; H, 5.86. Found: C, 45.47; H, 5.95.

6.11.12. Cyclohexene ***88***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (tt, *J*=2.0, 4.4 Hz, 1H), 3.73 (s, 6H), 2.73 (td, *J*=2.2, 4.0 Hz, 2H), 2.32 (dtt, *J*=2.2, 2.2, 6.4 Hz, 2H), 2.16 (t, *J*=6.4 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 171.3, 138.0, 133.2, 52.9, 52.5, 47.6, 31.1, 29.9, 28.3, 27.3, 21.6. HRMS (CI^+) calcd for $C_{15}H_{23}O_5S$ (M+): 315.12718, Found: 315.12662. FTIR (neat): 2954, 1735, 1645, 1257 cm^{-1}. Anal. Calcd for $C_{15}H_{23}O_5S$: C, 57.30; H, 7.05. Found: C, 57.66; H, 7.21.

6.11.13. Bromide ***89***. ^1H NMR (500 MHz, $CDCl_3$): δ 6.70 (dd, *J*=8.17, 15.67 Hz, 1H), 6.13 (dd, *J*=1.0, 15.67 Hz, 1H), 3.40 (ABt, *J*=9.72,

6.5 Hz, 1H), 3.33 (ABt, *J*=9.72, 6.5 Hz, 1H), 2.95 (q, *J*=7.4 Hz, 2H), 2.57 (m, 1H), 1.94 (ABdt, *J*=13.95, 6.97, 6.97 Hz, 1H), 1.91 (ABdt, *J*=13.95, 6.97, 6.97 Hz, 1H), 1.28 (t, *J*=7.4 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 147.5, 127.9, 43.9, 38.2, 34.7, 30.9, 26.6, 25.8, 23.2, 22.9, 18.8, 14.6, 14.5, 14.4. HRMS (FAB^+) calcd for $C_9H_{15}OBrNaS$ (M+Na): 272.99276, Found: 272.99247. FTIR (neat): 2965, 1670, 1631, 1453 cm^{-1}. Anal. Calcd for $C_9H_{15}OBrS$: C, 43.03; H, 6.02. Found: C, 43.29; H, 6.23.

6.11.14. Bromide ***91***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dd, *J*=9.2, 15.5 Hz, 1H), 6.23 (dd, *J*=0.7, 15.5 Hz, 1H), 3.25 (dd, *J*=7.1, 10.0 Hz, 1H), 3.14 (dd, *J*=8.2, 10.0 Hz, 1H), 2.959 (ABq, *J*=15.0, 7.5 Hz, 1H), 2.956 (ABq, *J*=15.0, 7.5 Hz, 1H), 2.78 (dddd, *J*=4.0, 4.0, 8.0, 9.1 Hz, 1H), 1.98 (ddddd, *J*=4.0, 4.0, 7.1, 8.2, 10.8 Hz, 1H), 1.29 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 143.1, 130.0, 42.6, 40.1, 36.6, 30.2, 27.2, 24.8, 23.1, 21.6, 14.7. HRMS (FAB^+) calcd for $C_{12}H_{19}OBrSNa$ (M+Na): 313.02361, Found: 313.02377. FTIR (neat): 2930, 2856, 1670, 1628, 1449 cm^{-1}. Anal. Calcd for $C_{12}H_{19}OBrS$: C, 49.49; H, 6.58. Found: C, 49.70; H, 6.53.

6.11.15. Cyclopentene ***92***. HRMS (CI^+) calcd for $C_{12}H_{19}OS$ (M+Na): 211.1152, Found: 211.1157. Anal. Calcd for $C_{12}H_{19}OS$: C, 68.52; H, 8.63. Found: C, 68.27; H, 8.67.

6.12. Procedure for catalytic reaction of enones

To the halide in a 0.5 M solution of *tert*-butyl alcohol/methylene chloride (1:1), was added a 0.2 M KOH solution (1 equiv) and $BnEt_3NCl$ (10 mol %). The reaction mixture was then treated with tributylphosphine (20 mol %) and allowed to stir at ambient temperature until the reaction was complete (TLC analysis). Entries 1, 4 and 5, Table 12—a 1.0 M solution of *tert*-butyl alcohol/methylene chloride (1:1) was employed for the catalytic reaction.

6.12.1. Bromide ***93***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (m, 1H, Ar), 8.02 (m, 1H, Ar), 7.98 (m, 1H, Ar), 7.90 (m, 2H, Ar), 7.56 (m, 2H, Ar), 7.12 (td, *J*=6.0, 15.45 Hz, 1H), 7.07 (d, *J*=15.45 Hz, 1H), 3.46 (t, *J*=6.6 Hz, 2H), 2.41 (dt, *J*=6.0, 7.3 Hz, 2H), 1.97 (tt, *J*=6.6, 7.5 Hz, 2H), 1.74 (tt, *J*=7.3, 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 148.5, 135.3, 135.1, 132.4, 129.9, 129.4, 128.4, 128.3, 127.7, 126.7, 126.2, 124.4, 32.3, 32.1, 31.8, 26.6. HRMS (FAB^+) calcd for $C_{17}H_{17}OBrNa$ (M+Na): 339.0368, Found: 339.0360. FTIR (neat): 2934, 1691, 1665, 1615, 1460, 1295 cm^{-1}. Anal. Calcd for $C_{17}H_{17}OBr$: C, 5.40; H,. Found: C, 64.44; H, 5.46.

6.12.2. Bromide ***95***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (m, 2H, Ar), 8.05 (m, 2H, Ar), 7.10 (td, *J*=6.8, 15.4 Hz, 1H), 6.89 (td, *J*=1.5, 15.4 Hz, 1H), 3.44 (t, *J*=6.6 Hz), 2.40 (ddt, *J*=1.5, 6.6, 7.2 Hz, 2H), 1.94 (tt, *J*=6.6, 7.2 Hz), 1.73 (tt, *J*=7.2, 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 150.8, 149.7, 142.4, 129.4, 129.2, 125.6, 123.6, 123.5, 33.1, 31.9, 31.7, 26.3. HRMS (FAB^+) calcd for $C_{13}H_{15}O_3BrNa$ (M+Na): 312.0237, Found: 312.0235. FTIR (neat): 3106, 2937, 2861, 1673, 1620, 1601, 1523, 1344 cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_3Br$: C, 50.02; H, 4.52. Found: C, 50.05; H, 4.67.

6.12.3. Bromide ***97***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (m, 1H, Ar), 8.03 (m, 1H, Ar), 7.98 (m, 1H, Ar), 7.90 (m, 2H, Ar), 7.58 (m, 2H, Ar), 7.14 (d, *J*=15.38 Hz, 1H), 7.07 (td, *J*=6.6, 15.38 Hz, 1H), 3.49 (t, *J*=6.6 Hz, 2H), 2.56 (dt, *J*=6.6, 7.3 Hz, 2H), 2.13 (tt, *J*=6.6, 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.8, 146.8, 135.2, 134.8, 132.3, 129.8, 129.3, 128.3, 128.2, 127.6, 126.6, 126.5, 124.2, 32.7, 30.9, 30.7. FTIR (neat): 3055, 2930, 1665, 1617, 1291 cm^{-1}. Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.38; H, 4.99. Found: C, 63.39; H, 4.93.

6.12.4. Bromide ***99***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (m, 2H, Ar), 8.05 (m, 2H, Ar), 7.08 (td, *J*=7.1, 15.4 Hz, 1H), 6.93 (td, *J*=1.5, 15.4 Hz, 1H), 3.46 (t, *J*=7.0 Hz, 2H), 2.55 (dtd, *J*=1.5, 7.0, 7.1 Hz, 2H), 2.11 (tt, *J*=7.0, 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.8, 149.9, 149.4, 142.4, 129.3, 126.3, 123.7, 35.5, 31.0, 30.6. FTIR (neat): 2936, 2854, 1674, 1622, 1602, 1436, 1248, 1028 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_3N_2Br$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.67; H, 4.34; N, 4.75.

6.12.5. Cyclohexene ***94***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (m, 1H, Ar), 7.92 (m, 1H, Ar), 7.87 (m, 2H, Ar), 7.75 (m, 1H, Ar), 7.55 (m, 2H, Ar), 6.64 (tt, *J*=2.0, 7.3 Hz, 1H), 2.49 (dtt, *J*=2.0, 2.4, 6.1 Hz, 2H), 2.30 (ttd, *J*=2.4, 6.1, 7.2 Hz, 2H), 1.78 (tt, *J*=6.1, 6.1 Hz, 2H), 1.71 (tt, *J*=6.1, 6.1 Hz, 2H). FTIR (neat): 2918, 2849, 1638, 1465, 1282 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.10; H, 6.43.

6.12.6. Cyclohexene ***96***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (m, 2H, Ar), 7.73 (m, 2H, Ar), 6.57 (tt, *J*=2.0, 7.4 Hz, 1H), 2.43 (dtt, *J*=2.0, 2.4, 6.2 Hz, 2H), 2.30 (ttd, *J*=2.4, 6.2, 7.6 Hz, 2H), 1.75 (tt, *J*=6.2, 6.2 Hz, 2H), 1.69 (tt, *J*=6.2, 6.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 149.0, 146.5, 144.4, 138.6, 129.6, 123.2, 26.2, 23.4, 21.7, 21.4. HRMS (EI^+) calcd for $C_{13}H_{13}O_3N$: 231.08948, Found: 231.08955. FTIR (neat): 2933, 1648, 1301, 1522, 1350 cm^{-1}. Anal. Calcd for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67. Found: C, 67.30; H, 5.74.

6.12.7. Cyclopentene ***98***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (m, 1H, Ar), 7.94–7.83 (m, 4H, Ar), 7.59–7.52 (m, 2H, Ar), 6.61 (tt, *J*=1.7, 2.5 Hz, 1H), 2.81 (dtt, *J*=1.7, 2.2, 7.5 Hz, 2H), 2.67 (tdt, *J*=2.2, 2.5, 7.5 Hz, 2H), 2.06 (tt, *J*=7.5, 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 146.7, 144.6, 136.1, 134.9, 132.2, 129.9, 129.1, 128.0, 127.8, 127.7, 126.5, 125.1, 34.3, 32.0, 22.7. HRMS (FAB^+) calcd for $C_{16}H_{14}ONa$ (M+Na): 245.0948, Found: 245.0942. FTIR (neat): 2952, 1636, 1355, 1299 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.41; H, 6.33.

6.12.8. Cyclopentene ***100***. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (m, 2H, Ar), 7.84 (m, 2H, Ar), 6.57 (tt, *J*=2.0, 12.4 Hz, 1H), 2.76 (dtt, *J*=2.4, 7.6, 12.4 Hz, 2H), 2.66 (tdt, *J*=2.0, 2.4, 7.6 Hz, 2H), 2.04 (tt, *J*=7.6, 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 149.5, 149.1, 144.5, 144.3, 129.5, 123.4, 34.6, 31.5, 22.7. HRMS (EI^+) calcd for $C_{12}H_{11}O_3N$: 217.07378, Found: 217.07390. FTIR (neat): 2957, 2871, 1646, 1601, 1522, 1348 cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10. Found: C, 66.21; H, 5.10.

6.13. Catalysis of reactions of α,β-unsaturated thioesters in the MBH reaction: general procedure of the catalytic MBH alkylation reaction of thioesters

A solution of thioester **75** (237 mg, 1 mmol) in CH_2Cl_2/*t*-BuOH (1:1) (2 mL, 0.5 M), and H_2O (10 mL, 0.1 M) with $BnEt_3NCl$ (23 mg, 0.1 mmol) and KOH (56 mg, 1 mmol) was treated with tributylphosphine (0.45 mL, 0.2 mmol). The reaction was stirred in a resealable tube until complete consumption of starting material as indicated by TLC. The organic layer was then extracted with CH_2Cl_2, dried over anhydrous sodium sulfate and concentrated in vacuo. Purification via column chromatography gave the desired product **78** (152 mg, 99%).

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