Unprecedented reactivity in the Morita–Baylis–Hillman reaction; intramolecular α-alkylation of enones using saturated alkyl halides†

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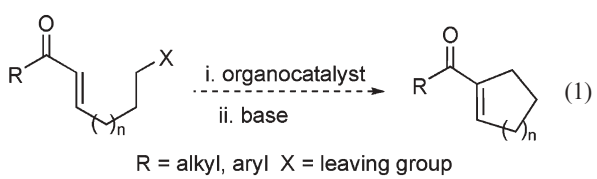
sp^3 Hybridized electrophiles, never before used in the organomediated Morita–Baylis–Hillman reaction, now facilitate the formation of five- and six-membered enone cycloalkylation products.

Discovering new high yielding, 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 not only noteworthy but are also fundamental for the construction of organic molecular frameworks. The Morita–Baylis–Hillman reaction (MBH)[1,2] 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.[3] During the last 15 years, the Morita–Baylis–Hillman reaction has seen tremendous growth and development of all three components and now encompasses the use of a wide variety of activated alkenes, electrophiles and nucleophilic catalysts.[3] 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.[4,5]

A diverse group of electrophiles, all sp^2 hybridized at the reacting center, including aldehydes, α-keto esters, 1,2-diketones, aldimines, α-bromo methyl enoates,[6] allylic acetates under Pd catalysis,[7a] arenes,[7b] vinyl sulfones,[7c] and allylic halides[8] have been studied extensively in this intriguing reaction. The MBH reaction has long been limited to reactions of highly reactive sp^2 hybridized electrophiles whereas the less reactive sp^3 hybridized electrophiles have been overlooked and never before utilized as the electrophilic partner in the Morita–Baylis–Hillman coupling. In view of our previously developed method for the organomediated MBH reactions of allylic chlorides,[8] we investigated the feasibility of the related, yet completely unprecedented, cycloalkylation reaction using an sp^3 hybridized electrophile (eqn. 1).



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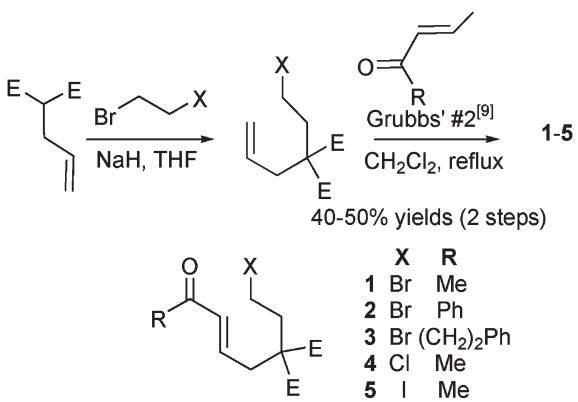
Herein, we report an entirely new organomediated Morita–Baylis–Hillman cycloalkylation reaction representing a direct, intramolecular α-alkylation of enones. To assess its viability, initial studies were performed using enones bearing different halide leaving groups, which were readily prepared beginning from diethyl allylmalonate (Scheme 1). Alkylation of diethyl allylmalonate with 1,2-dibromoethane or 1-bromo-2-chloroethane gave the substituted malonate. Subsequent cross-metathesis with the appropriate enone using Grubbs' 2nd generation catalyst[9] furnished the desired cycloalkylation precursors **1–5** in good overall yield.

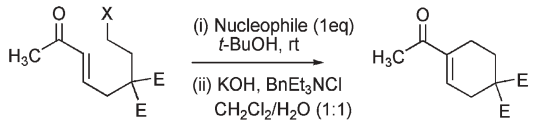
Amine nucleophiles such as DABCO and quinuclidine,[10] which are commonly employed in the traditional Morita–Baylis–Hillman, were found to be ineffective at promoting the cycloalkylation of **1** in various solvents at temperatures from ambient to 63 °C. However, treatment of bromide **1** with Bu_3P 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 **6** in excellent yield (entry 3, Table 1). In light of the transient nature of the putative MBH zwitterionic intermediate, this result is truly remarkable since reactions with sp^2 hybridized electrophiles, found in traditional MBH reactions, are typically much more favorable than those with sp^3 hybridized electrophiles.

Intrigued by this extraordinary initial cycloalkylation result, we set out to investigate the efficiency of the electrophilic partner. Reaction of chloride **4** with Bu_3P or Me_3P resulted in low recoveries of both starting material and cyclized enone (entries 1 and 2, Table 1). Evidently, the chloride is too weak a leaving group to undergo facile displacement by the transiently formed zwitterionic enolate thus giving rise to low yields of enone **6**. For the reaction of iodide **5** with Bu_3P, the cycloalkylation product was obtained in a slightly diminished yield when compared to reaction



Scheme 1 Synthesis of alkyl halides **1–5**.

Table 1 Optimization of cycloalkylation



1, X = Br; **4**, X = Cl; **5**, X = I — **6**

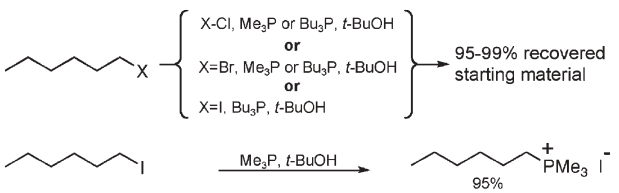
Entry	X	Nucleophile	Time (h)	Yield (%)[a]
1	Cl	Bu_3P	72	12[b]
2	Cl	Me_3P	72	46[c]
3	Br	Bu_3P	3	99
4	Br	Me_3P	5	96
5	I	Bu_3P	3	87
6	I	Me_3P	24	[d]

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

of the bromide (entry 5, Table 1). Use of Me_3P led to the disappearance of starting material, but no recognizable products were isolated after treatment with base. These results clearly point out the delicate balance of reactivity between the nucleophile and electrophilic centers in the molecule.

With the cycloalkylation results in hand, it was necessary to discount the possibility that the phosphine reacted initially with the halide generating a phosphonium salt. Hexyl bromide or chloride, when treated with one equivalent of either Bu_3P or Me_3P in *t*-BuOH at room temperature for 5 h, resulted in quantitative recovery of the starting material (Scheme 2). 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 cycloalkylation results in Table 1, entries 5 and 6 with alkyl iodides and their reaction with Bu_3P or Me_3P.

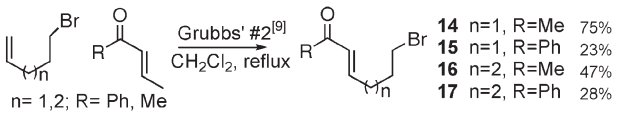
Having established the bromide to be the optimal leaving group and that the phosphonium salt was not a likely intermediate, we further probed the generality of this enone cycloalkylation. Remarkably, increasing the enone steric bulk had little consequence on the isolated yield of the six-membered ring cycloalkylation adducts (Table 2, entries 1–3).[11] 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 **10** and **11**. As expected, treatment of enone **10** with one equivalent 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 **12** in good yield. This cyclization protocol also cleanly provided bicyclic enal **13** in similarly high yield from enal



Scheme 2

Table 2 Optimization of cycloalkylation[11]

Entry	Alkyl bromide	Product	Yield (%)
1	**1**	**6**	99
2	**2**	**7**	90
3	**3**	**8**	79
4	**10**	**12**	90
5	**11**	**13**	83
6	**14**	**18**	80
7	**15**	**19**	99
8	**16**	**20**	81
9	**17**	**21**	95



Scheme 3 Synthesis of alkyl halides **14–17**.

11. 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, **14–17**, in moderate to good yields (Scheme 3). Subjecting these compounds to the optimized cyclization conditions also gave the five- and six-membered cycloalkylation adducts in excellent yields (Table 2, entries 6–9).

We next set out to investigate the nature of the two-stage cycloalkylation process. Upon reaction of bromide **1** 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 **6**. Under identical conditions, reaction of bromide **1** with 0.5 equiv. of Me_3P gave rise to 44% of enone **6** and 51% recovery of starting material. To probe the identity of the intermediate material, enone **15** (Table 2) was treated with one 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 **19** 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 suggests that cyclization had occurred prior to the addition of base, which serves only to promote elimination to the enone.

In summary, we have successfully developed the first, entirely organomediated one-pot Morita–Baylis–Hillman α-alkylation of enones using sp^3 hybridized electrophiles. This method tolerates modification of the enone and the tether length and substitution pattern to form both five- and six-membered rings in excellent yields. Further studies will focus on related transformations and modifications of the electrophilic partner and substitution on the tether.

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