New directions for the Morita–Baylis–Hillman reaction; homologous aldol adducts *via* epoxide opening†

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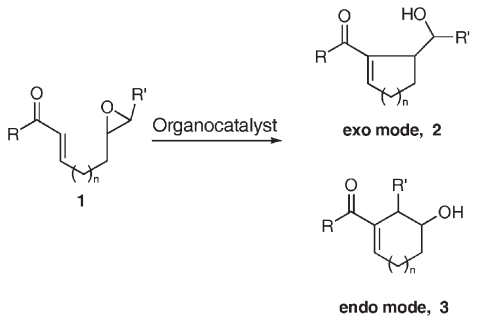
Under trialkylphosphine catalyzed Morita–Baylis–Hillman reaction conditions, epoxides react with enones to give rise to homologous aldol adducts.

The Morita–Baylis–Hillman (MBH) reaction[1] is an organocatalytic process that generates aldol adducts *via* reaction at the α-carbon of an unsaturated carbonyl moiety. Existing conditions for the MBH reaction now permit the use of a wide variety of alkenes, electrophiles and nucleophilic catalysts, including both tertiary phosphines and amines. The types of electrophiles that have been shown to react under MBH conditions include aldehydes, ketones, aldimines, arenes, unsaturated ketones[2] and vinyl sulfones.[3] Recently, we have extended the traditional MBH reaction to include allylic halides[4] and alkyl halides.[5] Epoxides however, have been overlooked as an electrophile in the MBH reaction despite being considered an important organic functional group. 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.[6] A number of examples illustrate effective epoxide opening resulting in skeletal enhancement under either Lewis acidic or base-catalyzed reaction conditions.[7]

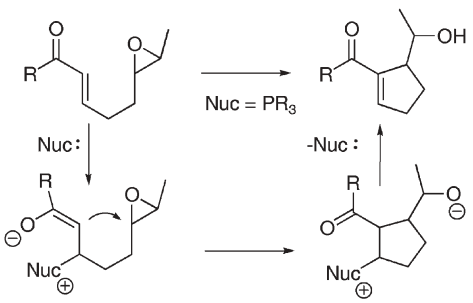
In the presence of nucleophilic catalysts, epoxides have demonstrated variable stability and reactivity. An early communication reported that epoxides failed to yield recognizable products in the tertiary amine-catalyzed intermolecular MBH reaction with acrylates[8] whereas α,β-epoxy aldehydes, on the other hand, underwent efficient DABCO catalyzed coupling giving a traditional MBH aldol adduct.[9] To date, there have been no reports of attempted phosphine-catalyzed MBH reactions with epoxides. Under tributylphosphine catalysis, epoxides have been shown to react with deoxygenation (160 °C),[10] or react with the phosphine resulting in ring opening under mild conditions (rt → refluxing *t*-BuOH).[11] In addition, epoxides react with acetate generated by reaction of Ac_2O with tributylphosphine in refluxing toluene, thus illustrating the stability of epoxides in the presence of a trialkylphosphine when competing processes are possible.[12] These examples demonstrate that the reactivity of epoxides in the presence of trialkylphosphines or tertiary amines is highly dependent on the reaction environment. Herein we report our unprecedented work on the use of epoxides in the MBH reaction resulting in the first homologous intramolecular MBH reaction, which represents a $C(sp^2)$–$C(sp^3)$ coupling with concomitant cyclization.

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 (eqn (1)) *via* a traditional MBH organocatalyzed mechanism (Scheme 1).

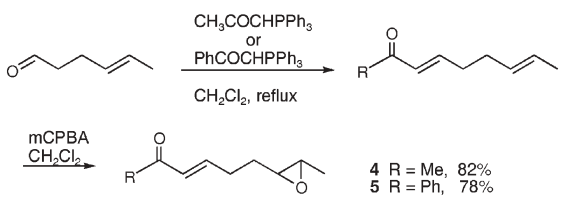


(1)

Substitution on the epoxide or the tether would be expected to bias which cyclization mode will operate. Initial studies were conducted with epoxy enones **4** and **5** that were prepared as described in Scheme 2.[13] Treatment of epoxide **4** with 1 equiv. of PBu_3 in *t*-BuOH at rt led to the isolation of 25% of cyclic enone **6** in addition to a significant amount of unrecognizable materials



Scheme 1



Scheme 2

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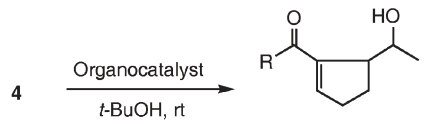
Table 1



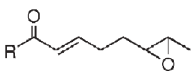
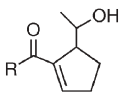
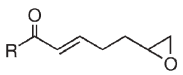
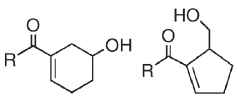
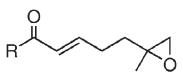
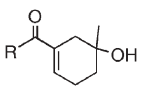
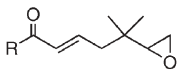
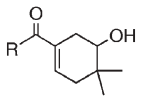
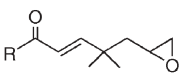
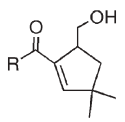
(2)

Concentration/M	PR_3 (equiv.)	Time/h	Yield (%)
0.50	PBu_3 (0.25)	72	25
0.50	PBu_3 (1.0)	30	25
0.20	PMe_3 (1.0)	30	38
0.10	PMe_3 (0.10)	72	41
0.10	PMe_3 (1.0)	30	44
0.05	PMe_3 (0.10)	72	48
0.025	PBu_3 (0.10)	72	n.r.
0.025	PMe_3 (0.10)	72	65
0.025	PMe_3 (1.0)	30	67

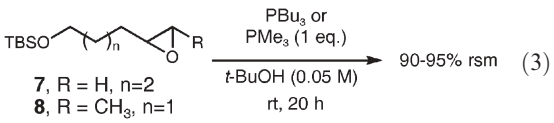
(eqn (2)). None of the endo epoxide opening adduct was observed. While this was a promising result because it represented the first epoxide opening using a zwitterionic enolate under MBH conditions, further refinement of reaction conditions was warranted. Optimization studies involving variations in both solvent concentration and equivalents of trialkylphosphine led to conditions for efficient epoxide opening (Table 1, eqn (2)). These results showed that PMe_3 was a more effective organocatalyst than PBu_3. At higher concentrations (0.5 M), loss of material and generation of unrecognizable products[14] was a problem regardless of whether catalytic or stoichiometric amounts of PMe_3 or PBu_3 were used. At lower concentrations (0.025 M) only PMe_3 was an effective organocatalyst giving rise to 65–67% of the desired cyclized adduct. Both stoichiometric and catalytic conditions gave the same result at 0.025 M concentration using PMe_3, but the stoichiometric reaction required less time. The use of higher temperatures was not advantageous to the reaction outcome. It was therefore beneficial to continue further studies using stoichiometric amounts of trialkylphosphine in order to keep the reaction time to a minimum.

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 rt for 20 h resulted in the recovery of 90–95% of the epoxide (eqn (3)).

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

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

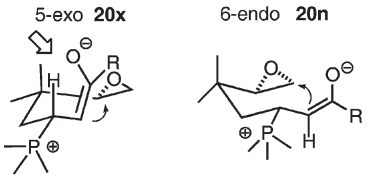
[a] Reactions were conducted at a concentration of 0.025 M in *tert*-butanol at room temperature.



(3)

These results strongly suggest that the traditional MBH organocatalyzed mechanism[1] 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). Unsubstituted enone-epoxides **10** and **13** gave almost equimolar mixtures of the endo and exo modes of opening due to minimal steric interactions influencing one mode of opening. In the cyclizations of either epoxide **10** or **13**, the products of a 5-exo mode of opening, alcohols **12** or **15** respectively, would be expected to be favored kinetically. However, with the unsubstituted epoxide terminus, the 6.5-endo mode of cyclization apparently competes favorably giving rise to alcohols **11** or **14**. 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**. Reaction of the γ-disubstituted enone was expected to be slow if the reaction were to occur at all. Substitution adjacent to the site of nucleophilic addition of trimethylphosphine should make the addition difficult and thus decrease the zwitterion concentration. Reaction of methyl ketone **24** was extremely slow requiring 7 d and 10 equiv. of phosphine for complete consumption of starting material. The corresponding phenyl ketone was consumed during the course of 72 h although 10 equiv. of phosphine were also required. However, 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. Opening to form the five-membered ring *via* the exo mode was preferred over the endo mode generating the cyclohexenol. At this point we have been unable to promote cyclizations where 6-exo adducts are expected.



We have described an unprecedented opening of epoxides under Morita–Baylis–Hillman reaction conditions. While epoxides are often considered an important functional group in organic synthesis, they have been overlooked as an electrophile in the MBH reaction. Nucleophilic epoxide openings are key reactions in the construction of carbon skeletons and this new reaction enhances the synthetic utility of epoxides. The MBH epoxide opening results in the formation of homologous aldol products efficiently and embodies a $C(sp^2)$–$C(sp^3)$ coupling with concomitant cyclization. Further work on the scope of this reaction is currently in progress.

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Notes and references

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