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Influence of Michael Acceptor Stereochemistry on Intramolecular Morita−Baylis−Hillman Reactions

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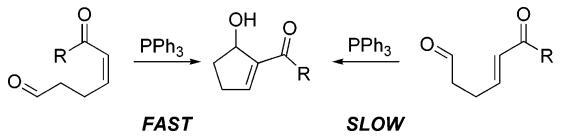

A study of the effect of Michael acceptor stereochemistry on the efficiency of intramolecular Morita−Baylis−Hillman (MBH) reactions has been performed. The reactions were catalyzed by a phosphine, and the reaction substrates studied were enones containing a pendant aldehyde moiety attached at the β-position of the alkene group. In all cases examined with PPh_3 as the catalyst, cyclization substrates possessing (*Z*)-alkene stereochemistry afforded a much higher yield of the desired product than did the *E* isomeric substrates under identical reaction conditions. This was also true when a polymer-supported phosphine catalyst was used. While both alkene isomers afforded the same product, in parallel reactions, the *Z* isomer afforded 2.5−8.5 times higher yield than did the corresponding *E* isomer. It is proposed that steric effects are a possible source of this dramatic difference in reactivity. Substrates where the β-substituent is cis to the electron-withdrawing substituent are relatively more accessible to react with the nucleophile catalyst than are their trans counterparts. These findings are expected to be useful in the design of synthetic intermediates, as intramolecular MBH reactions are being increasingly used in the preparation of complex synthetic targets.

The Morita−Baylis−Hillman (MBH) reaction has become an important tool in organic synthesis, since it allows for the formation of densely functionalized carbon−carbon bonds under mild, organocatalytic reaction conditions (Figure 1).[1,2] While early versions of this reaction were marked by some irreproducible results and long reaction times, recent years have seen much advancement in the understanding of its mechanism[3] and the identification of highly efficient catalysts[4] and reaction media.[5] We have had a longstanding interest in this reaction,[6] especially versions in which N-sulfonated imines are used as the electrophile,[7] and the use of polymer-supported reagents to catalyze them.[8] While hundreds of reports have described intermolecular MBH reactions, examples of intramolecular MBH[9−19] and related Rauhut−Currier reactions[20,21] are very few (Figure 1).

Perhaps one reason for the limited number of examples of intramolecular MBH reactions in the literature is the sensitivity of MBH reactions in general to steric effects at the β-position of the Michael acceptor. It has been reported that, when a β-subsituent is present, either high pressure or microwave irradiation is necessary for the desired reaction to occur.[22,23] In most intermolecular MBH reactions, the conjugated electrophile is unsubstituted at this position. Therefore, when the reaction is rendered intramolecular by tethering of the electrophile to the Michael acceptor at its β-position (Figure 1, Type A reaction), it can be expected that the reaction would be relatively inefficient.[9−16] However, when the electrophile is attached to the Michael acceptor at its carbonyl center (Figure 1, Type B reaction), no such steric hindrance occurs.[17−19]

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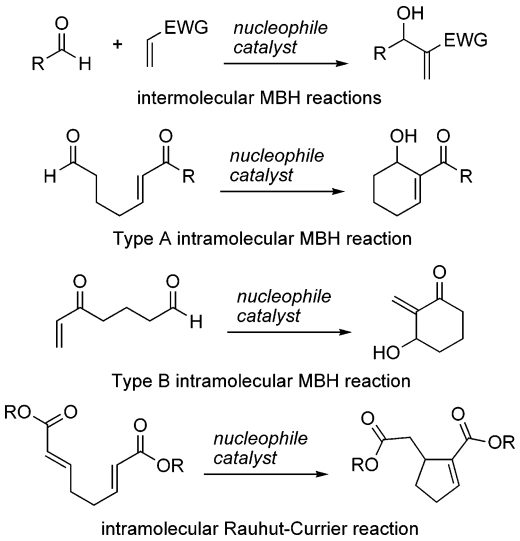
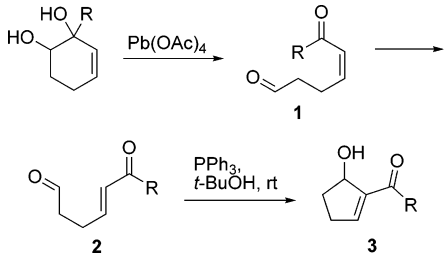


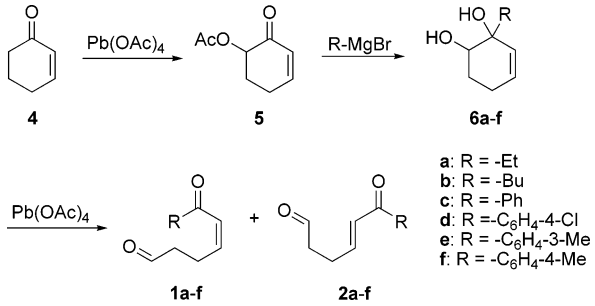
FIGURE 1. Representative intramolecular Morita−Baylis−Hillman reactions.

During a survey of the literature we noted that despite the potential importance of substrate stereochemical effects in intramolecular MBH reactions, no analysis of the effect of the Michael acceptor alkene stereochemistry on the reaction rate of Type A reactions has been performed. Perhaps this is due to the fact that both *E* and *Z* isomers of the starting material afford the same cyclized product and, thus, ease of synthesis prevailed in determining substrate stereochemistry. In all reports, the cyclization precursors only possessed (*E*)-alkene stereochemistry. This is due to the fact that most of the reported intramolecular MBH reaction substrates studied were prepared by the Wittig reaction of an aldehyde with a stabilized phosphorus ylide to form the Michael acceptor moiety. One notable exception to this is the work by Koo et al., where the cyclization substrates were prepared by oxidative cleavage of vicinal diols.[14] Under the reaction conditions used, the initially formed *Z* isomers **1** rearranged to the corresponding *E* isomers **2** (Scheme 1). In their work, only *E* isomers **2** were subjected to intramolecular MBH reactions, and they observed that optimized reaction conditions for formation of **3** involved the use of a stoichiometric amount of PPh_3 as the catalyst in *t*-BuOH at room temperature.

SCHEME 1



SCHEME 2



Considering the importance of intermolecular MBH reactions and the potential power of intramolecular versions for preparing densely functionalized cyclic structures, we sought to fill the gap in the literature and determine what role, if any, Michael acceptor stereochemistry has in determining the outcome of such intramolecular MBH reactions. Herein we report the results of comparative studies in which reactions of isomerically pure *E* and *Z* ω-formyl α,β-unsaturated carbonyl compounds were subjected to nucleophilic phosphine catalysis under identical reaction conditions to form the corresponding intramolecular MBH adduct and in which the isolated yields were used to judge the efficiency of the reactions.

The methodology reported by Koo et al.[14] was used to prepare separable mixtures of cyclization substrates **1a**−**f** and **2a**−**f** from 2-cyclohexene-1-one (**4**) (Scheme 2). Treatment of **4** with $Pb(OAc)_4$ in refluxing toluene afforded 6-acetoxy-2-cyclohexene-1-one (**5**).[24] Reaction of **5** with greater than 2 equiv of the appropriate Grignard reagent, either alkyl or aryl, resulted in simultaneous acetate cleavage and 1,2-addition to the ketone group to afford **6a**−**f**. Controlled oxidative cleavage of the vicinal diol groups of **6a**−**f** with $Pb(OAc)_4$ afforded mixtures of **1a**−**f** and **2a**−**f**. As noted previously, it was important to control the duration of these oxidative cleavage reactions in order to ensure that both *E* and *Z* isomers were present in the isolated product mixture. By limiting the reaction times to approximately 15 min, it was possible to obtain **1**:**2** ratios ranging from 1.9:1 to 9.7:1 (see Table 1 in the Supporting Information). If the reactions were allowed to continue for too long, only **2a**−**f** were recovered. Regardless of the mixture composition, **1** and **2** were easily separable by silica gel column

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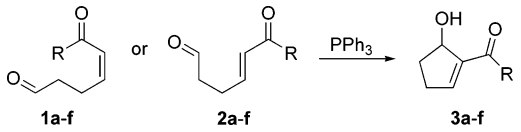
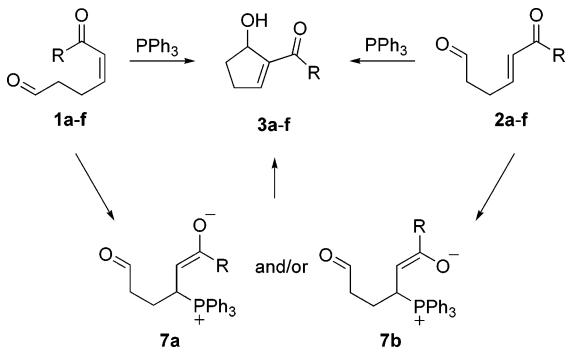
TABLE 1. Intramolecular MBH Reaction Results



entry	substrate	solvent	concn (M)	temp (°C)	time (h)	product	yield (%)[a]
1	**1a,** R = Et	*t*-BuOH	0.1	40	60	**3a**	72
2	**2a,** R = Et	*t*-BuOH	0.1	40	60	**3a**	12
3	**1a,** R = Et	CH_3CN	0.1	40	48	**3a**	59
4	**2a,** R = Et	CH_3CN	0.1	40	48	**3a**	12
5	**1b,** R = Bu	*t*-BuOH	0.1	40	24	**3b**	69
6	**2b,** R = Bu	*t*-BuOH	0.1	40	24	**3b**	13
7	**1c,** R = Ph	CH_3CN	0.1	room temp	32	**3c**	69
8	**2c,** R = Ph	CH_3CN	0.1	room temp	32	**3c**	8
9	**1c,** R = Ph	*t*-BuOH	0.1	room temp	12	**3c**	55
10	**2c,** R = Ph	*t*-BuOH	0.1	room temp	12	**3c**	9
11	**1d,** R = C_6H_4-4-Cl	CH_3CN	0.1	room temp	96	**3d**	55
12	**2d,** R = C_6H_4-4-Cl	CH_3CN	0.1	room temp	96	**3d**	15
13	**1e,** R = C_6H_4-3-Me	CH_3CN	0.1	room temp	72	**3e**	50
14	**2e,** R = C_6H_4-3-Me	CH_3CN	0.1	room temp	72	**3e**	21
15	**1f,** R = C_6H_4-4-Me	CH_3CN	0.1	room temp	72	**3f**	54
16	**2f,** R = C_6H_4-4-Me	CH_3CN	0.1	room temp	72	**3f**	17
17	**1b,** R = Bu	*t*-BuOH	0.2	40	24	**3b**	79
18	**1b,** R = Bu	*t*-BuOH	0.1	room temp	36	**3b**	66
19	**1e,** R = C_6H_4-3-Me	CH_3CN	0.05	room temp	72	**3e**	50
20	**1e,** R = C_6H_4-3-Me	CH_3CN	0.1	40	72	**3e**	69
21	**1f,** R = C_6H_4-4-Me	CH_3CN	0.05	room temp	72	**3f**	48
22	**1f,** R = C_6H_4-4-Me	CH_3CN	0.1	40	72	**3f**	59
23	**1c,** R = Ph	DCE[b]	0.1	room temp	48	**3c**	43[c]
24	**2c,** R = Ph	DCE	0.1	room temp	48	**3c**	10[c]

[a] Isolated yield. [b] DCE = 1,2-dichloroethane. [c] *J*anda*J*el-PPh_3 (1 equiv) was used as the catalyst.

SCHEME 3



chromatography. The relatively modest product yields obtained (39−66%) were a result of the inherent propensity of these compounds to decompose on standing to form polar side products.

With the reaction substrates in hand, we compared reaction yields afforded by **1a**−**f** and **2a**−**f** under identical reaction conditions (Scheme 3). The parallel intramolecular MBH reactions comparing **1a** to **2a**, **1b** to **2b**, etc. were performed using 1 equiv of PPh_3 catalyst at 0.1 M concentration in either *t*-BuOH or CH_3CN at 40 °C or room temperature for the indicated time, since these are the conditions previously reported to be optimal for such reactions.[14] Both of the reactions were stopped when all of the starting material **1a**−**f** had completely disappeared, as determined by TLC analysis. These reaction conditions are similar to those used previously, where *t*-BuOH at slightly elevated temperature was the solvent for the alkyl-substituted substrates and room temperature CH_3CN was used for substrates containing aryl substituents;[14] however, we found that, for a limited number of substrates, changing the reaction solvent from CH_3CN to *t*-BuOH or changing the reaction temperature did not appear to dramatically affect reaction yields. The results of these comparative reactions are summarized in Table 1. It should be noted again that the reactions of **2a**−**f** were stopped when the corresponding reaction with **1a**−**f** was complete, so that the yields afforded under identical conditions could be compared. Thus, in addition to the desired product **3a**−**f**, and small amounts of undesired byproducts, much unreacted **2a**−**f** remained in these reactions. Furthermore, it should also be noted that, in the reactions of **1a**−**f**, trace amounts of **2a**−**f** were detected by thin-layer chromatography, but no **2a**−**f** to **1a**−**f** isomerization appeared to have occurred in the reactions of **2a**−**f**.

It is clearly evident from the data that, in all cases, the *Z* isomer **1** exhibited much greater reactivity than did the *E* isomer **2** under the reaction conditions used and PPh_3 was a better catalyst than PBu_3, as might have been expected[14] (see Table 2 in the Supporting Information). Furthermore, the choice of solvent did not dramatically influence the product distribution (entries 1−4 and 7−10). The greatest reactivity disparity was exhibited by substrates **1c** and **2c**, containing vinyl phenyl ketone moieties, where **1c** afforded more than 8.5 times the amount of the desired product **3c** than did substrate **2c** (entries 7 and 8). Substrates giving the most similar yields were the pairs **1d** and **2d**, **1e** and **2e**, and **1f** and **2f**, where the *Z* isomers only afforded approximately 2.5−3.7 times the amount of desired product **3d**−**f** than did the *E* isomers (entries 11−16). The vinyl alkyl ketone substrate pairs **1a** and **2a** and **1b** and **2b** exhibited intermediate differences in reactivity with their yield ratios ranging from 6.0 to 4.9 (entries 1−6).

We also examined the effect of substrate concentration for representative examples of *Z* isomers **1**. For example, when the concentration for cyclization of **1b** was doubled to 0.2 M, the yield somewhat surprisingly increased slightly to 79% from 69% at 0.1 M (entry 17). It might be expected that increasing substrate concentration for such an intramolecular cyclization reaction would lower, not increase, the yield as bimolecular reactions become more favored. On the other hand, as expected, lowering the temperature for the cyclization of **1b** from 40 °C to room temperature meant a longer reaction time was necessary for complete disappearance of **1b** (entry 18). For substrates **1e** and **1f**, lowering the concentration from 0.1 to 0.05 M did not have any appreciable influence on reaction yield or time (entries 19 and 21). However, increasing the reaction temperature from room temperature to 40 °C increased the yield of **3e** from **1e** from 50% to 69% (entry 20) but did not significantly affect the yield of **3f** from **1f** (entry 22). Regardless of the various changes in reaction conditions, the pattern of *Z* substrate affording much more product than did the corresponding *E* substrate held true.

Considering that a full 1 equiv of the catalyst was necessary for all of the reactions of **1a**−**f** to go to completion in a reasonable amount of time, they are ideally suited for the use of an easy to remove polymer-supported phosphine catalyst.[25] Thus, polystyrene cross-linked with 1,4-bis(4-vinylphenoxy)-butane[26] functionalized by triphenylphosphine groups (*J*anda*J*el-PPh_3, 1.0 mmol of P/g)[27] was used to catalyze the cyclization reactions of **1c** and **2c** in 1,2-dichloroethane, a good swelling solvent for this polymeric reagent, since this reagent/solvent combination has previously produced good results in related intermolecular aza-MBH reactions (entries 23 and 24).[8b] The use of a polymer-supported catalyst in these reactions greatly simplified product isolation, as it was removed at the end of the reactions by simple filtration. Therefore, chromatographic removal of 1 equiv of PPh_3 was not necessary. While the yield ratio between **1c** and **2c** obtained in these reactions dropped compared to the ratio when PPh_3 was the catalyst (4.3:1 vs 8.5:1), it remained consistent with the entirety of the data, in that **1c** afforded much more **3c** than did **2c**.

It is striking to note that, considering the large amount of research dedicated to understanding and exploiting the MBH reaction, no analysis regarding Michael acceptor stereochemistry and its effect on reaction efficiency had been previously performed. However, a survey of the literature reveals that only few examples of intermolecular MBH reactions with acyclic β-substituted Michael acceptors such as crotononitrile and methyl methacrylate have been reported,[22,23] while a large body of literature exists describing the use of cyclic alkenenones (predominantly five- and six-membered rings) in such reactions.[28] In fact, even the number of reported intramolecular MBH reactions of Type A far surpasses that of intermolecular MBH

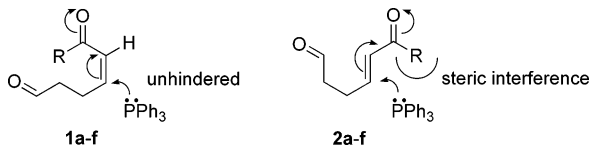


FIGURE 2. Steric effects in type A intramolecular MBH reactions.

reactions with acyclic β-substituted Michael acceptors. While the success of these intramolecular reactions is at least due in part to entropic factors, it seems reasonable to expect that alkene stereochemistry should influence their efficiency to some extent. Therefore, a better understanding of the stereochemical effects on such reactions should increase their applicability and utility.

On the basis of current understanding of the mechanism of the MBH reaction, the initial step of the process is nucleophilic addition of the catalyst to the β-position of the Michael acceptor. In the cases of the different alkene isomers **1** and **2**, this results in the zwitterionic intermediates **7a** and/or **7b** (Scheme 3), which cyclize to eventually form the desired product **3**. One reasonable explanation for the observed differences in reactivity between the *E* and *Z* isomers of the reaction substrates in this study is that the initial nucleophilic attack by the phosphine catalyst is relatively more hindered in the cases of the *E* isomers compared to the *Z* isomers (Figure 2). Another possible source for the different rates of reaction of **1** and **2** is that depending on their preferred conformation (s-cis or s-trans), they may preferentially form enolate **7a** or **7b** and that these two reactive species have substantially different nucleophilic reactivities, resulting in the observed lower reaction rates for the *E* isomers **2**.

In conclusion, we have observed that dramatic differences in reactivity exist between alkene isomers in intramolecular MBH reactions. The *Z* isomers uniformly afford more desired product than did the corresponding *E* isomers in identical reactions, and we believe that the basis for this difference in reactivity is either the relative accessibility of the β-positions of the Michael acceptors to the nucleophile catalyst or a difference in reactivity of potentially different enolate reactive intermediates. These findings should improve the utility of the intramolecular MBH reaction for the synthesis of complex cyclic structures by guiding the design of the cyclization substrates.

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Supporting Information Available: Text, tables, and figures giving experimental details, characterization data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) In addition to refs 4a−d and 5c, for representative examples of intermolecular MBH reactions where cycloalkenenones are used as the Michael acceptor, see the Supporting Information.