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The Vinylogous Intramolecular Morita−Baylis−Hillman Reaction: Synthesis of Functionalized Cyclopentenes and Cyclohexenes with Trialkylphosphines as Nucleophilic Catalysts

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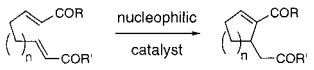
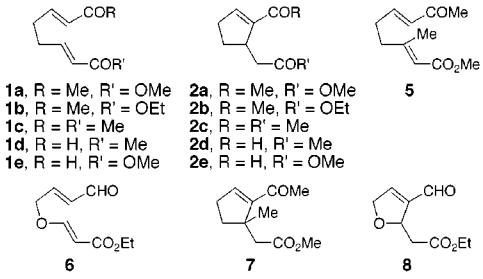
The Morita−Baylis−Hillman (MBH) reaction involves the α-hydroxyalkylation and α-aminoalkylation of Michael acceptors by electrophilic carbonyl compounds or imines in the presence of a nucleophilic catalyst such as a tertiary amine or phosphine.[1−5] Surprisingly, there have been relatively few applications of this technology to cyclization processes.[6−9] We are also unaware of examples of a potentially important variant, which we term the vinylogous intramolecular Morita−Baylis−Hillman reaction, in which an α,*β*-unsaturated carbonyl compound serves as a Michael acceptor in the electrophile capture step (see **1** → **2** or **3** → **4**). It is known that acrylates and enones will dimerize under MBH reaction conditions,[10−13] and that enones can be α-alkylated in a Michael reaction with acrylates and acrylonitrile in the presence of DBU at 185 °C.[14] Ring closing reactions are known that proceed via 1,4-addition of organometallic and heteronucleophilic reagents to enones or enoates such as **1** and **3**, with subsequent addition of the initial enolate to the second Michael acceptor.[15−17] Lithium amides and thiolates have been used to initiate such cyclizations; however, the nucleophiles remain covalently attached in the cyclization products.[18,19] In principle, a subsequent elimination step could be employed to access the targeted unsaturated ring systems **2** and **4**.[9] The advantages of using a nucleophilic catalyst to effect cyclizations of **1** → **2** and **3** → **4** under mild conditions are readily apparent. We report herein the first examples of the vinylogous intramolecular Morita−Baylis−Hillman reaction for the synthesis of substituted cyclopentenes and cyclohexenes **2** and **4**.



1, n = 1
3, n = 2

2, n = 1
4, n = 2

Initial studies were performed with enone-enoate **1b** as the substrate (see Supporting Information). Amine nucleophiles such as DABCO, DBU, Et_2NH, and DMAP, which are commonly employed in the traditional Morita−Baylis−Hillman reaction, were ineffective in promoting the cyclization of **1b** in solvents such as THF, MeOH, and CH_2Cl_2 at temperatures from ambient to 65 °C. Similarly, stoichiometric Ph_3P (CH_2Cl_2, 23 °C) gave no reaction with **1b**, while use of 0.25 equiv of (*c*-Hex)$_3$P gave only 15% conversion to **2b** over a 6 h period. Ultimately, we found that excellent results were obtained by using catalytic amounts of Bu_3P in CH_3CN or, better still, Me_3P in *tert*-amyl alcohol (Table 1). A direct comparison of these catalysts and conditions with **1a** as the substrate (Table 1, entries 1−7) demonstrated that 0.1 equiv of Me_3P in *tert*-amyl alcohol was optimal, a combination that provided **2a** in 95% yield with 97:3 regioselectivity (entry 6). Reactions catalyzed by Me_3P were faster in *tert*-amyl alcohol than in CH_3CN (entries 4 and 6).[20] While the cyclizations were also faster when performed at higher reaction concentrations, the efficiency suffered under these conditions (compare entries 1−2 and 6−7), presumably as a consequence of competitive bimolecular reactions of **1a**.



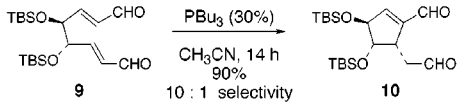
1a, R = Me, R' = OMe
1b, R = Me, R' = OEt
1c, R = R' = Me
1d, R = H, R' = Me
1e, R = H, R' = OMe

2a, R = Me, R' = OMe
2b, R = Me, R' = OEt
2c, R = R' = Me
2d, R = H, R' = Me
2e, R = H, R' = OMe

5

6 **7** **8**

Results of the Me_3P-catalyzed cyclizations of **1c**−**e**, **5**, and **6** are summarized in Table 1. Substrates **1c**−**e** underwent efficient cyclizations under conditions closely resembling those developed for **1a**. However, it was necessary to use CH_2Cl_2 as the solvent to achieve efficient cyclization of **1c**; the competitive aldol cyclization of the product **2c** that was observed in *tert*-amyl alcohol was suppressed in CH_2Cl_2 (entries 8 and 9). It also proved necessary to perform the cyclization of enal-enoate **1e** at 0.01 M, owing presumably to the tendency of **1e** to self-condense in the presence of Me_3P at higher concentrations. In all cases, the major product resulted from a sequence in which the phosphine catalyst added to the most electrophilic of the two Michael acceptors, with the less electrophilic unsaturated carbonyl system serving as the Michael acceptor for the ring-closing step. This regioselectivity was also observed in the Me_3P-promoted cyclizations of **5**, in which case the *β*,*β*-disubstituted enoate served as the electrophilic acceptor for the ring closure step with establishment of a quaternary center in product **7**, and of **6** where the vinylogous ester served as the acceptor unit for the Michael cyclization. Finally, the Bu_3P-catalyzed cyclization reaction of bis-enal **9** proceeded in excellent yield with synthetically useful diastereoselectivity.[16]



9 **10**

Applications of this methodology to the cyclization of substituted heptadienes **3a**−**d** and **11** are summarized in Table 2. Typically 0.25−1.0 equiv of the phosphine catalyst was required for these reactions to proceed at reasonable rates. While **3a**−**b** (entries 1−3), **3d** (entries 6,7), and **11** (entry 8) cyclized in moderate to good yields, cyclization of **3c** was less productive (entries 4,5) owing to its tendency to undergo bimolecular coupling reactions, as well as the propensity of the product **4c** to undergo an intramolecular aldol

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Table 1. Synthesis of Substituted Cyclopentenes via the Intramolecular Vinylogous Morita−Baylis−Hillman Reaction[a]

entry	substrate	catalyst (%)	solvent	concn (M)	time (h)	product	yield[b]	regioselectivity[c]	% aldol[d]
1	**1a**	PBu_3 (10)	CH_3CN	0.05	24	**2a**	80	95:5	
2	**1a**	PBu_3 (10)	CH_3CN	0.1	8	**2a**	61	95:5	
3	**1a**	PBu_3 (10)	*tert*-amyl-OH	0.1	11	**2a**	88	96:4	
4	**1a**	PMe_3 (10)	CH_3CN	0.1	4	**2a**	71	94:6	
5	**1a**	PMe_3 (10)	*tert*-amyl-OH	0.05	3	**2a**	91	97:3	
6	**1a**	PMe_3 (10)	*tert*-amyl-OH	0.1	1	**2a**	95	97:3	
7	**1a**	PMe_3 (10)	*tert*-amyl-OH	1.0	0.75	**2a**	81	96:4	
8	**1c**	PMe_3 (10)	*tert*-amyl-OH	0.05	4	**2c**	54		13
9	**1c**	PMe_3 (10)	CH_2Cl_2	0.05	2	**2c**	96		0
10	**1d**	PMe_3 (20)	*tert*-amyl-OH	0.01	0.75	**2d**	79	89:11	trace
11[e]	**1d**	PMe_3 (20)	*tert*-amyl-OH	0.1	2	**2d**	48	93:7	trace
12	**1e**	PMe_3 (20)	*tert*-amyl-OH	0.1	0.25	**2e**	43	only	-
13	**1e**	PMe_3 (20)	*tert*-amyl-OH	0.01	4	**2e**	90	only	-
14	**5**	PMe_3 (100)	*tert*-amyl-OH	0.05	17	**7**	32	only	-
15	**5**	PMe_3 (100)	*tert*-amyl-OH	0.01	44	**7**	51	only	-
16	**5**	PMe_3 (200)	*tert*-amyl-OH	0.01	44	**7**	60	only	-
17	**6**	PMe_3 (50)	CH_3CN	0.01	2	**8**	38	only	-

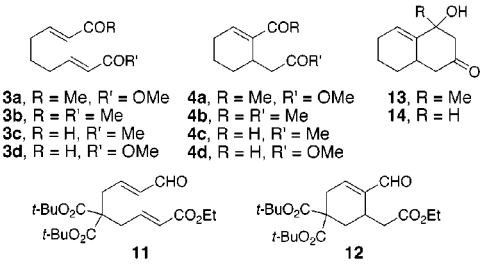
[a] All reactions were performed by addition of the phosphine reagent to a solution of substrate in the indicated solvent at 23 °C, unless noted otherwise. [b] Isolated yield of product. Compounds **2a** and **2d** were isolated as mixtures with the regioisomeric cyclopentene product. [c] Regioselectivity refers to the ratio of the two regioisomeric cyclopentenes. [d] Products **2c** and **2d** underwent aldol cyclization under the reaction conditions (see text). [e] Substrate **1d** was added via syringe pump to the phosphine catalyst over 1 h.

Table 2. Synthesis of Substituted Cyclohexenes via the Intramolecular Vinylogous Morita−Baylis−Hillman Reaction[a]

entry	substrate	catalyst (%)	solvent	concn (M)	time (h)	product	yield[b]	regioselectivity	% aldol
1	**3a**	PMe_3 (25)	*tert*-amyl-OH	0.1	8	**4a**	83	92:8	
2	**3b**	PMe_3 (25)	*tert*-amyl-OH	0.05	1.5	**4b**	46		23
3	**3b**	PMe_3 (25)	CH_2Cl_2	0.05	20	**4b**	64		20
4	**3c**	PBu_3 (50)	CH_3CN	0.06	0.5	**4c**	55	90:10	-
5	**3c**	PMe_3 (50)	*tert*-amyl-OH	0.01	0.75	**4c**	45	95:5	11
6	**3d**	PMe_3 (100)	*tert*-amyl-OH	0.01	6	**4d**	47	95:5	
7	**3d**	PMe_3 (100)	CH_3CN	0.01	8	**4d**	67	97:3	
8	**11**	PMe_3 (50)	CH_3CN	0.01	22	**12**	74	97:3	

[a] All reactions were performed as described in Table 1. [b] All products were isolated as mixtures with the regioisomeric cyclohexenes except for **4b**.

cyclization to **14**. Aldol cyclization of **4b** was also problematic under all conditions examined (entries 2,3); regioisomeric aldols (cf. **13**), as well as the derived dienones, were obtained. Acetonitrile was the optimal solvent for cyclization of **3d** and **11**.



In conclusion, a new variant of the Morita−Baylis−Hillman reaction has been developed for the synthesis of substituted cyclopentenes **2** and cyclohexenes **4** by trialkylphosphine-catalyzed cyclizations of diactivated 1,5-hexadienes **1** and 1,6-heptadienes **3**. Applications of the vinylogous intramolecular Morita−Baylis−Hillman reaction in the synthesis of natural products will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for **2a**, **2c**−**e**, **4a**−**d**, **8**, **10**, and **12**; summary of catalyst and solvent selection with **1b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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