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Phosphine-Catalyzed Reactions of Activated Olefins Tethered to Cycloalkanones. Substrate- and Solvent-Controlled Synthesis of Bicyclo[3.2.1]octanones, Mixed Acetals, and Morita–Baylis–Hillman Products

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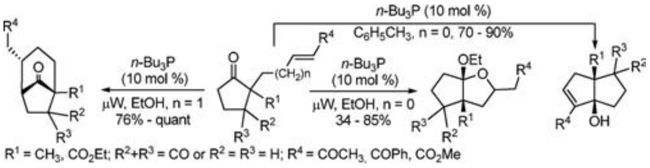
ABSTRACT



The n-Bu$_3$P organocatalyzed reaction of cycloalkanones, i.e., cyclopentanones or 1,3-cyclopentanediones tethered to actived olefins, afforded selectively and in high yields three different types of products: bicyclo[3.2.1]octanones, mixed acetals, and Morita–Baylis–Hillman products. The progress of the reaction was closely related to the reaction medium and to the length of the tether located between the cyclopentanone (-dione) and the activated olefin.

The addition of trivalent phosphines as Lewis base organocatalysts to electron-deficient olefins/alkynes represents the initial step of several catalytic processes such as Morita–Baylis–Hillman (MBH)[1] and the Rauhut–Currier (RC) reactions.[2] The intramolecular version of the MBH reaction was pioneered by Frater et al. who showed that the addition of n-Bu$_3$P to compound **1** gave the MBH product **2** in moderate yield.[3] Later on, the intramolecular MBH and RC became a powerful method to construct carbocyclic compounds starting from various combinations of activated alkenes (enal, enone, enoate, enamide, vinylsulfone) tethered mostly to acyclic aldehydes or to α,β-unsaturated ketones.[4] However, to the best of our knowledge, there have been no reports about trialkylphosphine organocatalyzed intramolecular reactions of α,β-unsaturated electrophiles tethered to cycloalkanones. Accordingly, an investigation of the reactivity of the latter resulted in unexpected reaction outcomes, i.e., the formation in high yields and in high (diastereo)selectivities of bridged bicyclo[3.2.1]octanones, mixed acetals, and MBH products (Figure 1).

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(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D.German Patent 2155113, 1972; *Chem. Abstr.* 1972, *77*, 34174q. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574. (d) Rao, A. J.; Satyanaranaya, T. *Chem. Rev.* **2003**, *103*, 811–891. (e) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674. (f) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659–6690.

(2) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084.

(3) Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 1045–1048.

(4) (a) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236–237. (b) Dino, F.; Richards, E.; Murphy, P. J *Tetrahedron Lett.* **1999**, *40*, 3279–3282. (c) Richards, E. L.; Murphy, P. J.; Dinon, F.; Tratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771–7784. (d) Brown, P. M.; Käppel, N.; Murphy, P. J.; Coles, S. J.; Hursthouse, M. B. *Tetrahedron* **2007**, *63*, 1100–1106. (e) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (f) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *124*, 2402–2403. (g) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683. (h) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687–3690.

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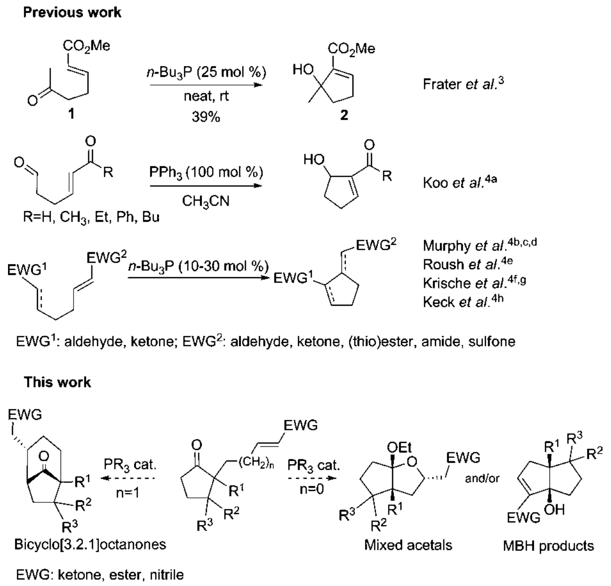
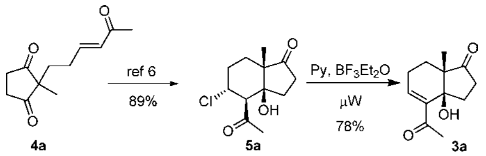


Figure 1. Trialkylphosphine and MBH reactions.

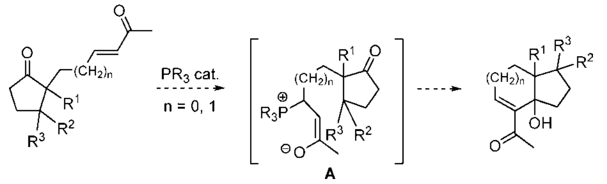
Our interest in the trialkylphosphine organocatalyzed reaction was motivated by an ongoing program dealing with synthetic approaches to prepare the C−D ring present in bioactive 14β-hydroxypregnanes,[5] especially hydrindane **3a**. In this context, we have shown that the TiCl$_4$ treatment of an α,β-unsaturated ketone tethered to 1,3-cycloalkanedione **4a** promoted a halo Michael aldol reaction to afford the halohydrindane derivative **5a**.[6] A dehydrohalogenation was carried out with pyridine in the presence of BF$_3$·Et$_2$O and under microwave activation, yielding hydrindane **3a** in 69% overall yield (Scheme 1).

Scheme 1. Halo Michael Aldol and Deshydrohalogenation Reactions



To improve access to hydrindane **3a** and related compounds and to avoid the use of a stoichiometric amount of titanium tetrachloride as well as the dehydrohalogenation step, we became interested in a new synthetic route calling for an organocatalytic process. Indeed, we expected that the addition of a catalytic amount of trialkyl phosphine to α,β-unsaturated electrophiles tethered to cycloalkanones should afford MBH products via the key intermediate **A** (Scheme 2).

Scheme 2. Expected MBH Reaction



For our preliminary studies, we focused our initial effort on the reactivity of triketone **4a** under different reaction conditions. No reaction occurred in the presence of triphenylphosphine (Table 1, entries 1 and 2). However, in the presence of 0.1 equiv of n-Bu$_3$P in toluene, a 1.4/1 mixture of two compounds was obtained: the expected hydrindane **3a** (yield 28%) and the unexpected bicyclo[3.2.1]octanone **6a** (yield 20%)[7] which were obtained as single isomers along with 25% of the starting material (Table 1, entry 3). It is reasonable to state that compound **6a** is probably the thermodynamically favored diastereomer bearing the side chain in the equatorial position.[8] However, in the presence of 1 equiv of n-Bu$_3$P, the MBH product **3a** became the major product (Table 1, entry 4). To study the influence of the solvent, the reaction was conducted in an aprotic polar solvent, acetonitrile, leading this time to bicyclo[3.2.1]-octanone **6a** as a major product (Table 1, entries 5 and 6). Finally, the reaction was carried out in a protic polar solvent, ethanol, affording the bicyclo[3.2.1]octanone **6a** as a single isomer in high yield along with less than 5% of hydrindane **3a** (Table 1, entries 7 and 8). These results clearly showed that the nature of the solvent[9] was crucial to the progress of the reaction and that the microwave activation decreases significantly the length of the reaction (entries 7 and 8).[10] No reaction took place in the presence of DABCO (Table 1, entry 9), and decomposition occurred in the presence of sodium ethylate (Table 1, entry 10).

The scope and limitations of our n-Bu$_3$P organocatalyzed reaction were then investigated. First, the reactivity of n-Bu$_3$P with compounds **4a**−**f** bearing a two methylene tether located between the cycloalkanone (-dione) and the activated olefin was examined (Scheme 3). The bicyclo-[3.2.1]octanones **6a**−**f** were isolated as single products and as single isomers (except for compound **6b**) in high yields (76% quant) using either ethanol or toluene as solvent. However, the behavior of the nitrile derivative **4d** was different compared to the other substrates. Indeed, in

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(5) (a) Geoffroy, P.; Ressault, B.; Marchioni, E.; Miesch, M. *Steroids* **2011**, *76*, 702–708. (b) Geoffroy, P.; Ressault, B.; Marchioni, E.; Miesch, M. *Steroids* **2011**, *76*, 1166–1175.

(6) Ressault, B.; Jaunet, A.; Geoffroy, P.; Goudedranche, S.; Miesch, M. *Org. Lett.* **2012**, *14*, 366–369.

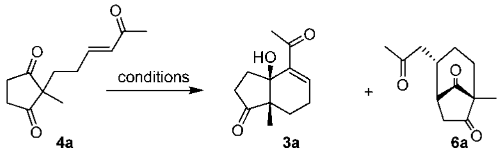
(7) Bicyclo[3.2.1]octanes review: Presset, M.; Coquerel, Y.; Rodriguez, J. *Chem. Rev.* **2013**, *113*, 525–595.

(8) The relative configuration of compound **6** was determined by HMBC, HSQC, and NOESY experiments.

(9) *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Reichardt, C., Welton, T., Eds.; Wiley-VCH: Weinheim, 2011.

(10) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim; 2006.

Table 1. Optimization of Reaction Conditions

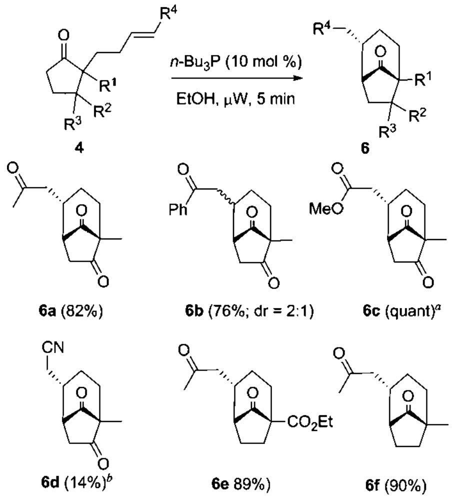


entry	conditions	MBH product **3a** (%)	bicyclo[3.2.1]octanone **6a** (%)
1	PPh_3, (10 mol %) toluene, 75 °C, 8 h	no reaction[a]	no reaction[a]
2	PPh_3 (100 mol %) toluene, 75 °C, 8 h	no reaction[a]	no reaction[a]
3	n-Bu_3P (10 mol %) toluene, 75 °C, 8 h	28[b]	20[b]
4	n-Bu_3P (100 mol %) toluene, 75 °C, 8 h	57	6
5	n-Bu_3P (10 mol %) CH_3CN, 82 °C, 3 h	7	60
6	n-Bu_3P (10 mol %), CH_3CN, 85 °C, μW (500 W), 5 min	5	62
7	n-Bu_3P (10 mol %) EtOH, 80 °C, 3 h	3	81
8	n-Bu_3P (10 mol %) EtOH, 90 °C, μW (500 W), 5 min	5	82
9	DABCO (10 mol %) EtOH, 90 °C, μW (500 W), 2 h	no reaction[a]	no reaction[a]
10	EtONa (10 mol %) EtOH, 90 °C, μW (500 W), 2 h	decomposition	decomposition

[a] Starting material was recovered. [b] 25% starting material was recovered.

ethanol, the reaction was sluggish, and an unseparable mixture of bicyclo[3.2.1]octanone **6d** and MBH product **9a** was obtained. However, the MBH product **9a** was isolated as the sole product in toluene.

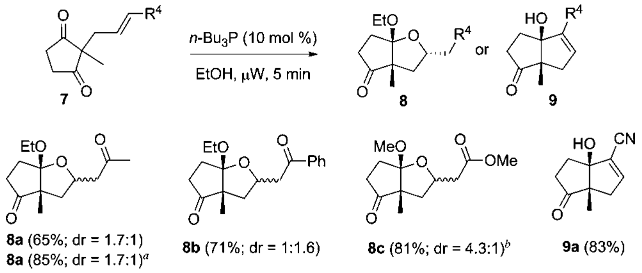
Scheme 3. Formation of Bicyclo[3.2.1]octanones



[a] n-Bu_3P (10 mol %), toluene, 75 °C, 3 h; when the reaction was carried out in MeOH, **6c** was isolated in 28% yield along with 27% starting material. [b] **9a** and **4d** were also isolated in 42% and 14% yield, respectively; when the reaction was carried out in toluene, **9a** was isolated as sole product in 55% yield.

To extend the scope and limitations of our n-Bu_3P-organocatalyzed reaction, we first examined the reactivity of compounds **7a**–**d** derived from 2-methyl-1,3-cyclopentanedione and bearing a one methylene tether. In ethanol, the formation of mixed acetals **8a**–**c** took readily place.[11] We never observed the formation of bicyclo[2.2.1]heptanones nor the formation of MBH products except when **7d** was utilized as the starting material. In this case, the MBH product **9a** was exclusively formed (Scheme 4).

Scheme 4. Formation of Mixed Acetals or MBH Products



[a] n-Bu_3P (1 equiv), EtOH, μW, 5 min. [b] The reaction was carried out in MeOH.

Finally, it was possible to obtain exclusively the MBH products (i.e., polyfunctionalized diquinanes **9a**–**f**) when the n-Bu_3P-organocatalyzed reaction was carried out in toluene, except for compound **9f** where the reaction was conducted in ethanol. The yield was slightly higher in the presence of 1 equiv of n-Bu_3P. Once again, the formation of the bicyclo[2.2.1]heptanones never took place (Scheme 5).

To explain the formation of these different products, it is reasonable to postulate the catalytic cycle shown in Figure 2.[12] The addition of n-Bu_3P to substrates **4a**–**f** generates the phosphonium enolate **A** which evolves toward the ion pair **B**.[13] Of course, a direct prototropy of **A** to **C** cannot be excluded. The resulting alkoxide (which behaves like a base) is now able to deprotonate the cyclopentanone

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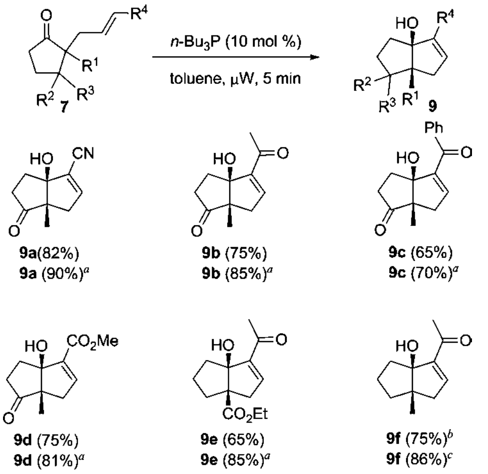
(11) The addition of EtONa in EtOH (90 °C, 5 min, microwave 500 W) to compound **7a** yielded a complex mixture of compounds from which the mixed acetal **8a** was isolated in less than 5% yield.

(12) (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (b) Xu, J. *THEOCHEM* **2006**, *767*, 61–66.

Scheme 5. Formation of MBH Products



9a(82%) **9a** (90%)[a]

9b (75%) **9b** (85%)[a]

9c (65%) **9c** (70%)[a]

9d (75%) **9d** (81%)[a]

9e (65%) **9e** (85%)[a]

9f (75%)[b] **9f** (86%)[c]

[a] n-Bu$_3$P (1 equiv), toluene, μW, 5 min. [b] n-Bu$_3$P (0.1 equiv), EtOH, μW, 5 min. [c] n-Bu$_3$P (1 equiv), EtOH, μW, 5 min

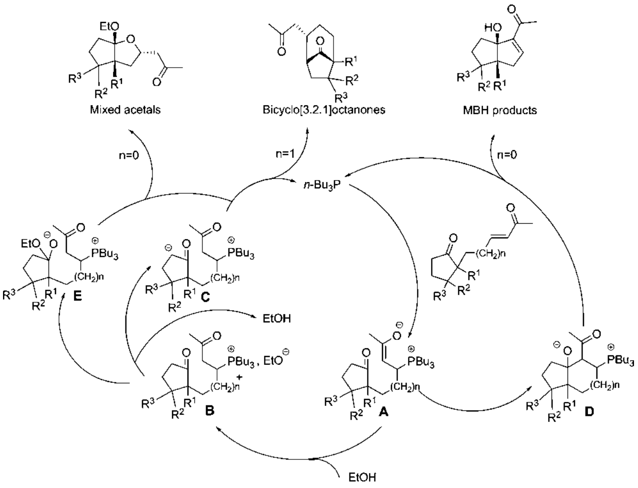


Figure 2. Proposed mechanism for the formation of bicyclo[3.2.1]octanones, MBH products, and mixed acetals.

to yield the zwitterion **C**, which undergoes an intramolecular cyclization to yield the bicyclo[3.2.1]octanones **6a**–**f**. Our results are in sharp contrast with those reported by Toste[14] and Jiang,[15] who showed that n-Bu$_3$P promotes the 1,4-addition of the alkoxide (generated in situ) to α,β-unsaturated ketones. We never observed such a reaction. On the other hand, starting from compounds **7a**–**f** bearing a shorter tether, it is reasonable to postulate that the formation of the corresponding bridge compounds, i.e., bicyclo[2.2.1]heptanones, was disfavored for strain reasons and unfavorable stereoelectronic constraints. Thus, in ethanol, the formation of the ion pair **B** still took place but the alkoxide behaves now like a nucleophile inducing the formation of the corresponding mixed acetals **8a**–**c**. In an apolar solvent, the MBH reaction occurred; the phosphonium enolate **A** undergoes an intramolecular cyclization to give intermediate **D**, which evolves toward MBH products **9a**–**f**.

In summary, we have developed an unprecedented substrate and solvent controlled n-Bu$_3$P organocatalyzed reaction starting from cycloalkanones (-diones) tethered to activated olefins to afford in high yields and high (diastereo)-selectivities bicyclo[3.2.1]octanones or polyfunctionalized diquinanes and mixed acetals. Studies of synthetic applications as well as an asymmetric version of these reactions are in progress and will be reported in due course.

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Supporting Information Available. Experimental details and ^{1}H and ^{13}C spectra for compounds **6a**–**f**, **8a**–**c**, and **9a**–**f**.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) The reaction pathway of the amine catalyzed MBH reactions in the presence of protic species (MeOH) was extensively studied by Kappe et al.: Cantillo, D.; Kappe, C. O. *J. Org. Chem.* **2010**, *75*, 8615–8626 and references cited therein. It is reasonable to postulate that this pathway can be extended to trialkylphosphine catalyzed MBH reactions.

(14) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697.

(15) Liu, H.-L.; Jiang, H.-F.; Wang, Y.-G. *Chin. J. Chem.* **2007**, *25*, 1023–1026.