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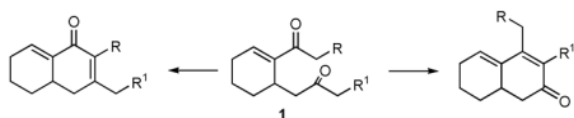
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Remarkable Phosphine-Effect on the Intramolecular Aldol Reactions of Unsaturated 1,5-Diketones: Highly Regioselective Synthesis of Cross-Conjugated Dienones

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As part of a target-oriented synthetic study, we were interested in developing selective syntheses of linear- and cross-conjugated dienones via aldol cyclizations of diketones (eq 1). Methods for the regioselective aldol reaction of such diketones are scarce, especially in cases where the steric environments of the two carbonyl groups are very similar.¹ 1,5-Diketones such as **1** were of interest because they are readily prepared via the phosphine-catalyzed intramolecular vinylogous Morita-Baylis-Hillman (MBH) cyclization of bis- α,β -unsaturated carbonyl compounds,² a reaction that was developed simultaneously in the Krische group³ and in our laboratory^{4,5}. During the course of our studies of the vinylogous MBH reaction, competitive intramolecular aldol cyclizations were observed for vinylogous MBH products **1** bearing enolizable carbonyl units when these reactions were performed in protic solvents such as *t*-Amyl alcohol.^{4a} This observation is consistent with the notion that the aldol reactions are catalyzed by alkoxide generated via deprotonation of alcoholic solvent by the zwitterionic phosphonium enolate intermediates.⁶ During efforts to optimize this tandem MBH/aldolization process, we discovered and report herein remarkable and unprecedented regioselectivity in the aldol step, resulting in extremely high selectivity for the less stable cross-conjugated dienones. We also provide evidence for the involvement of the phosphonium unit of the phosphine-enone Michael adduct (e.g., **6**) in controlling the regiochemistry of these reactions.

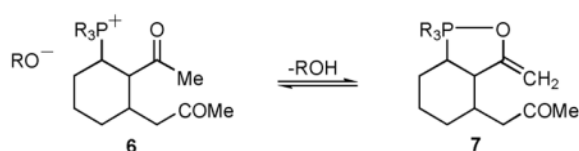


(1)

Symmetrical bisenone **2** was selected for initial reaction development studies (Table 1). The cyclization of **2** at room temperature in the presence of 1 equiv of PBU₃ in MeOH as the solvent produced regioisomeric aldol condensation products **4** and **5** with excellent selectivity (**4** : **5** = 94 : 6) for the cross-conjugated isomer **4** (entry 1). The Bu₃P loading can be decreased to 0.25 equiv if the reaction is performed at 60 °C, and the selectivity is only slightly lower (**4** : **5** = 93 : 7, entry 2). Unfortunately, these products were contaminated with inseparable adducts of MeOH-Michael addition to **4** and **5**.⁷ Use of *t*-AmylOH as the reaction solvent resulted in inefficient aldol condensation (entry 3), while use of *i*-PrOH gave a very clean, high yield (80%) of products, but with poor selectivity (**4** : **5** = 71 : 29, entry 4). Remarkably, however,

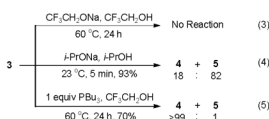
use of $\text{CF}_3\text{CH}_2\text{OH}$ as solvent for the tandem reaction gave clean aldol condensation product with exclusive selectivity for **4**; isomer **5** was undetected by ^1H NMR analysis (entry 5). PMe_3 can also be used to promote this reaction with identical selectivity to that obtained using $\text{P}t\text{Bu}_3$ (entry 6).

The very high regioselectivity for **4** in these reactions was unexpected. A priori, we had anticipated that poor kinetic selectivity would occur in the aldol step due to the similarity in $\text{p}K_{\text{a}}$ and steric environment of the two ketone units in intermediate **3**; moreover, the linearly-conjugated isomer **5** was expected to predominate if the reaction was subject to thermodynamic control.¹ Therefore, it is noteworthy that we observe such high regioselectivity and that the reaction is highly selective for the less stable cross-conjugated isomer.⁸ We postulate that the high degree of selectivity derives from an interaction between the phosphonium unit and the adjacent carbonyl in intermediate **6**. This would increase the acidity of the β -phosphonium-substituted methyl ketone such that it is deprotonated regioselectively by the alkoxide (**6** \rightarrow **7**; eq 2).⁹



(2)

Experimental evidence for this phosphine effect was obtained by subjecting MBH product **3** to a catalytic amount of $\text{CF}_3\text{CH}_2\text{ONa}$ in $\text{CF}_3\text{CH}_2\text{OH}$ (eq 3). No reaction was observed, indicating that $\text{CF}_3\text{CH}_2\text{ONa}$ is not basic enough to deprotonate **3** in the absence of phosphine. While **3** undergoes efficient aldol cyclization when treated with *i*-PrONa (eq 4), the selectivity (**4** : **5** = 18 : 82) is opposite to that observed using $\text{P}t\text{Bu}_3$ /*i*-PrOH (**4** : **5** = 71 : 29). Furthermore, treatment of **3** with $\text{P}t\text{Bu}_3$ in $\text{CF}_3\text{CH}_2\text{OH}$ affords **4** exclusively (eq 5), demonstrating that **3** is a viable intermediate in the conversion of **2** to **4**. These results support our proposal that **6** plays a key role in controlling the regioselectivity of the aldol step.



Other bisenone substrates cyclize to afford exclusively the cross-conjugated isomers (Table 2). Bisenone **8**, bearing a shorter tether, cyclizes to dienone **9** in 76% yield (Table 2, entry 2). Substrate **10** can theoretically afford two vinylogous MBH adducts (c.f., **1**), each of which in principle can cyclize to give two aldol regioisomers. Remarkably, **10** cyclized to afford only one out of four possible products (**11**) in 71% yield (entry 3). Evidently, the vinylogous MBH cyclization of **10** occurs with selectivity that is consistent with initial phosphine addition to the least hindered enone, while the selectivity of the aldol step is governed by the phosphine effect outlined above.

Sterically differentiated bisenones **12**, **14**, **16**, and **18** (Table 2, entries 7–10), which contain a hindered β,β -disubstituted enone, undergo efficient and selective MBH cyclization and subsequent aldol condensation to give the cross-conjugated products. Again, only one out of four possible products is formed. For these substrates, the optimal conditions involved use of 5 equiv of PMe_3 in *t*-AmylOH at 80 $^\circ\text{C}$; the MBH cyclization in these cases was unsuccessful using $\text{CF}_3\text{CH}_2\text{OH}$ as solvent. In all cases, products bearing quaternary centers were generated in good yield (58–64%).

MBH product **20**, which can be isolated from the cyclization of bisenone **18**, undergoes phosphine-mediated aldol cyclization with the most hindered enolate serving as the nucleophile to generate isomer **19** (Scheme 1). Interestingly, a base-promoted aldol cyclization of **20** in the absence of phosphine results in a complete reversal of selectivity, and the linearly-conjugated isomer **21** is obtained in >95:5 selectivity. This example highlights the striking complementarity of the phosphine-mediated aldol condensation to a traditional aldol process.

In summary, we have discovered a phosphine-mediated intramolecular aldol cyclization of unsaturated diketones **1** that proceeds with extremely high levels of regioselectivity for the cross-conjugated bicyclic dienone products. The sense of regioselectivity observed in this reaction is unattainable using traditional aldol conditions, and is governed by the chemistry of the phosphine Michael adduct **6**. Applications of this method to the synthesis of natural products will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

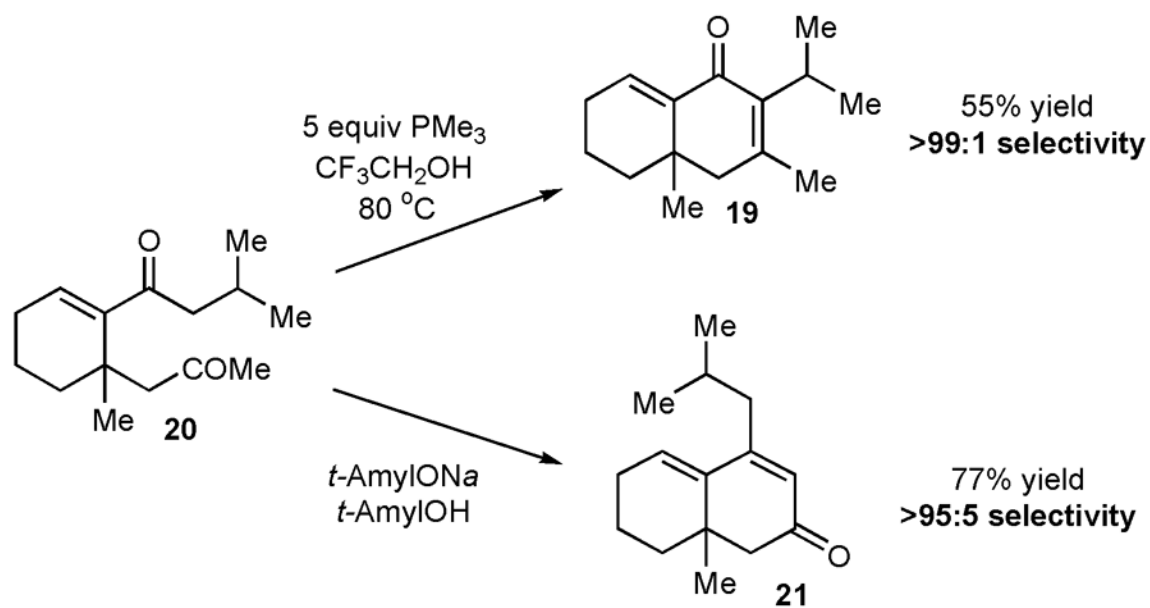
Acknowledgements

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7. Solvent mixtures of THF, MeCN, or MeOH significantly reduced CH₂Cl₂ the amount of MeOH Michael adducts (from 20% to 3%), but conversions and/or selectivities were lower in these solvent systems.
8. Isomers **4** and **5** do not equilibrate under the reaction conditions.
9. For known examples of structures related to **7**, see: (a) Bentrude WG, Johnson WD, Khan WA. *J Am Chem Soc* 1972;94:923–932. (b) Arbuzov BA, Zoroastrova VM, Tudrii GA, Fuzhenkova AV. *Bull Acad Sci USSR Div Chem Sci* 1973;22:2513. (c) Aksnes G, Frøyen P. *Acta Chem Scand*

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Scheme 1.
Synthesis of Cross-Conjugated *or* Linear Dienones

Table 1

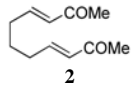
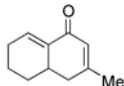
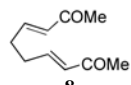
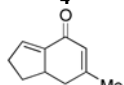
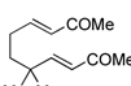
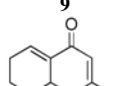
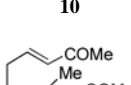
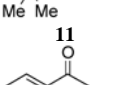
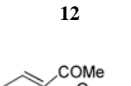
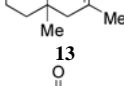
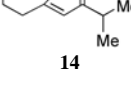
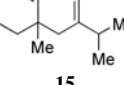
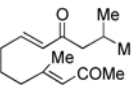
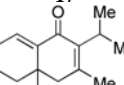
Survey of Solvents for the Tandem Cyclization^a

entry	Solvent	T (°C)	time (h)	% 4+5	Ratio (4 : 5)
1 ^b	MeOH	25	24	83 ^c	94 : 6
2	MeOH	60	10	82 ^c	93 : 7
3	<i>t</i> -AmylOH	60	48	10 ^d	90 : 10
4	<i>i</i> -PrOH	60	3	80	71 : 29
5 ^b	CF ₃ CH ₂ OH	60	24	80	>99 : 1
6 ^e	CF ₃ CH ₂ OH	60	22	76	>99 : 1

^a Conditions: 0.25 equiv PBu₃, 0.05 M **2**.^b 1 equiv PBu₃ was used.^c Contaminated with 20% MeOH-adducts of **4** and **5**.^d Aldol product (**19%**) and **3** (42%) were also isolated.^e 1 equiv PMe₃ was used.

Table 2

Substrate Scope of the Tandem Cyclization

Entry	Substrate	product(s)	Yield(%) ^a
1 ^b	 2	 4	80
2 ^b	 8	 9	76
3 ^b	 10	 11	71
4 ^c	 12	 13	60 ^d
5 ^c	 14	 15	64 ^d
6 ^c	 16	 17	58 ^d
7 ^c	 18	 19	58 ^d

^aThe only product isomers detected by ¹H NMR analysis of the crude material are those indicated.

^bMethod A: 1 equiv PMe₃, 0.05 M substrate in CF₃CH₂OH, 60 °C.

^cMethod B: 5 equiv PMe₃, 0.05 M substrate in *t*-AmylOH, 80 °C.

^dThe MBH intermediate (c.f., **1**) was isolated in 7–8% yield.