Synthetic Methods

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Highly Diastereoselective Synthesis of Bicyclo-[3.2.1]octenones through Phosphine-Mediated Condensations of 1,4-Dien-3-ones**

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New methods for the construction of highly substituted carbocycles with a defined configuration are important for the synthesis of natural products and drugs.[1] The synthesis of cyclic compounds that possess all-carbon quaternary centers is a challenge that has been primarily addressed by the alkylation of enolates,[2] the Diels–Alder reaction,[3] and radical cyclizations.[4] One elegant approach is the [4+3] cycloaddition of oxyallyl cations with substituted dienes and furans to afford bicycles that contain quaternary carbon centers.[5] Complementary approaches to simple carbocycles from acyclic precursors include phosphine-mediated methods such as [3+2] annulations[6] as well as intramolecular Rauhut–Currier,[7] Morita–Baylis–Hillman,[8] and S_N2 reactions.[9] Despite the myriad approaches afforded by these reactions,[10] few synthetic methods that produce quaternary carbon-containing bicyclic structures by using nucleophilic promoters exist.[11] Herein we report the phosphine-mediated highly diastereoselective synthesis of bicyclo[3.2.1]octenones[12] that bear two bridgehead quaternary carbon centers from 1,4-dien-3-ones by a formal [4+2] cycloaddition–Wittig reaction process.

1,4-Dien-3-ones are useful multifunctional building blocks in the synthesis of carbocyclic compounds. A recent report illustrated their utility in the synthesis of cyclohexenones through an electrocyclic ring closure following base-mediated formation of the corresponding hexatriene.[13] Intermolecular Diels–Alder reactions[14] of 1,4-dien-3-ones as electron-deficient dienophiles also afford carbocyclic structures. Cyclopentenones and highly substituted bicycles are readily accessed through another type of electrocyclic ring closure of dienones, the Nazarov reaction.[5a–d,15] On the basis of the multifunctional nature of 1,4-dien-3-ones, we believed that they could serve as latent 1,3-dienes in [4+2] annulation reactions.

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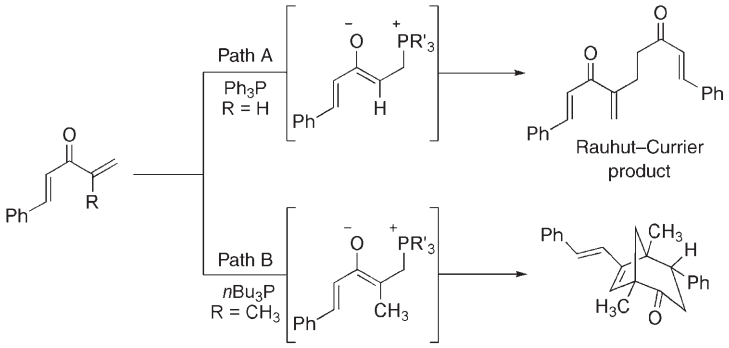
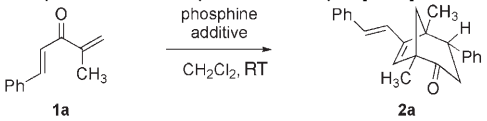
We began our investigations with the reaction of phosphines with 1,4-dien-3-ones to determine the feasibility of a phosphine-catalyzed all-carbon [4+2] annulation (Scheme 1). When styryl vinyl ketone (R = H) is mixed with Ph_3P in THF,



Scheme 1. Phosphine-promoted reactions of 1,4-dien-3-ones.

the Rauhut–Currier product is formed in 53% yield (Path A). Although this result confirms that the enolate can be generated in situ, α-proton transfer leads to the Rauhut–Currier reaction pathway. To investigate other reaction pathways of this type of latent 1,3-diene, we synthesized α-substituted 1,4-dien-3-ones (Path B). When styryl isopropenyl ketone (**1a**) was treated with nBu_3P in CH_2Cl_2 at room temperature, we found that bicyclo[3.2.1]octenone **2a** formed as a single diastereomer in 15% yield (Table 1, entry 1). Bicyclo[3.2.1]octanes are subunits of a variety of biologically active terpenes, including the scopadulcic acids,[16] gibberellins,[17] and aphidicolane diterpenes.[18] We screened various electronically and sterically different phosphines[19] and found that 1 equivalent of Et_2PhP mediated the condensation reaction in 65% yield after 20 h (Table 1, entry 3). Substoichiometric amounts of phosphine resulted in extended reaction times and lower yields. Although the reaction proceeded in most polar, non-ether solvents ($CHCl_3$, $PhCF_3$,

Table 1: Phosphine-mediated synthesis of bicyclo[3.2.1]octenone **2a**.[a]



1a **2a**

Entry	Phosphine	Additive	Yield [%][b]
1	nBu_3P	–	15[c]
2	Cy_3P	–	–[d]
3	Et_2PhP	–	65
4	$EtPh_2P$	–	–[e]
5	Ph_3P	–	–[e]
6	Et_2PhP	DBU	44
7	Et_2PhP	Et_3N	65
8	Et_2PhP	pyridine	76

[a] Reactions were run with ketone (0.3 mmol), phosphine (0.3 mmol), and additive (0.3 mmol) in CH_2Cl_2 (0.5 M) at room temperature for 20 h under Ar, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Reaction time was 5 min. [d] Decomposition of **1a**. [e] No reaction observed by ^1H NMR spectroscopy. Cy = cyclohexyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

CH_3CN), the best yields were obtained with anhydrous CH_2Cl_2. Basic additives affected the reaction yield (Table 1, entries 6–8). The use of 1 equivalent of pyridine improved the yield to synthetically useful levels while maintaining the high diastereoselectivity (Table 1, entry 8); no reaction was observed when pyridine was used in the absence of phosphine.[20] Therefore, we selected 1 equivalent each of Et_2PhP and pyridine in CH_2Cl_2 at room temperature as general reaction conditions.

These reaction conditions proved general for a variety of 1,4-dien-3-ones (Table 2). Halogen- and alkyl-substituted aryl substrates **1b–d** cleanly underwent condensation in yields greater than 70%. Heteroaromatic and electron-donating aromatic dienones afforded the bicyclo[3.2.1]octenone products in good yields, although gentle heating was required for the 4-methoxy derivative **1h** (Table 2, entries e–h). Substitutional effects were more pronounced at other positions of the 1,4-dien-3-one backbone. The condensation of 2-ethyl-1,4-dienone **1i** resulted in lower yields, although heating to 50°C in $CHCl_3$ afforded the desired product in 41% yield after 20 h (Table 2, entry i). Substrates bearing alkyl substituents (Table 2, entries j,k) did not react under the general conditions; however, the use of more-nucleophilic phosphines such as nBu_3P resulted in effective condensation of these less-electrophilic enones to afford the bicyclic products. Dienones **1l–n** underwent condensation under similar reaction conditions; Et_2PhP was the nucleophilic promoter for aromatic **1l** and **1m** [Eq. (1)], whereas geranal-derived **1n** required nBu_3P for optimal yields [Eq. (2)]. In an experiment designed to explore the reactivity of the dienones, the reaction of **1e** with Et_2PhP and pyridine in the presence of a stoichiometric amount of **1n** resulted in the exclusive formation of **2e**, the condensation product of 2 equivalents of **1e**. The heterodimer product, afforded by the reaction of 1 equivalent each of **1e** and **1n**, was not observed. This might have been due to the higher electrophilicity of aromatic over aliphatic substrates toward both the nucleophilic addition of Et_2PhP and the reaction of the resulting 1,3-diene.

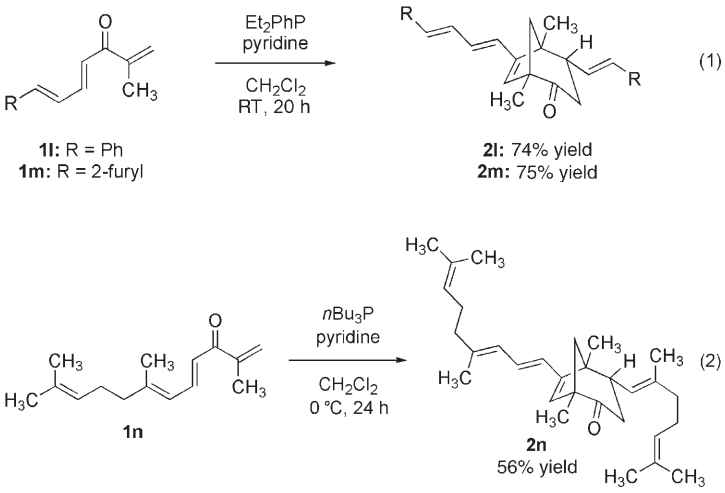
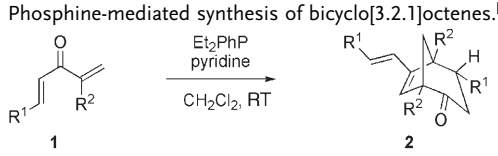


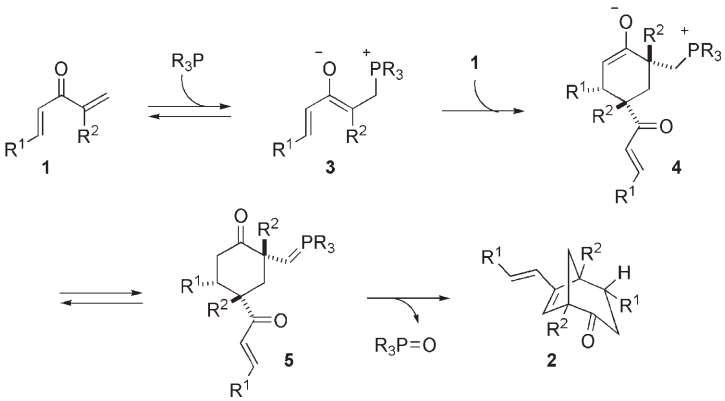
Table 2: Phosphine-mediated synthesis of bicyclo[3.2.1]octenes.[a]



Entry	R^1	R^2	Yield [%][b]
a	C_6H_5	CH_3	76
b	4-F-C_6H_4	CH_3	70
c	4-Br-C_6H_4	CH_3	70
d	4-Me-C_6H_4	CH_3	75
e	2-furyl	CH_3	75
f[c]	2-MeO-C_6H_4	CH_3	70
g	3-MeO-C_6H_4	CH_3	73
h[d]	4-MeO-C_6H_4	CH_3	66
i[e]	C_6H_5	CH_2CH_3	41
j[f]	$H_3C(CH_2)_6$	CH_3	60
k[f]	2-furyl-$(CH_2)_2$	CH_3	60

[a] Reactions were run with ketone (0.3 mmol), pyridine (0.3 mmol), and Et_2PhP (0.3 mmol) in CH_2Cl_2 (0.5 M) at room temperature for 20 h under Ar, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Reaction time was 30 h. [d] Reaction was run at 30°C. [e] Reaction was run in $CHCl_3$ at 50°C. [f] nBu_3P, added over 6 h, was used at 0°C.

We propose herein a mechanism for the condensation reaction in which the phosphine fulfills two roles (Scheme 2).[21] Nucleophilic addition of the phosphine to **1** affords diene **3**.[22] A formal [4+2] cycloaddition of **3** with another 1 equivalent of **1** in an *endo* fashion yields cycloadduct **4** as one diastereomer. We postulate that pyridine facilitates the proton transfer to protonate enolate **4** and form phosphorus ylide **5**.[23] When the reaction of **1a** was conducted in $CDCl_3/D_2O$ (9:1), we observed deuterium incorporation at the methylene α to the carbonyl group and at the cyclic-olefin methine positions of **1b** (both 82% D incorporation), suggesting that the protonation of **4** may occur by an intermolecular process and that formation of **5** is reversible. Notably, deuterium incorporation was not observed at the bridgehead methylene or the exocyclic vinyl hydrogen atoms,



Scheme 2. Proposed mechanism for the phosphine-mediated synthesis of bicyclo[3.2.1]octenones.

which indicates that the [4+2] cycloaddition may not be reversible. Finally, intramolecular Wittig olefination[24] of **5** and the α,β-unsaturated carbonyl group located on the same face of the cyclohexanone ring afforded the bicyclo-[3.2.1]octenone **2** and phosphine oxide, as observed by ^{31}P NMR spectroscopy. Given this proposed mechanism, we conducted experiments to test whether **5** could undergo intermolecular Wittig olefinations with aldehydes in situ. The reaction of **1a** with Et_2PhP in the presence of benzaldehyde, acetaldehyde, or paraformaldehyde resulted solely in the formation of the bicyclic product **2a**. Intermolecular Wittig olefination products were not formed, suggesting a fast intramolecular olefin-formation step.

In summary, we have developed a highly diastereoselective phosphine-mediated synthesis of bicyclo[3.2.1]octenones that contain two quaternary carbon centers by a domino [4+2] cycloaddition–Wittig reaction process. The phosphine acts as both a nucleophilic promoter to generate a 1,3-diene and a mediator of intramolecular olefination. Experiments designed to explore the scope and limitations of this reaction are ongoing and will be reported in due course.

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