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Organocatalytic Michael Cycloisomerization of Bis(enones): The Intramolecular Rauhut−Currier Reaction

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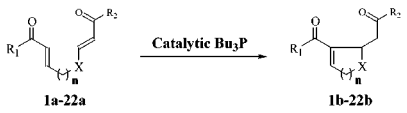
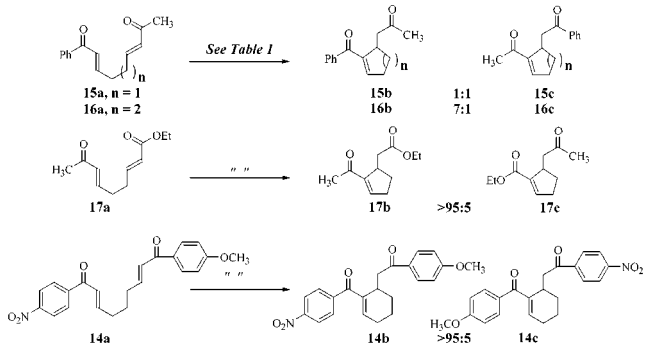
The utilization of enones as latent enolates enables regioselective enolate formation from chemically robust precursors. Seminal studies by Stork establish enones as enolate precursors in stoichiometric processes.[1] Recently, metal-catalyzed methods for the nucleophilic activation of enones have been described, e.g. catalytic reductive aldol[2] and Michael processes.[2g] As demonstrated by the Morita−Baylis−Hillman reaction, nucleophilic organic compounds also may serve as efficient catalysts for enone activation.[3] Though realized in the context of aldehyde addition, the mechanistic motif embodied by the Morita−Baylis−Hillman reaction may encompass other electrophilic partners, including electron-deficient alkenes.[4−6] Indeed, the phosphine-catalyzed dimerization of electron-deficient alkenes reported by Rauhut and Currier predates the Morita−Baylis−Hillman reaction.[5a] While the intramolecular Morita−Baylis−Hillman reaction is known,[7] the intramolecular Rauhut−Currier reaction has not been described.[8,9] In this account, we report an intramolecular variant of the Rauhut−Currier reaction, i.e. an organocatalytic Michael cycloisomerization of bis(enones). Upon exposure to 10 mol % of tributylphosphine, bis(enone) substrates afford both five- and six-membered-ring products. Notably, unsymmetrical bis(enones) possessing sufficient steric or electronic bias yield single isomeric products.

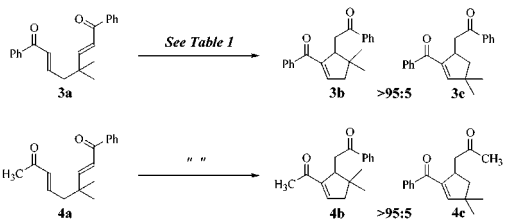


Initial efforts focused on defining optimal conditions for the catalytic cycloisomerization of bis(enone) **5a**. ^{1}H NMR analysis of reactions conducted in $CDCl_3$, d_6-acetone, and d_6-DMSO allowed a variety of nucleophilic catalysts to be assayed. Through this preliminary screen, tributylphosphine was identified as the catalyst of choice. Additionally, this study revealed a dramatic increase in reaction rate with increasing solvent polarity. Reactions performed in DMSO were complete in less than 10 min, but gave rise to substantial quantities of oligomerized products. Oligomerization is suppressed in a less polar medium and, for aroyl-substituted substrates, acetone was found to be the best solvent. However, for highly electrophilic bis(enones), e.g. furyl-substituted bis(enone) **11a**, a less polar medium is required. In such cases, ethyl acetate was found to promote cleaner conversion. Under these optimized conditions, both aroyl- and heteroaroyl-containing bis(enones) undergo cycloisomerization in good to excellent yields. Aliphatic bis(enones) and mixed bis(enones) incorporating enoate moieties also are viable substrates. However, owing to their reduced electrophilicity, more forcing conditions are required to induce cycloisomerization. Here, refluxing *tert*-butyl alcohol proved to be the most effective medium.

Electronic differentiation of the reacting partners was investigated as a means of enabling the chemoselective cycloisomerization of unsymmetrical substrates. Aromatic−aliphatic mixed bis(enone) **15a** provides the cyclopentenes **15b** and **15c** as a 1:1 mixture of isomers, while the homologous substrate **16a** affords the cyclohexenes **16b** and **16c** in a 7:1 ratio, respectively. These data suggest the initial formation of tributylphosphine adducts is indiscriminate. For five-membered ring formation, the kinetic phosphine adducts are trapped via cyclization. In the case of six-membered ring formation, an attenuated cyclization rate enables a preequilibrium of tributylphosphine adducts to be established, whereby cyclization becomes the product- and rate-determining step. Further electronic differentiation of the enone partners completely suppresses the competitive cyclization manifold. For mono-enone mono-enoate **17a**, a single cycloisomerization product **17b** is obtained.[10] The ability to select cyclization manifolds on the basis of electronic effects is underscored by the cyclization product **14a**. Here, remote para substituents direct the formation of a single isomeric cycloisomerization product, cyclohexene **14b**. The isomeric material **14c** was not detected.[10]



In the absence of a significant electronic bias, steric factors direct selectivity. The cycloisomerization of bis(enone) **3a**, which incorporates a resident geminal dimethyl moiety in the tether, provides **3b** as the exclusive cycloisomerization product. Similarly, mixed bis(enone) **4a** provides a single isomeric cycloisomerization product **4b**.



Stereoselectivity is an issue for systems incorporating stereocenters in the tether. The optically pure xylose-derived mono-enone mono-enoate **22a** provides pentasubstituted cyclohexene **22b** as a single isomer.[10] A model accounting for the observed stereoselectivity is indicated.

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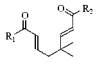
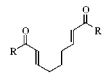
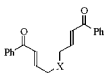
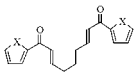
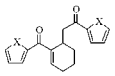
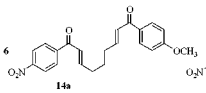
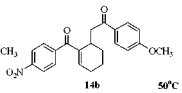
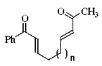
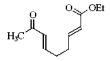
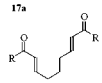
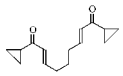
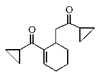
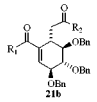
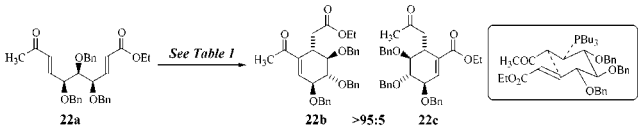
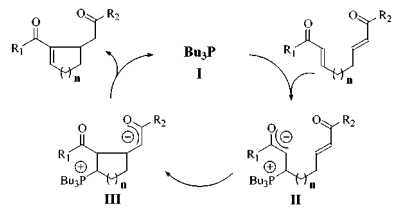
Table 1. Phosphine-Catalyzed Cycloisomerization of Bis(enones)[a]

Entry	Substrate	Product	T (°C)	Solvent	Isolated Yield (%)
1					
	1a, R = Ph	1b	50°C	EtOAc	86
	2a, R = 2-Furyl	2b	40°C	EtOAc	95
2					
	3a, $R_1 = R_2 = Ph$	3b	50°C	EtOAc	85
	4a, $R_1 = CH_3$, $R_2 = Ph$	4b	76°C	EtOAc	81
3					
	5a, R = phenyl	5b	25°C	Acetone	82
	6a, R = 4-methoxyphenyl	6b	50°C	Acetone	78
	7a, R = 4-trifluoromethylphenyl	7b	25°C	EtOAc	79
	8a, R = 3-naphthyl	8b	50°C	EtOAc	88
4					
	9a, X = O	9b	25°C	Acetone	95
	10a, X = NTs	10b	25°C	EtOAc:Acetone (1:1)	90
5					
	11a, X = O	11b	50°C	EtOAc	90
	12a, X = S	12b	25°C	EtOAc	82
	13a, X = NCH_3	13b	56°C	Acetone	88[b]
6					
	14a	14b	50°C	EtOAc	75
7					
	15a, n = 1	15b/16b, R_1 = Ph, $R_2 = CH_3$	76°C	EtOAc	79
	16a, n = 2	15c/16c, $R_1 = CH_3$, R_2 = Ph	76°C	EtOAc	77
		15b:15c (1:1)			
		16b:16c (7:1)			
8					
	17a	17b	25°C	^{t}BuOH	87
9					
	18a, R = CH_3	18b	84°C	^{t}BuOH	61
	19a, R = $CH_2CH(CH_3)_2$	19b	84°C	^{t}BuOH	70
10					
	20a	20b	84°C	^{t}BuOH	82
11					
	21a, $R_1 = R_2 = CH_3$	21b	84°C	^{t}BuOH	81[c]
	22a, $R_1 = CH_3$, R_2 = OEt	22b	102°C	^{t}AmylOH	71[c]

[a] Procedure: Tributylphosphine was added to a 0.1 M solution of substrate in the indicated solvent and the reaction was allowed to stir at the indicated temperature until complete. [b] Yield based on recovered starting material. [c] 20 mol % PBu_3 used.



Though detailed mechanistic studies have not been undertaken, a plausible mechanism for the phosphine-catalyzed cycloisomerization of bis(enones) is proposed below.[6] Conjugate addition of tributylphosphine **I** to the indicated bis(enone) provides enolate **II**. Subsequent intramolecular conjugate addition to the appendant enone yields zwitterionic intermediate **III**. Finally, proton-transfer enables β-elimination of tributylphosphine to complete the catalytic cycle. Cycloisomerization performed in d_6-acetone did not yield products incorporating deuterium, indicating that proton transfer occurs between substrate molecules either inter- or, more likely, intramolecularly.



In summary, we have developed a simple and effective organic catalyst system for the cycloisomerization of bis(enones). This methodology overcomes many limitations of metallic diene cycloisomerization catalysts: both five- and six-membered-ring formations occur readily, conformationally predisposed substrates are not required, products of alkene isomerization are not formed, and finally, functional group compatibility is broadened. An enantioselective variant of the phosphine-catalyzed cycloisomerization of bis(enones) will be the subject of a forthcoming report.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Isomeric ratios were determined by ^{1}H NMR. For ratios of >95:5, the minor isomer was not observed.

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