

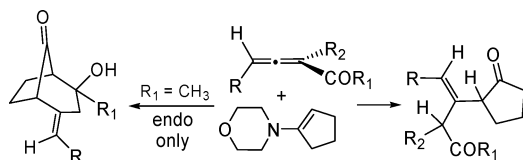
## Michael–Stork Addition of Cyclopentyl Enamine to Allenyl Ketones and Esters

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We report the first examples of a Michael–Stork enamine addition to allenyl esters and ketones. Studies reveal that 2 equivalents of enamine are required for optimal yields. In the case of an allenyl methyl ketone, cyclopentyl enamine addition led to 8-oxobicyclo[3.2.1]octane formation, providing evidence for the *in situ* formation of an enamine intermediate following the initial Michael–Stork reaction.

Despite their potential as versatile intermediates in organic synthesis, studies relating to the preparation and reactivity of allenyl carbonyls have been few in number. Recently we reported the development of an efficient method for the conversion of a variety of conjugated alkynyl esters to  $\alpha$ -substituted conjugated allenyl esters through the use of strong amide bases.<sup>1</sup> We have also investigated the mechanism of a complementary approach pioneered by Franck–Neumann<sup>2</sup> involving the isomerization of manganese alkynyl carbonyls to the corresponding allenes.<sup>3</sup> Allenyl 1,3-dicarboxylates are known to react as both dienophiles<sup>4,5</sup> and Michael acceptors.<sup>5</sup> Likewise, studies involving related systems such as vinyl esters,<sup>6</sup> aldehydes,<sup>7</sup> and ketones<sup>8</sup> also indicate that these species readily undergo Michael–Stork addi-

tion with enamines. Schreiber<sup>9</sup> and Jorgensen<sup>10</sup> have demonstrated that vinyl aldehydes and ketones react as heterodienes in Diels–Alder reactions with enamines. Thus it was not clear from this related literature if allenyl carbonyls would behave as heterodienes or as Michael acceptors in the presence of enamines. In this note, we examine the reaction of *N*-(1-cyclopenten-1-yl)-morpholine (**2**) with a variety of allenyl carbonyls.

We began our studies with racemic silyl allene **1a**, which is obtained in good yields and in scalable quantities from alkynyl ester.<sup>1</sup> The addition of enamine **2** to allenyl ester **1a** proceeded at ambient temperature in benzene to yield adduct **3** and its desilylated analogue **4** in a low overall yield of 26% (Table 1, entry 1). Initial attempts to optimize the addition of enamine to **1a** by varying the reaction solvent (CH<sub>2</sub>Cl<sub>2</sub>, THF, and CH<sub>3</sub>CN) were unsuccessful. Only modest improvements of the reaction yield were realized by varying temperature and reaction concentration and altering the order of reagent addition. We reasoned that the low yield might be related to the appearance of desilylated product **4**. In a separate experiment, pure adduct **3** was readily converted to **4** (in 65% yield) when treated with enamine **2** in benzene at room temperature. This finding suggested that the poor conversion of **1a** to adduct **3** may be due to a side reaction involving the depletion of enamine **2** employed in the conversion of **3** to **4**. Alternatively, we have observed that enamine **2** decomposes in solution over several hours. A significant improvement in yield was observed when two or more equivalents of enamine **2** were utilized in the addition reaction (Table 1). Proton NMR experiments of products **3** and **4** involving NOE enhancement were used to establish the geometry of the double bond for each molecule. In each case, the benzyloxyethyl group was oriented *trans* relative to the cyclopentanone moiety.

To examine the scope of this new synthetic method, enamine **2** was reacted with a variety of allenyl carbonyls **1** using the optimized reaction conditions. In each case, the reaction proceeded rapidly to yield the expected addition products in moderate to good yields (Table 2, entries 1–5). The reaction of  $\alpha$ -stannylallenyl ester **1b** with enamine **2** afforded product **4** in 82% yield (Table 2, entry 1).

In contrast to the outcome of the allenyl silane addition reaction, product **4** was obtained as a 3:1 mixture of *E/Z* isomers and with complete loss of the  $\alpha$ -substituent. Interestingly, the addition of enamine **2** to methylallenyl ester **1c**,  $\alpha$ -unsubstituted allenyl ester **1d**, and ketone **1e** led to single alkene isomers, with the benzyloxyethyl group oriented *trans* relative to the cyclopentanone moiety (*E* isomer), albeit in lower yields (entries 2–4).

The addition of enamine **2** with methyl allenyl ketone **1f** gave a low yield (30%) of addition product **7** as the *E* stereoisomer (Table 2, entry 5). This reaction also produced 8-oxobicyclo[3.2.1]octane **8** (31%) as a single diastereomer (Scheme 2). An NMR analysis of bicyclooctane

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**TABLE 1.** Effect of Enamine Equivalents on the Yield of the Michael–Stork Addition Reaction

entry	equiv	% isolated yield		
		3	4	combined
1	1.0	11	15	26
2	1.5	28	7	35
3	2.0	41	25	66
4	2.5	30	30	60
5	5.0	35	25	60

**TABLE 2.** Addition of Cyclopentyl Enamine to Allenyl Carbonyls

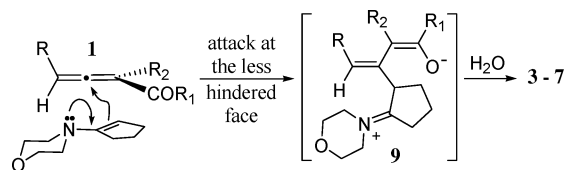
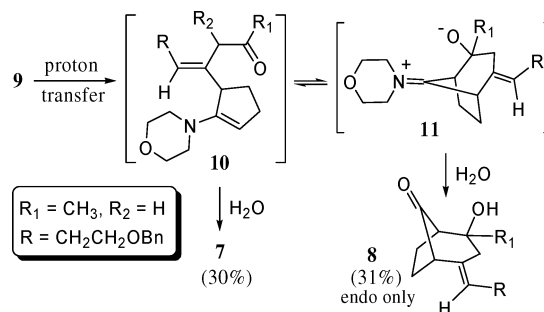
entry	allene <sup>a</sup>	R <sub>1</sub>	R <sub>2</sub>	product	% yield <sup>b</sup>
1	<b>1b</b>	SnBu <sub>3</sub>	OMe	<b>4</b>	82 <sup>c</sup>
2	<b>1c</b>	Me	OMe	<b>5</b>	68 <sup>d</sup>
3	<b>1d</b>	H	OMe	<b>4</b>	37
4	<b>1e</b>	H	<i>t</i> -Bu	<b>6</b>	53
5	<b>1f</b>	H	Me	<b>7/8</b>	61 <sup>e</sup>

<sup>a</sup> Allenes synthesized according to reported literature procedures (refs 1 and 3). <sup>b</sup> Isolated yields. <sup>c</sup> Product **4** was isolated as a 3:1 ratio of *E/Z* stereoisomers. <sup>d</sup> Product **5** was isolated as a 2:1 mixture of *syn/anti* diastereoisomers. <sup>e</sup> Overall yield for a 1:1 mixture of **7** and oxobicyclo product **8** (Scheme 2).

**8** using NOE enhancement experiments revealed an *E* double bond geometry and a methyl substituent in the endo orientation. While oxobicyclic products have been obtained from vinyl ketones<sup>11</sup> and pentacarbonyl[alkenyl-(alkoxy)]carbene complexes,<sup>12</sup> their formation from allenyl ketones is unprecedented.

The mechanism of enamine additions to allenyl carbonyls does not appear to proceed via a Diels–Alder process primarily because cycloaddition adducts were not isolated. In addition, Diels–Alder products were not observed by NMR when monitoring various enamine additions to allenyl carbonyls in deuterated benzene. Therefore, on the basis of related precedent,<sup>6</sup> we envision that products **3–7** are obtained by a Michael–Stork mechanism to yield intermediate **9** followed by hydrolysis (Scheme 1). The *E*-selectivity in the formation of compounds **3–7** suggests that the cyclopentyl enamine approaches allenyl carbonyls **1** from the less hindered allene face of the molecule to avoid undesirable steric interactions with the benzyloxyethyl side chain (Scheme 1).

The formation of bicyclooctane **8** from allenyl ketone **1f** can also be reasoned on the basis of a Michael–Stork

**SCHEME 1.** Rationale for Alkene Geometry in **3–7****SCHEME 2.** Proposed Mechanism for the Formation of Oxobicyclo **8** from Allenyl Methyl Ketone **1f**

mechanism. We envision an initial enamine addition to form intermediate **9** (R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H) followed by a proton transfer to yield enamine intermediate **10** (Scheme 2). Enamine intermediate **10** is then believed to undergo an intramolecular condensation to yield iminium **11**, which upon hydrolysis should furnish functionalized 8-oxobicyclo[3.2.1]octane **8**. While the *E* stereochemistry of bicycle **8** is likely established in the initial Michael–Stork addition leading to **9**, the origins of the *endo* preference are less clear. Force field calculations of the *exo* isomer of **11** reveal a destabilization energy of 32 kcal/mol relative to intermediate **11**. Since ionic interaction terms predominate in the ground-state energy calculation of both **11** and its *exo* isomer, we surmise that the large energy difference is primarily due to the reduced charge separation in **11**. An earlier report involving enamine additions to vinyl methyl ketones suggests that the formation of oxobicyclo products proceeds under thermodynamic control.<sup>11b</sup> If the formation of **11** proceeds by a similar mechanism, the exclusive formation of **8** (*endo* only) can be understood in light of the substantially reduced energy of intermediate **11** relative to its *exo* isomer.

In conclusion, we have demonstrated the first examples of Michael–Stork enamine additions to allenyl esters and ketones. Moderate yields were achieved with two or more equivalents of enamine at room temperature in benzene. The addition of enamine **2** to allenyl methyl ketone **1f** led to the formation of oxobicyclic **8** most likely through the intermediacy of an enamine intermediate derived from the initial Michael–Stork reaction. Further studies of allenyl carbonyl reactivity are currently in progress.

## Experimental Section

**Representative Procedure: Synthesis of 2-[1-(Benzyloxy)-6-oxohept-3-en-4-yl]-cyclopentanone (7) and 4-(3-(Benzyloxy)propylidene)-2-methyl-2-hydroxy-bicyclo[3.2.1]-octan-8-one (8).** A round-bottomed flask (25 mL) under an argon atmosphere was equipped with a magnetic stir bar and charged with **1f** (180 mg, 0.83 mmol) and benzene (0.8 mL) via

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syringe. *N*-(1-Cyclopenten-1-yl)-morpholine (**2**) (0.280 mL, 1.74 mmol) was then added dropwise to the reaction mixture via syringe. This reaction solution was stirred at ambient temperature for 1 h followed by solvent removal in vacuo to yield a crude oil that was purified using silica gel (70 g, 2 × 10 cm) under gradient elution (2–15% EtOAc/hexanes). Like fractions were combined, and solvent was removed in vacuo to yield two products. 2-[1-(Benzyloxy)-6-oxohept-3-en-4-yl]-cyclopentanone (**7**) ( $R_f = 0.24$  in 30% EtOAc/hexanes) (57 mg, 30%):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.27 (m, 5 H), 5.49 (t,  $J = 5.5$  Hz, 1 H), 4.50 (s, 2H), 3.50 (t,  $J = 6.9$  Hz, 2H), 3.40 (d,  $J = 16.7$  Hz, 1H), 3.24 (d,  $J = 16.6$  Hz, 1H), 2.8 (t,  $J = 10.7$  Hz, 1H), 2.38–2.27 (m, 4 H), 2.21–2.17 (m, 4H), 2.07–1.99 (m, 1 H), 1.94–1.84 (m, 1 H), 1.82–1.71 (m, 1 H);  $^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  218.1, 206.3, 138.4, 131.0, 128.4, 127.7, 127.6, 127.2, 72.9, 69.4, 56.4, 44.9, 38.3, 29.7, 29.1, 28.8, 20.0; HRMS (ESI)  $m/z$  323.1630  $[\text{M} + \text{Na}]^+$ , mass calcd for  $\text{C}_{19}\text{H}_{24}\text{O}_3 = 323.1618$ . 4-(3-(Benzyloxy)propylidene)-2-methyl-2-hydroxy-bicyclo[3.2.1]octan-8-one (**8**) ( $R_f = 0.11$  in 30% EtOAc/hexanes) (59 mg, 31%):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37–7.27 (m, 5 H), 5.42–5.37 (m, 1 H), 4.49 (s, 2H), 3.47–3.25 (m, 2H), 2.81–2.80 (m, 1H), 2.54–2.50 (m, 2H), 2.46–2.36 (m, 1H), 2.32 (d,  $J = 15.4$ , 1H), 2.21–2.14 (m, 2H), 2.04–1.93 (m, 2H), 1.80–1.69 (m, 2 H), 1.32 (s, 3 H);  $^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  213.4, 138.8, 137.9, 128.4, 127.8, 127.7, 123.4, 77.2, 72.9, 68.9, 56.1, 55.0, 35.3, 28.5, 26.7, 22.4, 20.7; HRMS (CI)  $m/z$  301.1801  $[\text{M} + \text{H}]^+$ , mass calcd for  $\text{C}_{19}\text{H}_{24}\text{O}_3 = 301.1804$ .

**Methyl 6-(Benzyloxy)-3-(2-oxocyclopentyl)-2-(trimethylsilyl)-hex-3-enoate (3):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34–7.31 (m, 5 H), 5.02 (t,  $J = 7.4$  Hz, 1 H), 4.5 (s, 2H), 3.62 (s, 3H), 3.52–3.41 (m, 2 H), 3.37 (s, 1H), 3.11 (t,  $J = 10.4$  Hz, 1H), 2.45 2.12 (m, 5 H), 2.04–1.97 (m, 1H), 1.81–1.69 (m, 2H), 0.13 (s, 9H);  $^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  217.4, 173.2, 138.4, 136.1, 128.3, 127.6, 127.5, 124.7, 72.9, 69.6, 55.4, 41.5, 39.0, 34.2, 29.3, 20.5, –1.7; HRMS (CI)  $m/z$  388.2060  $[\text{M}]^+$ , mass calcd for  $\text{C}_{22}\text{H}_{32}\text{O}_4\text{Si} = 388.2070$ .

**Methyl 6-(Benzyloxy)-3-(2-oxocyclopentyl)-hex-3-enoate (4):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35–7.30 (m, 5 H), 5.5 (t,  $J = 7.2$  Hz, 1 H), 4.51 (s, 2H), 3.63 (s, 3H), 3.51 (t,  $J = 7.0$  Hz, 2H), 3.29 (d,  $J = 15.8$  Hz, 1H), 3.11 (d,  $J = 15.7$  Hz, 1H), 2.9 (t,  $J = 9.0$  Hz, 1H), 2.45–1.73 (m, 8 H);  $^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  218.1, 171.7, 138.4, 130.4, 128.3, 127.9, 127.6, 127.5, 72.9, 69.3, 56.7, 51.8, 38.2, 35.0, 28.9, 28.8, 20.5; HRMS (CI)  $m/z$  317.1744  $[\text{M} + \text{H}]^+$ , mass calcd for  $\text{C}_{19}\text{H}_{24}\text{O}_4 = 317.1753$ .

**2-(1-(Benzyloxy)-7,7-dimethyl-6-oxooct-3-en-4-yl)-cyclopentanone (6):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.27 (m, 5 H), 5.47 (t,  $J = 7.0$  Hz, 1 H), 4.49 (s, 2H), 3.2 (d,  $J = 18.1$  Hz, 1H), 3.46 (t,  $J = 7.1$  Hz, 2H), 3.37 (d,  $J = 18.1$  Hz, 1H), 2.78 (t,  $J = 9.2$  Hz, 1H), 2.32–2.22 (m, 3H), 2.15–2.10 (m, 2H), 2.05–1.98 (m, 1H), 1.98–1.70 (m, 2H), 1.16 (s, 9H);  $^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  218.4, 213.2, 138.4, 131.5, 128.3, 127.6, 127.5, 125.9, 72.9, 69.6, 56.1, 44.5, 38.4, 37.7, 28.9, 28.7, 26.6, 20.5; HRMS (CI)  $m/z$  343.2267  $[\text{M} + \text{H}]^+$ , mass calcd for  $\text{C}_{22}\text{H}_{30}\text{O}_3 = 343.2273$ .

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**Supporting Information Available:** Copies of  $^1\text{H NMR}$  spectra for compounds **3–8**, including NOE data for **3** and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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