

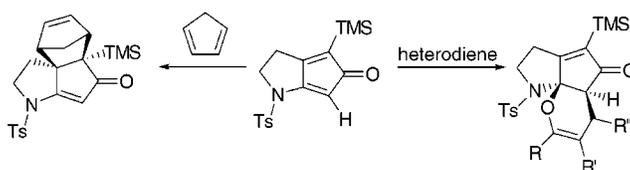
# Synthesis and Chemoselective Reactivity of 3-Aminocyclopentadienones

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## ABSTRACT



This Letter describes the synthesis and chemoselective cycloaddition chemistry of 3-aminocyclopentadienones.

Cyclopentadienones have been widely recognized as having a high degree of synthetic potential.<sup>1–3</sup> Unfortunately, their propensity to dimerize<sup>1,2</sup> has limited their use in synthesis to masked cyclopentadienones<sup>3</sup> or to those containing multiple aromatic rings.<sup>4</sup> As part of our program targeting the use of cyclopentadienones in the synthesis of complex molecules, we became interested in 3-aminocyclopentadienones<sup>5</sup> since the divergent electronic properties present in the two enone double bonds would provide us with the opportunity to carry out chemoselective manipulations. Outlined herein are our preliminary results that not only describe the synthesis of 3-aminocyclopentadienones but also their unique properties in cycloaddition chemistry.

(1) For a discussion of the properties and reactivity of cyclopentadienones, see: Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261.

(2) For a recent example of the dimerization of a non-aryl-substituted cyclopentadienone, see: West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 5043.

(3) (a) For oxime-protected cyclopentadienones, see: Mackay, D.; Papadopoulos, D.; Taylor, N. J. *J. Chem. Soc., Chem. Commun.* **1992**, 325. (b) For cyclopentadiene-protected cyclopentadienones, see: Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515 and references therein. (c) For a review discussing cyclopentadienones masked as 4-acetoxycyclopentenones, see: Harre, M. Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480.

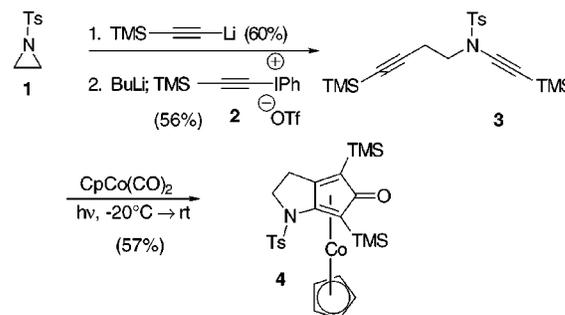
(4) See ref 1 and (a) Yamashita, Y.; Miyauchi, Y.; Masumura, M. *Chem. Lett.* **1983**, 489. (b) Yamashita, Y.; Masumura, M. *Tetrahedron Lett.* **1979**, 1765.

(5) For an example of a tetraamine-substituted cyclopentadienone, see: Lepage, T.; Nakasuji, K.; Breslow, R. *Tetrahedron Lett.* **1985**, *26*, 5919.

We envisioned 3-aminocyclopentadienones as arising from cobalt-mediated [2 + 2 + 1] cycloaddition reactions between nitrogen acetylenes (ynamines) and alkynes.<sup>6,7</sup> We were hopeful that any dimerization problems could be avoided through the judicious choice of the nitrogen protecting group as well as through trimethylsilyl substitution on the cyclopentadienone.<sup>8</sup>

We initially targeted aminocyclopentadienone complex **4** from a cobalt-induced intramolecular cycloaddition reaction (Scheme 1).<sup>9</sup> The requisite yne–ynamine cyclization precursor **3** was synthesized in two steps from tosylaziridine (**1**).

**Scheme 1** Generation of Aminocyclopentadienone Complex **4**



Namely, ring opening of **1** with trimethylsilylacetylide

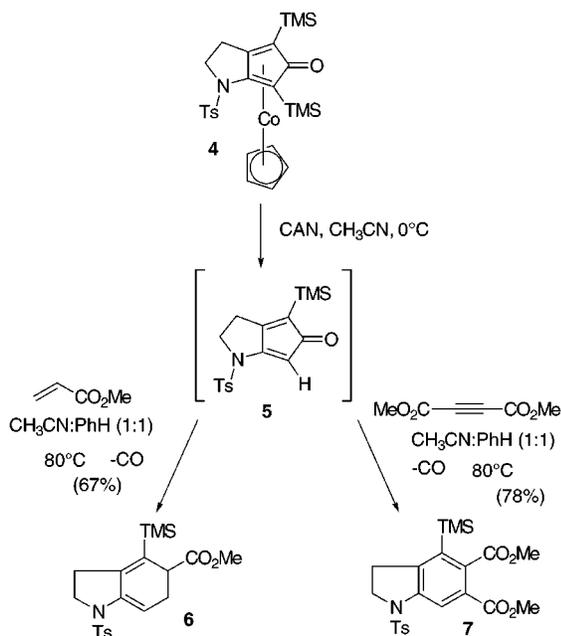
followed by ynamine formation using Stang's protocol gave yne-ynamine **3** in synthetically useful yields.<sup>7,10</sup> To our delight, when **3** was subjected to CpCo(CO)<sub>2</sub> and photolysis at low temperature we were able to isolate complexed cyclopentadienone **4** in 57% yield (Scheme 1).

With ready access to **4**, we set out to explore its reactivity. Oxidative decomplexation with ceric ammonium nitrate (CAN)<sup>9</sup> at 0 °C provided a bright yellow solution of **5** after aqueous workup. Interestingly, CAN had not only decomplexed the cobalt but it had also chemoselectively protodesilylated the vinylogous amide.<sup>11</sup>

Although **5** was reasonably stable in solution, it decomposed upon concentration.<sup>12</sup> For this reason **5** was characterized via its reactivity with dienophiles.<sup>13</sup> Exposure of a solution of **5**, CH<sub>3</sub>CN, and benzene to dimethyl acetylenedicarboxylate (DMAD) at 80 °C for 12 h resulted in the formation of indolene **7** in 78% yield (from cobalt complex **4**). Likewise, addition of methyl acrylate to **5** resulted in diene **6** in 67% yield after decarbonylation.

While pleased with our ability to use **5** as the 4π component in cycloadditions,<sup>14</sup> the experiments outlined in Scheme 2 do not demonstrate the chemoselectivity of interest

**Scheme 2.** 3-Aminocyclopentadienone **5** in Diels–Alder Reactions with Dienophiles

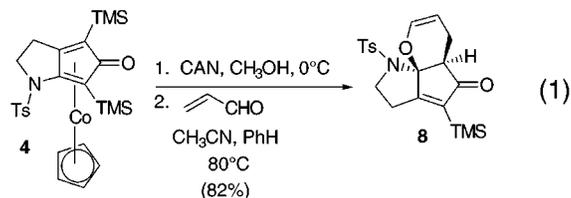


to us. With this in mind, we turned to the use of **5** in hetero-Diels–Alder cycloadditions with unsaturated aldehydes and

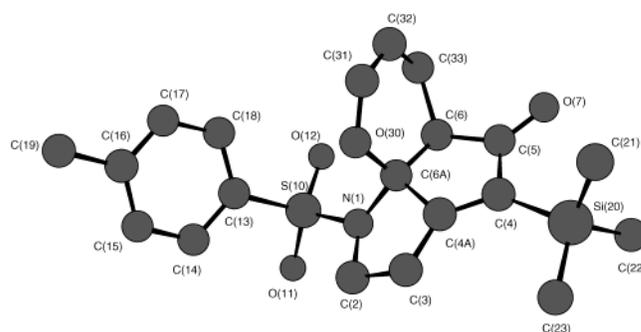
(6) For reviews discussing the chemistry of ynamines, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (b) Himbert, G. *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; p 3267.

(7) For recent ynamine cycloaddition reactions, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (c) Witulski, B.; Stengel, T. *J. Chem. Soc., Chem. Commun.* **1999**, 1879. (d) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237.

ketones.<sup>15,16</sup> We were gratified to isolate adduct **8** in 82% yield when cyclopentadienone **5** was condensed with acrolein (eq 1). This experiment represents one of the very few examples of the chemoselective functionalization of a non-aryl-substituted cyclopentadienone.<sup>1,17</sup>



The structure of **8** was determined both spectroscopically as well as through X-ray crystallography (Figure 1).



**Figure 1.** X-ray crystal structure of **8**.

The reaction appears to be general as **5** also reacted with methyl vinyl ketone, crotonaldehyde, and methacrolein to give adducts **9**, **10**, and **11**, respectively (Table 1).

**Table 1.** Hetero Diels–Alder Cycloaddition of **5**

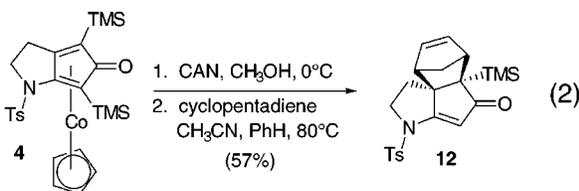
entry	heterodiene	R	R'	R''	adduct	Yield
1	methylvinyl ketone	CH <sub>3</sub>	H	H	<b>9</b>	74%
2	crotonaldehyde	H	H	CH <sub>3</sub>	<b>10</b>	36%
3	methacrolein	H	CH <sub>3</sub>	H	<b>11</b>	66%

Having successfully demonstrated the enhanced reactivity of the vinylogous amide with unsaturated aldehydes and

(8) Both 2,3,5- and 2,3,4-tris(trimethylsilyl)cyclopentadienones are reasonably stable at room temperature. See: Maier, G.; Lage, H. W.; Reisenauer, H. P. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 976.

(9) Vollhardt has synthesized the corresponding all-carbon cyclopentadienone. See: Gesing, E. R. F.; Tane, J. P.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1023.

ketones, we set out to selectively functionalize the isolated enone in the presence of the vinylogous amide. Once again we were interested in taking advantage of the divergent properties of the two alkenes in **5** and examined the reaction of **5** with cyclopentadiene.<sup>16b</sup> To our delight, enone adduct **12** was isolated in 57% yield when **5** was exposed to cyclopentadiene (eq 2).



To conclude, 3-aminocyclopentadienone **5** can be efficiently synthesized from a cobalt mediated yne-ynamine cycloaddition reaction. By varying its coupling partner, we

(10) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds; VCH: Weinheim, 1995.

(11) The position of the remaining trimethylsilyl group in **5** was initially determined spectroscopically (NOE experiments) on indolene **7**. A subsequent X-ray structure of **8** confirmed this assignment.

(12) Cyclopentadienone **5** was stable at 80 °C for up to 24 h in a 1:1 acetonitrile-benzene solution but decomposed to unrecognizable products upon concentration.

(13) For the use of cyclopentadienones as dienes in Diels-Alder cycloadditions, see ref 1 and Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1984**, 1049.

(14) A similar vinylogous ester was unreactive in analogous cycloaddition reactions. See: Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, 38, 59.

have demonstrated that **5** can serve as both the  $4\pi$  and  $2\pi$  component in cycloaddition reactions. We are currently focused on the optimization of the reactions that have been discovered, the use of other 3-aminocyclopentadienones in cycloaddition chemistry, and the use of the substrates from these reactions in the synthesis of interesting targets.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds **4** and **6–12**. This material is free of charge via the Internet at <http://pubs.acs.org>.

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(15) For an example of the use of an enamine in a hetero-Diels-Alder cycloaddition reaction, see: Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, 78, 5129.

(16) For the use of cyclopentadienones as  $2\pi$  components in cycloaddition chemistry, see ref 1 and (a) Gavina, F.; Costero, A. M.; Gil, P.; Palazon, B.; Luis, S. V. *J. Am. Chem. Soc.* **1981**, 103, 1797. (b) Depuy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. *J. Org. Chem.* **1964**, 29, 3503.

(17) Herndon has been able to carry out the in situ protonation of the corresponding reduced vinylogous esters, see: Herndon, J. W.; Zhu, J. *Org. Lett.* **1999**, 1, 15 and references contained therein.