The Synthesis and Chemoselective Reactivity of 3-Aminocyclopentadienones

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Iron and cobalt complexes of 3-aminocyclopentadienones have been synthesized from the [2 + 2 + 1] cycloadditions of nitrogen acetylenes and pendant alkynes. Following decomplexation, the resulting 3-aminocyclopentadienones have been subjected to chemo- and regioselective cycloadditions with dienophiles and heterodienes.

Introduction

Although cyclopentadienones are widely recognized as having a high degree of synthetic potential, their relative instability has limited their use in organic synthesis.[1] Because of this, a significant amount of effort has targeted the synthesis and use of masked cyclopentadienones. A few of these are illustrated in Figure 1 and include the following: (a) cyclopentadienone-cyclopentadiene Diels–Alder adducts (e.g., **1**);[2] (b) 4-alkoxycyclopentenones (e.g., **2**);[3] (c) oxime adducts (e.g., **3**);[4] (d) cyclopentadienone–transition metal complexes (e.g., **4**).[5]

While the masking strategies depicted in Figure 1 are cleverly designed and clearly of utility, from our perspective a better synthetic strategy would be one that used cyclopentadienones directly. With this as one of our goals, we have recently targeted and communicated the generation and use of 3-aminocyclopentadienones (e.g., **5**, Figure 2).[6,7] This came out of the notion that the divergent electronic properties of the two enones (one being a vinylogous amide) might enable us to use them in chemo- and regioselective reactions and ultimately in the synthesis of interesting alkaloids. As we are aware of very few examples of the use of cyclopentadienones in complex molecule synthesis,[8,9] the success of these ventures would demonstrate that strategies incorporating cyclopentadienones are of merit.

Clearly, the aforementioned goals required that (a) we have an efficient entry into 3-aminocyclopentadienones (e.g., **5**) and (b) that **5** be stable enough to isolate or to trap. With respect to the latter requirement, it has been
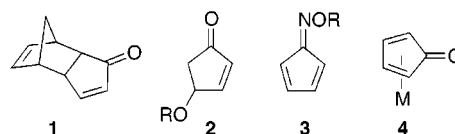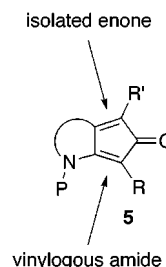

Figure 1.

Figure 2.

well documented that substitution about the cyclopentadienone leads to its stabilization.[1] As our ultimate interests included the use of **5** in the synthesis of interesting alkaloids, we placed the additional constraint on **5** that R, R′, and P be of general synthetical utility.

With regard to their synthesis, we became fascinated with the generation of 3-aminocyclopentadienones from cobalt- and iron-mediated [2 + 2 + 1] cycloaddition reactions of nitrogen acetylenes (ynamines) and pendant alkynes. While ynamines had not been utilized in this context prior to our work,[10,11] they had been used by Witulski in cobalt-mediated Pauson–Khand reactions[12] and in independent studies by Ficini[13] and Witulski[14] in Ni- and Rh-mediated cycloaromatization reactions, respectively. In addition to efficiency of synthesis, we were

(1) Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965,** *65,* 261.

(2) Dols, P. P. M. A.; Lacroix, L.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1991,** *32,* 3739.

(3) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 480.

(4) Mackay, D.; Papadopoulos, D.; Taylor, N. J. *J. Chem. Soc., Chem. Commun.* **1992,** 325.

(5) For a review of metal cyclopentadienone complexes, see: Knölker, H.-J. *Chem. Soc. Rev.* **1999,** *28,* 151.

(6) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999,** *1,* 2037.

(7) We are aware of one other aminocyclopentadienone. See: LePage, T.; Nakasuji, K.; Breslow, R. *Tetrahedron Lett.* **1985,** *48,* 5919.

(8) Knölker has utilized a cyclopentadienone in the synthesis of corranulene. See: Knölker, H.-J.; Braier, A.; Bröcher, D. J.; Jones, P. G.; Piotrowski, H. *Tetrahedron Lett.* **1999,** *40,* 8075.

(9) Herndon has utilized reduced cyclopentadienones in synthesis, see: Herndon, J. W.; Zhu, J. *Org. Lett.* **1999,** *1,* 15 and references contained therein.
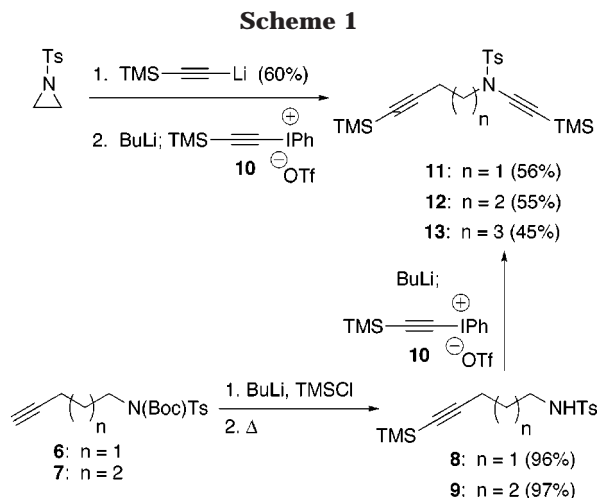
(10) For reviews on the chemistry of nitrogen acetylenes, see: (a) Ficini, J. *Tetrahedron* **1976,** *32,* 1448. (b) Himbert, G. *Methoden der Organischen Chie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; p 3267.

(11) For recent examples of the use of nitrogen acetylenes in cycloaddition chemistry, see refs 12, 14, and: Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999,** *1,* 1237.

(12) (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1998,** *37,* 489. (b) Witulski, B.; Gößmann, M. *J. Chem. Soc., Chem. Commun.* **1999,** 1879.

(13) Ficini, J.; d'Angelo, J.; Falou, S. *Tetrahedron Lett.* **1977,** 1645.

(14) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1999,** *38,* 2426.

Scheme 1

Table 1.

entry	product	M	R	yield (%)
1	**14**	CoCp[a]	TMS	57
2	**15**	Fe(CO)₃[b]	TMS	84

[a] CpCo(CO₂), $h\nu$, $-20\,°C \rightarrow$ rt. [b] Fe(CO)₅, PhCH₃, 110 °C.

Scheme 2

attracted to the use of metal-mediated [2 + 2 + 1] cycloadditions because the cyclopentadienones would be generated as isolable metal complexes that might be interesting in their own right.[15,16]

Outlined herein is a full report of our investigations demonstrating that cobalt and iron complexes of [3.3.0]-, [4.3.0]-, and [5.3.0]aminocyclopentadienones can be synthesized from yne−ynamine cycloaddition reactions.[6] Also described is the decomplexation of the cyclopentadienones and their capture with dienophiles as well as dienes in chemo- and regioselective cycloaddition reactions.
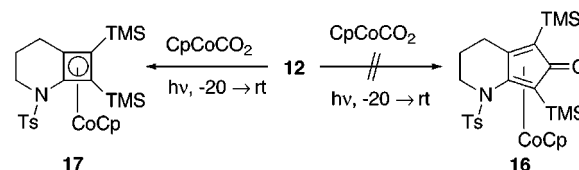
Results and Discussion

Yne−Ynamine Synthesis. We have synthesized yne−ynamine cycloaddition precursors having 2-, 3-, and 4-carbon tethers between the alkyne and ynamine as depicted in Scheme 1. Yne−ynamine cyclization precursor **11** was synthesized in two steps from *N*-tosylaziridine. Namely, ring opening of *N*-tosylaziridine with lithium trimethylsilylacetylide followed by ynamine formation using Stang's iodoacetylene salt **10** provided yne−ynamine **11** in synthetically useful yields.[17] The homologous yne−ynamines **12** and **13** were synthesized from the corresponding alkynols. Mitsunobu coupling of (BOC)-NH(Ts) with 4-pentyn-1-ol and 5-hexyn-1-ol provided

amino alkynes **6** and **7**, respectively. Conversion of **6** and **7** into the corresponding ynamine precursors **8** and **9** involved TMS-alkyne formation and selective thermal removal of the Boc group.[18] Ynamine formation provided **12** and **13**, respectively.

Yne−Ynamine Cycloadditions to Cyclopentadienone Complexes. With access to yne−ynamine cycloaddition precursors, we investigated their conversion into the corresponding cobalt and iron cyclopentadienone complexes via [2 + 2 + 1] cycloaddition reactions. To our delight, when **11** was subjected to Vollhardt's conditions for the corresponding all-carbon cycloaddition (CpCo(CO)₂ and photolysis at low temperature)[15b] we isolated cobalt cyclopentadienone complex **14**[6] as a dark red solid in 57% yield (Table 1). Yne−ynamine **11** also proved amenable to iron-mediated cycloaddition. Yellow cyclopentadienone complex **15** was generated in 84% yield upon exposure of **11** to Fe(CO)₅ and elevated temperatures (Table 1).

Having generated iron and cobalt [3.3.0] complexes **14** and **15**, we targeted the corresponding [4.3.0]- and [5.3.0]-cyclopentadienone complexes. Thus far, all of our attempts to generate [4.3.0]cobalt complex **16** from **12** using the conditions that were successful for the synthesis of **14** have resulted in the formation of cyclobutadiene complex **17** (Scheme 2).

In contrast, the corresponding iron-mediated [2 + 2 + 1] cycloadditions provided iron [4.3.0]- and [5.3.0]cyclopentadienone complexes in respectable yields (Table 2). When yne−ynamine **12** was subjected to Fe(CO)₅ and heat, we isolated mono- and bis-TMS cobalt [4.3.0] complexes in a 2.2:1 ratio in 96% overall yield.[19] Similarly, the 3-amino[5.3.0]cyclopentadienone iron complex **20** was obtained in 54% yield from the cycloaddition of yne−ynamine **13**.

These cycloadditions compare favorably with the corresponding all-carbon variants. In independent studies, both Pearson and Knölker have generated the all-carbon [4.3.0]- and [5.3.0]cyclopentadienone−iron complexes but in 57% and 50−59% yield (Pearson)[20] and 82% and 15%

(15) Co-cyclopentadienone complexes: (a) McDonnell Bushnell, L. P.; Evitt, E. R.; Bergman, R. G. *J. Organometallic Chem.* **1978** *157*, 445. (b) Gesing, E. R. F.; Tane, J. P.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1023. (c) For a Co-mediated [2 + 2 + 1] cycloaddition of bis-alkynes where decomplexation occurs in situ, see: Shibata, T.; Ohta, T.; Soai, K. *Tetrahedron Lett.* **1998**, *39*, 5785. (c) Fe-cyclopentadienone complexes: (b) Pearson, A. J.; Dubbert, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 371. (c) Knölker, H.-J.; Heber, J.; Mahler, C. H. *Synlett.* **1992**, 1002. (b) Pearson, A. J.; Shively, R. J., Jr.; Dubbert, R. A. *Organometallics* **1992**, *11*, 4096. (c) Pearson, A. J.; Shively, R. J., Jr. *Organometallics* **1994**, *13*, 578. (d) Brookhart, M.; Chandler, W. A.; Pfister, A. C.; Santini, C. C.; White, P. S. *Organometallics* **1992**, *11*, 1263. Ru-cyclopentadienone complexes: (d) Mauthner, K.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1994**, *13*, 5054. (e) Mo- and W-cyclopentadienone complexes: Slugovc, C.; Mauthner, K. Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 2954. Ox-cyclopentadienone complexes: Washington, J.; McDonald, R.; Takats, J.; Menashe, N.; Reshef, D.; Shvo, Y. *Organometallics* **1995**, *14*, 3996. Ni-cyclopentadienone complexes: (e) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539.

(16) Metal cyclopentadienone complexes have been shown to be amenable to reactions on the cyclopentadienone. (a) Tane, J. P.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 617. (b) Pearson, A. J.; Shively, R. J., Jr.; Dubbert, R. A. *Organometallics* **1992**, *11*, 4096.

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

(18) (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (b) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096.

(19) It is not clear at the present time whether mono-TMS adduct **19** results from an acid mediated desilylation reaction of **18** or one of the intermediates leading to **18**.

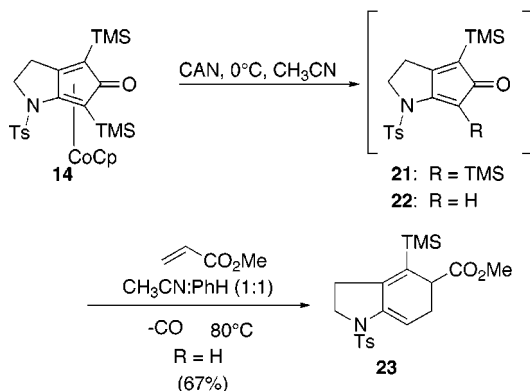(20) Pearson, A. J.; Yao, X. *Synlett* **1997**, 1281.

Table 2.

entry	product	n	R	yield (%)
1	**18**	2	TMS	96[a]
	19	2	H	
2	**20**	3	TMS	54

[a] Ca. 2.1:1 ratio of **18**:**19** was isolated from the cycloaddition of **12**.

Scheme 3

yield (Knölker), respectively.[21]

Decomplexation and Cycloadditions of 3-Aminocyclopentadienones. With relatively efficient syntheses of metal cyclopentadienone complexes in hand, we were prepared to test our hypothesis that 3-aminocyclopentadienones might be valuable intermediates in complex molecule synthesis. We initially targeted cycloaddition reactions of metal-free 3-aminocyclopentadienones because of the possibility that the divergent electronic properties of the two enone alkenes would enable us to carry these out chemo- and regioselectively.

Before examining the properties of 3-aminocyclopentadienones, it was necessary to find conditions to effect the decomplexation of **14**, **15**, **18**, and **20**. Upon exposure of cobalt complex **14** to ceric ammonium nitrate (CAN) at 0 °C for 1 h, we were able to generate a bright yellow solution of cyclopentadienone **22** (Scheme 3).[6] We subsequently discovered that CAN had not only decomplexed the cobalt but that it had also chemoselectively protodesilylated the vinylogous amide. While we have been able to access mixtures of mono-TMS cyclopentadienone **22** and bis-TMS cyclopentadienone **21** by subjecting **14** to CAN for shorter periods of times, we have not been able to selectively generate bis-TMS cyclopentadienone **21** from the CAN oxidative decomplexation of **14**. In subsequent studies, we were able to isolate **21** from the decomplexation of iron cyclopentadienone **15** (vide infra).

Due to our lack of success in our early attempts to isolate **22** and its presumed instability to concentration, we chose to immediately subject **22** to cycloaddition reactions with dienophiles (Scheme 3 and Table 3) or heterodienes (eq 2). Aqueous workup and dilution of the yellow solution from decomplexation with an equal volume of benzene followed by exposure to methyl acry-
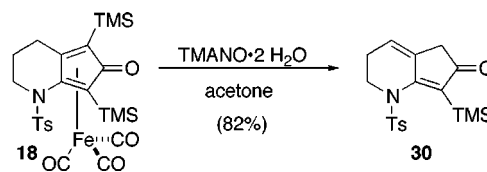
(21) Knölker, H.-J.; Heber, J. *Synlett* **1993**, 924.

late resulted in the formation of dihydroindolene **23** as a single regioisomer in 67% yield from **14** (Scheme 3).[22] As it is widely accepted that C-5 substitution greatly stabilizes cyclopentadienones,[23] the efficient entry into **23** is made all the more remarkable by the lack of vinylogous amide substitution in **22**.

Similarly, when a solution of cyclopentadienone **22** was exposed to DMAD and heat indolene **24** was isolated in 78% yield from complex **14** (Table 3).[24] Presumably, decarbonylation was occurring in the course of the synthesis of both **23** and **24** as we have not been able to isolate the adduct prior to loss of CO.

Having successfully carried out the decomplexation of cobalt complex **14** and subsequent cycloaddition of the corresponding cyclopentadienone we then took aim at iron cyclopentadienones **15**, **18**, and **20**. As has been the experience of others,[25] we have found the decomplexation of the iron complexes to be somewhat more problematic in comparison to cobalt complex **14** and have investigated a number of decomplexation protocols. Thus far, we have examined the oxidative decomplexation using trimethylamine *N*-oxide (TMANO) and morpholine *N*-oxide (NMO) along with the base-induced decomplexation using NaOH. In reactions that nicely complement the decomplexation of **14**, the decomplexation of bis-TMS cyclopentadienone complex **15** with TMANO, NMO, or NaOH provided a solution of bis-TMS cyclopentadienone **21**. As was the case in the cobalt decomplexation reaction, we did not isolate **21** but instead immediately subjected it to cycloaddition reactions with DMAD (Table 3) or unsaturated carbonyl compounds (Table 4). In a fashion similar to **22**, the cycloaddition of **21** with DMAD resulted in the formation of indolene **25** in moderate yield. Higher yields were obtained when [3.3.0]- and [4.3.0]cyclopentadienones **18** and **20** were carried through the decomplexation and cyclization sequence with DMAD. Cycloaddition of [3.3.0]cyclopentadienone **26** gave a 54% overall yield of cycloadduct **27** while [4.3.0]cyclopentadienone **28** gave a 70% overall yield of adduct **29**.

We believe that the facility with which the highly substituted aromatic heterocycles **24**, **25**, **27**, and **29** have been generated will be of significance for the synthesis of these ring systems. Of interest is the observation that the methylene protons in the ^{1}H NMR spectra of **25**, **27**, and **29** are magnetically inequivalent, implying a high inversion barrier at the nitrogen atom when the ortho position of the aryl ring is substituted with TMS.[26]

Interestingly, the decomplexation of **18** using TMANO in acetone instead of CH₂Cl₂ provided dienone **30** as the only product in 82% yield (eq 1). Knölker and Pearson have observed a similar phenomenon in the decomplexation of the all carbon variant of **18**.[27]
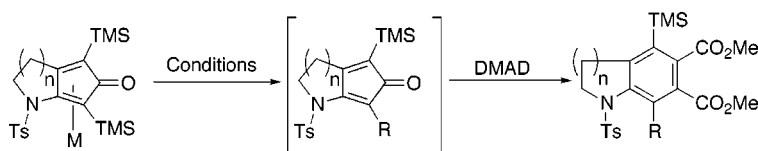

Having utilized 3-aminocyclopentadienones as the 4π component in cycloadditions, we turned to their use as

(22) For the use of cyclopentadienones as dienes in cycloaddition reactions see ref 1 and: (a) Knölker, H.-J.; Baum, E.; Heber, J. *Tetrahedron Lett.* **1994**, *35*, 578. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1984**, 1049.
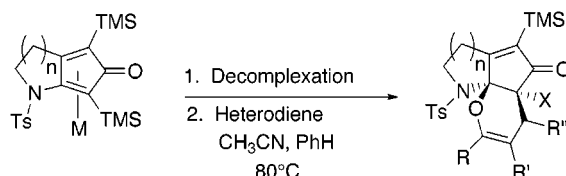
Table 3.

entry	M	conditions[a]	n	cyclopenta-dienone	R	product	yield (%)
1	CoCp	A	1	22	H	24	78
	Fe(CO)$_3$	B	1	21	TMS	25	36
2	Fe(CO)$_3$	D	1	21	TMS	25	28
4	Fe(CO)$_3$	B	2	26	TMS	27	57
5	Fe(CO)$_3$	C	2	26	TMS	27	48
6	Fe(CO)$_3$	C	3	28	TMS	29	70
7	Fe(CO)$_3$	D	3	28	TMS	29	36

[a] Key: A, CAN, B, TMANO; C, NMO; D, NaOH.

Table 4.

entry	heterodiene	M	n	X	R	R′	R″	adduct	yield[d] (%)
1	acrolein	Fe(CO)$_3$[a]	1	TMS	H	H	H	**32**	54[e]
2	acrolein	Fe(CO)$_3$[b]	1	**21**	TMS	H	H	**32**	44[e]
3	acrolein	Fe(CO)$_3$[b]	2	**21**	TMS	H	H	**33**	66
4	methylvinyl ketone	CoCp[c]	1	H	CH$_3$	H	H	**34**	74
5	crotonaldehyde	CoCp[c]	1	H	H	H	CH$_3$	**35**	36
6	methacrolein	CoCp[c]	1	H	H	CH$_3$	H	**36**	66

[a] Decomplexed with NMO. [b] Decomplexed with TMANO. [c] Decomplexed with CAN. [d] Yield over two steps. [e] 4:1 mixture with the corresponding enone adduct.

dienophiles in hetero-Diels–Alder cycloadditions with unsaturated aldehydes and ketones.[28,29] We were thrilled to isolate adduct **31** in 82% yield from cobalt complex **14** when cyclopentadienone **22** was condensed with acrolein (eq 2). This experiment truly demonstrates the utility of 3-aminocyclopentadienones as we have utilized them chemo- and regioselectively as both dienes and dienophiles.
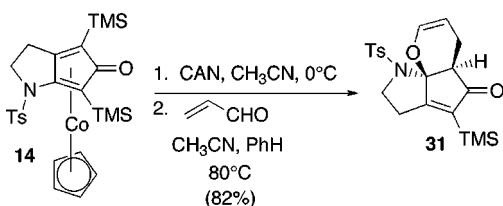
Both bis-TMS-substituted cyclopentadienones **21** and **26** also acted as 2π components in their reaction with

acrolein. In a fashion similar to **22**, cyclopentadienone **26** reacted exclusively at the vinylogous amide to give **33** in 66% yield for the two steps (Table 4, entry 3). The reaction of cyclopentadienone **21** was not as selective. While its reaction with acrolein resulted in the formation of vinylogous amide adduct **32** as the major product, it also gave a small amount of a byproduct whose structure we have tentatively assigned to the corresponding iso-lated enone adduct (Table 4, entries 1 and 2).[30] While the enhanced selectivity of **22** relative to **21** can be rationalized as being due to the presence of the vinylo-gous amide TMS group in **21**, at the present time it is not clear why **26** is more selective than **21**. The reaction of **22** with heterodienes at the vinylogous amide appears to be general. Aminocyclopentadienone **22** reacts with methyl vinyl ketone (entry 4), crotonaldehyde (entry 5), and methacrolein (entry 6) to give adducts **34**, **35**, and **36**, respectively in reasonable yields for the two-step process.

Surprisingly, 3-amino[5.3.0]cyclopentadienone **28** un-derwent cycloaddition with acrolein at the isolated enone instead of at the vinylogous amide to give **37** in 52% yield (eq 3).[31]

(23) See ref 1 and Maier, G.; Lage, H. W.; Reisenauer, H. P. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 976.

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

(25) (a) Knölker, H.-J.; Goesmann, H.; Klauss, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 702. (b) Knölker, H.-J.; Baum, I.; Goesmann, G.; Klauss, R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2064.

(26) The methylene signals did not coalesce at 80 °C.

(27) See ref 21 and: Pearson, A. J. Perosa, A. *Organometallics* **1995**, *14*, 5178.

(28) 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*, 5128.

(29) For the use of cyclopentadienones as 2π components in cycload-dition 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.

(30) Thus far, we have been unable to separate vinylogous amide adduct **32** from the corresponding enone adduct without selectively destroying the enone adduct. The structure of the enone adduct was assigned based upon the similarity of its ^{1}H and ^{13}C NMR spectra to **37**.
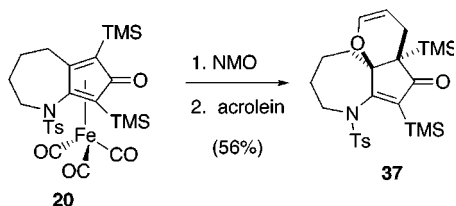
In addition to the heterodiene investigations described above, we have examined the cycloaddition of cyclopentadienone **21** with cyclopentadiene. To our delight, endo-adduct **38** was isolated in 57% yield when **21** was exposed to cyclopentadiene (eq 4). In contrast to our heterodiene results with **21**, cyclopentadiene had reacted exclusively at the isolated enone of **21**.
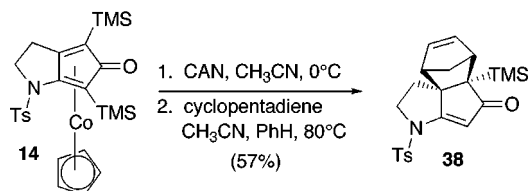
Conclusions

To conclude, we have demonstrated that 3-aminocyclopentadienones can be efficiently synthesized from

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(31) We also isolated an additional 30% of unrecognizable material from this reaction. The reason for the disparate reactivity of **28** with acrolein is not apparent to us at the present time.

metal mediated yne-ynamine [2 + 2 + 1] cycloaddition reactions. In addition, we have shown that metal free 3-aminocyclopentadienones can serve as both the 4π and 2π component in chemoselective cycloaddition reactions. We are currently focused on the optimization of the reactions that have been discovered, the use of iron and cobalt complexed cyclopentadienones in addition reactions, and the use of the substrates from these reactions in the synthesis of interesting targets.

Supporting Information Available: Experimental procedures and characterization data, along with ^{1}H and ^{13}C NMR spectra for compounds **6**−**9**, **12**, **13**, **15**, **17**, **18**, **20**, **25**, **27**, **29**, **30**, **32**, **33**, and **37**. ORTEP figures, atomic coordinates, thermal parameters, bond lengths, and bond angles for **14**, **37**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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