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Formation of Aminocyclopentadienes from Silyldihydropyridines: Ring Contractions Driven by Anion Stabilization

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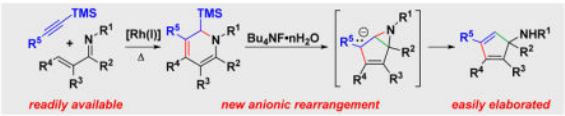
Abstract

Highly functionalized aminocyclopentadienes are formed by rearrangement of anions generated from readily prepared 6-silyl-1,2-dihydropyridines by desilylation with fluoride. The scope and generality of the reaction are defined, and diverse transformations are performed on the highly functionalized products. A mechanism and driving force for rearrangement is identified from experiment and DFT calculations.

A new contract(ion)

Densely functionalized aminocyclopentadienes are efficiently accessed by anionic rearrangement of 6-silyl-1,2-dihydropyridines. DFT calculations have been performed to elucidate the mechanism of this transformation.



Keywords

rearrangement; amines; ring contraction; density functional calculations; reaction mechanisms

We previously reported the Rh(I)-catalyzed C–H bond addition/electrocyclization cascade reaction of readily available α,β-unsaturated imines **1** with trimethylsilyl alkynes, providing efficient access to diverse 6-trimethylsilyl-substituted 1,2-dihydropyridines (DHPs) **3** (Scheme 1).[1] Subsequent protonation/desilylation of the silyl-substituted DHPs **3** generated unstabilized ylides **4** that were converted to pharmaceutically relevant tetrahydropyridines **5** and tropanes **6**.

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Supporting information for this article is given via a link at the end of the document

Upon investigation of the desilylation of DHPs **3** under basic conditions using tetrabutylammonium fluoride hydrate, we were surprised to obtain aminocyclopentadienes **8**. This transformation provides rapid entry to densely substituted derivatives that would be difficult to access by other methods.[2] Notably, aminocyclopentanes are present in many natural products[3] and pharmaceuticals such as the recently approved drugs Ticagrelor[4] and Peramivir.[5] We now report on the scope and limitations of this new transformation and demonstrate that products **8** are versatile intermediates for further elaboration. We have determined a mechanism for this transformation from experiment and computation.

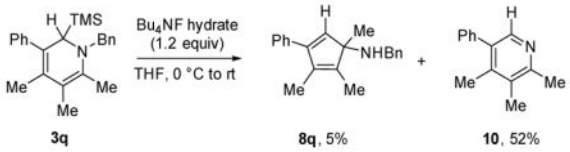
A variety of conditions were explored for mediating desilylative rearrangement of silyl DHP **3** (see Table S1). Bu_4NF hydrate proved to be the optimal reagent for effecting this transformation, but the presence of water was also necessary. The optimized conditions were next applied to a number of silyl-substituted DHPs **3** (Table 1). We first evaluated DHPs with an ester group at the R^5 position to provide aminocyclopentadienes **8a–8e**. DHPs **3a** with R^1, R^2 and R^3 = Me and **3b** with R^1 and R^2 = Me and R^3 = H provided products **8a** and **8b**, respectively, in high yields. The bicyclic product **8c** was similarly obtained in a high yield. Moreover, the aminocyclopentadiene product **8d** demonstrates efficient access to densely substituted products with differential substitution at all five of the R^1 to R^5 sites. Replacement of the methyl ester (**8a**) with the more sterically encumbered *tert*-butyl ester (**8e**) resulted in minimal reduction in yield.

Different R1-nitrogen substituents could be incorporated successfully into the aminocyclopentadiene product, including benzyl (**8f**), alkyl (**8g** and **8h**), and even aryl (**8i**) *N*-substituents. The structure of the rearrangement product was rigorously confirmed to be the aminocyclopentadiene motif by X-ray structural analysis of the amine salt of **8i**.[6] As demonstrated with aminocyclopentadienes **8f** to **8l**, an aryl group could be incorporated at the R^5 position instead of the ester group, including trifluoromethylphenyl (**8f–8i**), phenyl (**8j**), 2-fluorophenyl (**8k**), and 3-chlorophenyl (**8l**) groups.

To enhance synthetic utility, the reaction sequence from imine **1** was carried out without isolation of DHPs **3** (Table 2). Previously prepared aminocyclopentadienes **8a** and **8f** were obtained in 52% and 67% overall yields from **1a**, respectively. The additional aminocyclopentadienes, **8m** displaying different alkyl substituents from R^2 to R^4 and bicyclic **8n**, further establish that these densely functionalized products can be rapidly prepared from readily available TMS alkynes and imines.

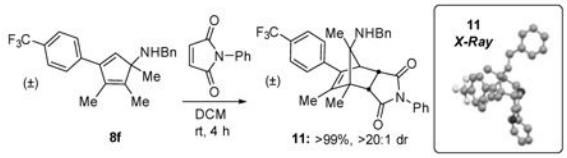
While not all substitution patterns for DHPs **3** underwent clean rearrangement to aminocyclopentadienes **8**, the side products obtained for these derivatives provided very useful information for ascertaining a mechanism for this new transformation (*vide infra*). For DHP **3o** with an R^5 methyl group, no reaction occurred under the standard conditions, and upon heating to 50 °C, while the rearrangement product **8o** was not observed, 1,4-dihydropyridine **9o** was obtained in moderate yield (Scheme 2).[7] In contrast, DHP **3p** with the electron-rich 4-methoxyphenyl group at the R^5 position, gave a mixture of rearrangement product **8p** and 1,4-dihydropyridine **9p** (entry 2).

The *N*-benzyl DHP **3q** with an R^5 phenyl group also resulted in an unexpected outcome. The aminocyclopentadiene **8q** was produced in very low yield with the pyridine byproduct **10** obtained in 52% isolated yield instead (eq 1). Extrusion of the tolyl anion from the *N*-benzyl substituent likely occurred due to the considerable resonance stabilization achieved by aromatization after generating the anion upon silyl cleavage. In support of this hypothesis, pyridine **10** was not detected for the reaction of DHP **3j**, which possesses an *N*-cyclohexyl instead of an *N*-benzyl group (see **8j**, Table 1). Extrusion of the more basic cyclohexyl anion would be less favorable in this case.



(1)

Synthetic transformations were performed upon the aminocyclopentadiene products **8** to demonstrate their utility as intermediates for further elaboration. Diels-Alder reaction of aminocyclopentadiene **8f** with *N*-phenyl maleimide provided the norbornene adduct **11** as a single isomer with the facial and endo selectivity rigorously determined by X-ray crystallography (eq 2).[8,2b]



(2)

More extensive elaboration of the fused bicyclic aminocyclopentadiene **8c** was also carried out (Scheme 3). Diels-Alder cycloaddition with *N*-phenyl maleimide and methyl acrylate gave the polycyclic adducts **12** and **13**, respectively, in good yields and with very high regio- and diastereoselectivity. Dihydroxylation with catalytic osmium under acidic conditions occurred exclusively at only one of the two double bonds and proceeded with moderate diastereoselectivity to provide **14**.[9] Selective reduction of the ester to the corresponding alcohol **15** was accomplished in high yield with DIBAL. Finally, straightforward acetylation of the secondary amine gave amide **16**.

The most closely related transformation is that reported by Fusi and Adamo for ring contraction of highly electron-deficient *N*-trifluoroacetyl-3,5-dicyano-1,4-dihydropyridines (Scheme 4).[10,11]

We investigated the mechanism of the ring-contraction of **3** to aminocyclopentadiene **8** with DFT calculations. The mechanism in Pathway A (Scheme 5), analogous to that proposed by Fusi and Adamo, is consistent with the experimental observation that an electron-withdrawing R^5 substituent is necessary to obtain **8** in a good yield. After desilylation of dihydropyridine **3** to yield anion **17**, 6π disrotatory electrocylization occurs via **TS1** to afford aziridine intermediate **18**, with its formal negative charge stabilized by the electron-withdrawing R^5 substituent. Aziridine intermediate **18** opens regioselectively in the presence of a proton source to furnish **8**. An alternative mechanism, Pathway B, where the C6–N1 bond cleaves heterolytically to yield a carbene intermediate **19** that undergoes 6π-electrocyclization to provide **8** was also considered. We calculated the energy profiles for each pathway with the results shown in Table 3. DFT computations were performed with B3LYP geometry optimizations and M06-2X energy evaluations[12] in implicit CPCM solvent.[13] Computational details and discussion on the possible TMS elimination pathways to give **18** are given in the Supporting Information.[14]

The relative energies of the two pathways A and B were determined with a trifluoromethylphenyl group at the R^5 position and with the *N*-R^1 substituent modeled with a methyl group to simplify the calculations (Table 3). The $\Delta G^{\ddagger}$ of the aziridine-forming transition state **TS1a** was calculated to be 5.9 kcal/mol, indicating the feasibility of Pathway A. In contrast, the $\Delta G^{\ddagger}$ of the carbene-forming transition state **TS2a** was calculated to be 48.2 kcal/mol, clearly excluding Pathway B from consideration.

For electron-withdrawing substituents at the R^5 position the ring-contracting step along Pathway A was calculated to have free energies of activation **TS1a–c** ranging from 1.2 kcal/mol ($R^5 = CO_2Me$) to 7.9 kcal/mol (R^5 = Ph), with the length of the forming C2–C6 bond ranging from 1.92 Å (R^5 = Ph) to 2.01 Å ($R^5 = CO_2Me$). With a methyl group as the R^5 substituent, the free energy of activation **TS1d** is much higher at 15.3 kcal/mol,[15] and the forming C2–C6 bond length of 1.79 Å indicates a considerably later transition state. The formation of **18** was found to be exergonic for all electron-withdrawing R^5 substituents, with ΔG for **17a–c** to **18a–c** ranging from −14.7 kcal/mol for $R^5 = CO_2Me$ to −2.8 kcal/mol for R^5 = Ph. In contrast, for **17d** with R^5 = Me, the formation of **18d** is endergonic with a ΔG of +11.3 kcal/mol. These results indicate that both **TS1** and **18** are strongly stabilized by an electron-withdrawing R^5 substituent. For **17a** with $R^5 = 4\text{-}CF_3\text{-Ph}$, the free energy of activation is 2.0 kcal/mol lower and the reaction is >5 kcal/mol more exergonic than for R^5 = Ph, showing that for R^5 groups with similar steric profiles, stronger electron-withdrawing ability provides better stabilization.

The calculated energies are consistent with the experimental results. In particular, when **3o** with R^5 = Me was submitted to the reaction conditions, the aminocyclopentadiene product **8o** was not observed and DHP **9o** was instead obtained (Scheme 2). This result is in agreement with high endergonicity of **17d** to **18d**, with direct protonation of **17d** occurring to give **9o** rather than rearrangement.

The energy profiles of the two regiodivergent pathways, C and D, of opening up **18a** are shown in Figure 1, with Pathway C leading to the experimentally observed aminocyclopentadiene isomer **8a**. Spontaneous opening of the aziridine ring in **18a** would

result in a highly basic amide anion, which is calculated to be unstable. This result indicates that a proton source is required for the ring-opening, consistent with the observation that anhydrous fluoride sources result in greatly diminished yields (Table S1). Computed geometries of **TS4** involve mainly C–N bond breaking with very little proton transfer. At the level of theory used for geometry optimizations, hydrogen-bonded amide intermediates **20** were located, but these local minima disappear at the higher level of theory used for the energetics (Figure 1), suggesting that the C–N breaking and proton transfer are likely energetically concerted but highly asynchronous. While the energetics are not expected to be accurate, these results do provide information on how hydrogen bonding and proton transfer influence the reaction barrier. At both levels of theory, the calculations show the C–N breaking to be rate-determining, with **TS4a** being lower than **TS4b** by 2.2 kcal/mol. This result is in excellent agreement with the experimentally observed product, isomer **8a**.

We sought to provide direct experimental support for the aziridine intermediate **18** based upon the observation that silyl DHP **3p** provided a mixture of **8p** and **9p** albeit in low yield (Scheme 2). We hypothesized that deprotonation of the secondary amine in **8p** might result in the aziridine intermediate, which upon protonation could provide a mixture of **8p** and **9p**. One caveat is that rearrangement of **3** requires that Bu_4NF be employed as the hydrate while deprotonation of **8p** requires a strong base under anhydrous conditions. Perhaps for this reason, we did not detect the formation of 1,4-DHP **9p** upon deprotonation under a variety of conditions. However, deprotonation with BuLi and 12-crown-4[16] at −40 °C followed by protonation with acetic acid gave the aminocyclopentadiene isomer **21p** along with **8p**, providing significant support for aziridine intermediate **18p** (Scheme 6).

In conclusion, we have discovered a new type of ring-contraction of 6-azacyclohexadienyl anions to obtain densely functionalized aminocyclopentadienes **8** from readily accessible silyl DHPs **3**. The scope and limitations of the reaction were defined with many different types of products **8** obtained in good to excellent yields. The mechanism of this transformation was elucidated by DFT computations. A variety of regio- and stereoselective transformations of aminocyclopentadienes demonstrate the versatility of these products as synthetic intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH Grant R35GM122473 (to J.A.E.) and NSF Grant CHE-1059084 (to K.N.H.). We gratefully acknowledge Eric Paulson (Yale) for NMR assignment of **21p** and Dr. James Phelan (Yale) for helpful discussions. Density functional theory (DFT) calculations were performed on the Hoffman2 cluster at the University of California, Los Angeles, and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the National Science Foundation (Grant OCI-1053575).

References

1. a) Chen S, Bacauanu V, Knecht T, Mercado BQ, Bergman RG, Ellman JA. J Am Chem Soc. 2016; 138:12664. [PubMed: 27642766] b) Ischay MA, Takase MK, Bergman RG, Ellman JA. J Am Chem Soc. 2013; 135:2478. [PubMed: 23398467]

2. For alternative methods to prepare aminocyclopentadienes, see: Wu YT, Flynn B, Schirmer H, Funke F, Müller S, Labahn T, Nötzel M, de Meijere A. Eur J Org Chem. 2004:724.Macaulay JB, Fallis AG. J Am Chem Soc. 1990; 112:1136.

3. For leading references and reviews on select natural products that incorporate tertiary carbinamine-based aminocyclopentanes, see: Pactamycin Malinowski JT, Sharpe RJ, Johnson JS. Science. 2013; 340:180. [PubMed: 23580525] Halochlorine and pinnaic acids Liu R, Gutierrez O, Tantillo DJ, Aubé J. J Am Chem Soc. 2012; 134:6528. [PubMed: 22490078] Clive DLJ, Yu M, Wang J, Yeh VSC, Kang S. Chem Rev. 2005; 105:4483. [PubMed: 16351051] Himandrine and himgaline Movassaghi M, Tjandra M, Qi J. J Am Chem Soc. 2009; 131:9648. [PubMed: 19555115] Evans DA, Adams DJ. J Am Chem Soc. 2007; 129:1048. [PubMed: 17263383] Cylindricines Pandey G, Janakiram V. Chem Eur J. 2015; 21:13120. [PubMed: 26220441] Weinreb SM. Chem Rev. 2006; 106:2531. [PubMed: 16771458] Cephalotaxines Abdelkafi H, Nay B. Nat Prod Rep. 2012; 29:845. [PubMed: 22714632] Notoamide B Artman GD, Grubbs AW, Williams RM. J Am Chem Soc. 2007; 129:6336. [PubMed: 17455936]

4. Wiviott SD, Steg PG. Lancet. 2015; 386:292. [PubMed: 25777663]

5. McLaughlin MM, Skoglund EW, Ison MG. Expert Opin Pharmacother. 2015; 16:1889. [PubMed: 26153242]

6. Synthetic details, characterization, and molecular structures obtained by X-ray structural analysis are described in the Supporting Information. CCDC 1816814 (**8i**), 1817118 (**11**) and 1817123 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif.

7. Protodesilylation of certain types of 6-silyl-1,2-DHPs provide desilylated DHPs, see: Fallon BJ, Garsi J-B, Derat E, Amatore M, Aubert C, Petit M. ACS Catal. 2015; 5:7493.

8. Kim S, Ciufolini MA. Org Lett. 2011; 13:3274. [PubMed: 21615101]

9. Dupau P, Epple R, Thomas AA, Fokin VV, Sharpless KB. Adv Synth Catal. 2002; 344:421.

10. Fusi S, Ponticelli F, Ventura A, Adamo MFA. Tetrahedron Lett. 2008; 49:5820.

11. Azirdinyl cyclopentene derivatives have been prepared by irradiation of N-alkyl pyridiniums in protic solvents. For this photochemical process, an azirdinyl cyclopentallyl cation is proposed as an intermediate: Penkett CS, Simpson ID. Tetrahedron Lett. 2001; 42:1179.Penkett CS, Simpson ID. Tetrahedron. 1999; 55:6183.Ling R, Mariano PS. J Org Chem. 1998; 63:6072. [PubMed: 11672222] Ling R, Yoshida M, Mariano PS. J Org Chem. 1996; 61:4439. [PubMed: 11667350] Kaplan L, Pavlik JW, Wilzbach KE. J Am Chem Soc. 1972; 94:3283.

12. Zhao Y, Truhlar DG. Theor Chem Acc. 2008; 120:215.

13. Barone V, Cossi M. J Phys Chem A. 1998; 102:1995.

14. Frisch MJ, , et al. Gaussian 09 Gaussian Inc; Wallingford, CT: 2013

15. For a comparable activation barrier found in the analogous theoretical rearrangement of iodabenzene, see: Rawashdeh AM, Parambil PC, Zeng T, Hoffmann R. Am Chem Soc J. 2017; 139:7124.

16. Aggarwal VK, Wang MF, Zaparucha A. J Chem Soc, Chem Commun. 1994:87.

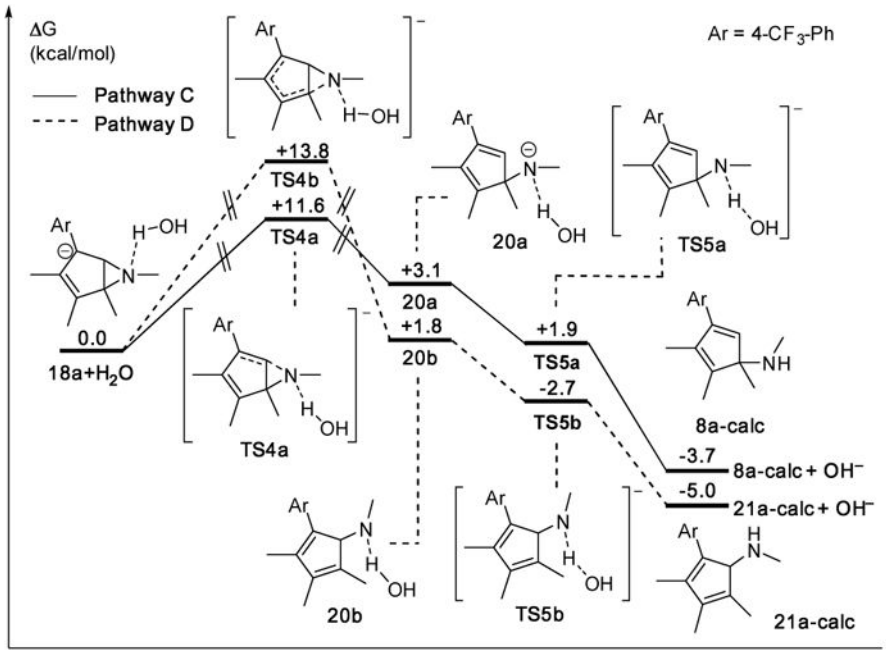
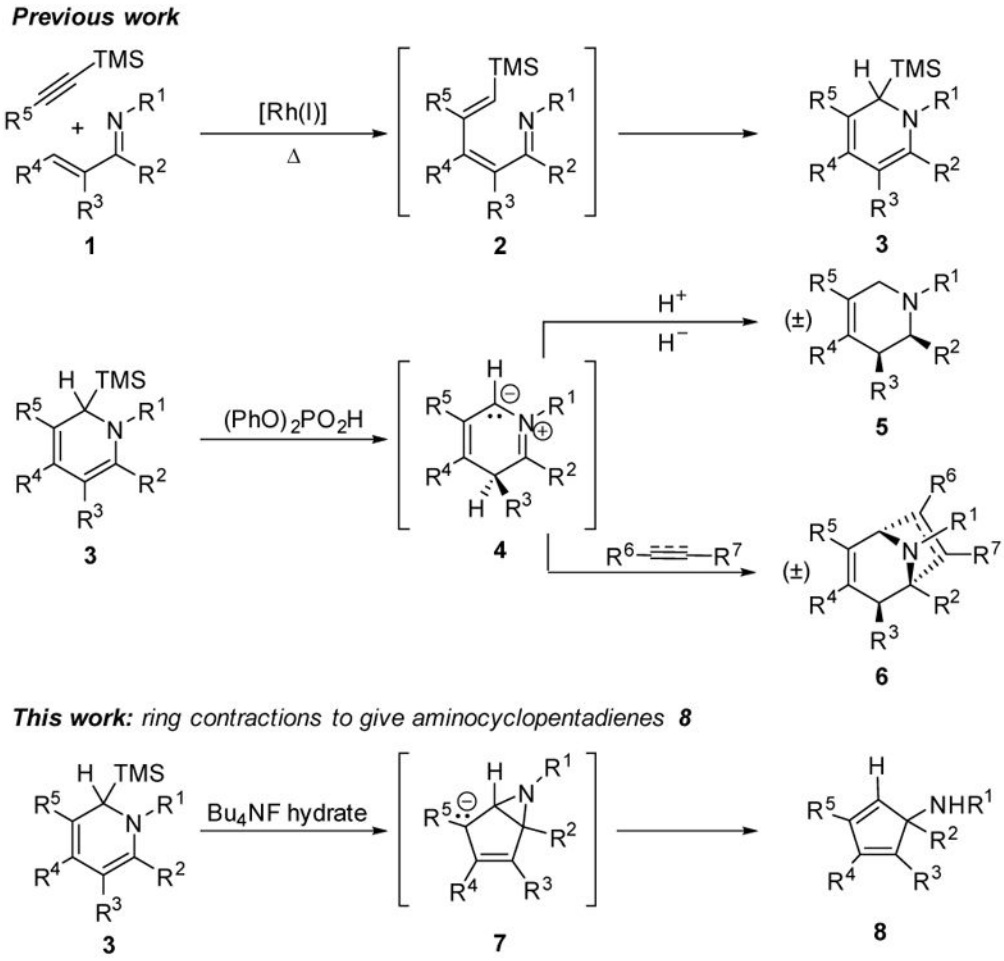
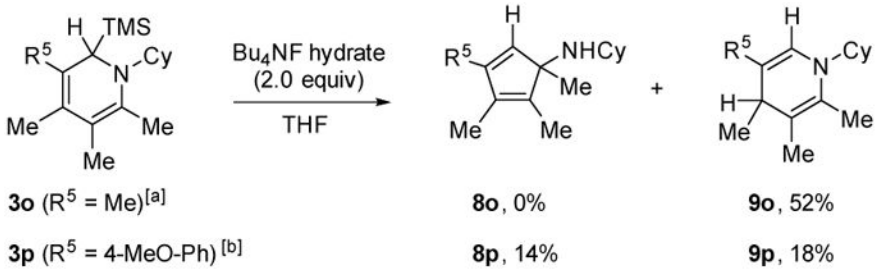


Figure 1.

Energy profiles (in kcal/mol) of Pathways C and D for the regiodivergent aziridine ring-opening of **18a** to yield aminocyclopentadiene isomers at the M06-2X/6-311G++(d,p)-CPCM (THF)// B3LYP/6-31G(d)-CPCM (THF) level of theory. Distances denoted in Angstroms.

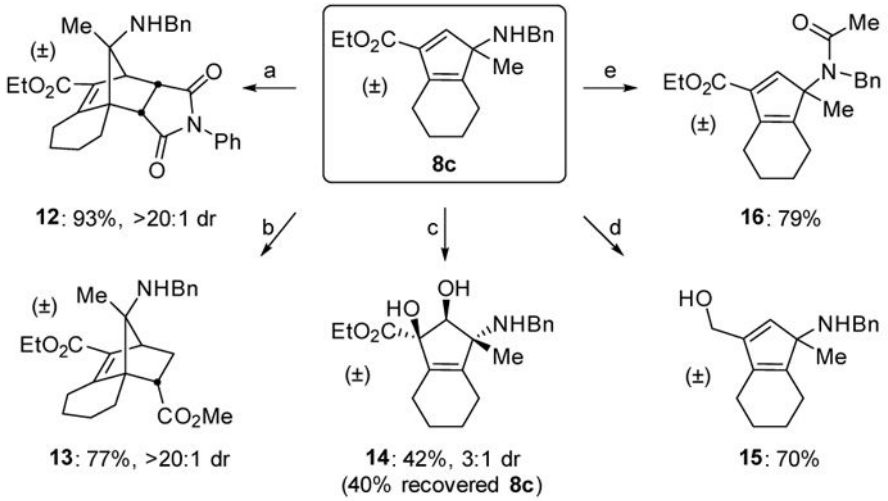


Scheme 1.
Reactions of silyl-substituted DHPs **3**.



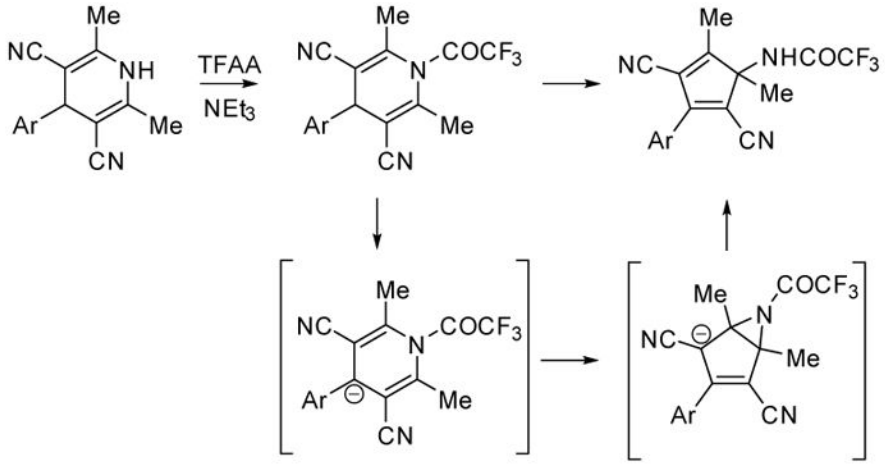
Scheme 2.

DHPs **3** that provide the 1,4-dihydropyridines. Conditions: **3** (1 equiv), Bu_4NF hydrate in THF (0.1 M). [a] 18 h at 50 °C. [b] 72 h at rt. Yields determined by ^1H NMR spectroscopy with 2,6-dimethoxytoluene as the external standard.

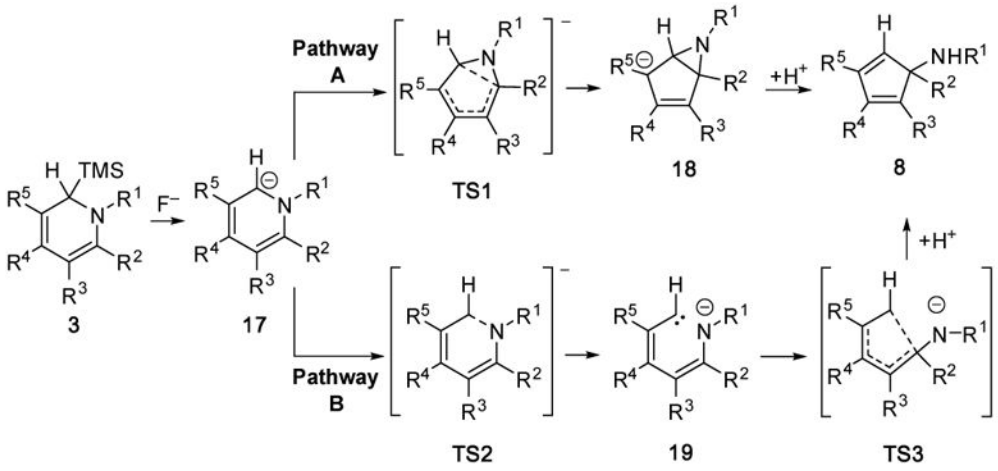


Scheme 3.

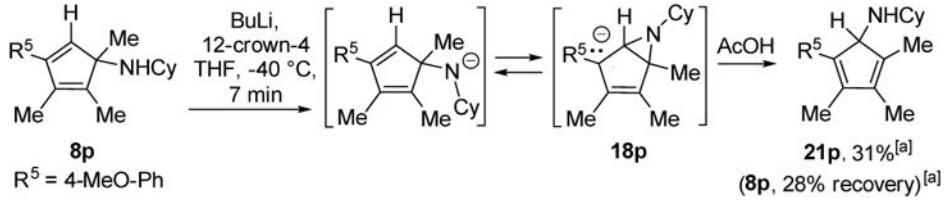
Elaboration of aminocyclopentadiene **8c**. Reaction conditions: a) *N*-phenylmaleimide, CH_2Cl_2; b) methyl acrylate; c) OsO_4, NMO, citric acid, *t*BuOH/H_2O; d) DIBAL, CH_2Cl_2; e) $(CH_3CO)_2O$, NEt_3, CH_2Cl_2.



Scheme 4.
Previously reported transformation by Fusi and Adamo.



Scheme 5.
Possible mechanistic pathways from DHP **3** to aminocyclopentadiene **8**.

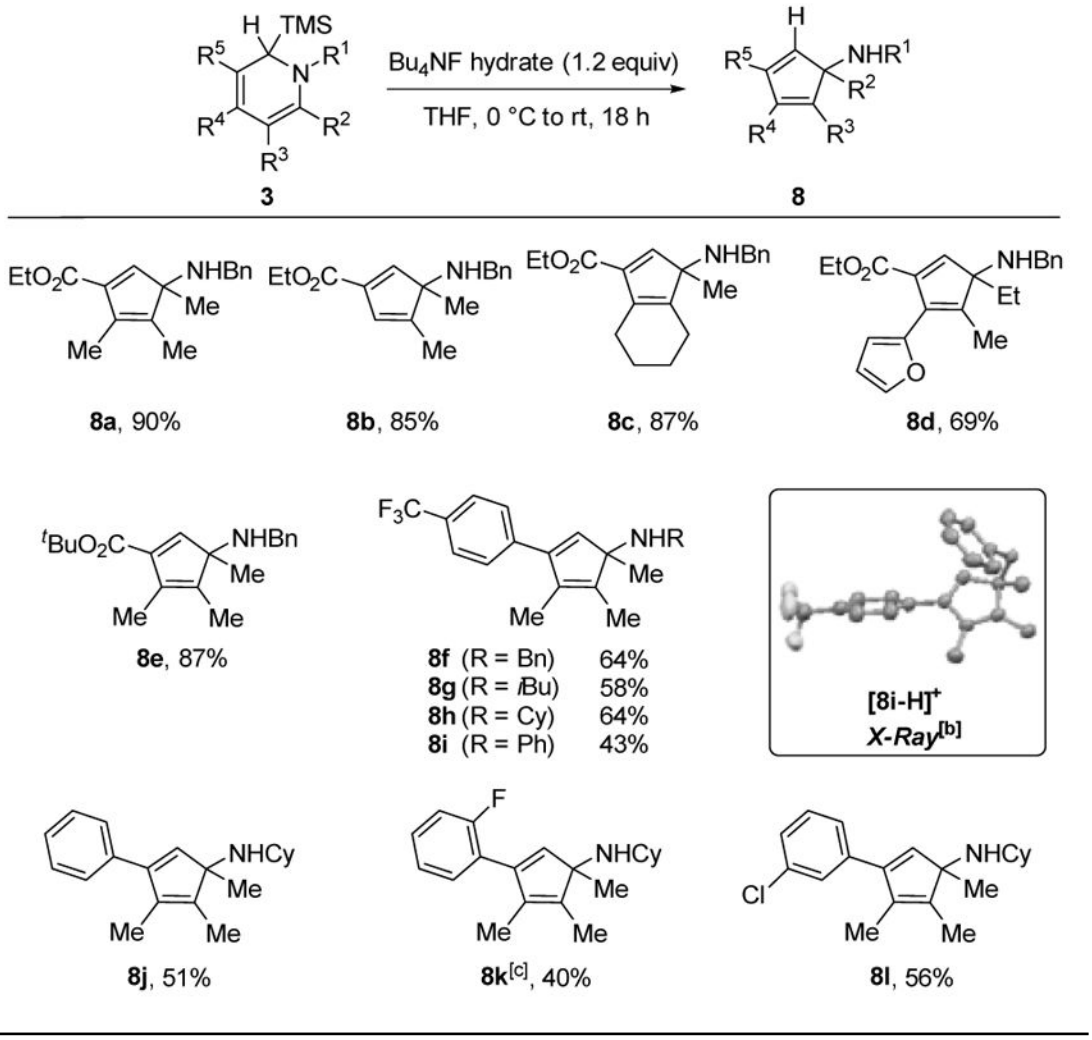


Scheme 6.

Support for aziridine intermediate. [a] Yields determined by ^{1}H NMR spectroscopy with 2,6-dimethoxytoluene as the external standard.

Table 1

Substrate scope.[a]



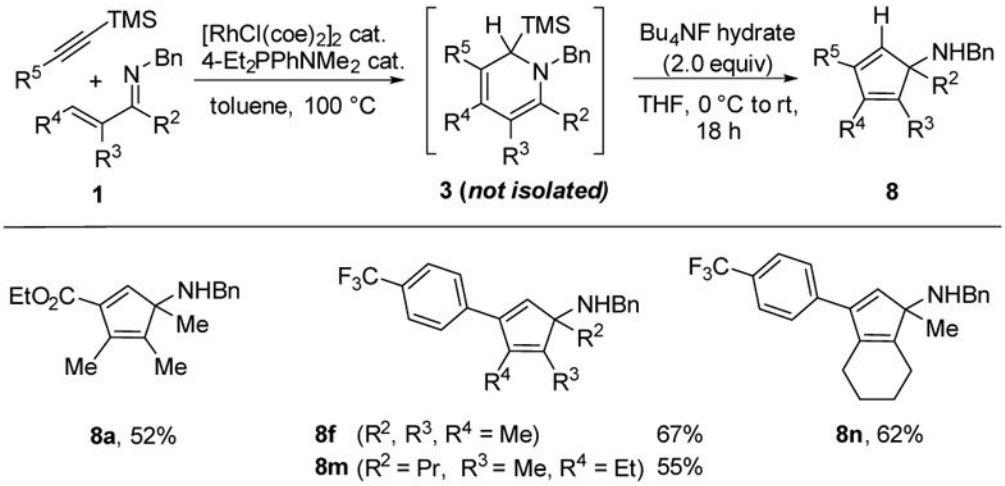
[a]Conditions: **3** (1 equiv), Bu_4NF hydrate (1.2 equiv) in THF (0.1 M). Reactions generally proceeded much more rapidly than 18 h, but for evaluating scope were allowed to continue for longer times. Isolated yields after silica gel chromatography.

[b]X-ray structure shown with anisotropic displacement ellipsoids at the 50% probability level. The pircrylsulfonate counterion and hydrogen atoms omitted for clarity.

[c]Conditions: Bu_4NF (2.0 equiv), 72 h.

Table 2

Direct synthesis of aminocyclopentadienes **8** from imine **1**.[a]



[a]Conditions: 1st step: alkyne (2 equiv), from 1.25 to 15 mol % of $[RhCl(coe)_2]_2$ with equimolar amounts of $4\text{-}Et_2PPhNMe_2$ and from 2 to 48 h depending on DHP **3** synthesized (see Supporting Information). 2nd step: Bu_4NF hydrate in THF (0.1 M). Isolated overall yield for sequence based on **1** after silica gel chromatography.

Table 3

Computed free energies (kcal/mol) at the M06-2X/6-311G++(d,p)-CPCM (THF)// B3LYP/6-31G(d) level of theory of transition states and intermediates along Pathways A and B relative to desilylated DHP **17** (R^1 to R^4 = Me).

R^5	Structure	$\Delta G^{\ddagger}$	Structure	ΔG
4-CF_3-Ph	**TS1a**	5.9	**18a**	−8.2
Ph	**TS1b**	7.9	**18b**	−2.8
CO_2Me	**TS1c**	1.2	**18c**	−14.7
Me	**TS1d**	15.3	**18d**	11.3
4-CF_3-Ph	**TS2a**	48.2	**19a**	18.6