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Nucleophilic Additions to a Spiro[2,4]hepta-4,6-diene 4-Nitrile: Synthesis of 1,2–Disubstituted Cyclopentenes

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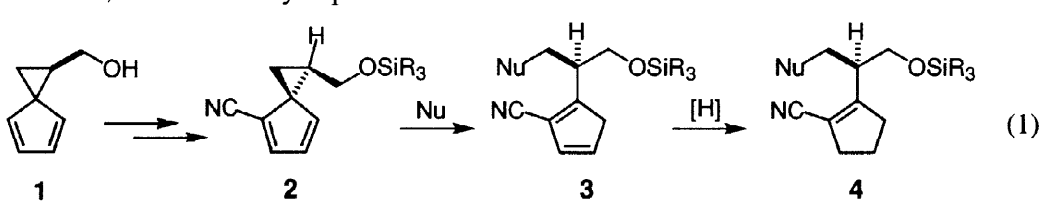
Abstract. Organocuprates react with spiro[2,4]heptadiene 4-nitrile to furnish ring-opened cyclopentadiene adducts which can be chemoselectively monohydrogenated to the corresponding unsaturated cyclopentene nitriles. The use of optically active spiro[2,4]heptadiene allows for the asymmetric synthesis of chiral cyclopentadienes and cyclopentenes that may serve as useful starting materials for asymmetric synthesis.

Keywords: cleavage reactions, cyclopropanes, cyclopentadienes, cyclopentenes

Stereochemically complex substituted cyclopentanes are prominent substructures of natural products such as the aminocyclopentitols allosamidin, trehazolin, and mannostatin,[1] the alkaloid palau'amine,[2] and the epithiopiperazinedione sirodesmin.[3] The general synthetic strategies that have been devised for the construction of stereochemically complex five–membered rings are typified by those used in the synthesis of aminocyclopentitols. These include cycloaddition reactions of cyclopentadienes;[4] desymmetrization reactions of cyclopentenyl–1,4–*meso*–diols;[5,6] and fragmentation and refunctionalization reactions of carbohydrate starting materials.[7] Recent work in this laboratory has documented a novel tactic involving optically active spiro[2,4]hepta-4,6-diene-1-methanol **1** as a versatile template for stereoselective amination and hydroxylation reactions as a key step in the total synthesis of trehazolin (Eq 1).[8]

In order to further expand the scope of **1** as a useful starting material for complex molecule synthesis, we have expanded the investigation of its reaction chemistry. This substituted, chiral homofulvene may be converted to the corresponding 4-cyanoderivative **2** which in turn displays unusual reactivity towards nucleophiles (Eq 1). In this letter we report that treatment of **2** with organo- magnesium or lithium reagents in the presence of CuI leads to chemoselective homoconjugate addition, furnishing the corresponding ring-opened cyclopentadienes **3** in 76-97% yield. The product diene subsequently undergoes selective reduction (H_2/10% Pd/C) to yield the 1,2-substituted cyclopentenes **4**.



1 2 3 4 (1)

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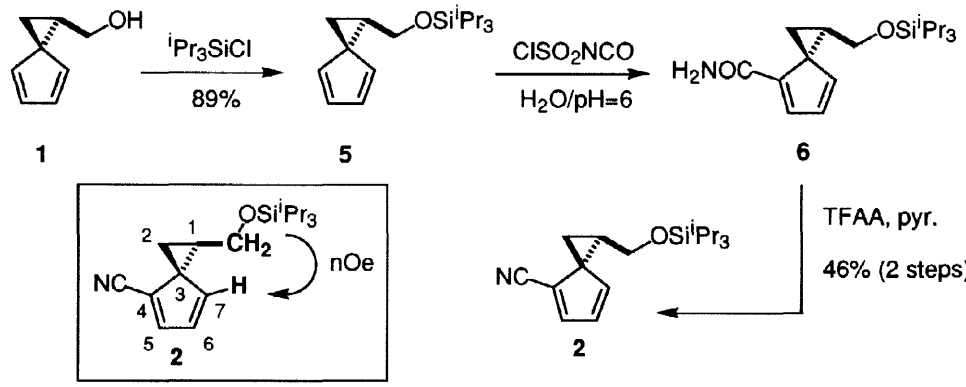
Our interest in developing methods that lead to functionalization of **1** through C-C bond formation led us to examine protected spirocycloheptadiene **5** as a substrate for chlorosulfonyl isocyanate.[9] Using the procedure we have previously described, the reaction of cyclopentadiene and epichlorohydrin furnished **1**, which was subsequently protected as the triisopropylsilyl ether **5** (89%).[8] Reaction of **5** with chlorosulfonyl isocyanate followed by aqueous workup at pH 6 afforded a mixture of diastereomers (89:11) from which primary amide **6** was obtained in 41% yield after purification on silica gel. Treatment of **6** with trifluoroacetic anhydride (TFAA) and pyridine in THF at –78 °C furnished nitrile **2** in 72% yield. A more efficient protocol was developed for the direct conversion of **5** to nitrile **2**; thus, the two-step sequence (**5** → **6** → **2**) could be conducted, without purification of the intermediate amide, to afford the desired nitrile **2** in 46% overall yield for both steps ([2+2] cycloaddition and dehydration $RCONH_2 \rightarrow RCN$). Examination of the ^1H NMR spectral data for **2** confirmed the formation of the C-4 regioisomer, a result consistent with the known regioselectivities in the reaction of sulfonyl isocyanates with dienes.[9] The relative stereochemistry of the nitrile and the silyloxymethylene substituent of the cyclopropane moiety was determined by the observation of a homonuclear ^1H NMR nOe between the C-1 methylene and C-7 vinyl proton in **2**.

Scheme 1



In our initial examination of the chemistry of **2** we observed a reluctance by this nitrile diene to undergo simple conjugate addition to the carbon-carbon double bonds under a variety of conditions. In lieu of conjugate addition, **2** preferentially underwent nucleophilic homoconjugate addition to furnish ring-opened adducts **7-12** in 76-97% yield (Eq 2, Table 1).[10,11] The ^1H NMR spectral data for products formed in each of the addition reactions was consistent with the formation of the single 1-cyano-2-substituted conjugated cyclopentadiene isomers shown for **7–12**. For one adduct the structure of the diene was unambiguously established by single crystal X-ray crystallographic analysis of the *p*–nitrobenzoate derivative formed from **11** following desilylation (HF/MeCN) and esterification (*p*–nitrobenzoyl chloride, CH_2Cl_2).

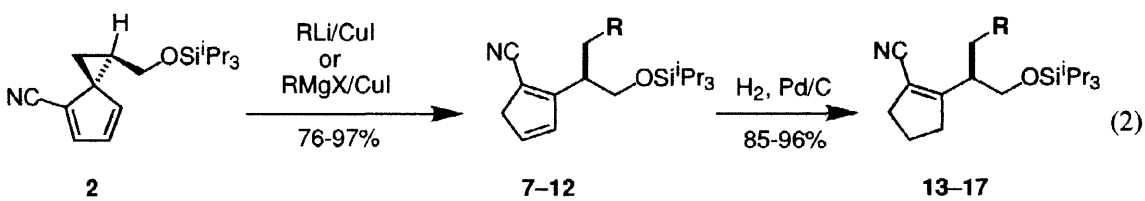


Table 1. Conversion of nitrile **2** to cyclopentadienes **7-12** and cyclopentenes **13-17**.

Entry	Nucleophile	Adduct	Yield	Reduction Product	Yield
1	CH_3MgBr/CuI	**7**	76%	**13**	93%
2	EtMgBr/CuI	**8**	83%	**14**	85%
3	^{i}PrMgBr/CuI	**9**	83%	**15**	86%
4	BuLi/CuI	**10**	90%	**16**	96%
5	PhMgBr/CuI	**11**	97%	**17**	96%
6	*iso*propenylMgBr/CuI	**12**	82%	-	-

In a typical procedure, a solution of organo lithium or Grignard reagent in THF (12 mL) cooled to 0 °C was treated with CuI (1.83 mmol), stirred 30 min, and then cooled to -78 °C. Following the dropwise addition of a solution of **2** (0.61 mmol in 0.19 mL THF), the reaction was stirred at –78 °C and subsequently warmed to 0 °C. The reaction was quenched with saturated aqueous ammonium chloride solution (15 mL) and extracted with pentane (3 x 30 mL). The combined organic solutions were dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. Purification by chromatography on silica gel (20:1 hexanes:EtOAc) afforded the desired products in 76-97% yield.

Cyclopentadiene nitriles **7-12** prepared from the addition of alkyl and aryl carbanions were amenable to selective monoreduction to give the α,β–unsaturated nitriles **13–17**. Under optimal conditions, reduction of dienes **7–12** in a suspension of 10% Pd/C in 25:1 cyclohexane/ EtOAc under an atmosphere of hydrogen furnished cyclopentenes **13-17** in 85-96% yield.

Although the reactions shown in Table 1 were conducted with racemic material, a test-substrate was chosen to determine whether the nucleophilic additions could be conducted with optically active **1** to furnish chiral cyclopentadienes and cyclopentenes as building blocks for enantioselective synthesis. The asymmetric synthesis of (*S*)–**2** was conducted following the procedure we have previously documented utilizing lithium cyclopentadienilide and (*R*)-epichlorohydrin.[8] When (*S*)–**2** was treated with MeMgBr/CuI and the adduct subjected to selective monohydrogenation, the isolated product **13** was shown to have been formed without loss of optical purity by analysis of the derived (*R*)–Mosher ester by gas chromatography.[12]

A novel addition reaction has been described involving the homoconjugate addition of carbanions to spiro[2,4]hepta-4,6-diene 4-nitrile. The nucleophilic additions are general for a range of carbanions, affording the unusual adducts in useful yields. Moreover, additions to non-racemic spiroheptadiene deliver optically active cyclopentadiene adducts without loss of optical purity. The ability to access substituted cyclopentadienes and cyclopentenes provides access to building blocks for enantioselective synthesis. The application of the chemistry described herein to the asymmetric synthesis of stereochemically complex molecules will be reported in the future.

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