

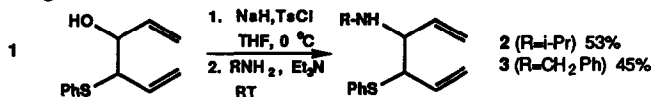
Charge-Accelerated Cope Rearrangements of 3-Amino-1,5-Dienes

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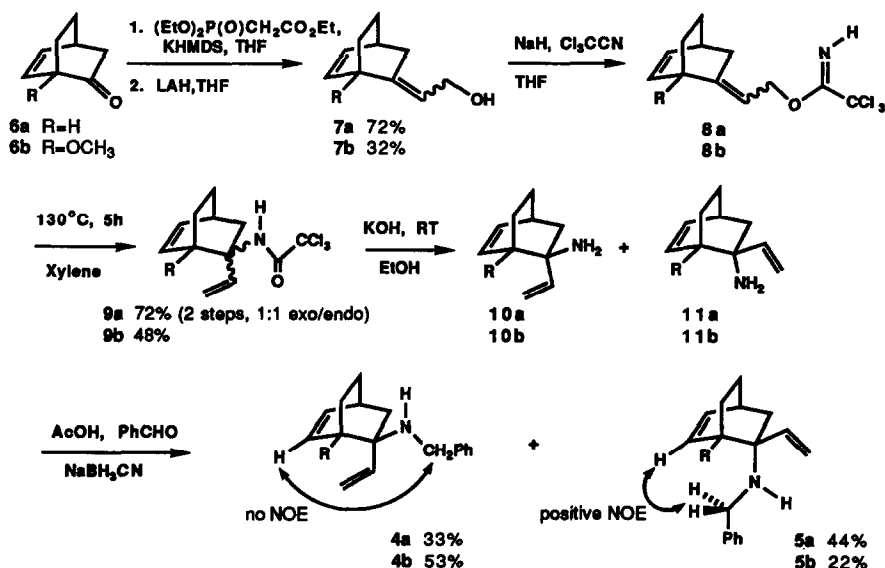
Abstract: The charge-accelerated [3,3] sigmatropic rearrangements of 3-amino-1,5-dienes are considerably more facile than those of the corresponding 3-hydroxy-1,5-dienes, requiring reaction temperatures 85 to 140 °C lower.

The [3,3] sigmatropic rearrangement of 3-hydroxy-1,5-dienes, "the oxy-Cope rearrangement," has been shown to be a powerful synthetic tool,¹ particularly the charge-accelerated alkoxy system.² On the other hand, very few examples of 3-amino-1,5-diene Cope rearrangements have been reported, and those that have involve thermolysis of the neutral compounds.³ Examples of the nitrogen anion rearrangement have not been reported. We anticipated that the increased basicity of the nitrogen anion, in comparison to an alkoxide, should produce an even greater rate acceleration. In this paper, we report the first examples of the extremely facile, charge-accelerated Cope rearrangements of 3-amino-1,5-dienes.



In order to evaluate the scope and limitations of the "amino-Cope" reaction and to compare them to those of the oxy-Cope, we chose to prepare the acyclic and bicyclic amino dienes 2, 3, 4, and 5. The corresponding alcohols are well studied oxy-Cope systems.² Alcohol 1 was converted to the *N*-isopropyl and the *N*-benzyl amines 2 and 3 by tosylation and displacement with the respective amines.⁴

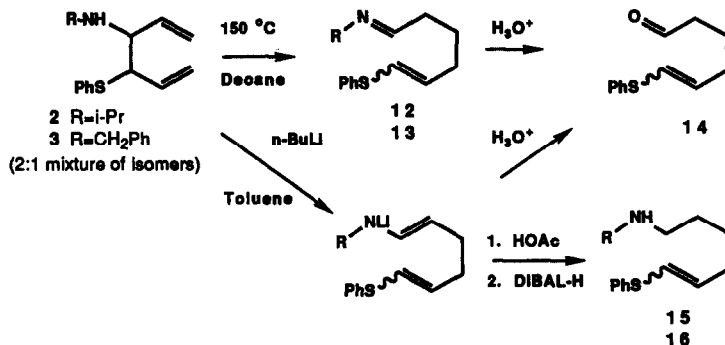
Scheme 1



A method involving the thermal rearrangement of allylic imino esters, developed by Overman,⁵ proved to be very effective in generating the required bicyclic allylic systems (Scheme 1). The ketone **6a**⁶ was converted to the allylic alcohol **7a** via reduction of the unsaturated ester. Coupling alcohol **7a** with trichloroacetonitrile using a catalytic amount of sodium hydride, and thermalizing the resulting imino ester **8a** at 130 °C in xylene gave a 1:1 *exo/endo* mixture of the allylic amides **9a**. Basic hydrolysis of the amides to amines **10a** and **11a**, followed by reductive amination with benzaldehyde afforded the *endo* and *exo* *N*-benzyl amines **4a** and **5a**. In a similar fashion, the methoxy ketone **6b**⁶ was converted to the *endo* and *exo* *N*-benzyl amines **4b** and **5b**. Stereochemical assignments of the *endo* and *exo* isomers were made on the basis of NOE experiments (Scheme 1).

Thermolysis of the acyclic systems **2** and **3** at 150 °C produced the Cope products **12** and **13**, affording aldehyde **14** in 48% and 45% yields after hydrolysis of the imines (Scheme 2). In contrast, the charge-accelerated reaction proved to be much more facile; thus treatment of **2** with *n*-BuLi at -40 °C followed by hydrolysis produced aldehyde **14** in 40% yield. It is noteworthy that the amino-Cope reaction of **2**, as the lithium amide, took place 65 °C lower than the corresponding anionic oxy-Cope using the potassium alkoxide of **1** (25°C).^{2b,7} The isolated yield of the product aldehyde **14** from the amino system **2** (40%) was similar to that from **1** (43%).^{2b} It was also possible to isolate the Cope products from **2** and **3** as their amines **15** and **16**, by quenching the *n*-BuLi mediated reactions with acetic acid followed by reduction of the resulting imines with DIBAL-H.

Scheme 2

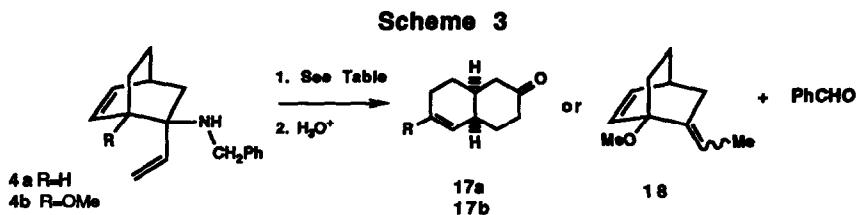


Compound	Conditions	Yield (%)	Product	cis/trans
2	decane, 3h, 150 °C	48	14	1:1
3	decane, 4h, 150 °C	45	14	1:1
2	<i>n</i> -Bu-Li, 4h, -40 °C	40	14	2:1
2	<i>n</i> -Bu-Li, 4h, -40 °C	20	15	2:1
3	<i>n</i> -Bu-Li, 2h, -20 °C	20	16	3:1

The bicyclic systems **4a** and **4b** were thermolyzed at 230 °C and 160 °C respectively to give the *cis*-fused ketones **17a** in 40% and **17b** in 50% yield, after hydrolysis of the resulting imines (Scheme 3). The thermal reactions of **4a** and **4b** are significantly more rapid than those of the corresponding oxy-Cope substrates, which require 320 °C and 195 °C respectively.^{2,6} This rate enhancement in the thermal Cope rearrangements of neutral 3-amino-1,5-dienes relative to 3-hydroxy-1,5-dienes is in accord with results previously reported, where the 3-(*N,N*-dimethylamino) substituent produced a rate enhancement relative to the 3-methoxy substituent.^{3c,d}

Treatment of **4a** and **4b** under conditions similar to those used for the charge-accelerated Cope rearrangement of **2** and **3** (*n*-BuLi, ≤ 25 °C) did not produce Cope products. Only starting material was obtained from **4a**, while **4b** gave what appears to be a retro-ene product **18**, in addition to benzaldehyde. Use

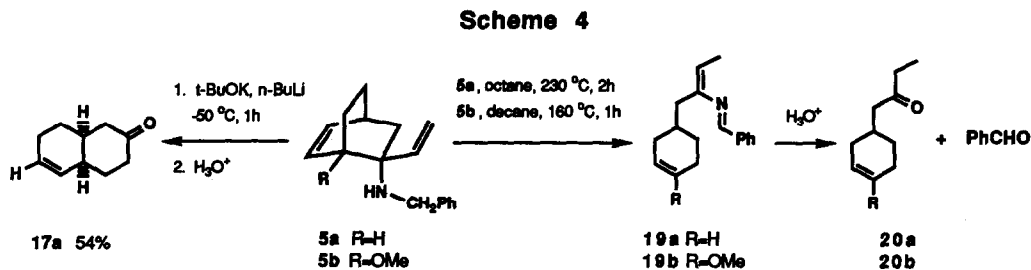
of *t*-BuOK/*n*-BuLi (conditions for generation of K-amides, such as potassium diisopropyl amide)⁸ at -50 °C and -60 °C produced smooth Cope rearrangement of **4a** and **4b**, to yield **17a** (73%) and **17b** (71%) after imine hydrolysis. In comparison, the temperature required for the corresponding anionic oxy-Cope using potassium alkoxides are 90 °C and 25 °C respectively;² thus the anionic amino-Cope reactions of **4a** and **4b** are



Compound	Conditions	Yield (%)	Product
4a	octane, 230 °C, 2h	40%	17a
4b	decane, 160 °C, 1h	50%	17b
4a	<i>n</i> -BuLi, THF, 25 °C	-	no reaction
4b	<i>n</i> -BuLi, THF, 0 °C	76%	18
4a	<i>t</i> -BuOK, <i>n</i> -BuLi, THF -50 °C, 2h	73%	17a
4b	<i>t</i> -BuOK, <i>n</i> -BuLi, THF -60 °C, 1h	71%	17b

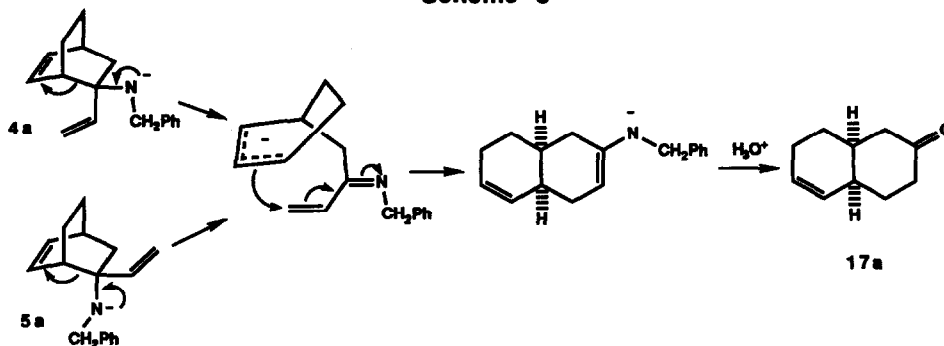
extremely facile. The potassium amides of **4a** and **4b** react at temperatures 280 °C and 220 °C lower than the corresponding neutral amines. This represents a significantly greater reaction temperature differential than that observed between the corresponding oxy-Cope and anionic oxy-Cope systems (230 °C and 170 °C respectively).⁹

The exo isomers **5a** and **5b** under thermolysis conditions (Scheme 4), produced the cleavage products **19a** and **19b**, which upon hydrolysis gave ketones **20a** and **20b** in addition to benzaldehyde. As in the case of the endo isomer **4a**, the exo isomers **5a** and **5b** gave no reaction upon treatment with butyllithium. Use of the *t*-BuOK/*n*-BuLi combination at -50 °C rapidly converted **5a** into the Cope product, while the methoxy isomer afforded only starting material, even after the temperature was raised to 25 °C.



The fact that *t*-BuOK/*n*-BuLi treatment of the exo isomer **5a** produced the same Cope product, under the same conditions as the endo isomer **4a**, is unusual. The corresponding hydroxy compound does not undergo the anionic oxy-Cope reaction, and this suggests that a fragmentation-Michael addition is occurring rather than a concerted sigmatropic process (Scheme 5).¹⁰

Scheme 5



In summary, the [3,3] sigmatropic rearrangements of 3-amino-1,5-dienes are considerably more facile than those of the corresponding 3-hydroxy-1,5-dienes. The amino systems undergo thermal [3,3] rearrangement at temperatures 35 to 90 °C lower than the hydroxy systems, while the corresponding anionic reactions take place at 85 to 140 °C lower. The lack of stereochemical requirements in one of the substrates suggests that a fragmentation-recombination process is taking place rather than a concerted mechanism.

Studies are underway to further examine the synthetic potential of this reaction, and in particular toward the synthesis of medium size nitrogen containing heterocycles.

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