Synthetic Methods Hot Paper

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Single-Electron/Pericyclic Cascade for the Synthesis of Dienes**

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Abstract: *The highly efficient and diastereoselective synthesis of E dienes has been accomplished through radical cyclization of bromoallyl hydrazones. This methodology has been further extended to generate these products through a one-pot condensation/radical cyclization/cycloreversion cascade from simple aldehyde starting materials in high yields (> 75 %) and high diastereoselectivities (> 95:5). Mechanistic investigations suggest that the cascade reaction proceeds through a cyclic diazene intermediate prior to the cycloreversion.*

Synthetic chemists have long exploited the ability to convert hydrazone derivatives into a wide variety of highly reactive diazo intermediates.[1] In the 1910s both Wolff[2] and Kishner[3] used the base-mediated conversion of a hydrazone into an alkyl diazene to effect an overall reduction (Figure 1).

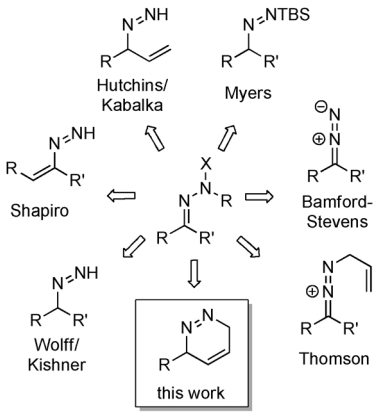
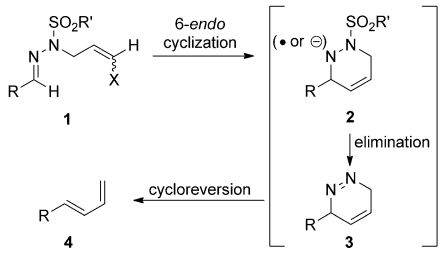


Figure 1. Representative diazo intermediates accessed from hydrazones. TBS = *tert*-butyldimethylsilyl.

Numerous other synthetic methodologies have also utilized diazene intermediates, including vinyl diazenes in the Shapiro reaction,[4] allyl diazenes in Hutchins[5] and Kabalka[6] reactions, and alkyl silylated diazenes from Myers et al.[7] Hydrazones have also been used to access diazoalkanes in Bamford–Stevens reactions[8] and allylated diazoalkanes in recent examples by Thomson and co-workers.[9] One transformation that is notably absent from the literature is the conversion of hydrazones into cyclic diazenes,[10] which readily undergo cycloreversions to access dienes in high diastereoselectivities.[11] Currently, there is only one method for the synthesis of dienes from hydrazones, and it is limited to aryl hydrazones.[9] A new and direct method for the conversion of hydrazines into dienes would not only represent the first example of accessing cyclic diazenes from hydrazones, but it also may provide a solution for the unsolved challenge of directly forming dienes from alkyl hydrazones.

We hypothesized that we may be able to rapidly access cyclic diazenes from the corresponding sulfonylated hydrazone **1** (Scheme 1). Generation of either an anion or radical



Scheme 1. Proposed route to dienes from hydrazones.

using the vinyl halide would lead to a 6-*endo* cyclization to form the cyclic hydrazide **2**,[12,13] followed by elimination of the sulfonamide to form the key cyclic diazene **3**.[14] The diazene **3** will then readily undergo a cycloreversion to form the desired diene **4**.[15] Each of these reactions will have low activation energies, thus the entire process should proceed during a single reaction step. The challenge with this route is finding an appropriate method for facilitating the key 6-*endo* cyclization. While 6-*endo* cyclizations of vinyl anions are known,[12] an anionic strategy may lead to undesired enolization or addition reactions. Furthermore, an anionic reaction requires a geometrically pure vinyl halide,[16] which places significant limitations on the availability of the key starting material. A radical-based approach is an intriguing alternative. Hydrazones are known acceptors for vinyl radicals,[17] and radicals avoid the complications of enolization[18] as well as the synthesis of a diastereomerically pure precursor.[19]

We focused our studies on alkyl hydrazones which currently cannot be readily converted into dienes (Scheme 2). The aldehyde **5a** was first condensed with bromoallyl hydrazine **6a**, which is readily prepared in a single step from tosyl hydrazine.[20] The corresponding hydrazone was then subjected to a refluxing solution of tributyltin hydride and azobis(isobutyronitrile) (AIBN) to afford the desired diene (**4a**) in 80 % conversion along with approximately 20 % of debrominated hydrazone **7a**. As **7a** is

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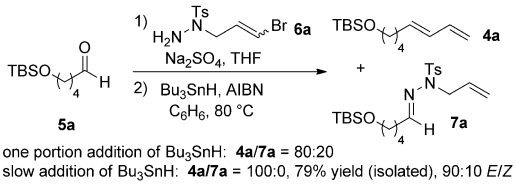
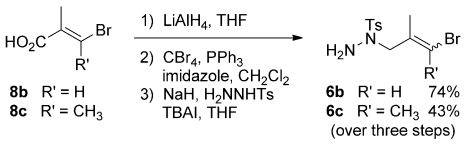


Scheme 2. Hydrazone formation and cascade diene synthesis starting from the siloxy butyl derivative **5a**. AIBN = azobis(isobutyronitrile), THF = tetrahydrofuran, Ts = *para*-toluenesulfonyl.

presumably formed from direct hydrogen transfer to the vinyl radical, we next investigated slow addition of tributyltin hydride to minimize this undesired pathway. Gratifyingly, under these slow addition conditions, only **4a** was observed by ^{1}H NMR spectroscopy and it could be isolated in 79% yield as a 90:10 mixture of *E* to *Z* isomers.[21,22]

For this methodology to be practical for the preparation of substituted dienes, the synthesis of the requisite substituted hydrazine must be highly efficient. We developed a rapid synthetic route beginning with the known carboxylic acids **8b** and **8c** (Scheme 3).[23] This readily available starting material

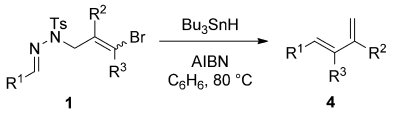


Scheme 3. Synthesis of tri- and tetrasubstituted bromoallyl hydrazines **6b** and **6c**. Ph = phenyl, TBAI = tetrabutylammonium iodide, THF = tetrahydrofuran.

can be rapidly converted into the desired hydrazine in three steps, which involve reduction of the carboxylic acid, Appel conversion into the allyl bromide,[24] and subsequent substitution using sodium tosyl hydrazinide to afford **6b** and **6c** in 74 and 43% yield, respectively.[25]

Investigations into the substrate scope commenced with the examination of the syntheses of more highly-substituted dienes (Table 1, entries 1–3). Subjecting both the resulting tri- (entry 2) and tetrasubstituted bromoallyl hydrazones (entry 3) to the optimized reaction conditions afforded the di- (**4b**) and trisubstituted (**4c**) diene products in 82% and 84% yields, respectively, and are comparable to the yield of the monosubstituted diene **4a** (entry 1). We next investigated increasing the steric bulk β to the hydrazone in citronellal hydrazones (entries 4–6). With the exception of an increase in yield for the monosubstituted diene **4d**, the yields were comparable for both the di- and trisubstituted alkenes (**4e** and **4f**). However, the diastereoselectivities observed were generally greater, with the *E*/*Z* ratios of all three greater than 95:5. Gratifyingly, no reaction was observed with the alkene on citronellal, which would be susceptible under oxidation reaction conditions.[9] Increasing the steric bulk α to the hydrazone (entries 7–9) led to no observed loss of yield or diastereoselectivity. Further increasing the steric bulk in the α-position provided the corresponding diene in good yield (entries 10–12). While the diastereoselectivity of trisubstituted diene **4l** was slightly diminished, the mono- and disubstituted dienes **4j** and **4k** were isolated with high diastereoselectivity. Finally, we investigated the synthesis of piperidyl dienes (entries 13–15) given the importance of nitrogen-containing heterocycles to the pharmaceutical industry.[26] Gratifyingly, the desired dienes could be synthesized in good yields[27] and high diastereoselectivities.

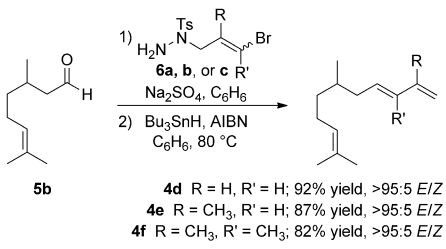
Table 1: Substrate scope of diene formation from bromoallyl hydrazones.



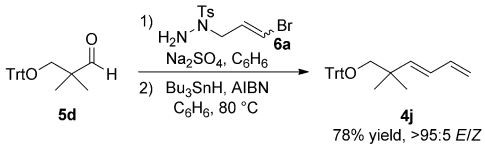
Entry[a]	R^1	R^2	R^3	Product	Yield [%][b]	d.r. (*E*/*Z*)[c]
1	TBSO-(CH$_2$)$_4$-	H	H	**4a**	79	90:10
2		CH_3	H	**4b**	82	>95:5
3		CH_3	CH_3	**4c**	84	90:10
4		H	H	**4d**	94	>95:5
5		CH_3	H	**4e**	84	>95:5
6		CH_3	CH_3	**4f**	79	>95:5
7		H	H	**4g**	82	>95:5
8		CH_3	H	**4h**	79	>95:5
9		CH_3	CH_3	**4i**	86	>95:5
10	TrtO-(CH$_2$)$_4$-	H	H	**4j**	80	>95:5
11		CH_3	H	**4k**	82	>95:5
12		CH_3	CH_3	**4l**	67	90:10
13	Boc-N-(CH$_2$)$_4$-	H	H	**4m**	76	>95:5
14		CH_3	H	**4n**	72	90:10
15		CH_3	CH_3	**4o**	74	>95:5

[a] Reactions were carried out on a >0.5 mmol scale. [b] Yield of the mixture of diastereomers isolated after flash chromatography. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Boc = *tert*-butoxycarbonyl, Trt = triphenylmethyl.

To be competitive with modern methods for the synthesis of dienes,[28] we next explored whether simple aldehydes could be directly converted into the corresponding diene in a single reaction pot. We began our studies with hydrazones derived from citronellal (Scheme 4). Subjecting the aldehyde **5b** to the one-pot, sequential procedure with bromoallyl tosyl hydrazines **6a**, **6b**, and **6c** afforded the dienes **4d**, **4e**, and **4f**, respectively, in comparable yields and diastereoselectivities to



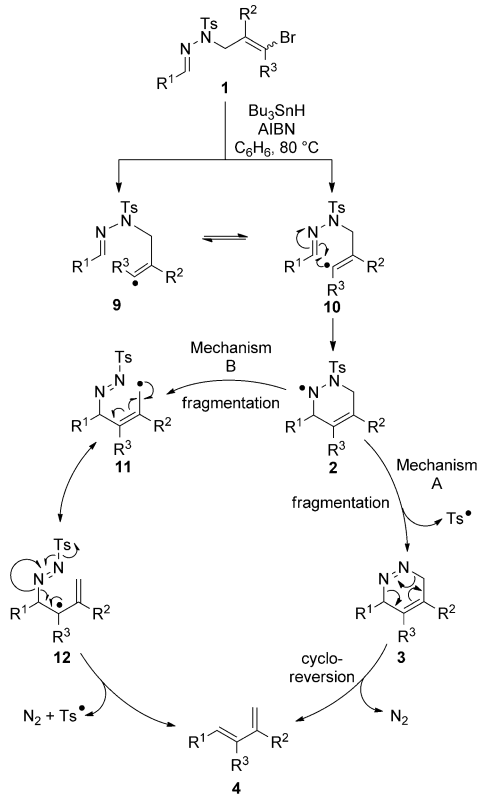
Scheme 4. One-pot hydrazone formation followed by one-electron/pericyclic cascade for the synthesis of dienes **4d**, **4e**, and **4f**.



Scheme 5. One-pot hydrazone formation followed by a one-electron/pericyclic cascade for the synthesis of the diene **4j**.

those of the two-step process (Table 1, entries 4–6). This one-pot process can also be applied to the reaction with the more sterically encumbered aldehyde **5d** (Scheme 5), whereas the one-pot procedure also provided the desired diene **4j** in comparable yield and diastereoselectivity to the two-step process.

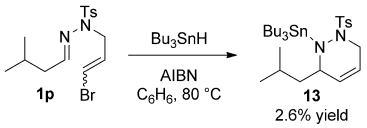
We next explored the mechanism of the radical cascade step. The first step of the radical cascade involves formation of the *E*- and *Z*-vinyl radicals **9** and **10** from **1** (Scheme 6).[29]



Scheme 6. Possible mechanistic pathways for the formation of the diene **4** from hydrazone **1**.

The two vinyl radicals readily interconvert[30] and only **10** has the requisite geometry to undergo the 6-*endo* cyclization to the diazenyl radical **2**. This geometry inversion is evident by the observation that *E*-enriched hydrazones (>20:1) only afford products resulting from 6-*endo* cyclizations.[31]

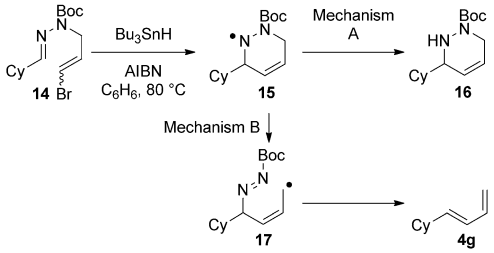
If the vinyl radical undergoes a 6-*endo* cyclization onto the hydrazone, we postulated that there may exist very small amounts of a tin-bound cyclic diazo adduct, such as **13** (Scheme 7), thus resulting from radical recombination of the



Scheme 7. Isolation of the tin-bound cyclic diazo adduct **13**.

tin radical and **2**. To investigate this possibility, we examined the radical cascade using a low-molecular-weight aldehyde, isovaleroaldehyde. This allows the facile removal of the diene product and would leave hydrazone and hydrazine intermediates. After cyclization of hydrazone **1p**, in vacuo removal of all non-nitrogen-containing products, and purification by column chromatography, the tin-bound cyclic hydrazine **13** was isolated in 2.6% yield.[32,33]

After the radical 6-*endo* cyclization, there are two mechanistic possibilities for diene formation (Mechanisms A and B; Scheme 6). We originally postulated that the diazenyl radical **2** would first undergo fragmentation to afford a sulfonyl radical and **3** (Mechanism A). This diazene would then rapidly undergo a cycloreversion to release nitrogen and afford the desired diene **4**. Alternatively, **2** may fragment to afford the stabilized radical **11** (Mechanism B). The resulting allylic radical could subsequently fragment to form a sulfonyl radical,[34] nitrogen gas, and the desired diene. To differentiate between these two mechanistic pathways, we examined the cyclization of the hydrazone **14**, which contains a Boc-hydrazone (Scheme 8). If Mechanism A is operative, the



Scheme 8. Isolation of the cyclic hydrazine **16**. Cy = cyclohexyl.

Boc group should slow fragmentation to the cyclic diazene relative to hydrogen transfer from tributyltin hydride.[35] Thus, the cyclic hydrazine **16** should be the predominant product and little to no diene should be observed. However, if Mechanism B is operative, the diazene intermediate **17** will form because the Boc group should have little effect on the fragmentation to the allyl radical. Once formed, **17** is unstable and should rapidly decompose to the diene. Treatment of **14** under our optimized reaction conditions exclusively afforded **16** in 86% yield, thus suggesting Mechanism A is the predominant pathway.

We have successfully demonstrated a new method that can be utilized for the rapid synthesis of *E* dienes in good yields and high diastereoselectivities starting from aldehydes. Not only is this methodology synthetically useful, but it is also the first example of directly converting tosyl hydrazones into cyclic diazene intermediates. The one-pot condensation/

cyclization/pericyclic cascade procedure further enhances the synthetic utility and makes it competitive with current diene syntheses from aldehydes. In addition to the synthesis of simple dienes, we are currently exploring this new methodology in a late-stage step for the synthesis of a natural product.

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[21] An erosion of diastereoselectivity was observed if the tributyltin hydride was not distilled prior to use.

[22] Replacing AIBN for 1,1′-azobis(cyclohexanecarbonitrile) (ABCN) yielded identical results. Other metal-hydride sources, such as triphenyltin hydride and tris(trimethylsilyl)silane, provided very low yields.

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[31] All of the starting hydrazines are *E* enriched. The hydrazine **6a** is isolated as a 3:1 mixture of *E*/*Z* isomers while the hydrazines **6b** and **6c** are isolated as a >20:1 mixture of *E* to *Z* isomers.

[32] Direct addition of the tributyltin radical to the nitrogen would be unable to form the nitrogen–tin adduct, as this would require the vinyl bromide to undergo a radical S_N2 displacement by the resulting intermediate carbon radical. No known examples of this transformation could be found in the literature.

[33] It is possible that **13** is formed by the addition of the cyclic hydrazine with tributyltin bromide. However, a control reaction, in which tributyltin bromide was generated in situ in the presence of Boc-hydrazine, did not afford the stannylated product.

[34] Sulfonyl radicals are well-known to form through fragmentation processes. For a review, see: I. Rosenstein in *Radicals in Organic Synthesis*, *Vol. 1*, 1st ed. (Eds.: P. Renaud, M. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 50 – 71.

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