

Stereoselective Synthesis of Dienes  
from *N*-Allylhydrazones

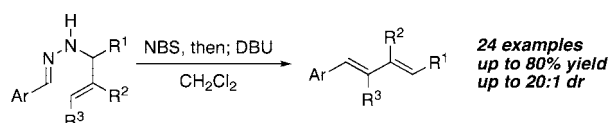
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## ABSTRACT



A new method for the stereoselective synthesis of dienes from aldehydes and *N*-allylhydrazine derivatives has been developed. High levels of (*E*)-stereoselectivity are obtained for a variety of substrates. Addition of a dienophile to the reaction mixture allows a one-flask diene synthesis–cycloaddition sequence.

The development of methods for the stereoselective synthesis of dienes has been an area of long-standing importance to chemists. This importance stems largely from the utility of dienes as substrates for powerful transformations, such as [4 + 2] cycloadditions<sup>1</sup> and Ziegler–Natta polymerizations.<sup>2</sup> Transition-metal-catalyzed  $sp^2$ – $sp^2$  cross-coupling reactions are especially powerful for diene synthesis but typically require that alkene geometry be set in the form of a vinyl derivative prior to bond formation.<sup>3</sup> Enyne cross-metathesis does not require such prefunctionalization but often necessitates that one reacting partner is used in excess.<sup>4</sup> Conversely, diene formation through Wittig, Horner–Wadsworth–Emmons, Julia, and Peterson olefinations can produce mixtures of both (*E*)- and (*Z*)-isomers.<sup>5</sup> Despite the utility of these transformations, there remains significant room for the development of additional complementary processes.

We recently reported a new copper(II) chloride promoted rearrangement of *N*-allylhydrazones (Figure 1).<sup>6</sup> This previ-

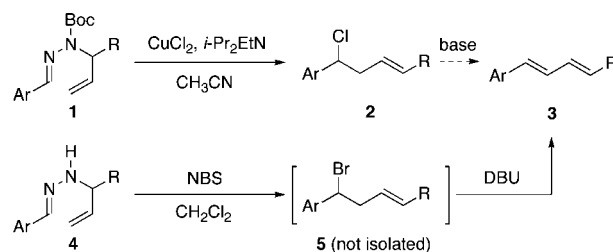


Figure 1. Diene synthesis from *N*-allylhydrazones.

ously unknown transformation provided a number of (*E*)-alkenes from precursors lacking stereodefined alkene geometries (i.e., **1** → **2**).

During the course of investigating this chemistry we wondered whether the chlorine atom, which is also incorporated during the reaction, might undergo stereoselective elimination to afford a diene product in one pot (i.e., **1** → **2**).

(1) For a recent review of [4 + 2] cycloadditions with many relevant dienes, see: Nicolaou, K. C.; Snyder, S. S.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

(2) For two recent reviews, see: (a) Friebe, L.; Nuyken, O.; Obrecht, W. *Adv. Polym. Sci.* **2006**, *204*, 1–154. (b) Fischbach, A. A.; Anwander, R. *Adv. Polym. Sci.* **2006**, *204*, 155–281.

(3) For a recent review of palladium-catalyzed cross-coupling reactions, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.

(4) For recent reviews of enyne metathesis, including sections on cross-metathesis, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18.

(5) For reviews, see the following. Wittig reaction: (a) Vedejs, E.; Peterson, M. J. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; Jai Press Inc.: Greenwich, CT, 1996; Vol. 2. Horner–Wadsworth–Emmons reaction: (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. Modified Julia olefination: (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. I* **2002**, 2563–2585. Peterson olefination: (d) Ager, D. J. *Org. React.* **1990**, *38*, 1–223.

(6) Mundal, D. A.; Lee, J. J.; Thomson, R. J. *J. Am. Chem. Soc.* **2008**, *130*, 1148–1149.

**Table 1.** Development of Initial Bromination Step

| entry | Br                | equiv Br | solvent                         | conversion (%) <sup>a</sup> |
|-------|-------------------|----------|---------------------------------|-----------------------------|
| 1     | CuBr <sub>2</sub> | 2.0      | CH <sub>3</sub> CN              | 95                          |
| 2     | Br <sub>2</sub>   | 2.0      | CH <sub>2</sub> Cl <sub>2</sub> | 0                           |
| 3     | CBr <sub>4</sub>  | 1.1      | CH <sub>2</sub> Cl <sub>2</sub> | no reaction                 |
| 4     | DBH               | 1.1      | CH <sub>2</sub> Cl <sub>2</sub> | >95                         |
| 5     | NBS               | 1.1      | CH <sub>2</sub> Cl <sub>2</sub> | >95                         |

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy.

→ **3**). Unfortunately, elimination of the chloride proved to be prohibitively slow, and the resulting diene was formed in low yield.<sup>7</sup> We had hoped to circumvent this problem by using copper(II) bromide, but this modification led to clean generation of an oxazolidinone through cyclization of the Boc-carbonyl group onto the pendant alkene. We now report the successful implementation of this strategy for diene synthesis, which requires only the sequential addition of *N*-bromosuccinimide (NBS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to *N*-allylhydrazones (i.e., **4** → **5** → **3**).

We initiated our research by preparing the *N*-allylhydrazone **6**, which was synthesized in near quantitative yield through the condensation of allylhydrazine<sup>8</sup> with 2-naphthaldehyde. Exposure of hydrazone **6** to a modification of our original conditions for chlorination, but using copper(II) bromide in place of copper(II) chloride, did provide the corresponding bromide **7**, but with significant formation of 2-naphthaldehyde (Table 1, entry 1). We suspected that this bromination may be occurring by activation of the hydrazone by an electrophilic bromonium ion (Br in Table 1);<sup>9</sup> we therefore treated hydrazone **6** with a variety of common brominating reagents. Bromine failed to provide the desired product and instead gave what appeared to be bromination of the alkene (Table 1, entry 2), whereas carbon tetrabromide induced no reaction (Table 1, entry 3). 1,3-Dibromo-5,5-dimethylhydantoin (DBH) did give the bromide **7** (Table 1, entry 4), but ultimately we found *N*-bromosuccinimide (NBS) to be superior in terms of product purity (Table 1, entry 5).

The addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) directly to the reaction mixture after treating hydrazone **9** (Ar = 2-naphthyl) with NBS and allowing the mixture to warm to room temperature smoothly converted the intermediate bromide to the desired diene **10a** in 78% yield over the two steps from 2-naphthaldehyde (**8a**, Table 2, entry 1). Importantly, the disubstituted alkene was formed with high (*E*)-selectivity (>20:1).<sup>10</sup> In this procedure, the intermediate

**Table 2.** Synthesis of 1-Arylbutadienes

| entry | Ar                                                | yield of <b>10</b> from <b>8</b> (%) <sup>a</sup> | <i>E</i> : <i>Z</i> <sup>b</sup> |
|-------|---------------------------------------------------|---------------------------------------------------|----------------------------------|
| 1     | 2-naphthyl ( <b>8a</b> )                          | 78 ( <b>10a</b> )                                 | 20:1                             |
| 2     | 1-naphthyl ( <b>8b</b> )                          | 75 ( <b>10b</b> )                                 | 20:1                             |
| 3     | Ph ( <b>8c</b> )                                  | 47 ( <b>10c</b> )                                 | 20:1                             |
| 4     | 4-Me-C <sub>6</sub> H <sub>4</sub> ( <b>8d</b> )  | 70 ( <b>10d</b> )                                 | 20:1                             |
| 5     | 3-Me-C <sub>6</sub> H <sub>4</sub> ( <b>8e</b> )  | 65 ( <b>10e</b> )                                 | 20:1                             |
| 6     | 2-Me-C <sub>6</sub> H <sub>4</sub> ( <b>8f</b> )  | 66 ( <b>10f</b> )                                 | 20:1                             |
| 7     | 4-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>8g</b> ) | 70 ( <b>10g</b> )                                 | 20:1                             |
| 8     | 3-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>8h</b> ) | 68 ( <b>10h</b> )                                 | 20:1                             |
| 9     | 2-OMe-C <sub>6</sub> H <sub>4</sub> ( <b>8i</b> ) | 69 ( <b>10i</b> )                                 | 20:1                             |
| 10    | 4-F-C <sub>6</sub> H <sub>4</sub> ( <b>8j</b> )   | 51 ( <b>10j</b> )                                 | 20:1                             |
| 11    | 4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>8k</b> )  | 58 ( <b>10k</b> )                                 | 20:1                             |
| 12    | 4-Br-C <sub>6</sub> H <sub>4</sub> ( <b>8l</b> )  | 46 ( <b>10l</b> )                                 | 20:1                             |

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

hydrazone species **9** was not purified but was subjected directly to the bromination–elimination conditions after evaporation of the solvent. With reliable conditions in hand, we examined the scope of this mild two-step procedure (Table 2).

The condensation–bromination–elimination sequence is tolerant of a wide variety of aromatic aldehydes. Generation of the diene from benzaldehyde (i.e., **8c**) proceeded in only 47% yield as a result of difficulties associated with product volatility. Substituents are tolerated at *ortho*, *meta*, and *para* positions (Table 2, entries 4–12). In all cases the diene products were formed with excellent levels of stereoselectivity (20:1 *E*:*Z* or greater). The successful conversion of electron-rich substrates, in particular 4-methoxybenzaldehyde (**8g**), was especially encouraging since these substrates had performed poorly in the previous copper(II) chloride promoted rearrangement.<sup>6</sup> Unfortunately, aliphatic aldehydes gave mixtures of products.

We next explored the use of a variety of hydrazine fragments to expand the scope of this chemistry to more highly substituted dienes (Table 3). Condensation of the easily prepared *N*-allylhydrazine hydrochloride salts (i.e., **12**)<sup>11</sup> with the desired aldehyde (**11**) in the presence of potassium carbonate gave the desired hydrazones (i.e., **13**). Because of the sensitivity of these hydrazones to decomposition upon prolonged standing, the NBS-initiated diene synthesis was conducted directly on the unpurified hydra-

(7) It seems likely that the base was not compatible with the excess copper(II) chloride used to promote the initial rearrangement.

(8) *N*-Allylhydrazine was purchased from Wako Chemicals.

(9) CuBr<sub>2</sub> is a known source of electrophilic bromide ions; see: Hammer, R. R.; Gregory, N. W. *J. Phys. Chem.* **1964**, 68, 314–317.

(10) This procedure is stereocomplementary to the diene synthesis developed by Yamamoto and co-workers; see: (a) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, 24, 4029–4032. (b) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, 43, 723–730. For an additional recent method for the synthesis of (*Z*)-dienes, see: Steinhart, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, 130, 7560–7561.

(11) Prepared by a modification of the procedure reported by Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *Tetrahedron Lett.* **2000**, 41, 205–207.

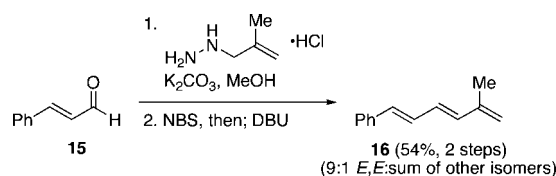
**Table 3.** Di- and Trisubstituted Dienes (Ar = 2-naphthyl)

| entry | diene | yield of <b>14</b> from <b>11</b> (%) <sup>a</sup> | dr <sup>b</sup> |
|-------|-------|----------------------------------------------------|-----------------|
| 1     |       | 68 ( <b>14a</b> )                                  | 20:1            |
| 2     |       | 59 ( <b>14b</b> )                                  | 20:1            |
| 3     |       | 60 ( <b>14c</b> )                                  | 3:1             |
| 4     |       | 63 ( <b>14d</b> )                                  | 10:1            |
| 5     |       | 71 ( <b>14e</b> )                                  | 10:1            |
| 6     |       | 75 ( <b>14f</b> )                                  | 11:1            |
| 7     |       | 80 ( <b>14g</b> )                                  | 10:1            |
| 8     |       | 52 ( <b>14h</b> )                                  | 13:1            |
| 9     |       | 64 ( <b>14i</b> )                                  | 6:1             |
| 10    |       | 66 ( <b>14j</b> )                                  | 20:1            |
| 11    |       | 59 ( <b>14k</b> )                                  | 20:1            |
| 12    |       | 68 ( <b>14l</b> )                                  | 20:1            |

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy; dr refers to *E*:*Z* ratio or major isomer:sum of others.

zones following aqueous workup. In this way, a number of diverse dienes were synthesized in a two-step procedure for the corresponding aldehydes in good yield (Table 3).

Using the previously developed conditions for bromination/elimination, 3-methyldiene **14a** was formed in 68% yield as a 20:1 mixture of *E*:*Z* isomers over the two steps from 2-naphthaldehyde. Similarly, the 2-bromo derivative **14b** could be generated in 59% yield (20:1 *E*:*Z*). The use of a terminally substituted hydrazine fragment **12** (R<sup>1</sup>, R<sup>2</sup> = H, R<sup>3</sup> = Me) provided the 2-methyldiene **14c** in 60% yield from 2-naphthaldehyde, in a 3:1 *E*:*Z* ratio. This ratio reflects the initial diastereoselectivity obtained during the formation of the intermediate bromide species: subsequent elimination of HBr is a stereospecific process affording the mixture of dienes. 1,4-Disubstituted dienes (i.e., **14d–14h**) were generated with good levels of stereoselectivity for the shown (*E,E*)-isomers. We also demonstrated that trisubstituted dienes (i.e.,

**Figure 2.** Triene synthesis.

**14i**) could be prepared from hydrazine **12** (R<sup>1</sup>, R<sup>2</sup> = Me, R<sup>3</sup> = H). While the regioselectivity of the carbon–carbon bond-forming step of the reaction is clearly seen by the regioselective synthesis of **14c** and **14d** from isomeric hydrazones, we provided further evidence in the form the deuterium-labeled diene **14l**. In addition to diene formation, we also showed that *trans*-cinnamaldehyde (**15**) may be converted to the triene **16** in 54% yield using our two-step procedure (Figure 2). This route to trienes may prove to be very useful, and we are investigating the scope of this method.

In our prior work relating to the chlorination of *N*-Boc hydrazones, we hypothesized that the initial carbon–carbon bond-forming step proceeded by a radical–cation induced sigmatropic rearrangement.<sup>6,12</sup> In this case, copper(II) chloride was likely acting as a single-electron oxidant, with chlorine incorporation possibly proceeding through a radical mechanism akin to a Sandmeyer reaction.<sup>13</sup> Although radical reactions are commonplace for NBS, they typically require light; our reaction proceeds in the dark. We therefore favor an ionic mechanism that involves initial bromination of the hydrazone **I** to afford **II**, followed by elimination of bromide ion to generate the unusual diazoallene species **III** (Figure 1).<sup>14</sup> Similar intermediates have been postulated by Barton and co-workers in their pioneering work on the decomposition of hydrazones<sup>15</sup> and may also be intermediates in the Myers and Furrow diazoalkane synthesis from TBS-hydrazones.<sup>16</sup> For our system, we hypothesize that a rapid [3,3] sigmatropic rearrangement<sup>17</sup> ensues to produce diazonium ion **IV**, followed by nucleophilic attack of bromide ion to form **V**. A chair-like transition state for such a rearrangement would lead to the observed (*E*)-selectivity for terminally substituted systems. Elimination of HBr by DBU through an E2-mechanism then affords the diene **VIII** via the conformation with the fewest eclipsing interactions (i.e., **VI** vs **VII**).

(12) Tantillo and Siebert have conducted DFT calculations on our experimental work that support our original hypothesis; see: Siebert, M. R.; Tantillo, D. J. *Org. Lett.* **2008**, *10*, 3219–3222.

(13) Kochi, J. K. *J. Am. Chem. Soc.* **1957**, *79*, 2942–2948.

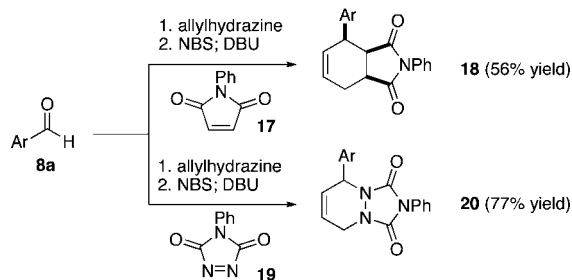
(14) A mechanism involving bromination at carbon, followed by loss of HBr to generate putative intermediate **III** cannot be ruled out at this time.

(15) (a) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470–476. (b) Barton, D. H. R.; Jaszberenyi, J. C.; Shinada, T. *Tetrahedron Lett.* **1993**, *34*, 7191–7194.

(16) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222–12223.

(17) A related sigmatropic rearrangement has been reported; see: Owens, K. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5973–5985. From orbital considerations, such rearrangements may be considered as the microscopic reverse of the well-known propargyl Claisen rearrangement.

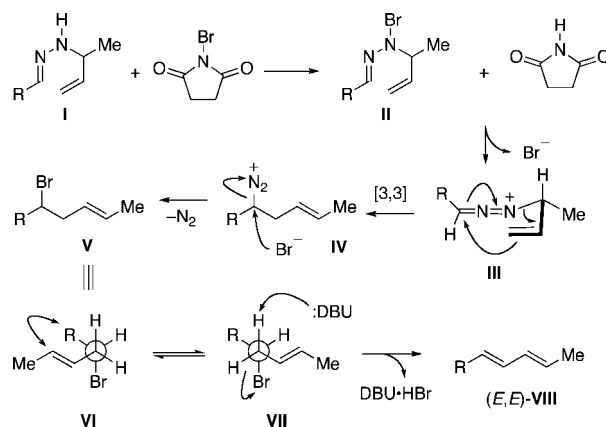
### Scheme 1. Merged Diene Synthesis and Diels–Alder Reaction



We wished to apply this method in conjunction with a subsequent Diels–Alder reaction to rapidly generate more complex molecules from relatively simple precursors (Scheme 1).

When using *N*-phenylmaleimide (**17**) as the dienophile, cycloadduct **18** was obtained in an overall yield of 56% from aldehyde **8a** (Ar = 2-naphthyl). In this case, 1,2-dichloroethane was used as the solvent for the bromination–elimination sequence to effect smooth cycloaddition at 80 °C. The more reactive aza-dienophile **19** underwent cycloaddition at room temperature to afford the diaminated adduct **20** in 77% yield from aldehyde **8a** (Ar = 2-naphthyl).

In summary, by investigating the chemistry of *N*-allylhydrazones we have developed a stereoselective synthesis of dienes from aldehydes that requires only simple precursors and reagents. This process may potentially be utilized for the synthesis of complex molecules, especially if the diene is employed in a subsequent bond-forming transformation,



**Figure 3.** Potential mechanism for diene synthesis.

such as a Diels–Alder cycloaddition. It will be interesting to see whether other electrophiles may be used to initiate this type of hydrazone rearrangement and thus allow for the incorporation of diverse functional groups.

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**Supporting Information Available:** Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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