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E-selective isomerization of stilbenes and stilbenoids through reversible hydroboration

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ABSTRACT

Hydroboration of a mixture of *E* and *Z* stilbenes and stilbenoids is followed by an elimination reaction to yield the *E* isomer with high stereoselectivity. The reaction tolerates aromatic substituents with varying stereoelectronic properties, occurs in one pot, and requires only commercially available reagents. An illustration of the isomerization reaction in a synthesis of resveratrol, a biologically active antioxidant, is presented.

Stilbenes and their substituted derivatives, stilbenoids, have attracted significant attention for their wide range of useful properties, which include applications in optics, biochemistry, and chemotherapy (Fig. 1).[1] Generally the two alkene stereoisomers of a particular *E*/*Z* stilbenoid pair exhibit meaningfully different physiochemical properties. Accordingly, methods for their stereoselective chemical synthesis and derivatization have been intensively investigated, along with strategies for the interconversion of the *E* and *Z* stereoisomers.

The most widely utilized strategy for stilbenoid synthesis[1,2] is the Wittig reaction along with its more modern variants, especially the Horner–Wadsworth–Emmons reaction. A mixture of *E* and *Z* stereoisomers is generally formed, though optimization of conditions can lead to highly selective formation of the *E* stereoisomer.[3]

Comparatively fewer methods have been developed for the selective production of the more thermodynamically stable *E* stilbenoid stereoisomers via isomerization of *E*/*Z* mixtures. The most extensively studied method for the interconversion of the E and *Z* stilbenoid stereoisomers is photoisomerization,[4] and conditions for both the *Z*-to-*E* and *E*-to-*Z* isomerizations have been developed for a wide range of stilbenoids. Competing photocyclization reactions[2a,4] are often observed, and *E*:*Z* ratios are generally quite sensitive to specific conditions, including the substituents on the substrate, solvent, and nature of additives such as sensitizers and quenchers. Nonetheless, the ability to tune conditions to favor production of the less stable *Z* isomer makes photoisomerization a powerful strategy for the stereoselective stilbenoid synthesis.

Radical-based isomerization methods, such as treatment with diaryldiselenides,[5] iodine,[6] or *N*-bromosuccinimide[7] (NBS) offer good *E* selectivity, but each method has limitations. For example, stilbenoids with electron-donating substituents sometimes suffer from competitive iodination of the aromatic rings when iodine is used as a catalyst.[5] Similarly, aromatic bromination was experienced with an NBS-dibenzoylperoxide-azobisisobutyronitrile system.[7] Selenide catalysis sometimes fails when strongly electron-withdrawing substituents are present.[5]

Recently, mild and practical palladium-catalyzed methods have been developed, but these reactions are not effective when electron-withdrawing substituents are present.[8] Collectively, these examples illustrate that additional methods for stilbenoid isomerization are still needed.

We envisioned a one-pot, *E*-selective stilbenoid isomerization sequence that takes advantage of the reversibility of hydroboration in the presence of strongly oxidizing electrophiles (Scheme 1). A mixture of *E* and *Z* stilbene isomers would undergo syn addition of 9-BBN to yield a trialkylborane. The mechanistic reverse of this addition, a syn elimination, must then occur from an eclipsed conformer, which would magnify the destabilizing effects of steric interactions on the conformational equilibrium. Syn elimination of 9-BBN with the powerful oxidant 2-methyl-2-nitrosopropane (MNP) from the least crowded eclipsed conformer should then regenerate the stilbenoid with high *E* stereoselectivity.[9] Elimination on the borane reagent itself is precluded with 9-BBN as it would lead to the generation of a bridgehead alkene, making

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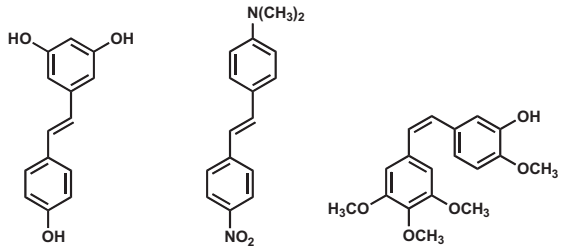
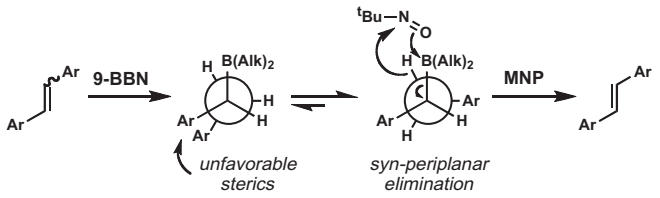
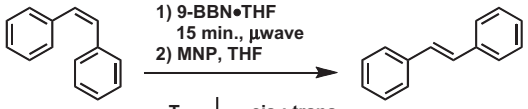


Figure 1. Three stilbenoids with useful chemical properties.



Scheme 1. Rationale for a stereoselective, one-pot, hydroboration–elimination route to *E* stilbenes.



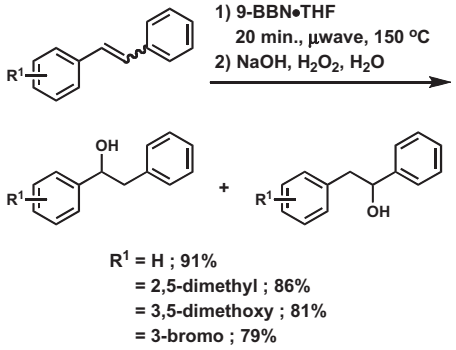
T	cis : trans
75 °C	0.63 : 1.0
100 °C	0.14 : 1.0
125 °C	0.01 : 1.0
150 °C	< 0.01 : 1.0

Scheme 2. Isomerization of cis-stilbene at various temperatures under microwave irradiation at 300 W for 15 min. Ratios were determined by integration of appropriate peaks in the crude product ^{1}H NMR.

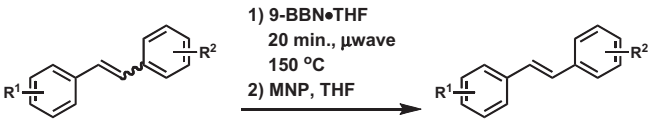
9-BBN a particularly good choice of dialkylborane for this methodology.

Execution of this strategy requires the development of an efficient stilbenoid hydroboration reaction with 9-BBN. Though hydroboration of stilbenes with boronic esters has been explored,[10] the resulting boronate ester intermediate is much less electrophilic than a trialkylborane and would not be expected to undergo facile elimination in the presence of MNP. We therefore chose to first investigate the hydroboration of a model system, *cis*-stilbene, with 9-BBN. Hydroboration of *cis*-stilbene with 9-BBN in THF at room temperature and at reflux was sluggish.[11] Considering that both 9-BBN and trialkylboranes decompose readily on exposure to air and moisture,[12] we felt accelerating the reaction time by heating the reagents in a sealed vessel at temperatures above the boiling point of THF would be advantageous. Accordingly, we investigated the extent of isomerization of *cis*-stilbene at various temperatures after 15 min of microwave irradiation using our two-step procedure (Scheme 2). At 75 °C, the isomerization was 61% complete, whereas at 125 °C the isomerization was essentially complete. No isomerization of *cis*-stilbene was observed after irradiation for 15 min at 150 °C in the absence of 9-BBN.

To verify the effectiveness of the hydroboration step itself, we next subjected *E*/*Z* stilbenoid mixtures to hydroboration followed by a standard peroxide-mediated oxidation (Scheme 3).[13] Product alcohols were obtained in good yields on a variety of stilbenoid



Scheme 3. Microwave-assisted hydroboration–oxidation of various stilbenoids. Yields are of the isolated mixtures of alcohol regioisomers.



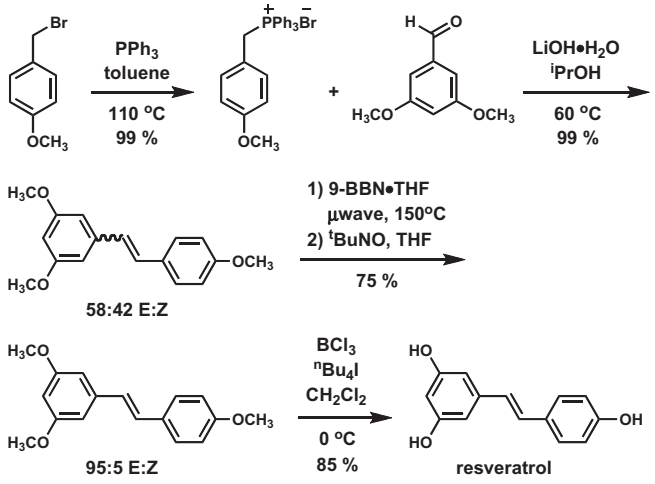
E:Z	R^1	R^2	Entry	E:Z	% Yield
50:50	H	H	1	99:1	75
50:50	2,5-diCH_3	H	2	97:3	73
54:46	2-CF_3	H	3	98:2	69
41:59	3-Br	H	4	99:1	46
52:48	2,5-diCH_3	4-OCH_3	5	97:3	69
58:42	3,5-diOCH_3	4-OCH_3	6	95:5	75
53:47	2-CF_3	4-OCH_3	7	97:3	67

Scheme 4. Microwave-assisted hydroboration–elimination of various stilbenoids. *E*/*Z* ratios were determined by integration of appropriate peaks in the corresponding ^{1}H NMR.

substrates, indicating that the hydroboration reaction is effective on stilbenoids bearing common aromatic substituents with varying steric and electronic properties. A mixture of alcohol regioisomers was obtained in every case, indicating hydroboration is not regioselective. Yields are comparable to those obtained via a rhodium-catalyzed hydroboration–oxidation of stilbenoids with boronate esters.[10]

We then subjected a similar range of substrates to the isomerization sequence and observed very high levels of *E* selectivity (Scheme 4).[14] The isomerization is tolerant of both electron-donating and electron-withdrawing substituents at various positions on the aromatic rings. The lower yields of the isomerizations relative to the oxidations (Scheme 3) indicate that the elimination step proceeds less efficiently than the corresponding oxidation step. We did not evaluate the substituents that are reduced in the presence of dialkylboranes[15] because a nitro group, which is relatively stable to dialkylboranes at lower temperatures, was competitively reduced to an amine at the elevated temperatures used in this study. A stilbenoid that was brominated in the meta position (entry 4) also isomerized with high *E* stereoselectivity but with an unusually low isolated yield.

To illustrate a complete synthesis route that utilizes this methodology we prepared resveratrol, which has generated significant interest in the synthesis community given its intriguing biological activity.[16] Given the high *E* selectivity of our isomerization reaction, we were able to utilize a mild, practical, and high-yielding Wittig reaction[17] despite its low inherent stereoselectivity (Scheme 5). Our isomerization reaction then yields (*E*)-trimethoxyresveratrol in 75% isolated yield. Boron trichloride-mediated deprotection of the methyl ethers produces resveratrol in 85% yield.[18]



Scheme 5. Illustration of a typical *E* stilbenoid synthesis sequence.

In sum, we have developed a new method for the hydroboration of stilbenes with 9-BBN and have applied this reaction to stereoselectively generate *E* stilbenoid stereoisomers from *E*/*Z* mixtures. While this methodology is not tolerant of functional groups that are reduced in the presence of dialkylboranes, it is tolerant of both electron-donating and electron-withdrawing substituents at various positions on the aromatic rings and does not suffer from aromatic substitution side reactions, making it complementary to the existing strategies for stilbenoid isomerization.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra are provided for all new compounds, along with ^{1}H NMR spectra of an example *E*/*Z* stilbenoid starting mixture and crude isomerization product from Scheme 4) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.046.

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13. *Typical procedure:* To 1 equiv of substrate *E*/*Z* mixture in a microwave vial under a positive pressure of Ar was added 9-BBN (0.5 M in THF, 1.1 equiv). The vial was subjected to microwave irradiation (300 W, 20 min.) and then cooled to room temperature. NaOH (1.5 M in H_2O, 2.9 equiv) was added, the solution was cooled to 0 °C, and H_2O_2 (30% in H_2O, 8.2 equiv) was added dropwise. The resulting solution was stirred for 30 min at 0 °C. Extractive work-up ($Et_2O \times 3$), followed by drying of the combined organic layers with $MgSO_4$ and concentration yielded the crude alcohols. Purification was accomplished via column chromatography on silica gel.
14. *Typical procedure:* To 1 equiv of substrate *E*/*Z* mixture in a microwave vial under a positive pressure of Ar was added 9-BBN (0.5 M in THF, 1.1 equiv). The vial was subjected to microwave irradiation (300 W, 20 min) and then cooled to room temperature. MNP dimer (0.6 equiv) dissolved in THF was added, and this solution was stirred for 90 min. The bright clue color of the MNP solution disappeared during this period, at which point the solvent was evaporated to yield the crude *E* stilbenoids. Purification was accomplished via column chromatography on silica gel.
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