



Published in final edited form as:

Angew Chem Int Ed Engl. 2017 December 22; 56(52): 16631–16635. doi:10.1002/anie.201708784.

## Asymmetric Traceless Petasis Borono-Mannich Reactions of Enals: Reductive Transpositions of Allylic Diazenes

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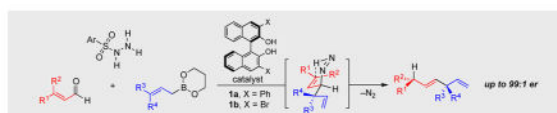
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### Abstract

The traceless Petasis borono-Mannich reaction of enals, sulfonylhydrazines, and allylboronates catalyzed by chiral biphenols results in an asymmetric reductive transposition of the in situ generated allylic diazene. Acyclic 1,4-diene products bearing alkyl- or aryl- substituted benzylic stereocenters are afforded in excellent yields and enantiomeric ratios up to 99:1. The use of crotylboronates in the reaction results in concomitant formation of two stereocenters in a 1,4-*syn* or *anti* relationship from the corresponding *E*- or *Z*-crotylboronate used in the reaction. The use of beta mono-substituted enals in the asymmetric traceless Petasis borono-Mannich reaction of crotylboronates installs tertiary methyl-bearing stereocenters in good yields and high enantioselectivities.

### Leave no trace



Tertiary stereogenic centers are installed by an asymmetric traceless reductive allylboration catalyzed by chiral biphenols. The reaction proceeds via transient enantioenriched allylic diazene species that break down through a sigmatropic rearrangement to generate 1,4-dienes bearing aryl- or alkyl-substituted tertiary stereocenters with high enantio- and diastereoselectivities.

### Keywords

asymmetric synthesis; organocatalysis; diazene; allylation; hydrazones

The retroene<sup>[1]</sup> rearrangement of diazenes proceeds with the loss of dinitrogen via a concerted pericyclic reaction pathway.<sup>[2]</sup> The stereospecific nature of the transformation results in the efficient transfer of chirality in a 1,3-atom transfer process.<sup>[3]</sup> We reported the

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catalytic enantioselective traceless Petasis reaction, a reaction that uses 1,3-chirality transfer from an enantioenriched propargylic diazene to generate an axially chiral allene.<sup>[4]</sup> Herein we describe the reaction of allylic diazenes to give rise to products bearing tertiary alkyl stereocenters,<sup>[5]</sup> following the allylic diazene rearrangement. The intermediate diazene is formed in situ by fragmentation of the corresponding allylic sulfonylhydrazide, synthesized by a chiral biphenol-catalyzed Petasis borono-Mannich reaction of sulfonylhydrazides, enals, and allylboronates (Scheme 1).<sup>[6][7]</sup> Subsequent rearrangement of the enantioenriched diazene, with concomitant extrusion of molecular nitrogen, results in the allylic transposition of chirality from the diazene stereocenter to the allylic, sp<sup>2</sup> hybridized carbon center. When a  $\gamma$ -substituted allylboronate (R<sup>3</sup> or R<sup>4</sup> = methyl) is employed, two tertiary stereocenters in a 1,4-relationship are generated in a stereoselective manner.

Strategies employing 1,3-chirality transfer by the allylic diazene rearrangement have been elegantly utilized in asymmetric synthesis, notably for the installation of stereocenters within cyclic systems.<sup>[8]</sup> For this approach, methods to access the requisite sulfonyl hydrazine precursor include trapping of carbonium ions<sup>[8a]</sup>, displacement of terminal alcohols<sup>[8b, 8c]</sup> by sulfonylhydrazides, asymmetric hydride reduction controlled by cyclic substrates,<sup>[8d-j]</sup> and Diels–Alder cycloadditions of 1-hydrazino dienes.<sup>[8k, 8l]</sup> While these advances are significant, an enantioselective catalytic reaction that provides access to acyclic allylic diazenes has been elusive. Only two methods describing the asymmetric synthesis of tertiary stereocenters via acyclic allylic diazenes exist. First, McIntosh and co-workers developed a diastereoselective reduction of an acyclic tosylhydrazone facilitated by a proximal  $\alpha$ -alkoxy stereocenter, resulting in a methyl-substituted tertiary stereocenter.<sup>[9]</sup> Second, Movassaghi and co-workers reported a palladium-catalyzed conversion of enantioenriched allylic epoxides to diazenes, which afforded methyl-substituted tertiary stereocenters adjacent to secondary alcohols.<sup>[10]</sup> Despite the efficient acyclic stereocontrol achieved by these methods, the formation of the enantioenriched allylic diazenes prior to the chirality transfer relied on the use of optically active starting materials containing oxygenated stereocenters. In order to access the desired chiral secondary hydrazine, we designed an approach that would directly generate acyclic allylic diazenes from achiral substrates using a BINOL-catalyzed traceless Petasis reaction.

We began by investigating the asymmetric Petasis allylation with  $\beta$ -methyl enals using chiral biphenols catalysts. The 3,3'-Ph<sub>2</sub>-BINOL catalyst **1a** proved ideal for enantiomeric control, consistent with our previous observations in the asymmetric allylation of imines (Scheme 2).<sup>[6a, 6e]</sup> In addition, the electron-deficient hydrazide **2a** was identified as optimal for producing the highest yields of the desired rearranged products **5**. The multicomponent reaction proceeded with initial generation of the hydrazone by condensation of enals **3** with hydrazide **2a** in the presence of 3 Å molecular sieves. After removal of the solvent in vacuo, the unpurified hydrazone was dissolved in toluene and to this mixture was added *t*-BuOH (3 equivalents), catalyst (*R*)-**1a** (7 mol%) and allyl boronate **4** at room temperature. The reaction generated the corresponding enantioenriched 1,4-dienes **5** after stirring at room temperature for 48 hours. The reaction tolerated  $\beta$ -aryl- $\beta$ -methyl enal substrates, furnishing allylated products bearing benzylic stereocenters in good yields and with excellent enantioselectivities (Scheme 2, **5a–5e**). The observed absolute stereochemistry was

consistent with the previously reported biphenol-catalyzed borono-Mannich allylation reaction (see Supporting Information for absolute stereochemical determination).<sup>[6c]</sup> 3-(Thiophen-2-yl)but-2-enal (**3f**) was also a suitable substrate, affording the product **5f** in 73% isolated yield and an enantiomeric ratio (e.r.) of 99:1. (*Z*)- $\beta$ -Silyl- $\beta$ -methyl enal **3g** yielded the corresponding chiral silane **5g** in high enantiomeric purity with the use of 5 equivalents of *t*-BuOH in the absence of toluene. The addition of *t*-BuOH as an additive was found to accelerate the catalytic pathway while impeding the uncatalyzed reaction, consistent with previous observations.<sup>[11]</sup> Geranial (**3h**), a  $\beta$ -alkyl- $\beta$ -methyl enal, proved to be a challenging substrate, affording product **5h** with modest enantioselectivity (85:15 e.r.). The lack of enantioselectivity observed was due to facile *E/Z* isomerization of the corresponding hydrazone intermediate, as either hydrazone isomer would give rise to opposite enantiomers.<sup>[12]</sup>

We sought to expand the scope of the reaction by placing other functional groups at the  $\beta$ -position of the enal (Scheme 3). Under the same conditions used for  $\beta$ -methyl enals, however,  $\beta$ -ethyl enal **6a** afforded the corresponding product in lower yield and with reduced enantioselectivity (41% yield, 82:18 e.r.). The nature of the sulfonylhydrazide and the biphenol catalyst proved crucial to the reactivity and selectivity of the traceless Petasis allylation. In a two-dimensional evaluation of arylsulfonyl hydrazides and catalysts (see Supplementary Information for details), 2-NO<sub>2</sub>-benzenesulfonyl hydrazide **2b** and 3,3'-Br<sub>2</sub>-BINOL catalyst **1b** proved to be optimal for  $\beta,\beta$ -disubstituted enals with substituents larger than a methyl group (Scheme 3). Under these conditions, the corresponding products were thereby accessed with excellent enantioselectivity (Scheme 3, **7a-7c**). The allylation product **7d** containing a stereogenic benzylic CF<sub>3</sub> group was formed in good yield and with high selectivity (85% yield, 97:3 e.r.), an approach complementary to existing strategies.<sup>[13]</sup> The monofluoromethyl-substituted product **7e** was also produced in good yield and with high enantiopurity. Under these reaction conditions, the olefin geometry of the enals determined the stereochemical outcome. Thus, the reaction of the *Z*-enal catalyzed by (*R*)-Br<sub>2</sub>-BINOL (**1b**) afforded the (*S*)-product **7c** in 82% yield and with a 98:2 enantiomeric ratio, while the same product [i.e., (*S*)-**7c**] was obtained by using (*E*)-enal **8** with the enantiomeric catalyst (*S*)-**1b**, albeit in lower yield and with slightly diminished enantiomeric purity (60% yield, 94:6 e.r.).

Tertiary diarylmethane stereocenters are a moiety that appears in natural products and pharmaceuticals.<sup>[14]</sup> While there have been recent notable advances in accessing these structures enantioselectively,<sup>[15]</sup> we envisaged that use of the traceless Petasis reaction would provide access to diarylmethane tertiary stereocenters through a complementary strategy.  $\beta,\beta$ -Diaryl enals proved to be good substrates for the optimized reductive allylation conditions. The corresponding 1,4-dienes bearing diaryl-substituted tertiary stereocenters were obtained with excellent yields and enantioselectivities, irrespective of the steric or electronic properties of the aryl substituents (Scheme 3, **7f-7k**).

We have previously disclosed that both *syn* and *anti*  $\alpha$ -methyl amines were accessible by an asymmetric Petasis borono-Mannich crotylation of aldehydes and amines.<sup>[6c]</sup> To investigate related reactivity in the reductive allylation,  $\beta$ -methyl cinnamaldehyde **3a** was subjected to the crotylation conditions using either (*E*)-crotylboronate **9** or (*Z*)-crotylboronate **10**

(Scheme 4). The Petasis products were postulated to provide access to both *syn* and *anti*  $\alpha$ -methyl diazene intermediates after the elimination of sulfinic acid. As anticipated, the reaction afforded diene products bearing two methyl-substituted tertiary stereogenic centers with a 1,4-*syn* or *anti* stereochemistry (Scheme 4, **11a** and **12a**).  $\beta,\beta$ -Diaryl enal **6k** also proved to be a viable substrate, providing access to both 1,4-disubstituted acyclic products **11b** and **12b** with good selectivity. The observed sense of enantio- and diastereoselectivity was consistent with the stereochemical outcome from the previously reported asymmetric Petasis crotylations.<sup>[6e]</sup> The lower diastereoselectivity for **12a** and **12b** resulting from (*Z*)-crotylboronate was presumably due to an unfavorable 1,3-diaxial interaction between the terminal methyl group from the boronate and the arylsulfonyl group on the nitrogen arising from a cyclic transition state.<sup>[16]</sup> Notably, this method achieved high levels of stereocontrol in acyclic hydrocarbons bearing 1,4-stereocenters without using any directing functional groups. The results compare favorably with existing methods to directly access tertiary alkyl stereocenters in a 1,4-relationship using asymmetric cycloadditions.<sup>[8l, 17]</sup> The observed diastereoselectivity was consistent with the previously reported biphenol-catalyzed borono-Mannich allylation reaction.<sup>[6e]</sup>

The methyl-substituted stereocenters generated in the crotylation reaction (Scheme 4) encouraged us to further explore the possibility of introducing branched methyl groups in 1,4-dienes. We investigated this strategy by subjecting cinnamaldehyde **13a** to the crotylboration conditions using hydrazide **2a**, 3,3'-Ph<sub>2</sub>-BINOL catalyst **1a**, and (*E*)-crotylboronate **9** (Scheme 5). The desired methyl-branched hydrocarbon product **14a** was isolated in 85% yield with a 97:3 enantiomeric ratio. Other cinnamaldehyde derivatives were successfully converted to the corresponding enantioenriched 1,4-dienes with excellent selectivities (Scheme 5, **14b–14e**). Enantioenriched 1,4,7-triene (**14g**) was also obtained under similar conditions albeit in moderate yield (54% yield, 98:2 e.r.). Similarly,  $\beta$ -alkyl enal **13h** displayed attenuated reactivity, affording the diene product **14h** in modest yield but with excellent enantioselectivity when using **1b** as the catalyst (54% yield, 99:1 e.r.). Given the operational ease of the reaction and the generally high level of selectivities, we anticipate that this methodology will find useful applications in the total synthesis of the natural products bearing the methyl-substituted stereocenters.<sup>[18]</sup>

In summary, we have developed an asymmetric reductive allylation of aldehydes that affords tertiary alkyl stereocenters using chiral biphenol catalysts. The reaction proceeds via the sigmatropic rearrangement of a transient enantioenriched allylic diazene intermediate; a process mechanistically distinct from the reductive coupling of boronic acids with tosylhydrazones via diazo intermediates.<sup>[19]</sup> Both allylation and crotylation reactions provide access to 1,4-dienes bearing tertiary alkyl-substituted stereocenters in excellent yields and high enantioselectivities. Key aspects of the methodology include the exclusive generation of (*E*)-alkenes by allylic transposition, and the traceless installation of two stereocenters within acyclic systems. Further exploration of the observed reactivity within the context of asymmetric catalysis is underway and will be reported in due course.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

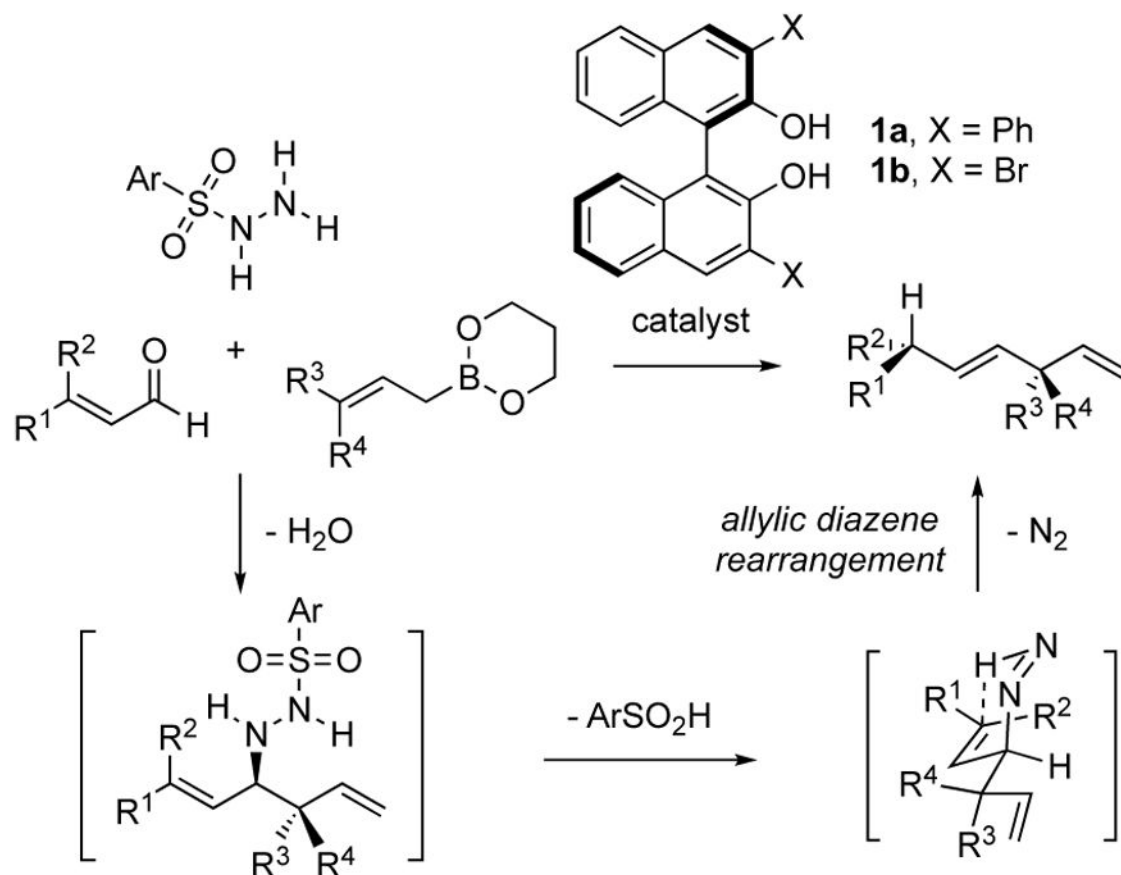
The research was supported by the National Institutes of Health (R01 GM078240 to SES) and the National Science Foundation (CHE1361173 to RJT).

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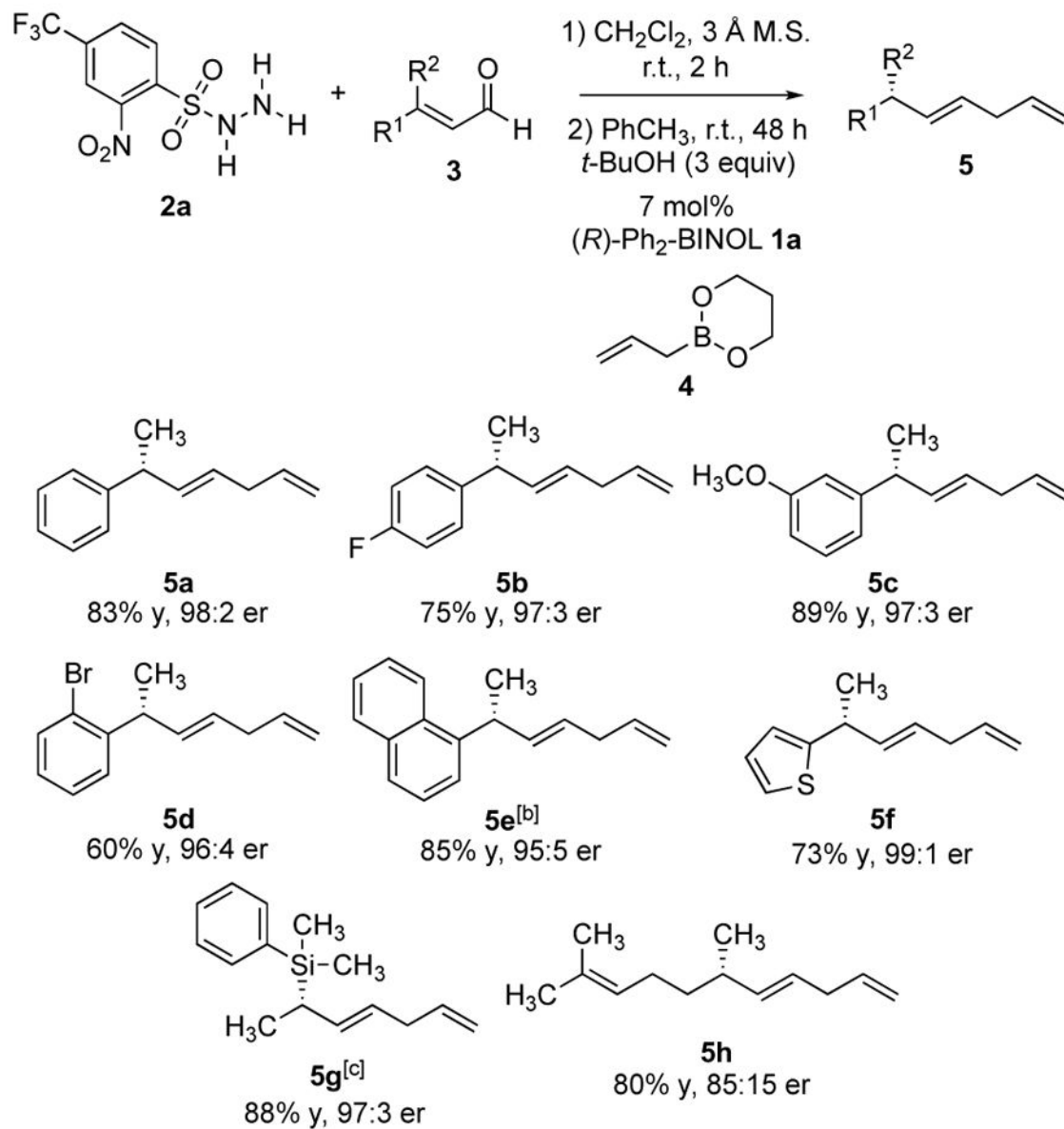
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**Scheme 1.**

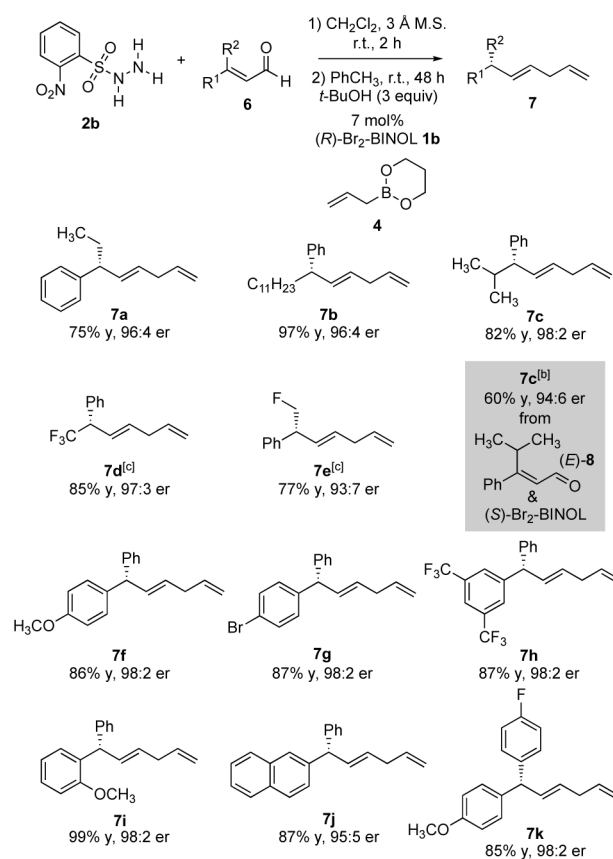
Asymmetric traceless Petasis borono-Mannich reactions of enals resulting in the reductive transpositions of allylic diazenes. The reaction generates 1,4-dienes bearing tertiary carbon stereocenters with high levels of enantioselectivity.



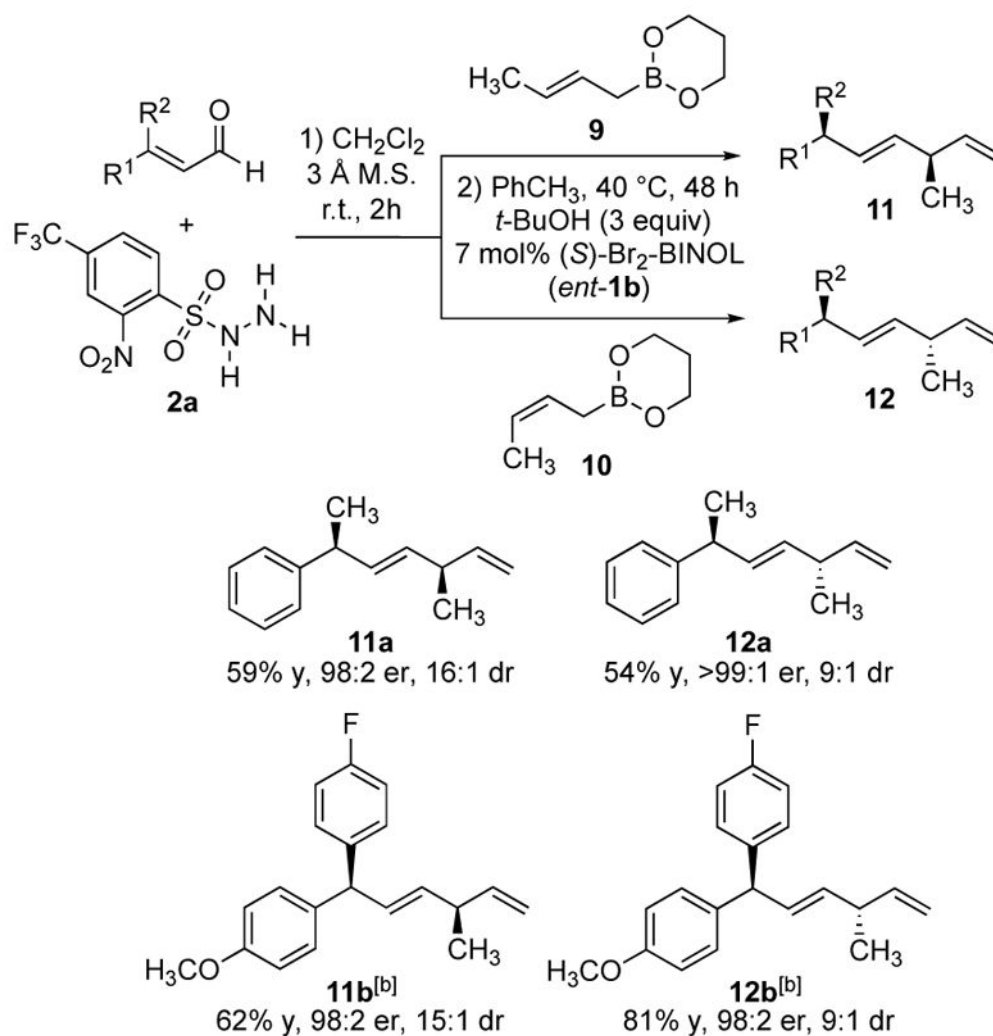
**Scheme 2.**

Enantioselective reductive allylation of  $\beta$ -methyl enals.<sup>[a]</sup> [a] All reactions were run on 0.4 mmol scale. Yields of isolated products are given. The e.r. values were determined by HPLC analysis using chiral stationary phases. [b] Reaction was run at 1 M concentration. [c] 5 equivalents of *t*-BuOH were used in the absence of toluene. The (*Z*)-silyl enal **3g** was used in the reaction. See Supplementary Information for experimental details and stereochemical proof.

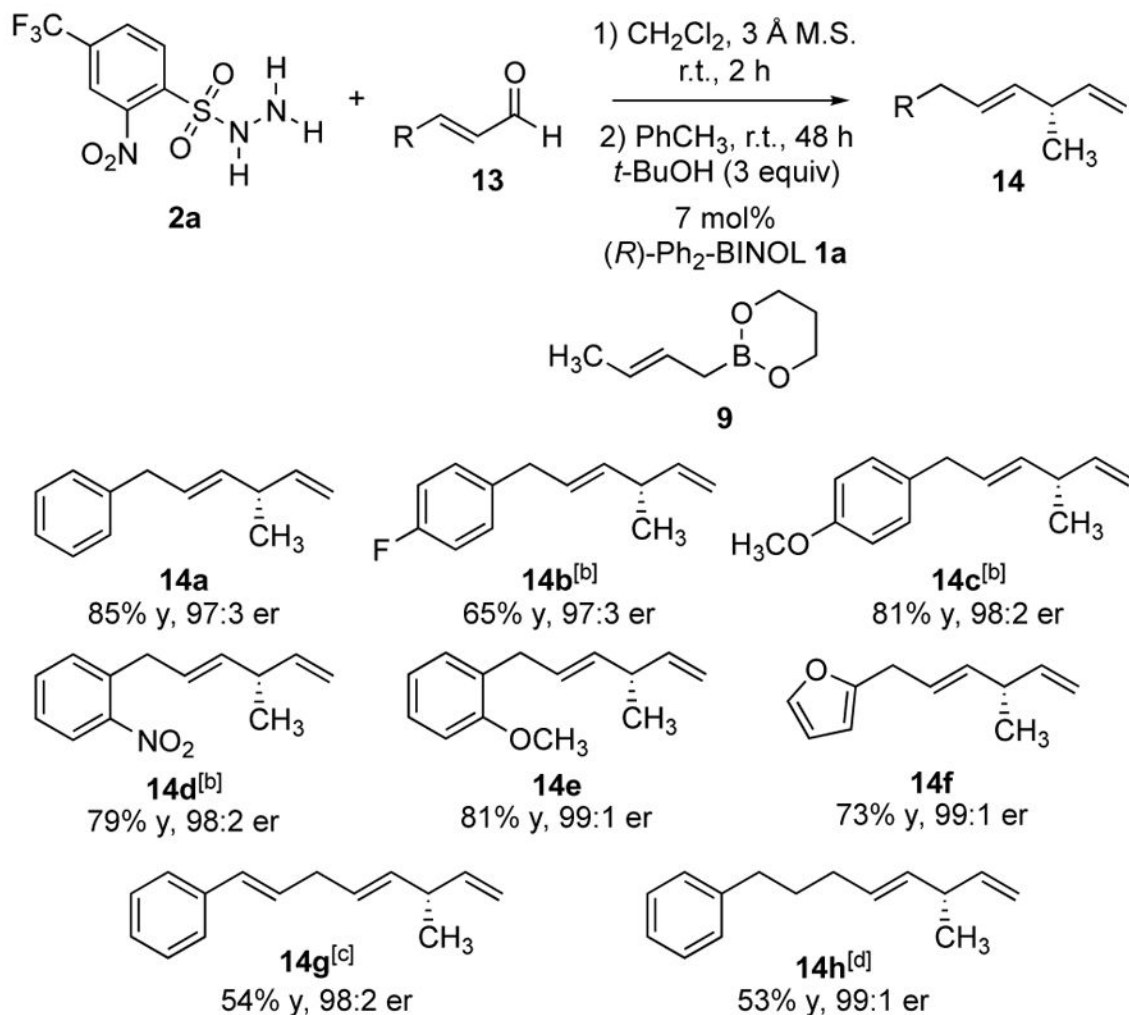


**Scheme 3.**

Enantioselective reductive allylation of  $\beta,\beta$ -disubstituted enals.<sup>[a]</sup> [a] All reactions were run at 0.4 mmol scale. Yields of isolated products are given. The e.r. values were determined by HPLC analysis using chiral stationary phases. [b]  $(S)$ - $\text{Br}_2$ -BINOL (*ent*-**1b**) and enal  $(E)$ -**8** were used. [c] 5 equivalents of *t*-BuOH was employed in the absence of toluene. See Supplementary Information for experimental details.

**Scheme 4.**

Diastereoselective reductive crotylations of  $\beta,\beta$ -disubstituted enals.<sup>[a]</sup> [a] All reactions were run on 0.4 mmol scale. Yields of isolated products are given. The values of e.r. and diastereomeric ratio (d.r.) were determined by HPLC analysis using chiral stationary phases. [b] 10 mol% catalyst was employed. See Supplementary Information for experimental details.

**Scheme 5.**

Enantioselective reductive crotylation of non-branched enals.<sup>[a]</sup> [a] All reactions were run on 0.4 mmol scale. Yields of isolated products are given. The e.r. values were determined by HPLC analysis using chiral stationary phases. [b] Reactions were run at 50 °C for 24 h. [c] 14 mol% of catalyst was employed. [d] 14 mol % of (*R*)-**1b** was employed. See Supplementary Information for experimental details and stereochemical proofs.