JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions

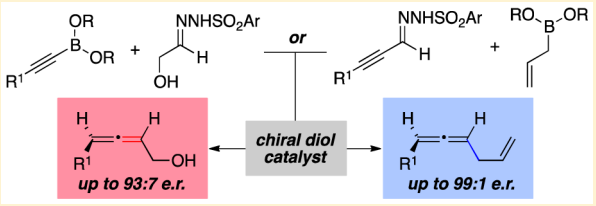
Yao Jiang,[†] Abdallah B. Diagne,[‡] Regan J. Thomson,*[,‡] and Scott E. Schaus*[,†]

[†]Center for Molecular Discovery, Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

[‡]Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, United States

Supporting Information

ABSTRACT: Allenes are useful functional groups in synthesis as a result of their inherent chemical properties and established reactivity patterns. One property of chemical bonding renders 1,3-substituted allenes chiral, making them attractive targets for asymmetric synthesis. While there are many enantioselective methods to synthesize chiral allenes from chiral starting materials, fewer methods exist to directly synthesize enantioenriched chiral allenes from achiral precursors. We report here an asymmetric boronate addition to sulfonyl hydrazones catalyzed by chiral biphenols to access enantioenriched allenes in a traceless Petasis reaction. The resulting Mannich product from nucleophilic addition eliminates sulfinic acid, yielding a propargylic diazene that performs an alkyne walk to afford the allene. Two enantioselective approaches have been developed; alkynyl boronates add to glycolaldehyde imine to afford allylic hydroxyl allenes, and allyl boronates add to alkynyl imines to form 1,3-alkenyl allenes. In both cases, the products are obtained in high yields and enantioselectivities.



INTRODUCTION

Allenes first appeared in the chemical literature over 140 years ago when van't Hoff predicted their existence in a now historic publication in 1875.[1] Twelve years later, in 1887, Burton and von Pechmann reported the first experimental preparation of an allene, although the structure of the prepared molecule was described incorrectly as an alkyne isomer.[2] Confirmation of the correct structure did not occur until 1954, following detailed spectroscopic investigations by Whiting and co-workers.[3] In a curious inversion of characterization, the correct structure of a natural product isolated from *Carlina acaulis* was shown to be an alkyne,[4] not the isomeric allene as had been originally proposed in 1906.[5] Perhaps because of such challenges in characterization, allenes were considered for many years to be unstable entities, more structural oddities than useful compounds. We now know that allenes are widely distributed in nature and featured as key structural elements in a diverse range of natural products, bioactive small molecules, and materials.[5,6] Allenes are highly versatile intermediates for synthesis, participating in numerous powerful chemical transformations.[7,8] The development of methods for the concise synthesis of allenes has therefore been an area of intense research for many years.[9] As predicted by van't Hoff in 1875,[1] the orthogonal relationship between the adjacent π systems within the allene structure gives rise to the possibility of axial chirality, which has inspired the development of methods that enable the enantioselective synthesis of allenes.[10−12] Traditional approaches have typically involved the stereospecific transformation of chiral propargylic precursors, such as [3,3][13,14] and [2,3][15] sigmatropic rearrangements, S_N2' displacements,[16−22] and reductive transposition.[23] Strategies using stoichiometric chiral reagents have also been developed,[24] as well as those employing kinetic resolution of preformed racemic allenes.[25] Contemporary efforts have focused on devising asymmetric catalytic reactions,[11] including useful metal-catalyzed approaches based on the transformation of achiral dienes,[26] conjugated enynes,[27,28] vinyl triflates,[29] and terminal alkynes,[30,31] as well as the dynamic kinetic resolution of chiral racemic allenes.[32] Organocatalytic methods have been developed recently,[33−36] such as an enantioselective alleno-Mannich reaction employing phase-transfer catalysis[35] and an enantioselective alkynylogous Mukaiyama aldol reaction using a chiral phosphoric acid catalyst.[36] While significant advances have been made, the development of broadly useful and convergent strategies to synthesize enantioenriched chiral allenes from achiral precursors remains a significant challenge.

In 2012, we reported an approach to the direct synthesis of allenes through what we termed a traceless Petasis reaction.[37,38] The reaction proceeds by the addition of an alkynyltrifluoroborate salt into a sulfonylhydrazone to generate an intermediate propargylic hydrazide. Fragmentation with loss of sulfinic acid produces an unstable propargylic diazene species that decomposes by a retro-ene reaction to form the corresponding allene as a racemate. Prior work by the Myers lab had shown that the retro-ene reaction of enantioenriched propargylic diazenes derived from the corresponding propargylic alcohols proceeds with complete chirality transfer to

Received: November 18, 2016
Published: January 25, 2017

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998−2005

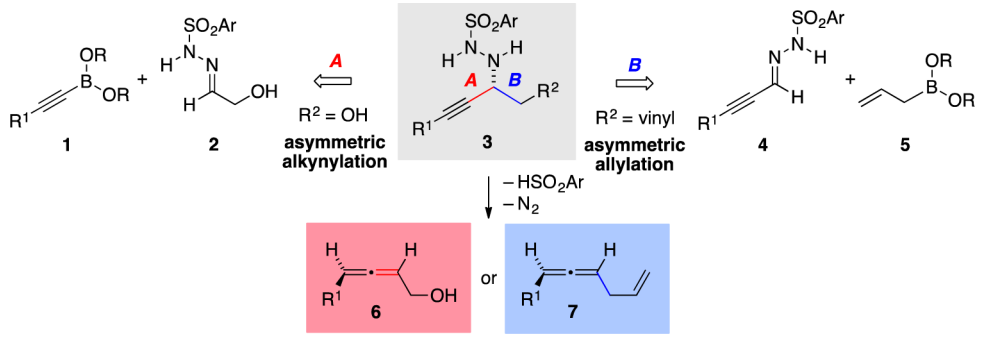
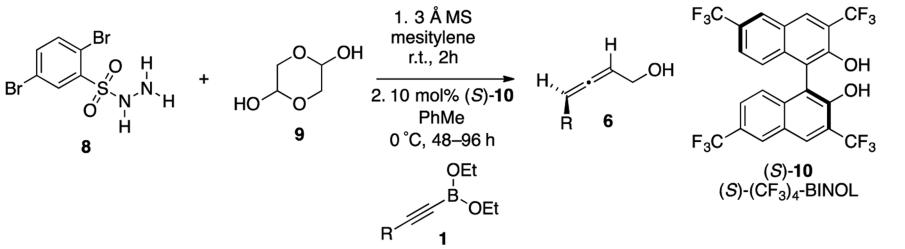
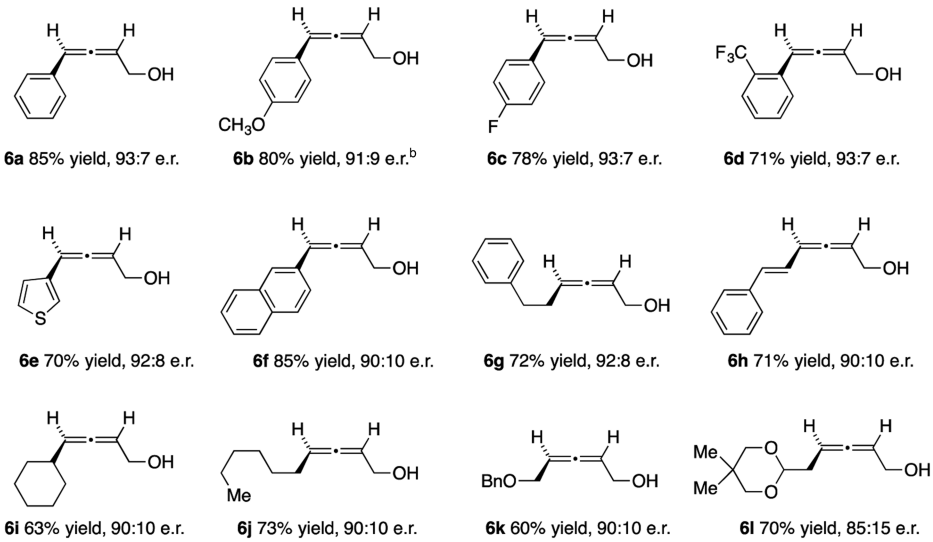


Figure 1. Development of an enantioselective allene synthesis reaction. Asymmetric routes to chiral allenes from (*A*) alkynyl boronate addition to glycolaldehyde imine and (*B*) allylation of alkynyl hydrazones.

Table 1. Substrate Scope of Enantioselective Allene Synthesis via Alkynyl Boronates[a]





[a]Under each product the percent yield and enantiomeric ratio (e.r.) or diastereomeric ratio (d.r.) are given. Yields are isolated yields (0.4 mmol scale). The e.r. or d.r. was determined by HPLC analysis using a chiral stationary phase. Abbreviations: Bn, benzyl; n-Bu, *n*-butyl; t-Bu, *tert*-butyl. See the Supporting Information for experimental details. [b]20 mol % catalyst was used at −10 °C for 48 h.

produce enantioenriched allenes.[23] We reasoned that it should be possible to develop an enantioselective traceless Petasis reaction by leveraging the known ability of chiral diols to catalyze regular Petasis reactions with high levels of asymmetric induction.[39−42]

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998−2005

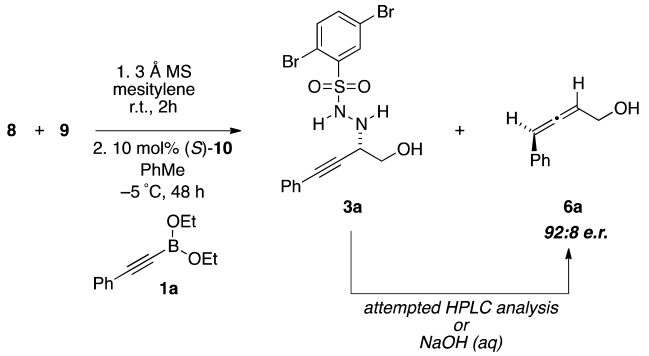


Figure 2. Isolation of hydrazide intermediate **3a**.

We sought to devise a strategy to access optically enriched propargylic hydrazides (i.e., **3**) by the addition of an appropriate boron reagent (Figure 1). An analysis of the two possible carbon–carbon bond disconnections on either side of the hydrazide functionality within **3** reveals the possibility of two distinct approaches to develop an enantioselective, catalytic traceless Petasis reaction depending on the nature of the R^2 substituent. When R^2 = OH, disconnection of bond ***A*** (red) within **3** leads back to alkynyl boronate **1** and hydrazone **2** as potential reaction partners in a manner that closely resembles the initial traceless Petasis reaction[37] and to the previously reported enantioselective alkynylation of acyl imines.[40] Like almost all Petasis-type reactions, including our initial traceless variant, the presence of the hydroxyl functional group within **2** is required for an effective reaction to proceed via coordination to the boron nucleophile.[43] Thus, path ***A*** (red) provides a direct and convenient method for accessing enantioenriched α-allenols that complements existing procedures.[10−12]

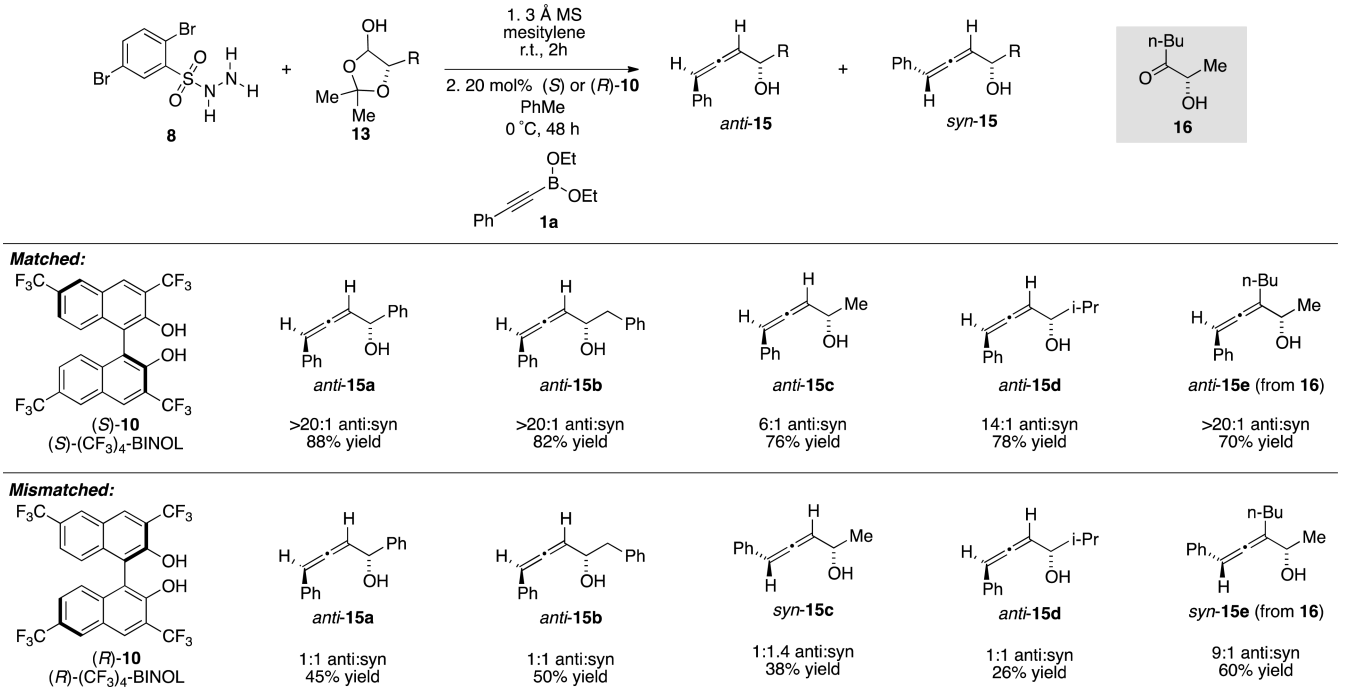
When R^2 = vinyl, the alternative disconnection of bond ***B*** (blue) within hydrazide **3** generates propargylic hydrazone **4** and nucleophilic allyl boronate component **5** as potential reaction partners. For this latter reaction, activation of the boronate by a hydroxyl substituent on the hydrazone was considered unnecessary because of the capacity of allylboron reagents to add via closed transition states, as observed in the corresponding asymmetric allylation of imines.[41,44] In a sense, this particular reaction is truly traceless in that the allene products obtained do not contain the remnants of functional groups required for the reaction to proceed (cf. the previous case that requires the hydroxyl group). The ease with which these simple chiral allenes can be accessed in a convergent manner is an especially powerful aspect of the reaction.

Herein we report the successful development of both approaches outlined in Figure 1, enabling direct access to two classes of enantioenriched allenes, **6** and **7**, from readily available precursors.

RESULTS AND DISCUSSION

Traceless Petasis Reaction of Alkynyl Boronates and Glycolaldehyde. We began by designing experiments to develop the asymmetric traceless Petasis Mannich reaction of alkynyl boronates catalyzed by chiral biphenols. Two parameters were determined to be most important: the identity of the sulfonyl hydrazide used to make the hydrazone and the chiral biphenol catalyst employed in the reaction. A two-dimensional evaluation of both parameters identified 2,5-dibromophenylsulfonyl hydrazide (**8**) and 3,3′,6,6′-$(CF_3)_4$-BINOL (**10**) to be optimal for the reaction, with enhanced selectivity observed using a toluene/mesitylene solvent mixture (see the Supporting Information for details). We found that quenching the reaction with aqueous NaOH and allowing the reaction mixture to warm

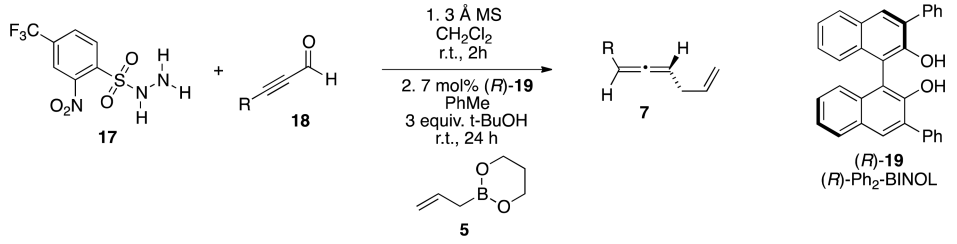
Table 2. Diastereoselective Allene Synthesis[a]

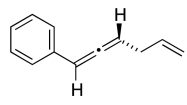


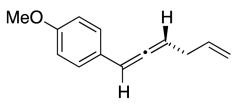
[a]Under each product, the percent yield and diastereomeric ratio (anti:syn) are given. Yields are isolated yields (0.4 mmol scale). The d.r. was determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. Abbreviations: n-Bu, *n*-butyl; Ph, phenyl. See the Supporting Information for experimental details and stereochemical proofs.

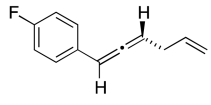
DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998–2005

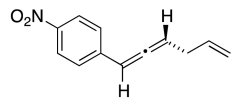
Table 3. Substrate Scope of Enantioselective Allene Synthesis from Alkynyl Aldehydes[a]

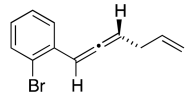


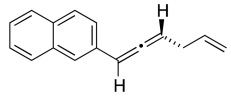

7a 83% yield, 99:1 e.r.

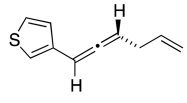

7b 88% yield, 98:2 e.r.

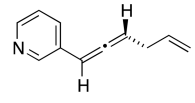

7c 87% yield, 99:1 e.r.

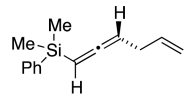

7d 87% yield, 98:2 e.r.

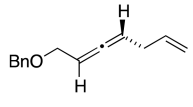

7e 60% yield, 99:1 e.r.

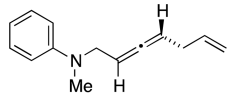

7f 89% yield, 98:2 e.r.

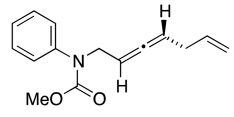

7g 87% yield, 99:1 e.r.

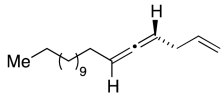

7h 27% yield[b], 98:2 e.r.

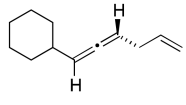

7i 73% yield, 98:2 e.r.

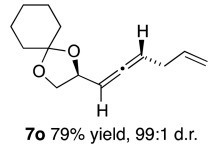

7j 90% yield, 98:2 e.r.


7k 50% yield[c], 99:1 e.r.


7l 85% yield[c], 99:1 e.r.


7m 98% yield, 98:2 e.r.


7n 62% yield, 99:1 e.r.


7o 79% yield, 99:1 d.r.

[a]Under each product the percent yield and enantiomeric ratio (e.r.) or diastereomeric ratio (d.r.) are given. Yields are isolated yields (0.4 mmol scale). The e.r. or d.r. was determined by HPLC analysis using a chiral stationary phase. Abbreviations: Bn, benzyl; Ph, phenyl. See the Supporting Information for experimental details and stereochemical proofs. [b]3 equiv of boronate was used. [c]40 h.

to room temperature facilitated efficient conversion of any undecomposed intermediate propargylic hydrazide to the desired allene product (see Figure 2). Under our optimized conditions, the reaction of phenylalkynyl boronate **1** (R = Ph) with glycolaldehyde using 10 mol % chiral biphenol catalyst **10** afforded the chiral allene in 85% isolated yield with 93:7 enantiomeric ratio (e.r.). The reaction proved general for electron-rich and electron-poor arylalkynyl boronates (**6a–f**) with enantioselectivities ranging from 90:10 to 93:7 (Table 1). Similarly, aliphatic and unsaturated boronates could be used in the reaction (**6g–k**), achieving commensurate levels of enantioselectivity. A trialkylsilylalkynyl boronate performed the reaction well, achieving the highest level of enantioselectivity (**6m**, 62% yield with 95:5 e.r.). α-Hydroxyacetone (**11**) could also be used as an electrophile to generate trisubstituted allene **6n** (91% yield with 90:10 e.r.). The reaction could also be adapted for more complex substrates requiring multistep synthesis of the boronates. Cyclic boronates such as **12** are stable toward chromatographic conditions but are less reactive toward exchange with the biphenol catalyst. We therefore developed a set of conditions that facilitates boronate exchange of cyclic boronate **12** by the addition of trialkoxyborate. These modified reaction conditions could be used to promote the catalyst-controlled diastereoselective traceless Petasis reaction of chiral alkynyl boronates (e.g., **12**) with good selectivity and yields (**6o**, 71% yield, 93:7 d.r. and **6p**, 68% yield, 91:9 d.r. for (*S*)-**10** and (*R*)-**10**, respectively).

During our experiments to optimize the reaction conditions, we identified and characterized the initial Petasis borono-Mannich reaction product (Figure 2). When the reaction mixture was kept at −5 °C, the addition of alkynyl boronate **1a** to the glycolaldehyde hydrazone derived from **8** and **9** formed the corresponding hydrazide **3a** and allenyl alcohol **6a** as a separable mixture (see the Supporting Information for details). Attempts to directly determine the enantiopurity of **3a** were unsuccessful; subjecting hydrazide **3a** to chiral HPLC analysis resulted in concomitant diazene formation and rearrangement to afford chiral allenyl alcohol **6a** in a 92:8 enantiomeric ratio. Furthermore, treating hydrazide **3a** with aqueous NaOH also resulted in the formation of allenyl alcohol **6a** in a 92:8 enantiomeric ratio. These observations support the original hypothesis that a stereoselective Petasis borono-Mannich reaction of sulfonyl hydrazones would result in the formation of enantioenriched chiral allenes via the formation of propargylic hydrazide intermediates. The isolation of hydrazide **3a** also clearly defines the developed reaction as mechanistically distinct from the reaction recently reported by Wang and co-workers, wherein sulfonyl hydrazones are transformed into enantioenriched allenes by initial conversion of the hydrazone to a diazo intermediate that undergoes a subsequent copper-catalyzed coupling with a terminal alkyne.[31]

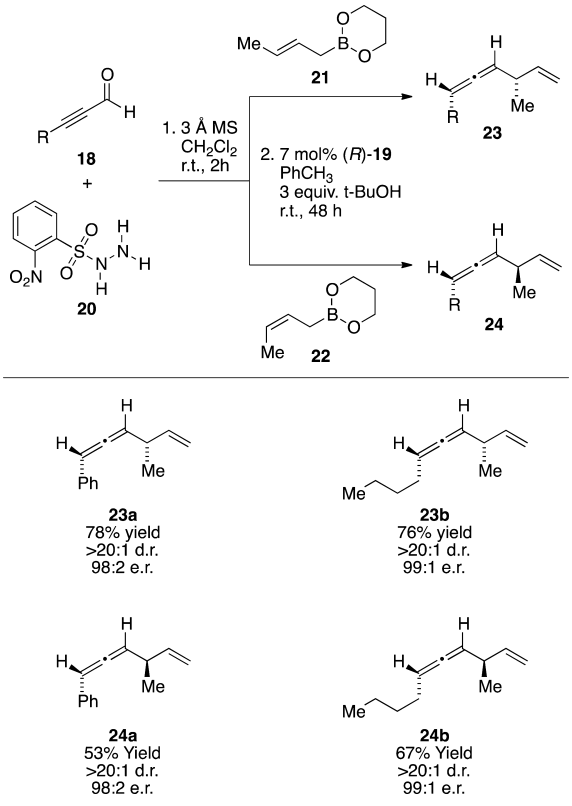
DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998–2005

Diastereoselective Traceless Petasis Reaction of Alkynyl Boronates and Chiral α-Hydroxy Aldehydes. We next investigated the use of chiral α-hydroxy aldehydes in the traceless Petasis reaction catalyzed by chiral biphenols (Table 2). For ease of preparation, stability, and general utility, the reaction employed 2,2-dimethyl-1,3-dioxolan-4-ol, a synthetic precursor that readily decomposes to the α-hydroxy imine in the presence of amines.[42] Our hope was that the diastereomeric outcome of the reaction could be controlled by the catalyst rather than by the substrate. The inherent selectivity, as we have shown before, ranges from 2−5 to 1 in the formation of the anti product, *anti*-**15**.[42] As we anticipated, one catalyst enantiomer, (*S*)-**10**, gave rise to enhanced selectivity in the formation of *anti*-**15** from the (*S*)-α-hydroxy aldehyde precursor **13**. Selectivities as high as 20:1 (anti:syn) could be achieved under optimal conditions in good overall yields (>70% isolated yield) for this matched scenario. However, the use of the (*R*)-**10** catalyst only resulted in a 1:1 mixture of diastereomers; the catalyst was unable to completely overturn the inherent selectivity. Correspondingly, the yields were lower for this case than for the (*S*)-**10**-catalyzed reaction, supporting the hypothesis of a catalyst-mediated process, albeit slower as a result of a diastereomeric transition state that does not promote the reaction because of mismatched steric constraints. Finally, the reaction of enantiopure α-hydroxy ketone **16** also resulted in excellent diastereoselectivity (*anti*-**15e**; Table 2); the anti product was obtained with >20:1 selectivity in 70% isolated yield. Unfortunately, the enantiomeric catalyst (*R*)-**10** was unable to affect the anti selectivity when used in the reaction, resulting in 9:1 diastereomeric ratio still favoring the anti diastereomer. While we were unable to achieve our desired goal of a completely catalyst-controlled diastereoselective process, the method reported herein will be useful for synthetic plans that require the anti isomer of an α-allenol.

Traceless Petasis Reaction of Alkynyl Aldehydes. We next sought to pursue a strategy that uses alkynyl aldehydes in the traceless Petasis Mannich reaction with allyl boronates as the nucleophile. Similar to our observations of alkynyl boronates reacting with glycolaldehyde, the identities of the sulfonyl hydrazide and the chiral biphenol catalyst employed in the traceless Petasis reaction proved to be important for the yield and selectivity. 2-Nitro-4-trifluoromethylphenylsulfonyl hydrazide (**17**) afforded the desired products in the highest yields and enantioselectivities (Table 3). The 3,3′-Ph_2-BINOL catalyst **19** proved to be ideal for the enantioselectivity, an observation we have also made in asymmetric imine allylboration reactions.[41] Typical reaction conditions involved the reaction of the alkynyl aldehyde 3-phenylpropiolaldehyde (**18a**) with hydrazide **17** at room temperature for in situ formation of the hydrazone. After concentration, the crude hydrazone was dissolved in toluene with the addition of *t*-BuOH (3 equiv), catalyst (*R*)-**19** (7 mol %), and allyl boronate **5** at room temperature for 24 h, affording the enantioenriched allene in 87% isolated yield with 99:1 enantiomeric ratio. The reaction was general for both electron-rich and electron-poor arylpropiolaldehyde substrates, affording the products (**7a**−**f**) with >98:2 enantiomeric ratio. Heterocyclic propiolaldehydes were also good substrates for the reaction (>98:2 e.r.), although the pyridylpropiolaldehyde resulted in a low yield (**7h**, 27% yield, 98:2 e.r.), presumably because the nitrogenated heterocycle acts as a Lewis base to inhibit the reaction. Silylpropiolaldehyde (**7i**, 73% yield, 98:2 e.r.) and propargylic heteroatom-bearing propiolaldehydes were also good substrates for the reaction (**7j**−**l**). Likewise, aliphatic propiolaldehydes were also effectively converted to the corresponding enantioenriched allenes (**7m** and **7n**) with >98:2 enantiomeric ratio. Finally, the diastereoselective reaction of a protected chiral 1,2-diol-substituted propionaldehyde afforded the product **7o** in good yield (79%) with excellent diastereoselectivity (99:1 d.r.). Overall, the asymmetric allylation of propiolaldehyde hydrazones in the traceless Petasis reaction is an excellent method to access structurally simple enantioeneriched allenes.

Stereodivergent and Diastereoselective Traceless Petasis Reaction of Alkynyl Aldehydes. In order to develop a stereodivergent approach toward the synthesis of α-substituted enantioenriched allenes (i.e., **23** and **24**), we investigated the use of crotyl boronates as nucleophiles. The reaction of propiolaldehyde **18a** with hydrazide **17** using (*E*)-crotyldioxaborinane (**21**) provided the syn diastereomer **23a** with excellent enantio- and diastereoselectivity. Disappointingly, under the same conditions, (*Z*)-crotyldioxaborinane (**22**) afforded the anti diastereomer **24a** with lower enantioselectivity (64:36 e.r.). Changing the hydrazide structure had a remarkable impact on the reaction generality, however. The use of hydrazide **20** with phenylpropiolaldehye and catalyst (*R*)-**19** enable highly stereoselective reactions with both **21** and **22** to deliver allenes (R_a,*S*)-**23a** and (R_a,*R*)-**24a**, respectively (Table 4). The reactions also worked well for hept-2-ynal to produce the corresponding aliphatic allenes (R_a,*S*)-**23b** and (R_a,*R*)-**24b**. Thus, under a standard set of reaction conditions, either diastereomeric

Table 4. Stereodivergent Synthesis of Chiral Allenes[a]



[a]Under each product the percent yield, diastereomeric ratio (d.r.), and enantiomeric ratio (e.r.) are given. Yields are isolated yields (0.4 mmol scale). The e.r. and d.r. were determined by HPLC analysis using chiral stationary phases. Ph, phenyl. See the Supporting Information for experimental details and stereochemical proofs.

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998−2005

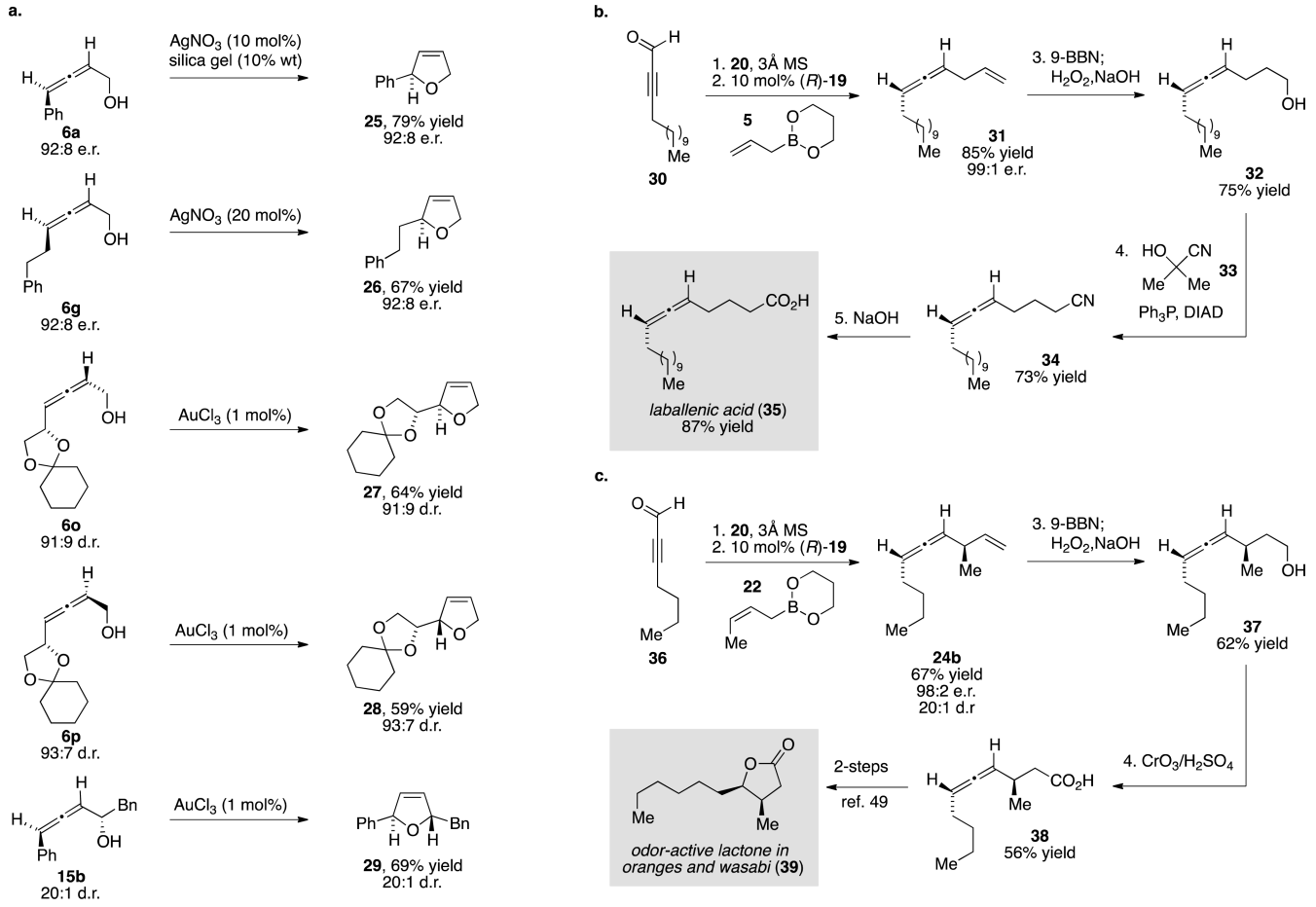


Figure 3. Utility of the chiral allene products prepared from traceless Petasis reactions. (a) Stereospecific cycloetherifications yield substituted dihydrofurans. (b) An efficient synthesis of laballenic acid (**35**), a major constituent of *Leonotis nepetaefolia* seed oil. (c) A formal total synthesis of **39**, an odor-active lactone component of oranges and wasabi, intercepting Ma's intermediate (i.e., **38**).

product, (R_a,*S*)-**23** or (R_a,*R*)-**24**, could be obtained simply by changing the olefin geometry of the boronate, indicating that transfer of chirality from the catalyst to the product most likely proceeds through a closed six-membered transition state. Use of the antipodal catalyst (*S*)-**19** under these conditions would provide access to the enantiomeric pair of diastereomeric allene products in this new stereodivergent traceless Petasis reaction.

Synthetic Utility of the Enantioenriched Allene Products. The enantioenriched allenes available through either one of the methods reported herein are versatile intermediates that may be further elaborated into a number of useful products (Figure 3). For example, when treated with either Au(III) or Ag(I) catalysts, the allenols formed by the traceless Petasis reaction with glycolaldehyde dimer underwent smooth cycloetherification to deliver enantioenriched dihydrofurans with complete transfer of stereochemical information (Figure 3a).[25,45,46] In some cases we noticed that the choice of catalyst was critical for complete stereochemical transfer. As an illustration, the attempted cyclization of phenyl-substituted allene **6a** using $AuCl_3$[45] led to significant erosion of the enantiopurity, while $AgNO_3$ (10 mol % on silica gel)[25] induced cyclization of **6a** with no change in the enantiomeric ratio. The use of $AgNO_3$ (20 mol %) in acetone/water[46] was the most effective for the cyclization of **6g**, while $AuCl_3$ (1 mol %)[45] was effective for most of the other substrates investigated (i.e., **6o**, **6p**, and **15b**) (see the Supporting Information for additional examples).

The allene products generated through the enantioselective allylation route (see Tables 3 and 4) were also converted to interesting natural products (Figure 3b,c). A key transformation that demonstrates the utility of these products is the chemoselective hydroboration of the terminal alkene over the less reactive internal allene π system using 9-borabicyclo[3.3.1]-nonane (9-BBN). Thus, allene **31** was transformed to alcohol **32** in 75% yield, and subsequent cyanation and hydrolysis delivered laballenic acid (**35**) in a highly efficient manner.[47,48] Similarly, allene **24b** could be converted to alcohol **37** by hydroboration with 9-BBN, and then carboxylic acid **38** was obtained from **37** by treatment with Jones reagent. Ma and coworkers previously demonstrated that acid **38** could be transformed in two steps to lactone **39** through a novel stereoselective iodolactonization,[49] and thus, access to acid **38** through our methodology completes a six-step formal synthesis of this natural product.[50]

■ CONCLUSIONS

Reactions that result in the direct formation of carbon−carbon bonds with the simultaneous generation of elements of stereochemistry are particularly powerful in synthetic pursuits. When applied in a rational manner to the synthesis of complex targets, such reactions enable the rapid generation of complexity from simple starting materials. The two catalytic enantioselective traceless Petasis reactions reported herein are powerful new examples of such fragment-coupling reactions that enable the

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998−2005

efficient asymmetric synthesis of chiral allenes from achiral precursors. Both reaction manifolds utilize boron nucleophiles that add to sulfonyl hydrazones to generate chiral propargylic hydrazides, which decompose to form unstable diazene intermediates. Retro-ene fragmentation of the enantioenriched diazene intermediates results in a stereospecific point-to-axial transfer of chirality, generating the allene products with concomitant loss of dinitrogen. The catalytic and enantioselective generation of transient chiral diazene intermediates represents a unique and somewhat nonobvious approach to asymmetric synthesis that is currently underdeveloped. Sorensen and co-workers have reported the asymmetric Diels–Alder reaction and subsequent retro-ene decomposition of 1-hydrazinodienes,[51] while the Movassaghi lab developed an enantioselective route to allylic diazenes through a palladium-catalyzed asymmetric alkylation of sulfonyl hydrazones.[52] Together with our work, these reactions represent rare examples of catalytically generated enantioenriched diazene intermediates. Further exploration of these species within the context of asymmetric catalysis is likely to reveal a range of similarly useful chemical transformations of broad utility for synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11937.

All experimental procedures, complete characterization (NMR, MS, IR, and optical rotation) of all new compounds, and HPLC assays for determination of enantiopurity (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*r-thomson@northwestern.edu

*seschaus@bu.edu

ORCID

Yao Jiang: 0000-0002-6137-1126

Regan J. Thomson: 0000-0001-5546-4038

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.E.S. and Y.J. gratefully acknowledge the NIH for research support (R01 GM078240) and instrumentation (P50 GM067041). R.J.T. and A.B.D. gratefully acknowledge the NSF for research support (CHE1361173) and the ARCS Foundation for the Daniel D. and Ada L. Rice Foundation Scholarship to A.B.D.

■ REFERENCES

(1) van't Hoff, J. H. *La Chimie dans L'Espace*; Bazendijk: Rotterdam, 1875.

(2) Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

(3) Jones, E. R. H.; Shaw, B. L.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3212.

(4) Crombie, L.; Harper, S. H.; Thompson, D. *J. Chem. Soc.* **1951**, 2906.

(5) Hoffmann-Roder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.

(6) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818.

(7) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(8) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *113*, 7287.

(9) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

(10) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259.

(11) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014**, *4*, 519.

(12) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 1210.

(13) Henderson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4736.

(14) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.

(15) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

(16) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(17) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083.

(18) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

(19) Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874.

(20) Tang, X.; Woodward, S.; Krause, N. *Eur. J. Org. Chem.* **2009**, *2009*, 2836.

(21) Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362.

(22) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. *Nat. Commun.* **2015**, *6*, 7946.

(23) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(24) Lü, R.; Ye, J.; Cao, T.; Chen, B.; Fan, W.; Lin, W.; Liu, J.; Luo, H.; Miao, B.; Ni, S.; Tang, X.; Wang, N.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Zhang, W.; Zhu, C.; Ma, S. *Org. Lett.* **2013**, *15*, 2254.

(25) Deska, J.; Backvall, J.-E. *Org. Biomol. Chem.* **2009**, *7*, 3379.

(26) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

(27) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12865.

(28) Wang, M.; Liu, Z.-L.; Zhang, X.; Tian, P.-P.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 14830.

(29) Crouch, I. T.; Neff, R. K.; Frantz, D. E. *J. Am. Chem. Soc.* **2013**, *135*, 4970.

(30) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. *Org. Lett.* **2012**, *14*, 1346.

(31) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2016**, *138*, 14558.

(32) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.

(33) Qian, H.; Yu, X.; Zhang, J.; Sun, J. *J. Am. Chem. Soc.* **2013**, *135*, 18020.

(34) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212.

(35) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240.

(36) Tap, A.; Blond, A.; Wakchaure, V. N.; List, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 8962.

(37) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2012**, *134*, 5782.

(38) Diagne, A. B.; Li, S.; Perkowski, G. A.; Mrksich, M.; Thomson, R. J. *ACS Comb. Sci.* **2015**, *17*, 658.

(39) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922.

(40) Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337.

(41) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.

(42) Muncipinto, G.; Moquist, P. N.; Schreiber, S. L.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8172.

(43) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169.

(44) Jiang, Y.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2017**, DOI: 10.1002/anie.201611332.

(45) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.

(46) Ye, J.; Fan, W.; Ma, S. *Chem. - Eur. J.* **2013**, *19*, 716.

(47) Bagby, M. O.; Smith, C. R.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 4227.

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998–2005

(48) Tang, X. J.; Huang, X.; Cao, T.; Han, Y. L.; Jiang, X. G.; Lin, W. L.; Tang, Y.; Zhang, J. S.; Yu, Q.; Fu, C. L.; Ma, S. M. *Org. Chem. Front.* **2015**, *2*, 688.
(49) Zhang, X.; Fu, C.; Yu, Y.; Ma, S. *Chem. - Eur. J.* **2012**, *18*, 13501.
(50) Masuzawa, Y.; Tamogami, S.; Kitahara, T. *Nat. Prod. Lett.* **1999**, *13*, 239.
(51) Xie, H.; Sammis, G. M.; Flamme, E. M.; Kraml, C. M.; Sorensen, E. J. *Chem. - Eur. J.* **2011**, *17*, 11131.
(52) Movassaghi, M.; Ahmad, O. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 8909.

DOI: 10.1021/jacs.6b11937
J. Am. Chem. Soc. 2017, 139, 1998−2005