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A Direct Synthesis of Allenes by a Traceless Petasis Reaction

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Supporting Information

ABSTRACT: A one-pot synthesis of allenes by the 2-nitrobenzenesulfonylhydrazide-mediated coupling of hydroxyaldehydes or ketones with alkynyl trifluoroborate salts is reported. This mild process involves in situ formation of a sulfonylhydrazone that reacts with alkynyl trifluoroborates to generate a transient propargylic hydrazide species. Decomposition of this unstable hydrazide via an intermediate monoalkyldiazine produces the allene products through an alkene walk mechanism.

The one-pot coupling of a boronic acid with an amine and an aldehyde, as first reported by Petasis and co-workers in 1993,[1] constitutes one of the most direct and mild methods for preparing stereogenic carbinamines.[2] Not only does this powerful reaction, now known as the Petasis borono-Mannich reaction, facilitate the generation of stereogenic carbinamines, it is also an exceptionally efficient fragment coupling reaction that can proceed with high levels of both enantioselectivity[3] or diastereoselectivity.[4] Our entry point into Petasis-type chemistry stemmed from our interest in developing fragment couplings via hydrazone intermediates.[5] We envisioned a scenario wherein an arenesulfonylhydrazide might participate in a Petasis-type coupling reaction with an α-hydroxyaldehyde and an alkynyl boron nucleophile, to generate an allene product instead of the usual amine adduct (Figure 1). The allene

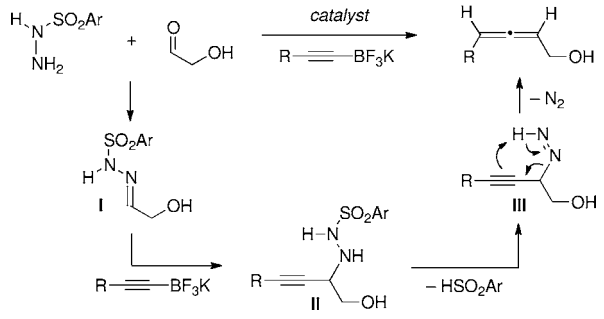

Figure 1. Traceless Petasis reaction.

substructure is found within numerous biologically active compounds[6] and is a versatile handle for a number of powerful transformations.[7] As such, new methods for the straightforward and efficient generation of allenes are highly desirable.

Key to the success of this proposed reaction would be the addition of the alkynyl nucleophile into hydrazone **I** to generate propargyl hydrazide **II**. Loss of sulfinic acid to afford diazine **III** and subsequent extrusion of nitrogen through an alkene walk pathway (retro-ene process) would produce the desired allene product. Related additions of organometal species into preformed tosylhydrazones have been reported,[8,9] while precedent for the reductive transposition of propargylic diazines is found within the elegant work by the Myers group, who reported the synthesis of allenes from propargylic alcohols via intermediates akin to **III**.[10] In this communication, we report the successful development of a new one-pot synthesis of allenes that proceeds through the coupling of a hydroxy aldehyde or ketone with 2-nitrobenzenesulfonylhydrazine (NBSH) and an alkynyl trifluoroborate salt. We refer to this new process as a traceless Petasis reaction.

We initiated our studies using the phenyl-substituted alkynyl trifluoroborate salt **1a**,[11,12] glycoaldehyde dimer (**2**), and *p*-tosylhydrazide (**3a**). Combining all three reagents in an equimolar ratio afforded none of the desired product (**4a**, Table 1, entry 1).

Lewis acids such as $Sc(OTf)_3$ are known to promote hydrazone formation,[13] and we anticipated that the addition of such a metal salt to our reaction mixture might facilitate both hydrazone formation and alkyne addition (i.e., the formation of **I** and **II** in Figure 1). Indeed, the addition of 10 mol % $Sc(OTf)_3$ led to formation of a new product we identified as the intermediate propargyl hydrazide (i.e., **II**), but it was found that elimination of the sulfinic acid residue was not facile under the reaction conditions (Table 1, entry 2). During their studies on the reductive transposition of propargylic alcohols, Myers and co-workers found that 2-nitrobenzenesulfonylhydrazides were superior precursors to diazine species, losing 2-nitrobenzenesulfinic acid much more rapidly than the corresponding *p*-tosyl derivatives.[10c,14] As we had hoped, using NBSH (**3b**, Ns = 2-nitrobenzenesulfonyl) in place of *p*-tosylhydrazide (**3a**) gave rise to the desired allene product (i.e., **4a**) in 49% yield in the absence of any catalyst (Table 1, entry 3). The addition of 10 mol % $Sc(OTf)_3$, however, gave a much cleaner reaction and allowed the isolation of allene **4** in 66% yield (Table 1, entry 4). A survey of various Lewis acids revealed that 10 mol % $La(OTf)_3$ provided allene **4** in the greatest isolated yield (78%, Table 1, entry 8). During this development stage and in preliminary investigations into the use of other alkyne salts, we noted that homogeneous reaction mixtures were never obtained, and product yields were inconsistent. A solvent screen revealed that acetonitrile provided superior solubility of all reagents with the added benefit of an improved isolated yield of 86% for **4a** (Table 1, entry 9).

A variety of aryl and alkyl acetylide salts[11] participated in the reaction to afford the corresponding allenes in good to excellent yield (Table 2). In general, aryl acetylides afforded

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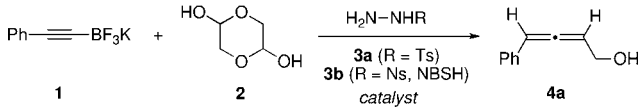
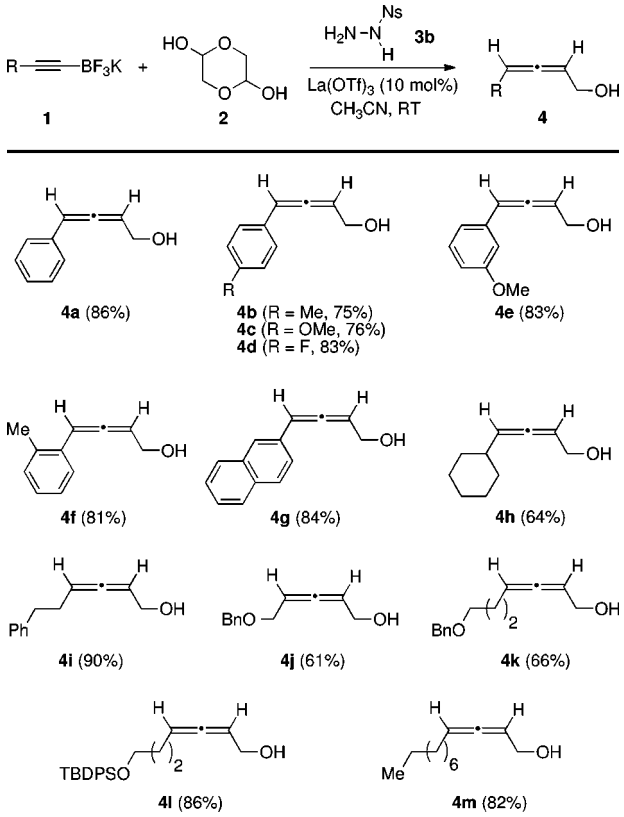
Table 1. Development of the Traceless Petasis Coupling[a]



entry	Hydrazide	catalyst (10 mol %)	yield 4a (%)[b]
1	**3a**	–	0
2	**3a**	$Sc(OTf)_3$	0 (90%)[c]
3	**3b**	–	49
4	**3b**	$Sc(OTf)_3$	66
5	**3b**	$Cu(OTf)_2$	0
6	**3b**	$Yb(OTf)_3$	73
7	**3b**	$Hf(OTf)_4$	62
8	**3b**	$La(OTf)_3$	78
9[d]	**3b**	$La(OTf)_3$	86

[a]**1** (0.75 mmol), **2** (0.25 mmol), **3** (0.5 mmol) in CH_2Cl_2, rt. [b]Isolated yield after chromatography. [c]Isolated yield of intermediate propargylic hydrazide. [d]Reaction conducted in CH_3CN.

Table 2. Alkynyl Partners in the Traceless Petasis Coupling[a]

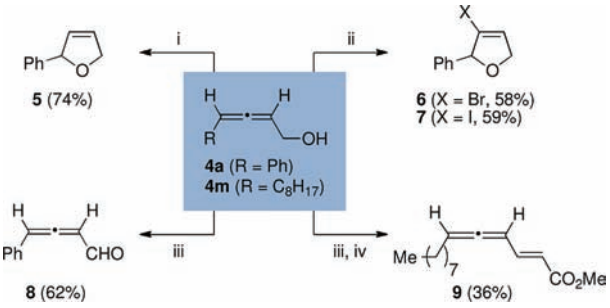


[a]**1** (0.75 mmol), **2** (0.25 mmol), **3b** (0.5 mmol) in CH_3CN, rt. Yields refer to isolated yields after chromatography.

the cleanest and highest yielding reactions (Table 2, **4a**–**4g**). These reactions also tended to proceed in the shortest time, an observation that is consistent with the enhanced migratory aptitude of the more electron-rich triple bond. A number of aliphatic alkynes underwent the reaction (Table 2, **4h**–**4m**). Benzyl ether derivatives behaved well (i.e., **4j** and **4k**), as did a TBDPS ether derivative (i.e., **4l**). In contrast, an alkynyl trifluoroborate possessing a TBS protected alcohol proved unstable and delivered the corresponding allene in low yield.

These allenes are useful precursors to a variety of compounds (Scheme 1), including dihydrofurans **5**–**7** and allenic aldehydes

Scheme 1. Utility of Allenyl Alcohol Products[a]



[a]Conditions: (i) $AgNO_3$ (20 mol %), acetone, reflux; (ii) Br_2 or I_2; (iii) Dess–Martin periodinane; (iv) $(EtO)_2P(O)CH_2CO_2Me$, NaH, −78 °C.

(i.e., **8**).[7] Allene **4m** could be prepared in 82% yield and converted to the sensitive triene **9**, which is the sex attractant of the dried bean beetle.[15]

Examples of the Petasis borono-Mannich reaction typically require the use of an aldehyde that has an α-hydroxyl group, or a related group that is capable of directing the addition of the boron species to the C–N π-bond (i.e., glyoxylic acid and salicaldehyde).[2] The traceless Petasis reaction did not work well with aldehydes lacking an α-hydroxyl group; benzyloxyacetaldehyde gave only a 23% isolated yield of the allene product (not shown). Thus, in a manner analogous to the proposed mechanism for the regular Petasis reaction,[2] the alkyne is most likely delivered to the intermediate hydrazone intramolecularly via an activated borate species. High levels of diastereocontrol for *anti*-amino alcohols, consistent with internal delivery, have been reported for several chiral α-hydroxyl aldehydes participating in the Petasis borono-Mannich reaction.[16] For the traceless Petasis reaction herein, we found that protected aldehyde **10** gave rise to allene **12** as a 2:1 mixture of diastereomers (88% yield, Scheme 2). Enantioenriched **10** could be employed with no loss of optical activity.[11] The major diastereomer was converted to tetrahydrofuran **13** by Au-catalyzed stereospecific cycloetherification[17] followed by an NBSH-derived diimide reduction (60% over 2 steps). The presence of strong reciprocal NOE signals between H2 and H5 indicated a 2,5-*syn* stereochemical arrangement in **13**. Thus, we established that the allene adduct **12** possessed the shown

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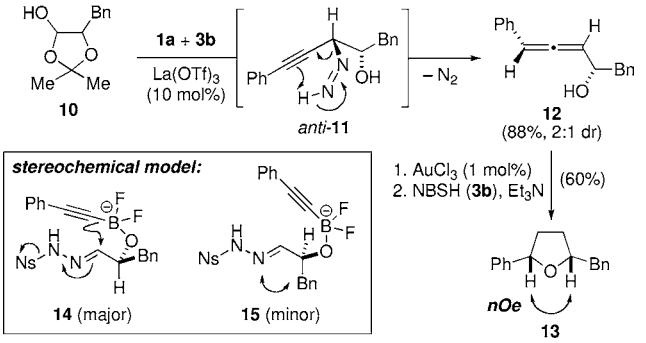
Scheme 2. Diastereoselective Allene Synthesis



relative configuration, a result consistent with the stereospecific extrusion of dinitrogen from the *anti*-configured diazine **11**. Since we had established that a free hydroxyl group was necessary for a highly efficient reaction, this stereochemical outcome can be rationalized by a preference for directed alkyne addition via A(1,2)-minimized conformer **14** in favor of conformer **15**.

Further studies showed that D-(+)-glyceraldehye could be used as a coupling partner to provide the corresponding allenes **16** and **17** with good efficiency (Figure 2). Moreover, we found

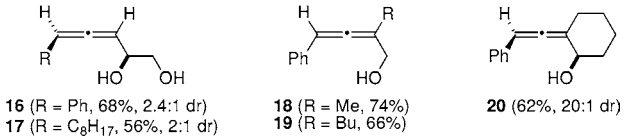
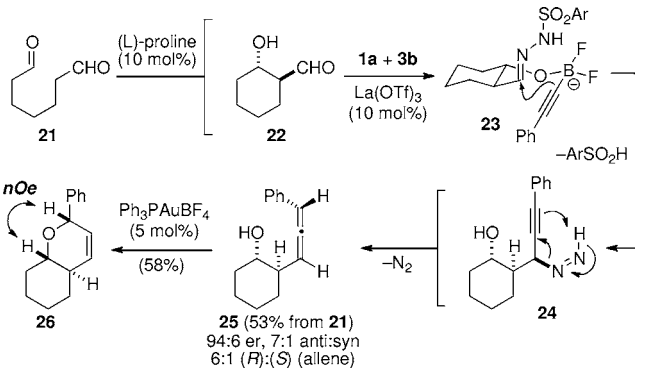


Figure 2. Additional substrates explored.

that α-hydroxyketones were competent reaction partners. α-Hydroxyacetone and 1-hydroxyhexan-2-one afforded allenes **18** and **19** in 74% and 66% yield, respectively. 2-Hydroxycyclohexanone gave the desired allene product **20** in 62% yield and with 20:1 stereoselectivity, indicating that high levels of stereoinduction are possible in these cyclic systems.[18]

We also investigated the possibility that β-hydroxy aldehydes might participate in this new allene synthesis, and to this end we report the one-pot enantioselective intramolecular aldol reaction/traceless Petasis reaction (Scheme 3). Treatment of dialdehyde **21** with L-proline[19] provided aldehyde **22** (10:1 dr), to which was added directly alkyne **1a**, NBSH (**3b**), and 10 mol % $La(OTf)_3$. In this manner, allene **25** was isolated in 53% yield with high levels of both enantio- and diastereoselectivity

Scheme 3. One-Pot Aldol/Traceless Petasis Reaction



for the three contiguous stereogenic elements constructed. The stereochemistry of the allene **25** was proved by stereospecific cyclization[20] to pyran **26**, indicating that the reaction sequence from **21** likely proceeded via diazine **24**, which in turn was generated by hydroxyl directed addition of the alkyne from an intermediate such as **23**.

In summary, we have developed an efficient $La(OTf)_3$-catalyzed synthesis of allenes by the sulfonylhydrazine-mediated coupling of hydroxyaldehydes and ketones with alkynyl trifluoroborates. This new traceless Petasis process offers significant advantages over the related Crabbé synthesis of allenes,[21] in that it proceeds under much milder reaction conditions and displays a wider substrate scope. The ability of chiral precursors to impart useful levels of stereoselectivity in this allene construction will pave the way for application of this reaction in complex synthetic sequences, especially when merged with a subsequent stereospecific etherification. Such applications, as well as the potential for developing catalytic enantioselective variants of the reaction, offer exciting prospects for the future.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, stereochemical proofs, and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (b) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.

(2) For a recent review of the Petasis borono-Mannich reaction, see: Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193.

(3) (a) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687. (b) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923. (c) Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337–4340.

(4) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635–3638. (b) Muncipinto, G.; Moquist, P. N.; Schreiber, S. L.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8172–8175.

(5) (a) Mundal, D. A.; Lee, J. J.; Thomson, R. J. *J. Am. Chem. Soc.* **2008**, *130*, 1148–1149. (b) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465–468. (c) Mundal, D A.; Avetta, C. A. Jr.; Thomson, R. J. *Nat. Chem.* **2010**, *2*, 294–297. (d) Lutz, K. E.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 4437–4440.

(6) For a review on the synthesis and properties of allenic natural products, see: Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216.
(7) For useful reviews on the synthetic utility of allenes, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829−2871. (b) Ma, S. *Aldrichimica Acta* **2005**, *40*, 91−102. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994−2009.
(8) (a) Vedejs, E.; Stolle, W. T. *Tetrahedron Lett.* **1977**, *18*, 135−138. (b) Bertz, S. H. *Tetrahedron Lett.* **1980**, *21*, 3151−3154. (c) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208−8210. (d) Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891−8892. (e) Smith, A. B.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423−7424.
(9) Barluenga and coworkers have reported a coupling of tosylhydrazones with boronic acids that proceeds under basic conditions via diazo-intermediates rather than monoalkyldiazines; see: Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494−499.
(10) (a) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *40*, 5747−5750. (b) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1990**, *112*, 9641−9643. (c) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493. Also see: (d) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838−1841.
(11) See Supporting Information for full experimental details.
(12) For examples of trifluoroborates participating in Petasis borono-Mannich reactions, see: (a) Stas, S.; Abbaspour Tehrani, K. *Tetrahedron* **2007**, *63*, 8921−8931. (b) Konev, A. S.; Stas, S.; Novikov, M. S.; Khlebnikov, A. F.; Abbaspour Tehrani, K. *Tetrahedron* **2008**, *64*, 117−123. (c) Stas, S.; Abbaspour Tehrani, K.; Laus, G. *Tetrahedron* **2008**, *64*, 3457. (d) Abbaspour Tehrani, K.; Stas, S.; Lucas, B.; Kimpe, N. D. *Tetrahedron* **2009**, *65*, 1957−1966. (e) Petasis, N. A.; Butkevich, A. N. *J. Organomet. Chem.* **2009**, *694*, 1747−1753. (f) Jury, J. C.; Swamy, N. K.; Yazici, A.; Willis, A. C.; Pyne, S. G. *J. Org. Chem.* **2009**, *74*, 5523−5527.
(13) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436−5445.
(14) For the preparation of NBSH, see: Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.
(15) Horler, D. F. *J. Chem. Soc. (C)* **1970**, 859−862.
(16) For selected examples of diastereoselective Petasis borono-Mannich reactions of α-hydroxy aldehydes, see refs 1d, 4, 12f, and the following: (a) Surya Prakask, G. K.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173−3176. (b) Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139−3143. (c) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097−7099. (d) Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352−8353. (e) Au, C. W. G.; Nash, R. J.; Pyne, S. G. *Chem. Commun.* **2010**, *46*, 713−715.
(17) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537−2538.
(18) Stereoselective approaches to such α-allenols by the nucleophilic opening of propargyl epoxides have been reported. For examples, see: (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677−1696. (b) Miura, T.; Shimada, M.; Ku, S.-Y.; Tamai, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101−7103. (c) Miura, M.; Shimada, M.; de Mendoza, P.; Deutsch, C.; Krause, N.; Murakami, M. *J. Org. Chem.* **2009**, *74*, 6050−6054.
(19) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785−2788. For a related one-pot aldol/Wittig reaction, see: Hu, D. X.; Clift, M. D.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 1799−1804.
(20) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485−4488.
(21) The Crabbé allene synthesis involves the high temperature decomposition of *N*-alkylpropargylic amines through a retro-ene fragmentation. Modest yields and a narrow substrate tolerance have limited the use of this interesting reaction. See: Crabbé, P.; Fillion, H.; André, D.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1979**, 859−860.