



An Efficient, Practical, and Enantioselective Method for Synthesis of Homoallenylamides Catalyzed by an Aminoalcohol-Derived, Boron-Based Catalyst

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Supporting Information

ABSTRACT: A practical catalytic method for enantioselective addition of an allene unit to aldimines is disclosed. Transformations are promoted by an in-situ-generated B-based catalyst that is derived from a simple, robust, and readily accessible (in multigram quantities) chiral aminoalcohol. A range of aryl-, heteroaryl-, and alkyl-substituted homoallenylamides can be obtained in 66–91% yield and 84:16 to >99:1 enantiomeric ratio through reactions performed at ambient temperature and in the presence of 0.1–3.0 mol% of the chiral catalyst and a commercially available allenylboron reagent. The catalytic protocol does not require strict anhydrous conditions, can be performed on gram scale, and promotes highly selective addition of an allenyl unit (vs a propargyl group). The utility of the approach is demonstrated through development of succinct approaches to syntheses of anisomycin and *epi*-cytoxazone.

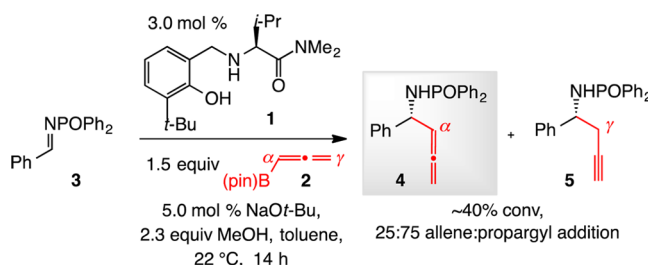
Reliable transformations that furnish N-containing organic molecules are crucial to advances in chemistry, biology, and medicine. Despite recent progress, several shortcomings are yet to be fully addressed, among which is the lack of availability of broadly applicable catalytic processes that afford homoallenylamines in high yield and enantioselectivity.¹ The significance of such protocols partly arises from the growing number of selective—and in many cases catalytic—procedures that are specific to allenes and generate valuable enantiomerically enriched organic molecules.^{2,3} Ground-breaking investigations have led to processes that provide access to homoallenylamides and derivatives; however, the extant methods are limited in scope, requiring specially activated substrates and/or aryl-substituted imines,⁴ or furnish the corresponding silyl-substituted products.⁵

Here, we outline a practical approach to catalytic enantioselective synthesis of aryl-, heteroaryl-, and alkyl-substituted homoallenylamides. Reactions can be performed at room temperature in the presence of 0.1–3.0 mol% of a readily accessible and robust chiral aminoalcohol and commercially available (pinacolato)allenylboron [allenyl-B(pin)], proceeding to completion in 2–14 h; the desired products are obtained often with complete group selectivity (5.0–10% propargyl addition in some cases), in 66–91% yield after purification and 84:16 to >99:1 enantiomeric ratio (er). The utility of the approach is illustrated in the context of applications to enantioselective synthesis of natural product anisomycin (antitumor and

antibacterial)⁶ and *epi*-cytoxazone (a member of cytokine modulator family of compounds).⁷

We recently described the design of aminoalcohol **1** (Scheme 1), which can be used as the precursor to a B-based chiral catalyst

Scheme 1. Initial Examination of the Catalytic Process^a



^aB(pin) = (pinacolato)boron.

that can effect the addition of allyl-B(pin) to phosphinoylimines and isatins as well as allenyl-B(pin) (**2**) to the latter set of bicyclic α -ketoamides.⁸ Transformations proceeded efficiently and with exceptional α selectivity. Furthermore, the C–B bond was directly converted to a C–C bond, which is unlike reactions of most organometallic complexes where γ addition often predominates.¹ We subsequently envisioned that the transition-metal-free catalytic system might be readily amenable to promoting highly α -selective additions of allenyl-B(pin) to phosphinoylimines. However, we were surprised to find that such is not the case (Scheme 1). Treatment of imine **3** with 3.0 mol% **1** and 1.5 equiv of **2**, under the conditions developed through the aforementioned initial investigations,⁸ resulted in a sluggish and nonselective transformation; only 40% conversion was observed after 14 h, and a 25:75 mixture of homoallenyl (**4**) and homopropargyl (**5**) amides was formed. Control experiments indicated that a significant portion of **5** is likely formed through a pathway that does not involve a species that is derived from **1** (ca. 20% conv, 14 h, 75% **5**).⁹

To gain additional insight vis-à-vis the origin of the unexpectedly low efficiency, we carried out a series of DFT calculations.¹⁰ These investigations revealed that, in contrast to an allylboron intermediate, transformation via a propargyl-boron compound (**II** vs **I**, Scheme 2) is energetically more demanding, thus allowing the competitive uncatalyzed process to

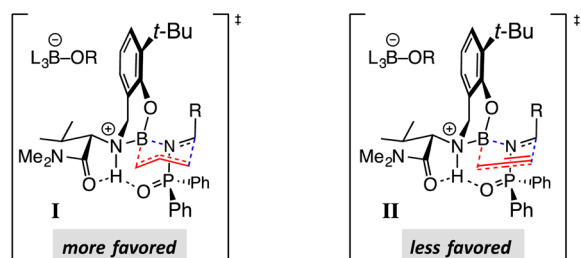
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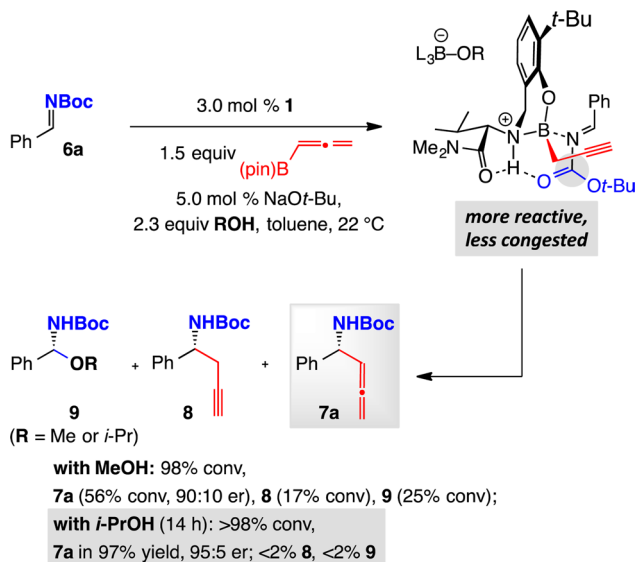
Scheme 2. Key Results of DFT Calculations

Less facile C–C bond formation with propargylboron intermediate:



become the major product-generating pathway. We conjectured that this complication might partly arise from the strain in the six-membered-ring transition state and/or the diminution in the degree of overlap between the appropriate alkyne π and imine π^* orbitals. To compensate for the diminished reactivity, we considered the use of Boc-imines, substrates believed to be somewhat more electrophilic¹¹ and that contain a less sterically hindered C=N unit (vs phosphinoylimines); moreover and importantly, carbamates are capable of establishing an H-bond contact within the active binary complex.⁸

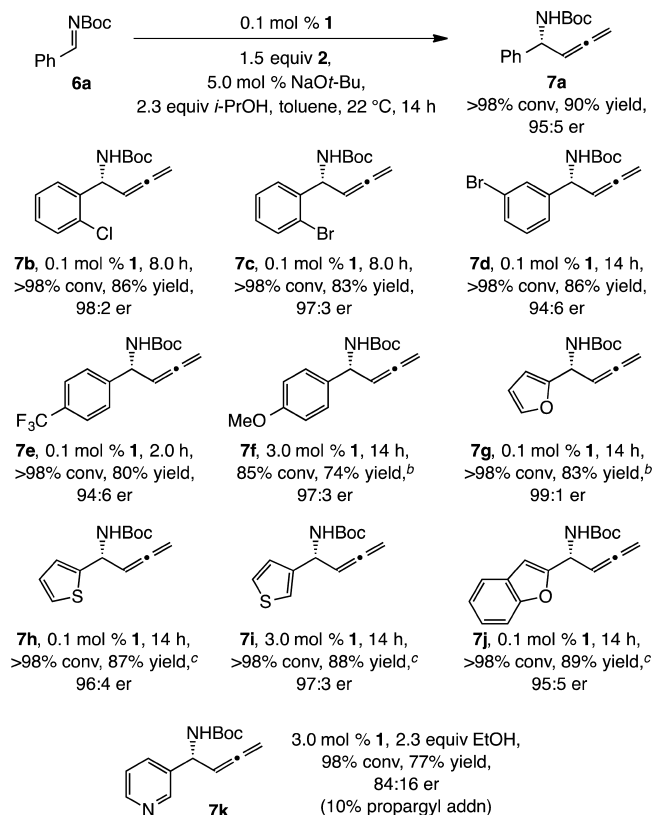
With carbamate **6a** as the starting material, under otherwise identical conditions (cf. Scheme 1), there was 56% conversion to **7a** (31% yield), which was generated in 90:10 er (Scheme 3);

Scheme 3. Reaction with a Boc-Imine Substrate^a

^aConversion was determined by analysis of ¹H NMR spectra of the unpurified product mixtures ($\pm 2\%$). Yields are of purified homoallenyl products ($\pm 5\%$). Enantioselectivities were determined by GC analysis. See the Supporting Information for details. Boc = *tert*-butoxycarbonyl.

significant amounts of homopropargylamide **8** (17% conv) and hemiaminal **9** (25% conv) were observed as well. To discourage the processes that are likely promoted by Lewis basic NaOMe, leading to the formation of *rac*-**8** and adventitious addition of the alcohol to the imine to generate **9**, we substituted MeOH with the more hindered *i*-PrOH. Under the modified conditions, **7a** was obtained as the exclusive product in 97% yield and 95:5 er (Scheme 3).

The transformation leading to **7a** can be performed with as little as 0.1 mol% **1**, affording the desired product in 90% yield, 95:5 er (Scheme 4); none of the propargyl addition product was

Scheme 4. Enantioselective Allene Additions to Aryl Imines^a

^aReactions were performed under N₂ atmosphere. Conversion was determined by analysis of ¹H NMR spectra of the unpurified products ($\pm 2\%$); <2% propargyl addition, unless noted otherwise. Yields are of purified homoallenyl products, except for **7g** and **7j** ($\pm 5\%$). Enantioselectivities were determined by GC or HPLC analysis. ^b~5% propargyl addition product formed. ^c~10% propargyl addition product formed. See the Supporting Information for details.

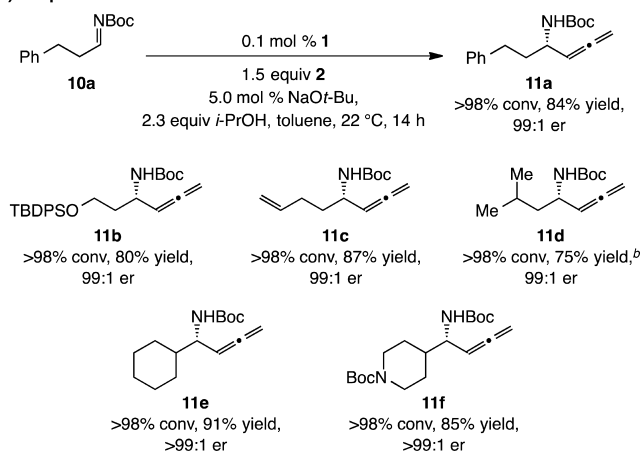
detected. Catalytic processes can be performed with different aryl-substituted imines, including those that carry an ortho (cf. **7b,c**), meta (cf. **7d**), or para (cf. **7e,f**) substituent. Transformations with electron-donating groups proceed at a diminished rate: whereas *p*-trifluoromethylphenyl-substituted **7e** was obtained in 80% yield and 94:6 er with 0.1 mol% **1** after 2.0 h, the *p*-methoxyphenyl-containing homoallenylamide **7f** required 3.0 mol% catalyst loading and 14 h to proceed to 85% conversion, and ca. 5% of the corresponding homopropargyl side product was formed (74% yield, 97:3 er; see below for more details). Syntheses of furyl- and thienyl-substituted products **7g–j** demonstrate that heterocyclic Boc-imines can serve as effective substrates; the expected homoallenylamides were isolated in 83–89% yield and 95:5–99:1 er, albeit, in certain instances, along with formation of ca. 5–10% of the propargyl addition side product. One shortcoming of the method is that additions to pyridyl imines proceed readily but are less enantioselective; as an example, transformation of **7k** in the presence of 3.0 mol% **1** and EtOH (otherwise the same as shown in Scheme 4) delivers the homoallenylamide in 77% yield and 84:16 er (ca. 10% homopropargylamide formed). Kinetic studies indicate that the C–C bond-forming addition is likely the turnover-limiting step

of the catalytic cycle;¹⁰ such findings support the contention regarding the positive influence of the more reactive Boc-imine substrates on reaction efficiency.

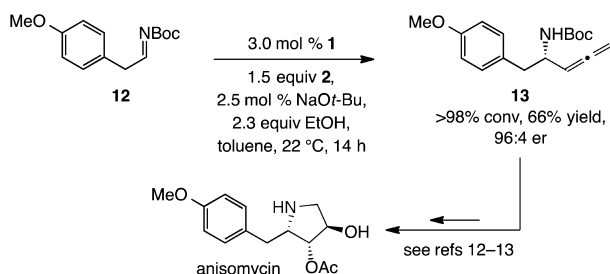
Catalytic α -selective and enantioselective additions extend to alkyl-substituted imines (cf. 11a–f, Scheme 5a); 0.1 mol% 1 is

Scheme 5. Enantioselective Allene Additions to Alkyl Imines^a

a) Scope:



b) Relevance to natural product synthesis:



^aFor reaction conditions, see Scheme 4. Yields refer to purified products. See the Supporting Information for details. ^b2.0–5.0% propargyl addition product observed. TBDPS = *t*-Bu(Ph)₂Si.

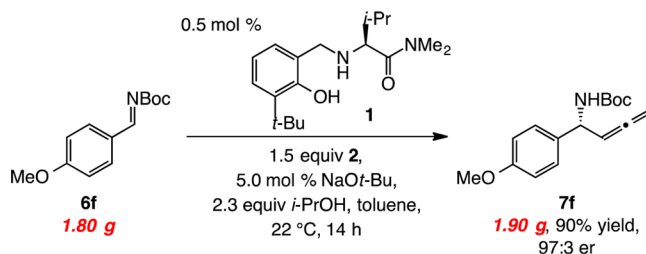
again sufficient for the transformations to proceed to >98% conversion at 22 °C after 14 h. The expected homoallenylamides, including those that contain functional groups such as a silyl ether, an alkene, or an amide, were obtained with exceptional enantioselectivity (99:1 er). Only in the case of 11d was 2–5% of the propargyl addition product detected (<2% otherwise). It should be noted that the present set of additions are substantially more efficient than those involving alkyl-substituted imines and allyl-B(pin) reagents.⁸

To demonstrate utility, the catalytic enantioselective addition to *p*-methoxybenzyl-substituted imine 12 was carried out; homoallenylamide 13, formerly used in an enantioselective synthesis of anisomycin,^{12,13} was isolated in 66% yield and 96:4 er (Scheme 5b). The previously reported route¹³ for obtaining enantiomerically enriched 13 entails a six-step sequence commencing from the aldehyde precursor, affording the desired product in ca. 9% overall yield and 95:5 er. The strategy presented in Scheme 5b, involving a three-step operation and generating 13 in ca. 30% overall yield (from the aldehyde) and 96:4 er, constitutes a more efficient approach.

A key attribute of the present approach is the ease with which the requisite chiral catalyst is prepared, the necessary reagents are accessed, and the transformations can be performed. The catalytic enantioselective allenyl addition illustrated in Scheme

6, carried out with 1.80 g of aldimine 6f, is noteworthy for several other reasons: (1) Rigorous exclusion of air and moisture was not

Scheme 6. Catalytic Enantioselective Allenyl Addition on Gram Scale^a



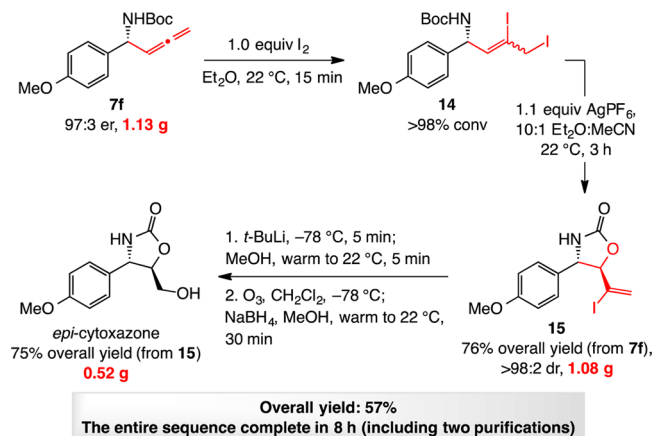
comparison to smaller scale reaction (~40 mg, cf. Scheme 4):
improved efficiency (0.5 vs 3.0 mol % 1)
improved yield (90% vs 74%)
improved group selectivity (<2% vs ~5% propargyl addition);
Rigorous exclusion of air/H₂O not required.

^aSee the Supporting Information for details.

required. (2) The desired product was isolated in 90% yield (1.90 g) and 97:3 er. That is, the efficiency of the reaction improved compared to the smaller-scale run (ca. 40–50 mg of 6f, Scheme 4) and despite the lower catalyst loading (0.5 mol% vs 3.0 mol% for 14 h; cf. Scheme 4). (3) Contrary to the smaller-scale experiments, on the occasions when the process was performed on ≥ 0.5 g scale, <2% of the undesired homopropargylamide was detected (vs ca. 5% in Scheme 4). The above findings suggest that the efficiency and selectivity of catalytic allene additions to Boc-imines are likely to be higher as the scale of a transformation is increased.

The feasibility of preparing gram quantities of homoallenylamides efficiently and in high enantiomeric purity, and the increasing variety of ways through which an allene can be functionalized, means that an assortment of valuable N-containing molecules can be accessed readily and in meaningful quantities. The enantioselective synthesis of *epi*-cytoxazone¹⁴ is a case in point (Scheme 7). Subjection of 1.13 g of 7f (97:3 er) to 1.0 equiv of iodine¹⁵ at ambient temperature for 15 min led to the formation of diiodide 14 with >98% site selectivity as an

Scheme 7. Application to Enantioselective Synthesis of *epi*-Cyttoxazone^a



^aSee the Supporting Information for details.

inconsequential 50:50 mixture of *E* and *Z* alkene isomers. Direct treatment of **14** (without purification) with 1.1 equiv of AgPF₆ for 3 h¹⁵ delivered heterocyclic alkenyl iodide **15** in 76% overall yield (1.08 g) and >98:2 diastereomeric ratio (dr). *epi*-Cytosazone was obtained after conversion of the alkenyl iodide to the requisite primary alcohol in two steps and 75% overall yield (Scheme 7). There are two additional noteworthy points regarding the sequence shown in Scheme 7: (1) The synthesis route was completed (including two chromatographic purifications) within 8 h to afford 0.52 g of *epi*-cytosazone (57% overall yield from **7f**). (2) The requisite diiodide (**14**) would not be easily accessible through modification of the alkene of a homoallylamine¹⁶ or the alkyne unit of a homopropargyl variant.¹⁷ The latter distinction also applies to the intermediates generated in Scheme 5b en route to anisomycin.

In conclusion, we put forth the first general method for efficient and enantioselective addition of an allenyl unit to a range of aldimines, including the more challenging alkyl-substituted substrates. The resulting Boc-protected amides can be readily converted to the corresponding amines in high yield.¹⁸ Applications to enantioselective syntheses of representative N-containing target molecules highlight the useful functionalization possibilities, rendered feasible by the presence of an allenyl unit, and which can be performed in a practical and reliable fashion on a significant laboratory scale. The present investigations further underscore the applicability of chiral B-based catalysts derived from the aminoalcohol family of compounds (e.g., **1**) to the development of new and selective protocols in chemical synthesis.

Investigations regarding the utility of the present B-based class of chiral catalysts and their applications in practical and enantioselective chemical synthesis are underway.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, spectral and analytical data for all products, as well as crystallographic (CIF) and computational data. 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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