Published in final edited form as:

Org Lett. 2012 March 2; 14(5): 1322–1325. doi:10.1021/ol300200m.

Transition-Metal Catalyzed Synthesis of Aspergillide B: An Alkyne Addition Strategy

Barry M. Trost and Mark J. Bartlett

Department of Chemistry, Stanford University, California 94305-5080

Barry M. Trost: bmtrost@stanford.edu

Abstract

A catalytic enantioselective formal total synthesis of aspergillide B is reported. This linchpin synthesis was enabled by the development of new conditions for Zn-ProPhenol catalyzed asymmetric alkyne addition. This reaction was used in conjunction with ruthenium-catalyzed *trans*-hydrosilylation to affect the rapid construction of a late-stage synthetic intermediate of aspergillide B to complete a formal synthesis of aspergillide B in a highly efficient manner.

The aspergillides are a family of bioactive natural products originally derived from the marine fungus *aspergillus ostianus*.¹ Aspergillide A, B and C, shown in Figure 1, share common macrolactone and pyran motifs but differ with respect to the stereochemistry at C3 and the unsaturation present in the pyran ring.²

These compounds exhibit cytotoxicity towards a number of different cancer cell lines including, HL-60 (human promyelocytic leukemia), MDA-MB-231 (human breast carcinoma) and HT1080 (human fibrosarcoma) cell lines.³ These properties, along with the challenging structural features present, have motivated a number of groups to pursue the synthesis of aspergillides A–C.^{4,5} Our interest in the aspergillides stems from the potential application of our zinc-catalyzed asymmetric alkynylation and ruthenium-catalyzed *trans*-hydrosilylation-desilylation methodologies (Scheme 1) to provide access to two chiral allylic alcohol moieties that would ultimately lead to an efficient synthesis of aspergillide B.

This alkyne-based strategy envisioned to synthesize aspergillide B is outlined in Scheme 2. Retrosynthetic disconnection of the macrolactone leads back to diester **6**, a late-stage intermediate used in a previous synthesis.^{4d} Diastereoselective formation of the pyran ring was expected to arise from intramolecular oxy-Michael addition of the C8 hydroxyl group and the pendant α,β -unsaturated ester in **7**. It was anticipated that the two chiral allylic alcohol moieties could be prepared using ruthenium-catalyzed hydrosilylation of the corresponding propargylic alcohols. Lastly, asymmetric alkyne addition would be used to

Correspondence to: Barry M. Trost, bmtrost@stanford.edu.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

access the aforementioned propargylic alcohols via separate addition of (*S*)-hept-6-yn-2-yl benzoate ((-)-**9**) and methyl propiolate (**10**) to each end of a butane dialdehyde equivalent **11** which is serving as a linchpin.

The invention of the ProPhenol ligand **4** has led to the development of a number of catalytic enantioselective transformations, including a direct aldol reaction.⁶ The ProPhenol ligand also facilitates the addition of a variety of alkynes to aryl and α,β -unsaturated aldehydes in excellent yield and enantioselectivity.⁷ Typically, these reactions require the use of 2.8 equivalents of alkyne and 2.95 equivalents of Me_2Zn to obtain high levels of enantioselectivity.⁸ At the outset, we recognized that the use of a super stoichiometric amount of alkyne (-)-**9** was particularly inefficient, given that this chiral intermediate is prepared using a multistep synthesis. Consequently, the use of a stoichiometric quantity of alkyne in ProPhenol-catalyzed alkynylations was investigated.

Using 1.2 equivalents of alkyne ($\pm$)-**9**,⁹ alkynylation of aliphatic aldehyde **11a** resulted in only 22% yield of the desired product in 54% ee (Entry 1, Table 1).¹⁰ The traditional super stoichiometric conditions provided only modest improvements in yield and enantioselectivity (Entry 2 & 3). Low yields of the desired product **12a** were primarily a consequence of competing aldol reactions.¹¹ The predominance of this side reaction led to the hypothesis that incomplete formation of the alkynylzinc nucleophile may be leaving significant amounts of basic dimethylzinc in the reaction mixture. Consequently, we examined a number of additives and methods that have been shown to facilitate the formation of alkynylzinc nucleophiles.¹² The use of *N*-methylimidazole (NMI), DMSO and DMF all resulted in lower yields of the desired product, **12a** (Entries 4–6). Increasing the alkyne/ Me_2Zn /*(S,S)*-**4** premix time and the catalyst loading provided improved yields of propargylic alcohol **12b** (Entry 7 & 8). While the excess alkyne could be recovered quantitatively, this inefficiency along with the moderate yield and enantioselectivity prompted the investigation of the analogous unsaturated aldehyde, **11c**. The ProPhenol-catalyzed addition of ($\pm$)-**9** to **11c** provided a much improved 84% yield and 95% ee (Entry 9). Reducing the stoichiometry of the alkyne to either 1.2 or 1.0 equivalents provided lower yield, although excellent ee was maintained in both cases (Entry 10 & 11). The moderate yield was presumably a consequence of poor reactivity and a solution to this problem was found in the use of fumaraldehyde dimethyl acetal (**11d**). The inductive effects of the dimethyl acetal create a more electrophilic aldehyde, and as a result, the desired propargylic alcohol **12d** was obtained in 82% yield (Entry 12).

The results in Table 1 provide a number of new insights into the proposed reaction mechanism for ProPhenol-catalyzed alkyne addition (Scheme 3). Incomplete formation of the alkynylzinc nucleophile was confirmed by ¹H-NMR analysis of a standard premix with 1-octyne, Me_2Zn and (*S,S*)-**4** in toluene-*d*₈.¹³ Despite the entropically favored release of methane gas, deprotonation of the terminal alkyne was not observed in the absence of ProPhenol ligand. The presence of significant amounts of dimethylzinc in the reaction mixture appears to have little effect on the outcome of alkyne additions to α,β -unsaturated aldehydes.¹⁴ However, enolizable aldehydes suffer from undesired aldol side reactions and typically only produce moderate yields of the desired propargylic alcohol. Methyl propiolate, a more acidic alkyne, has been shown to give significantly higher yields in additions to enolizable aldehydes under the standard conditions.¹⁵

The synthesis of aspergillide B commenced with the preparation of chiral alkyne (-)-**9** (Scheme 4),¹⁶ taking advantage of the Noyori asymmetric hydrogenation¹⁷ of ynone **14** and the alkyne zipper reaction of **16** to **17**.

Alkynylation of fumaraldehyde dimethyl acetal (**11d**)¹⁸ using just 1 equivalent of alkyne (–)-**9** and 10 mol% of the (*S,S*)-ProPhenol Ligand provided **12d** in 82% yield and 90% de (Scheme 5).¹⁹ Alkyne *trans*-hydrosilylation using benzyldimethylsilane (BDMS-H) and 2 mol% of Cp*Ru(CH₃CN)₃PF₆, provided vinyl silane **18**, regioselectively.²⁰ Hydrosilylation of propargylic alcohols under these conditions typically results in silylation at the β-position. The dramatic reversal in regioselectivity is thought to be a consequence of a coordinative interaction between ruthenium and the electron poor alkene. The presence of the silicon on one of the double bonds provides a key for their differentiation towards hydrogenation. The disubstituted olefin of allylic alcohol **18** was then chemoselectively hydrogenated using Wilkinson's catalyst and silyl protected to give **19**.²¹ Hydrolysis of the dimethyl acetal was performed under mild acid-catalyzed conditions, providing the desired aldehyde **20** for the second alkyne addition.

ProPhenol-catalyzed addition of methyl propiolate (**10**) to aldehyde **20** provided the desired propargylic alcohol **21** in 71% yield as a 5.2:1 mixture of diastereomers (Scheme 6).²² Protection of the propargylic alcohol was followed by a chemoselective alkyne reduction using our hydrosilylation/protodesilylation protocol for formation of E-double bonds.²³ The basic reaction conditions used for this transformation resulted in spontaneous intramolecular oxy-Michael addition. Consequently, the desired 2,6-*anti* tetrahydropyran **6** was isolated in 38% yield (77% brsm) over 2 steps.²⁴ Compound **6** can be transformed into aspergillide B in 3 additional steps.^{4d}

In summary, an enantioselective formal total synthesis of aspergillide B has been accomplished using sequential Zn-catalyzed alkyne addition and Ru-catalyzed *trans*-hydrosilylation-desilylation to access E-alkenes. The hydrosilylation – desilylation protocol not only provides the E geometry but also allows chemoselective differentiation of the two double bonds in a subsequent hydrogenation step. The development of new conditions for the Zn-ProPhenol catalyzed alkynylation has resulted in excellent yield and enantioselectivity using just a single equivalent of alkyne. Further research into the use of enolizable aldehydes in this methodology is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Science Foundation (CHE-0846427) and the National Institutes of Health (GM-33049) for their generous support of our programs. M.J.B thanks Victoria University of Wellington for the provision of a Ph.D. scholarship. We also thank Unicore for a generous gift of ruthenium salts.

References

1. Kito K, Ookura SY, Namikoshi M, Ooi T, Kusumi T. *Org. Lett.* 2008; 10:225. [PubMed: 18078344]
2. The structures of aspergillide A and B were revised in 2009 as a result of synthetic work by Hande and Uenishi. Hande SM, Uenishi J. *Tetrahedron Lett.* 2009; 50:189. The revised structures were later confirmed when X-ray crystal structures of the corresponding *m*-bromobenzoates were reported. Ookura R, Kito K, Saito Y, Kusumi T, Ooi T. *Chem. Lett.* 2009; 38:384.
3. Díaz-Oltra S, Angulo-Pachón CA, Murga J, Falomir E, Carda M, Marco JA. *Chem. Eur. J.* 2011; 17:675. [PubMed: 21207589]
4. For previous syntheses of aspergillide B, see: Nagasawa T, Kuwahara S. *Biosci. Biotechnol. Biochem.* 2009; 73:1893. [PubMed: 19661704] Díaz-Oltra S, Angulo-Pachón CA, Kneeteman MN, Murga J, Carda M, Marco JA. *Tetrahedron Lett.* 2009; 50:3783. Liu J, Xu K, He J, Zhang L, Pan X, She X. *J. Org. Chem.* 2009; 74:5063. [PubMed: 19485348] Fuwa H, Yamaguchi H, Sasaki M. *Org.*

- Lett. 2010; 12:1848. [PubMed: 20297800] Mueller Hendrix AJ, Jennings MP. Tetrahedron Lett. 2010; 51:4260. Kanematsu M, Yoshida M, Shishido K. Angew. Chem. Int. Ed. 2011; 50:2618. Kanematsu M, Yoshida M, Shishido K. Tetrahedron Lett. 2011; 52:1372. and also reference 2a.
5. For previous syntheses of aspergillides A and C, see: Nagasawa T, Kuwahara S. Org. Lett. 2009; 11:761. [PubMed: 19128025] Panarese JD, Waters SP. Org. Lett. 2009; 11:5086. [PubMed: 19817392] Sabitha G, Reddy DV, Rao AS, Yadav JS. Tetrahedron Lett. 2010; 51:4195. Kobayashi H, Kanematsu M, Yoshida M, Shishido K. Chem. Commun. 2011; 47:7440. Kanematsu M, Yoshida M, Shishido K. Tetrahedron Lett. 2011; 52:1372. Izuchi Y, Kanomata N, Koshino H, Hongo Y, Nakata T, Takahashi S. Tetrahedron: Asymmetry. 2011; 22:246. Nagasawa T, Nukada T, Kuwahara S. Tetrahedron. 2011; 67:2882. Zúñiga A, Pérez M, González M, Gómez G, Fall Y. Synthesis. 2011; 20:3301. Srihari P, Sridhar Y. Eur. J. Org. Chem. 2011:6690.
 6. Trost BM, Ito H. J. Am. Chem. Soc. 2009; 122:12003. For subsequent applications of this ligand, see: Trost BM, Hitce J. J. Am. Chem. Soc. 2009; 131:4572. [PubMed: 19281239] and references cited therein.
 7. a) Trost BM, Weiss AH, von Wangelin AJ. J. Am. Chem. Soc. 2006; 128:8. [PubMed: 16390095] b) Trost BM, Chan VS, Yamamoto D. J. Am. Chem. Soc. 2010; 132:5186. [PubMed: 20307084]
 8. For a recent review on the enantioselective addition of alkynes to aldehydes see: Trost BM, Weiss AH. Adv. Synth. Catal. 2009; 351:963.
 9. ($\pm$)-**9** was prepared in 4 steps from 3-methyl cyclohexenone. See Supporting Information for experimental details. Le Drain C, Greene AE. J. Am. Chem. Soc. 1982; 104:5473.
 10. The major method which can avoid such excesses is that of Carreira but sometimes that too will require them. See: Frantz D, Fässler R, Carreira EM. J. Am. Chem. Soc. 2000; 122:1806. Frantz D, Fässler R, Tomooka CS, Carreira EM. Acc. Chem. Res. 2000; 33:373. [PubMed: 10891055] Anand N, Carreira EM. J. Am. Chem. Soc. 2001; 123:9687. [PubMed: 11572696] Boyall D, Frantz DE, Carreira EM. Org. Lett. 2002; 4:2605. [PubMed: 12123387] Reber S, Knoepfel TF, Carreira EM. Tetrahedron. 2003:6813. Also see Jiang B, Chen Z, Xiong W. Chem. Commun. 2002:1524. Yue Y, Turlington M, Yu X-Q, Pu L. J. Org. Chem. 2009; 74:8681. [PubMed: 19860396] and reference 12c.
 11. The cross aldol side reaction produces a complex mixture of oligomers. The aldol side product **A** was isolated in 19% yield as a mixture of diastereomers from Entry 1 (Table 1). HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{34}H_{61}O_6Si_2$, 621.4001; found, 621.3996.

12. For selected discussions on the use of additives to facilitate alkynylzinc formation, see: Gao G, Xie R-G, Pu L. Proc. Natl. Acad. Sci. U.S.A. 2004; 101:5417. [PubMed: 15026570] Yang F, Xi P, Yang L, Lan J, Xie R, You J. J. Org. Chem. 2007; 72:5457. [PubMed: 17555361] Du Y, Turlington M, Zhou X, Pu L. Tetrahedron Lett. 2010; 51:5024.
13. Approximately 28% conversion to the alkynylzinc species was observed based on integration of the peaks at 0.29 (s, 3H, $CH_3ZnC\equiv C$) and -0.58 ppm (s, 6H, $(CH_3)_2Zn$).
14. Minor amounts of methyl addition side products have been isolated in only a small number of cases, see reference 7a for details.
15. Trost BM, Burns AC, Bartlett MJ, Tautz T, Weiss AH. J. Am. Chem. Soc. 2012; 134:1474. [PubMed: 22236456]
16. Parenty A, Campagne J-M, Aroulanda C, Lesot P. Org. Lett. 2002; 4:1663. [PubMed: 12000268]
17. Matsumara K, Hashiguchi S, Ikariya T, Noyori R. J. Am. Chem. Soc. 1997; 119:8738.

18. Fumaraldehyde dimethyl acetal (**11d**) was prepared in one step from commercially available fumaraldehyde bis(dimethyl acetal). Coppola GM. *Synthesis*. 1984:1021.
19. For examples of the few methodologies capable of efficient zinc-catalyzed asymmetric alkynylation with less than 1.2 equivalents of alkyne, see: Kojima N, Nishijima S, Tsuge K, Tanaka T. *Org. Biomol. Chem.* 2011; 9:4425. [PubMed: 21552582] Anand N, Carreira EM. *J. Am. Chem. Soc.* 2001; 123:9687. [PubMed: 11572696]
20. Trost BM, Ball ZT, Jöge T. *Angew. Chem. Int. Ed.* 2003; 115:3537. Trost BM, Ball ZT. *J. Am. Chem. Soc.* 2005; 127:17644. [PubMed: 16351094]
21. Young JF, Osborn JA, Jardine FH, Wilkinson G. *Chem. Commun.* 1965:131. O'Connor C, Wilkinson G. *J. Chem. Soc. A.* 1968:2665.
22. Diastereomeric ratio was determined by ¹H-NMR of the cyclized compound **6**.
23. Trost BM, Ball ZT, Jöge T. *J. Am. Chem. Soc.* 2002; 124:7922. [PubMed: 12095335]
24. The 2,6-*syn* diastereomer could not be observed by ¹H-NMR of the crude reaction mixture. Given that 88% yield of **6** was obtained, the diastereomeric ratio is >7.3:1, *anti:syn*.

aspergillide A (1)

aspergillide B (2)

aspergillide C (3)

Figure 1.
The Aspergillide Family of Natural Products.

Scheme 2.
Retrosynthetic Analysis of Aspergillide B.

Scheme 3.
Proposed Mechanism for ProPhenol-Catalyzed Alkyne Addition.

Scheme 4.
Preparation of Alkyne (-)-9.

Scheme 5.
First Alkyne Addition in the Synthesis of Aspergillide B.

Scheme 6.
Formal Synthesis of Aspergillide B.

Table 1

Optimization of Alkyne Addition.

entry	aldehyde	X/Y	conditions ^d	yield ^b	ee ^c
1	11a	1.2/1.5	20 mol% TPPO	22%	54%
2	11a	2.8/2.95	20 mol% TPPO	39%	62% (57%) ^d
3	11a	2.8/2.95	-	35%	45%
4	11a	1.2/1.3	30 mol% NMI	11%	72%
5	11a	1.2/1.4	4 eq. DMSO	4%	14%
6	11a	1.2/1.4	4 eq. DMF	10%	17%
7	11b	2.8/2.95	20 mol% TPPO, 24 h alkyne premix	58%	50% ^d
8	11b	2.8/2.95	40 mol% TPPO, 20 mol% ProPhenol, 24 h alkyne premix	69%	67% ^d
9	11c	2.8/2.95	c = 0.35 M	84%	95%
10	11c	1.2/1.5	20 mol% TPPO	56%	95%
11	11c	1.0/1.3	20 mol% TPPO	54%	95%
12	11d	1.0/1.3	20 mol% TPPO ^e	82%	90%

All reactions were run on 0.1625 mmol scale using the standard ProPhenol alkynylation procedure.

^aAll reactions were run at a concentration of 0.5 M with respect to alkyne unless otherwise noted.

^bIsolated yield.

^cEnantiomeric excess determined by chiral HPLC analysis.

^dEnantiomeric excess determined by ¹H-NMR analysis of the corresponding (*S*)-methyl mandelate.

^eReaction performed with (–)-**9** on a 0.45 mmol scale.

TPPO = triphenylphosphine oxide, NMI = *N*-methylimidazole