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Brønsted Acid-Catalyzed Highly Stereoselective Arene-Ynamide Cyclizations. A Novel Keteniminium Pictet–Spengler Cyclization in Total Syntheses of (±)-Desbromoarborescidines A and C

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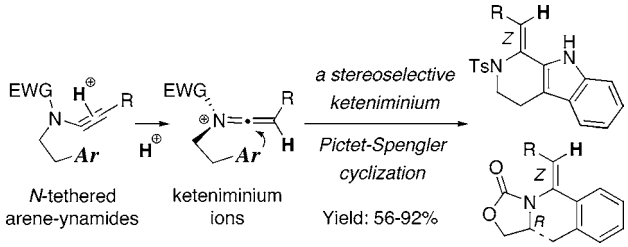
ABSTRACT



A Brønsted acid-catalyzed highly stereoselective arene-ynamide cyclization is described. These reactions constitute a keteniminium variant of Pictet–Spengler cyclizations, leading to efficient synthesis of nitrogen heterocycles and related alkaloids. Total syntheses of desbromoarborescidines A and C are illustrated here as first applications of this methodology.

Ynamides have become prevalent in organic synthesis.[1−6] Given that enyne cyclizations have become a powerful synthetic method for synthesizing complex carbo- or heterocycles,[7−10] en-ynamide cyclization using N-tethered

(1) For reviews, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

(2) For recent efforts in synthesis and applications of ynamides, see: (a) Rosillo, M.; Domínguez, G.; Casarrubios, L.; Amador, U.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084. (b) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (c) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783. (d) Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377. (e) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727. (f) Klein, M.; König, B. *Tetrahedron* **2004**, *60*, 1087. (g) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095. (h) Witulski, B.; Alayrac, C.; Tevzaadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *43*, 4392. (i) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (j) Witulski, B.; Lumtscher, J.; Bergsträsser, U. *Synlett* **2003**, 708. (k) Naud, S.; Cintrat, J.-C. *Synthesis* **2003**, 1391. (l) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281. (m) Saito, N.; Sato, Y.; Mori, M. *Org. Lett*. **2002**, *4*, 803. (n) Timbart, J.-C.; Cintrat. J.-C. *Chem. Eur. J.* **2002**, *8*, 1637.

(3) For a recent elegant account on $PtCl_2$-catalyzed en-ynamide cyclization, see: Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.

(4) For our recent contributions, see: (a) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209. (b) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353. (c) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A. Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663. (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H. A.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547. (e) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (f) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383.

(5) For copper-catalyzed amidations of alkynyl bromides, see: (a) Zhang, Y.; Hsung R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

(6) Also see: (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (b) Reference 2e.

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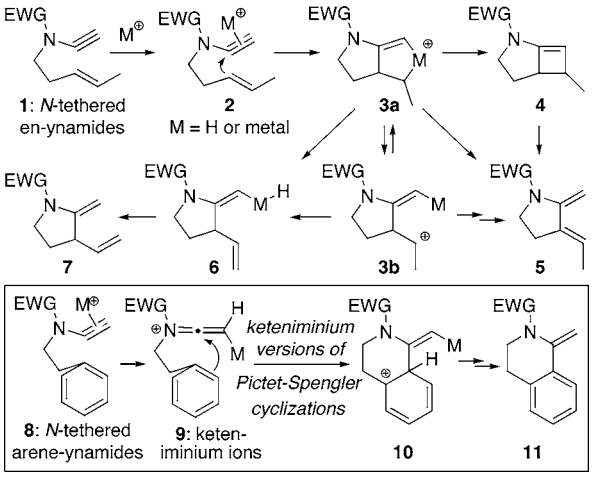
ynamides **1** should represent an attractive strategy for alkaloid syntheses.[3] As shown in Scheme 1, upon activations of en-

Scheme 1

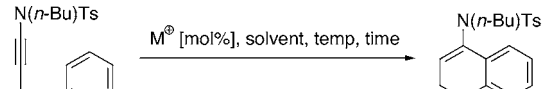


ynamides **1** using either Brønsted acids or transition metal π-acids, various possible pathways can lead to nitrogen heterocycles **4**, **5**, and **7**.[3]

In our pursuit of en-ynamide cyclizations, we have focused on employing arene-ynamides **8** that are tethered with aryl groups through the nitrogen atom because of the potential in constructing useful nitrogen heterocycles [Scheme 1]. In this regard, the keteniminium intermediate **9** could be generated upon activation with Brønsted acids or π-acids, and this particular arene-ynamide cyclization pathway would inspire a unique keteniminium Pictet−Spengler cyclization,[11−13] leading to heterocycles such as **11**. We report here a Brønsted acid-catalyzed, highly stereoselective cyclization of arene-ynamides and total syntheses of desbromoarborescidines A and C[14−17] as first applications of ynamides in natural product synthesis.

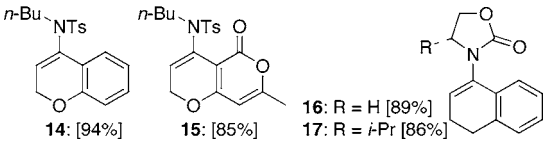
To establish the feasibility, the keteniminium Pictet−Spengler cyclization of C-tethered arene-ynamide **12**, prepared from Cu(II)-catalyzed coupling of the respective sulfonamide and alkynyl bromide,[5a] was examined [Scheme 2]. Surprisingly, transition metal π-acids such as $PtCl_2$, $PtCl_4$,

Scheme 2



entry	M⊕ [mol%]	solvent	temp	time	yield[a]
1	$PtCl_2$ [10%]	toluene	75 °C	16 h	ND
2	$PtCl_4$ [10%]	toluene	75	16	ND
3	$AgNTf_2$ [20%]	toluene	rt	1	<20%
4	$CuOTf_2$ [20%]	toluene	rt	1	<10%
5	PNBSA [10%][b]	toluene	75	16	ND
6	$HNTf_2$ [1%]	CH_2Cl_2	rt	3 min	91%

a. Isolated yields. **b.** PNBSA = *para*-nitrobenzenesulfonic acid.



and $AgNTf_2$ that are useful in various enyne cyclizations[3,7,8] were not successful here [entries 1−3], while Lewis acids such as $Cu(OTf)_2$ also failed [entry 4].

Instead, Brønsted acids[10] proved to be effective in initiating the cyclization of **12**. Only 1 mol % $HNTf_2$ [18] was needed, and dihydroamino-naphthalene **13**[19] was isolated in 91% yield after stirring in CH_2Cl_2 at room temperature for 3 min [entry 6]. A series of cyclized products **14**−**17** were obtained in good yields from their respective C-tethered arene-ynamides.

However, the success with C-tethered arene-ynamides did not translate completely to N-tethered arene-ynamides. As summarized in Table 1, N-tethered arene-ynamides **18a** and **18b** were only marginally successful in the keteniminium Pictet−Spengler [entries 1−5]. In fact, only π-acids such as $PtCl_2$ and $PtCl_4$ were modestly useful, providing cyclized products **19a** and **19b** in 30 and 40% yields, respectively [entries 2 and 5].

Since the cyclization of **18a** or **18b** could suffer from the strain in the oxazolidinone ring, we used ynamides **20a** and

(7) For a review, see: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

(8) For other reviews, see: (a) Méndez, M.; Mamane, V.; Fürstner, A. *ChemTracts* **2003**, *16*, 397. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.

(9) For recent examples of enyne cyclizations, see: (a) Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (c) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563. (d) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414. (e) Fürstner, A.; Mamune, V. *J. Org. Chem.* **2002**, *67*, 6264.

(10) For some examples of Brønsted acid catalysis, see: (a) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. (c) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45. (d) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851.

(11) (a) For an excellent review, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) For an excellent review on additions to *N*-acyl or *N*-sulfonyl iminium ions, see: Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(12) For some elegant examples of Pictet−Spengler cyclizations, see: (a) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565−7581. (b) Yu, J.; Wearing, X.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543.

(13) For a recent example on catalytic asymmetric Pictet−Spengler cyclization, see: Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(14) For isolation of 10-desbromoarborescidine A, see: Johns, S. R.; Lamberton, J. A.; Occolowitz, J. L. *Aust. J. Chem.* **1966**, *19*, 1951.

(15) For total syntheses of arborescidine A, see: (a) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (b) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108.

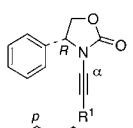
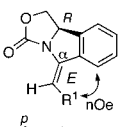
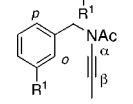
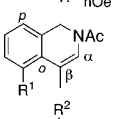
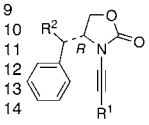
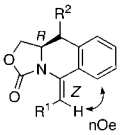
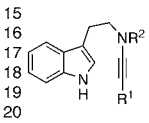
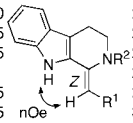
(16) For isolation of arborescidines A−D, see: Chbani, M.; Païs, M. *J. Nat. Prod.* **1993**, *56*, 99.

(17) For total syntheses of arborescidine C, see: (a) Burm, B. E. A.; Meijler, M. M.; Korver, J.; Wanner, M. J. Koomen, G.-J. *Tetrahedron* **1998**, *54*, 6135. (b) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283.

(18) For a study on the acidity of $HNTf_2$, see: Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264.

(19) Relevant procedures for all new compounds and their characterizations can be found in Supporting Information.

Table 1. N-Tethered Arene-Ynamide Cyclizations

entry	ynamides	R^1	R^2	$M^{\oplus}$ [mol%]	solvent	T °C	products	yield[a]
1		**18a** *n*-hex	-	$PtCl_2$ [5]	$[ClCH_2]_2$	70		**19a** ND
2		**18a** *n*-hex	-	$PtCl_4$ [5]	$[ClCH_2]_2$	70		**19a** 30
3		**18a** *n*-hex	-	PNBSA [20]	toluene	75		**19a** ND
4		**18a** *n*-hex	-	$HNTf_2$ [5]	CH_2Cl_2	rt		**19a** ND
5		**18b** *n*-Bu	-	$PtCl_4$ [5]	$[ClCH_2]_2$	70		**19b** 40
6		**20a** H	-	$PtCl_2$ [5]	$[ClCH_2]_2$	70		**21a** ND
7		**20a** H	-	$PtCl_2$ [5]	$[ClCH_2]_2$	70		**21a** ND
8		**20b** OMe	-	$PtCl_4$ [5]	$[ClCH_2]_2$	70		**21b**[b] 20
9		**22a** *n*-hex	H	$PtCl_4$ [20]	$[ClCH_2]_2$	75		**23a** ND
10		**22a** *n*-hex	H	PNBSA [15]	toluene	75		**23a** ND
11		**22a** *n*-hex	H	$HNTf_2$ [5]	CH_2Cl_2	30		**23a** 83
12		**22b** *n*-Bu	H	$HNTf_2$ [5]	CH_2Cl_2	30		**23b** 84
13		**24** Ph	H	$HNTf_2$ [5]	CH_2Cl_2	30		**25** 77
14		**26** *n*-hex	Ph	$HNTf_2$ [5]	CH_2Cl_2	30		**27**[c] 92
15		**28a** *n*-hex	Ts	$PtCl_2$ [10]	dioxane	80		**29a** 15
16		**28a** *n*-hex	Ts	PNBSA [10]	toluene	55		**29a** 20
17		**28a** *n*-hex	Ts	PNBSA [20]	toluene	55		**29a** 69
18		**28a** *n*-hex	Ts	$HNTf_2$ [1]	CH_2Cl_2	rt		**29a** <10
19		**28b** *n*-Bu	Ts	PNBSA [20]	toluene	55		**29b** 73
20		**30** *n*-hex	Ns	PNBSA [20]	toluene	55		**31** 84

a. Isolated yields only. **b.** As a mixture of rotamers and the isomer resulting from *para*-substitution [the *ortho*-isomer is shown]. **c.** The *dr* is ~ 9 : 1 but unassigned.

[a] Isolated yields only. [b] As a mixture of rotamers and the isomer resulting from para substitution [the ortho isomer is shown]. [c] Dr is ~9:1 but unassigned.

20b [entries 6−8], but these were met with similar difficulties. The only discernible product was **21b** from **20b**, which contains a more electron-rich arene [entry 8]. Interestingly, the regiochemistry of the cyclization also changed to favor the addition of the arene to the β-carbon of the ynamide, presumably because both α- and β-carbons can be electrophilic when the ynamide is complexed with a transition metal.

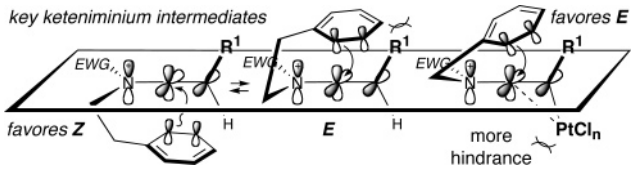
With an additional methylene unit as shown in **22a** and **22b** [entries 9−12], $HNTf_2$ in 5 mol % [entries 11 and 12] was again effective in promoting the cyclization to give the corresponding products **23a** and **23b** in good yields. Other related ynamides **24** and **26** also led to cyclized products **25** and **27**, respectively, with the latter providing a 9:1 diastereomeric ratio [entries 13 and 14].

When we examined indole-tethered ynamides **28a** and **28b**, we found that PNBSA [*p*-nitrobenzenesulfonic acid] was the best Brønsted acid in 20 mol % [entries 17 and 19], while $HNTf_2$ was not useful. This is presumably due to competing protonation of the indole ring when a much stronger Brønsted acid such as $HNTf_2$ is used.[18,20]

On the other hand, protonations of *N*-acyl ynamides require a stronger Brønsted acid because they are much less reactive than *N*-sulfonyl ynamides given that the nitrogen lone pair is more delocalized into the acyl carbonyl.[11b] Ynamide **30**, substituted with a Nosyl [Ns] group, worked equally well when using PNBSA [entry 17 vs 20].

It is noteworthy that cyclizations of N-tethered arene-ynamides are highly stereoselective. The (*Z*)-enamide formation is favored in all cases using Brønsted acids. Only for **18a** and **18b** was the (*E*)-enamide formation observed when using $PtCl_4$. These stereochemical outcomes can be accounted for as shown in Scheme 3.

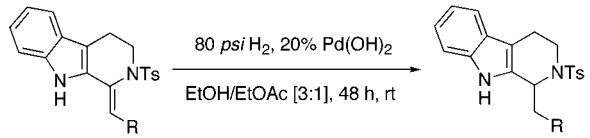
Scheme 3



When using Brønsted acids, the cyclization of the keteniminium intermediate that favors the (*Z*)-enamide [left] is devoid of the steric interaction between the R^1 group and the incoming arene [the (*E*)-model at center]. This selectivity is reversed when $PtCl_4$ was used since Pt is now more of a hindrance than the R^1 group [the (*E*)-model at right]. This would be especially true if the Pt metal could help stabilize the keteniminium carbon [see the dotted bond], thereby blocking even further the addition pathway at the bottom face.

The distinct advantage of this keteniminium Pictet−Spengler cyclization is the formation of a useful enamide motif that can be subjected to various transformations.[21−23] While these are among our current pursuits, we have here hydrogenated the rather hindered trisubstituted enamide in **29a** and **29b** at 80 psi H_2 using 20 mol % $Pd(OH)_2$ to complete the concept that this method represents a Pictet−Spengler equivalent [Scheme 4].

Scheme 4



29a: R = *n*-hex
29b: R = *n*-Bu

32a: R = *n*-hex [78%]
32b: R = *n*-Bu [84%]

To illustrate the synthetic potential of this methodology, total syntheses of desbromoarborescidines A and C were pursued. The synthesis of 10-desbromoarborescidine A [**36**],[16,24] which is a natural product in itself,[14] was completed, featuring the keteniminium Pictet−Spengler cyclization of ynamide **33** that contains a Cl group, albeit at 90 °C [Scheme 5]. To provide some alternatives for the reduction, the

(20) Attempts to disfavor the alleged competition were made. However, when the indole nitrogen atom in **28a** was protected with Boc, the cyclization still proceeded only with PNBSA.

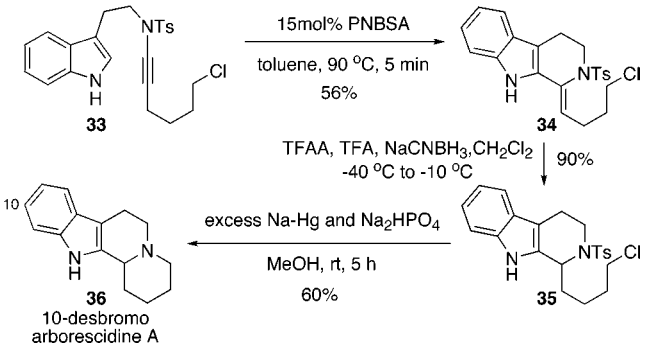
(21) For a review on enamides, see: Rappoport, Z. *The Chemistry of Enamines in The Chemistry of Functional Groups*; John Wiley and Sons: New York, 1994.

(22) For recent studies involving enamides, see: (a) Fuchs, J. R.; Funk, R. L. *Organic Lett.* **2001**, *3*, 3349. (b) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2000**, *3*, 1125.

(23) For oxdiations of enamides, see: (a) Xiong, H.; Hsung, R. P.; Shen, L.; Hahn, J. M. *Tetrahedron Lett.* **2002**, *43*, 4449. (b) Poon, T.; Turro, N. J.; Chapman, J.; Lakshminarasimhan, P.; Lei, X.; Jockusch, S.; Franz, R.; Washington, I.; Adam, W.; Bosio, S. G. *Org. Lett.* **2003**, *5*, 4951.

(24) Specific carbon numbering systems were based on Païs's isolation paper: see ref 16.

Scheme 5



enamide in **35** was reduced under cationic conditions using TFA and $NaCNBH_3$. Reductive removal of the Ts group occurred concomitantly with N-alkylation when using Smith's protocol involving Na−Hg and Na_2HPO_4.[25]

The synthesis of 11-desbromoarborescidine C [**42**][16,24] was more involved due to issues related to protecting groups. This is largely due to the fact that we had trouble in the preparation of ynamide **37** in which the nitrogen atom is substituted as a urethane group.

Ultimately, after hydrogenation of **38**, which was obtained in 67% yield from the keteniminium Pictet−Spengler cyclization of **37**, the Ts group was removed using Heathcock's sodium naphthalide protocol [Scheme 6].[26] We were surprised and uncertain why the benzyl ether in **38** survived the hydrogenation step. The secondary amine intermediate was then protected as a urethane using $ClCO_2Me$. Subsequent protection of the indole nitrogen with Boc anhydride gave **40** in 70% overall yield from **38**.

With the protecting group issue being resolved, 11-desbromoarborescidine C [**42**] was obtained in four steps from **40**, featuring (1) debenzylation via hydrogenation, (2) Swern oxidation, (3) removal of the indole Boc group concomitant with the aminal formation[27] using 8.0 N aq HCl,

(25) Smith, A. B., III; Kim. D.-S. *Org. Lett.* **2004**, *6*, 1493.

(26) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

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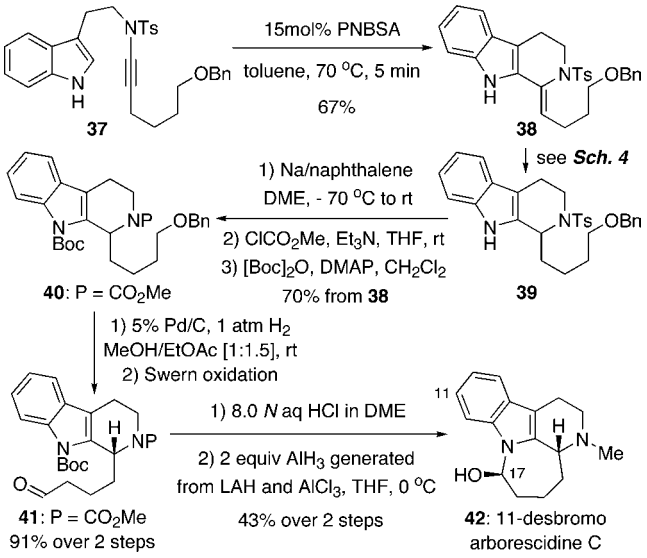
Scheme 6



and (4) reduction of the urethane to the corresponding methylamine using AlH_3 generated in situ from LAH and $AlCl_3$.[28] Both desbromoarborescidines A and C are spectroscopically identical to those reported.[15a,17a]

We have reported here a Brønsted acid-catalyzed, highly stereoselective arene-ynamide cyclization. Total syntheses of desbromoarborescidines A and C were accomplished from tryptamine in 5 and 11 steps, respectively, representing the first applications of ynamides in natural product synthesis. Future applications of this keteniminium Pictet−Spengler cyclization are currently underway.

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Supporting Information Available: Experimental and ^1H NMR spectral and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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