Multicomponent Synthesis

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Palladium(0)-Catalyzed Alkynyl and Allenyl Iminium Ion Cyclizations Leading to 1,4-Disubstituted 1,2,3,6-Tetrahydropyridines**

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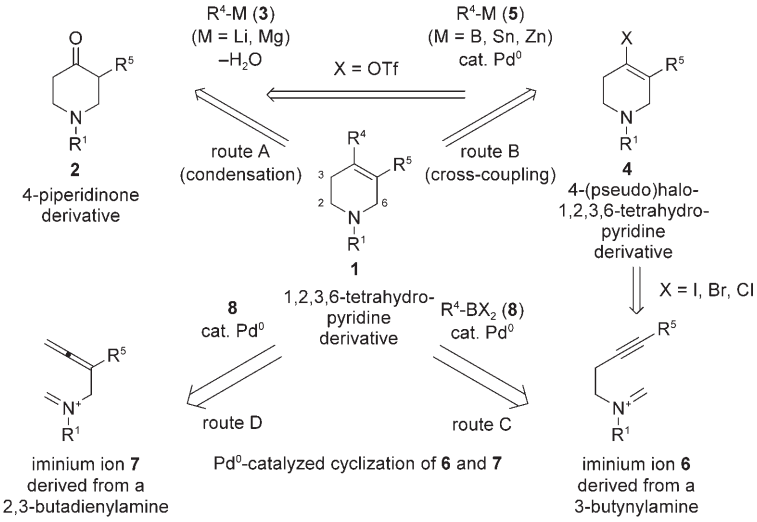
Piperidines, aliphatic six-membered nitrogen-containing heterocycles, are among the most promising therapeutic agents for a wide variety of diseases, including Alzheimer's disease and Parkinson's disease.[1] The development of new and efficient methods for the preparation of structurally diverse piperidine derivatives is desired for the drug-discovery process.[2] The introduction of a variety of substituent groups into preformed piperidine scaffolds is the conventional approach. This method has been applied to the synthesis of 1,4-disubstituted 1,2,3,6-tetrahydropyridines **1**, which are biologically important unsaturated piperidine derivatives[3] and useful synthetic intermediates for the preparation of saturated derivatives (Scheme 1). Synthetic routes to piperidines can be divided into the following two classes: 1) the condensation of a 4-piperidinone **2** with an organometallic reagent **3** (route A);[4] 2) the cross-coupling of a halogen- or triflate-containing piperidine **4** with an organometallic reagent **5** (route B).[5,6] Although the latter route is superior to the former in terms of its compatibility with a variety of functional groups, the preparation of the starting triflate **4** for route B requires regioselective deprotonation of a piperidinone **2** with a strong base,[5] a transformation that is not appropriate for unsymmetrical or base-labile piperidinones. Alternatively, the starting halide **4** can be prepared by a 6-*endo*-trig cyclization reaction of an alkynyl iminium ion **6** generated in situ from the parent secondary amine and formaldehyde.[7,8] However, a single-step procedure for the transformation of structurally simple acyclic precursors **6** into tetrahydropyridines **1** with diverse substituents has never been developed. Such a procedure would avoid the preparation of the cyclic intermediate **4** and make the overall process atom economical. Herein, we describe two newly developed three-component syntheses[9] of **1** based on a Pd^0-catalyzed "anti-Wacker"-type cyclization[10] of an alkynyl or allenyl iminium ion **6** or **7** generated in situ with an organoboron reagent **8**. These single-step routes C and D involving carbon–carbon bond formation at C4 and concomitant C5–C6–N1 and C3–C2–N1 bond formation, respectively, complement each other.[11]



Scheme 1. Retrosynthetic analysis of the 1,2,3,6-tetrahydropyridine structure **1**. Tf = trifluoromethanesulfonyl.

We first developed reaction conditions for the cyclization of the terminal-alkyne-containing amine **9a**[12] with the concomitant introduction of a *p*-methoxyphenyl group at C4 (Table 1) on the basis of those for the related 6-*exo*-trig cyclization of a 5-alkynal[10a] (Scheme 2). Upon heating at 50 °C in the presence of a slight excess of *p*-methoxyphenylboronic acid (**8A**), aqueous formaldehyde,[13] and a catalytic amount of $[Pd(PPh_3)_4]$, **9a** underwent arylative cyclization to afford a single cyclized product **1aA**. The yield of the product is affected dramatically by the solvent; **1aA** was formed in the highest yield in THF (Table 1, entries 1–5 versus entry 6). The reaction conditions are applicable to cyclizations of **9a** with the electron-rich and neutral aryl boronic acids **8B–E** (Table 1, entries 7–10). The heteroaryl boronic acids **8F**,**G** also served as nucleophiles in this process, with the formation of the cyclized products **1aF** and **1aG** in high yields (Table 1, entries 11 and 12). Importantly, no reaction takes place in the absence of the palladium catalyst.

The electron-deficient aryl boronic acid **8H** was found to be much less effective in the $[Pd(PPh_3)_4]$-catalyzed cyclization than electron-rich derivatives under the same reaction conditions (Table 2, entry 1). Ligand screening revealed that palladium ligated with $PPh(c\text{-}C_6H_{11})_2$ catalyzed effectively the cyclization reaction of **9a** with **8H** (Table 2, entry 4). Fur-

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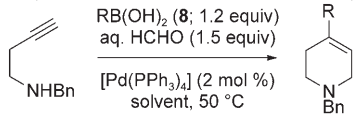
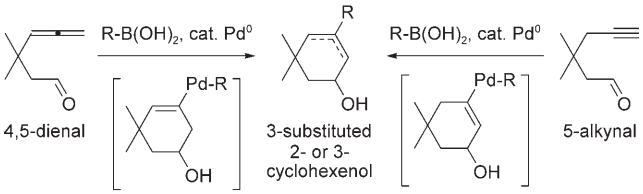
Table 1: Arylative cyclization of **9a** with electron-rich aryl boronic acids.[a]



9a **1aA–1aG**

Entry	8	Solvent	*t* [h]	1	Yield [%]
1	*p*-MeO-C_6H_4-$B(OH)_2$ (**8A**)	toluene	3	**1aA**	49
2	**8A**	$ClCH_2CH_2Cl$	2	**1aA**	10
3	**8A**	CH_3CN	3	**1aA**	7
4	**8A**	MeOH	8	**1aA**	66
5	**8A**	DMF	4	**1aA**	33
6	**8A**	THF	1	**1aA**	79
7	*p*-Me-C_6H_4-$B(OH)_2$ (**8B**)	THF	1	**1aB**	72
8	*o*-Me-C_6H_4-$B(OH)_2$ (**8C**)	THF	1	**1aC**	88
9	*m*-Me-C_6H_4-$B(OH)_2$ (**8D**)	THF	2	**1aD**	69
10	C_6H_5-$B(OH)_2$ (**8E**)	THF	2	**1aE**	71
11	2-thiophenyl boronic acid (**8F**)	THF	1	**1aF**	87
12	3-thiophenyl boronic acid (**8G**)	THF	1	**1aG**	83

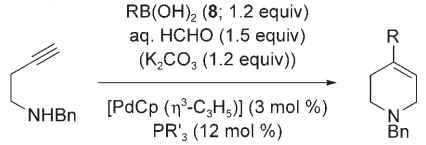
[a] Bn = benzyl, DMF = *N*,*N*-dimethylformamide.



Scheme 2. Pd^0-catalyzed alkylative cyclization of alkynyl and allenyl aldehydes.

thermore, the use of K_2CO_3 as a base resulted in an increase in the yield of the product (Table 2, entry 5).[14] Arylative cyclizations with unsubstituted **8E** and aryl boronic acids

Table 2: Cyclization of **9a** with electron-deficient aryl and vinyl boronic acids and trialkyl boranes.



9a **1aE, 1aH–1aN**

Entry	8	PR_3	*t* [h]	1	Yield [%]
1	*p*-Ac-C_6H_4-$B(OH)_2$ (**8H**)	PPh_3[a]	4	**1aH**	29
2	**8H**	$P(c\text{-}C_6H_{11})_3$	4	**1aH**	19
3	**8H**	$PPh_2(c\text{-}C_6H_{11})$	2	**1aH**	45
4	**8H**	$PPh(c\text{-}C_6H_{11})_2$	2	**1aH**	66
5[b]	**8H**	$PPh(c\text{-}C_6H_{11})_2$	1	**1aH**	80
6[b]	C_6H_5-$B(OH)_2$ (**8E**)	$PPh(c\text{-}C_6H_{11})_2$	1	**1aE**	79
7[b]	*p*-F-C_6H_4-$B(OH)_2$ (**8I**)	$PPh(c\text{-}C_6H_{11})_2$	1	**1aI**	85
8[b]	*p*-Cl-C_6H_4-$B(OH)_2$ (**8J**)	$PPh(c\text{-}C_6H_{11})_2$	1	**1aJ**	85
9[b]	*p*-CHO-C_6H_4-$B(OH)_2$ (**8K**)	$PPh(c\text{-}C_6H_{11})_2$	4	**1aK**	72
10[b]	*m*-NO_2-C_6H_4-$B(OH)_2$ (**8L**)	$PPh(c\text{-}C_6H_{11})_2$	1	**1aL**	69
11	(*E*)-Ph-CH=CH-$B(OH)_2$ (**8M**)	$PPh(c\text{-}C_6H_{11})_2$	1	**1aM**	85
12[c]	Et_3B (**8N**)	$PPh(c\text{-}C_6H_{11})_2$	6	**1aN**	78

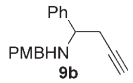
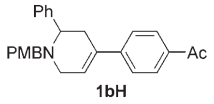
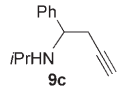
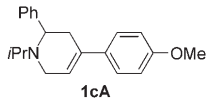
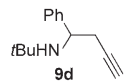
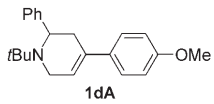
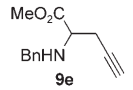
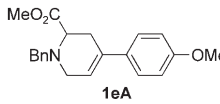
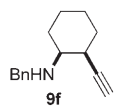
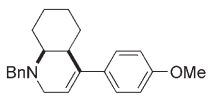
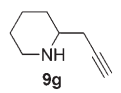
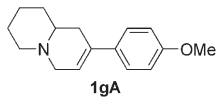
[a] The reaction was carried out with $[Pd(PPh_3)_4]$ (2 mol%). [b] The reaction was carried out with K_2CO_3. [c] The reaction was carried out with 1.5 equivalents of **8N** at 65 °C.

8I–L substituted with electron-withdrawing groups also proceeded under the optimized conditions (Table 2, entries 6–10), whereby the aromatic aldehyde in **8K** survived the reaction conditions (Table 2, entry 9). The cyclization reaction also took place with the vinyl boronic acid **8M** to afford the 1,3-diene **1aM** (Table 2, entry 11). Triethylborane (**8N**), which has β hydrogen atoms, participated in this process without undergoing competitive β-hydride elimination (Table 2, entry 12).

The 1-phenyl- and 1-methoxycarbonyl-substituted 3-butynylamines **9b–e** also underwent efficient cyclization reactions to provide 1,2,4-trisubstituted 1,2,3,6-tetrahydropyridines (Table 3, entries 1–4). The presence of a secondary alkyl substituent or a tertiary alkyl substituent on the nitrogen atom retards the reaction, but good product yields are maintained (Table 3, entries 2 and 3). Arylative cyclizations of the ethynyl-substituted cyclohexylamine **9f** and the piperidine **9g** afforded the bicyclic piperidines **1fA** and **1gA**, respectively (Table 3, entries 5 and 6). Unfortunately, amines with internal alkyne functionalities do not undergo cyclization to give 1,4,5-trisubstituted 1,2,3,6-tetrahydropyridines under these conditions.[15]

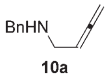
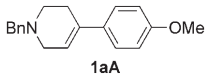
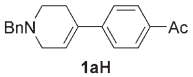
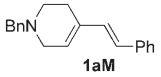
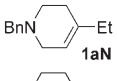
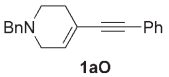
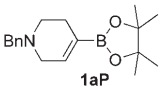
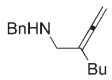
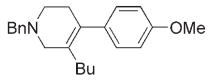
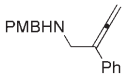
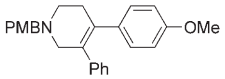
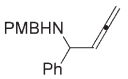
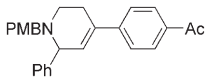
The use of 2,3-butadienylamines **10**[12] in place of 3-butynylamines **9** offers an alternative route to tetrahydropyridines **1** (Table 4). The three-component coupling reactions with the allenyl amines **10** proceed in the presence of $[Pd(PPh_3)_4]$[10c] and complement route C in Scheme 1 as

Table 3: Arylative cyclization of 3-butynylamines **9b–g**.[a]

Entry	9	8	*t* [h]	1	Yield [%]
1[b,c]	 **9b**	**8H**	1	 **1bH**	72
2	 **9c**	**8A**	8	 **1cA**	78
3	 **9d**	**8A**	8	 **1dA**	76
4[d]	 **9e**	**8A**	12	 **1eA**	67
5[d]	 **9f**	**8A**	12	 **1fA**	64
6[b]	 **9g**	**8A**	24	 **1gA**	64

[a] Reaction conditions: **8** (1.2 equiv), aqueous HCHO (37%; 1.5 equiv), $[Pd(PPh_3)_4]$ (2 mol%), THF, 50 °C. [b] The reaction was carried out with $[PdCp(\eta^3\text{-}C_3H_5)]$ (3 mol%) and $PPh(c\text{-}C_6H_{11})_2$ (12 mol%) in place of $[Pd(PPh_3)_4]$. [c] The reaction was carried out with K_2CO_3 (1.2 equiv). [d] The reaction was carried out with 5 mol% of $[Pd(PPh_3)_4]$ at 65 °C. PMB = *p*-methoxybenzyl.

Table 4: Cyclization of 2,3-butadienylamines **10** with the incorporation of various substituent types.[a]

Entry	**10**	**8**	**1**	Yield [%]
1	 **10a**	**8A**	 **1aA**	84
2[b]	**10a**	**8H**	 **1aH**	76
3	**10a**	**8M**	 **1aM**	83
4[c]	**10a**	**8N**	 **1aN**	66
5[d]	**10a**	PhCCH (**8O**)	 **1aO**	85
6[e]	**10a**	$(BPin)_2$ (**8P**)	 **1aP**	63
7	 **10h**	**8A**	 **1hA**	88
8	 **10i**	**8A**	 **1iA**	51
9[b]	 **10j**	**8H**	 **1jH**	81

[a] Reaction conditions: **8** (1.2 equiv), aqueous HCHO (37%; 1.5 equiv), $[Pd(PPh_3)_4]$ (2 mol%), THF, 50°C, 1 h. [b] The reaction was carried out with K_2CO_3 (1.2 equiv). [c] The reaction was carried out with 1.5 equivalents of **8N** for 2 h. [d] The reaction was carried out with 1.5 equivalents of **8O** in the presence of CuI (4 mol%). [e] The reaction was carried out with 2 equivalents of **8P**. Pin = pinacolato.

follows: 1) In addition to aryl, vinyl, and alkyl groups (Table 4, entries 1–4), alkynyl and boryl groups can be introduced at C4 by using a slight excess of the terminal alkyne in combination with a catalytic amount of CuI in the first case and a diboron reagent in the second (Table 4, entries 5 and 6); 2) 1,4,5-trisubstituted 1,2,3,6-tetrahydropyridines can be obtained from 2-substituted 2,3-butadienylamines (Table 4, entries 7 and 8); 3) regioisomers of the products formed with the 3-butynylamines can be synthesized (compare Table 4, entry 9 with Table 3, entry 1).

In summary, we have developed two efficient methods for the synthesis of 1,4-disubstituted 1,2,3,6-tetrahydropyridines from alkynyl or allenyl amines, formaldehyde, and organoboron reagents. The mild reaction conditions, broad functional-group compatibility, excellent regioselectivity, and ready availability of the reagents make this single-step procedure both practical and suitable for combinatorial synthesis. Symmetrical and unsymmetrical tetrahydropyridines generated in these reactions may be potent drug candidates and should be useful intermediates for the synthesis of saturated piperidines. Studies to probe the mechanism in detail and to expand the scope of the cyclization are under way.

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Keywords: heterocycles · iminium ions · multicomponent reactions · organoboron reagents · palladium

[1] a) B. Wenzel, D. Sorger, K. Heinitz, M. Scheunemann, R. Schliebs, J. Steinbach, O. Sabri, *Eur. J. Med. Chem.* **2005**, *40*, 1197–1205; b) A. P. Guzikowski, A. P. Tamiz, M. Acosta-Burruel, S. Hong-Bae, S. X. Cai, J. E. Hawkinson, J. F. Keana, S. R. Kesten, C. T. Shipp, M. Tran, E. R. Whittermore, R. M. Woodward, J. L. Wright, Z.-L. Zhou, *J. Med. Chem.* **2000**, *43*, 984–994, and references therein.

[2] a) L. Sabine, D. Tim, *Synthesis* **2000**, 1781–1813; b) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; c) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; d) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; e) J. Cossy, *Chem. Rec.* **2005**, *5*, 70–80.

[3] S. Przedborski in *Parkinson's Disease: Genetics and Pathogenesis* (Ed.: T. M. Dawson), Dekker, New York, **2007**, pp. 325–350.

[4] a) L. L. Martin, S. S. Klioze, M. Worm, C. A. Crichlow, H. M. Geyer III, H. Kruse, *J. Med. Chem.* **1979**, *22*, 1347–1354; b) C. J. Barnett, C. R. Copley-Merriman, J. Maki, *J. Org. Chem.* **1989**, *54*, 4795–4800.

[5] a) D. J. Wustrow, L. D. Wise, *Synthesis* **1991**, 993–995; b) U. S. Larsen, L. Martiny, M. Begtrup, *Tetrahedron Lett.* **2005**, *46*, 4261–4263; c) G. N. Boice, C. G. Savarin, J. A. Murry, K. Conrad, L. Matty, E. G. Corley, J. H. Smitrovich, D. Hughes, *Tetrahedron* **2004**, *60*, 11367–11374; d) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943–3949; for cross-coupling reactions between metalated piperidines and organic halides, see: e) J. S. Kiely, E. Laborde, L. E. Lesheski, R. A. Bucsh, *J. Heterocycl. Chem.* **1991**, *28*, 1581–1585; f) P. R. Eastwood, *Tetrahedron Lett.* **2000**, *41*, 3705–3708; g) C. Morrill, N. S. Mani, *Org. Lett.* **2007**, *9*, 1505–1508.

[6] For other synthetic routes to **1**, see: a) C. J. Schmidle, R. C. Mansfield, *J. Am. Chem. Soc.* **1956**, *78*, 425–428; b) C. J. Schmidle, R. C. Mansfield, *J. Am. Chem. Soc.* **1956**, *78*, 1702–1705.

[7] a) L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **1988**, *110*, 612–614; b) H. J. Arnold, L. E. Overman, M. J. Sharp, M. C. Witschel, *Org. Synth.* **1991**, *70*, 111–116; c) L. E. Overman, A. K. Sarkar, *Tetrahedron Lett.* **1992**, *33*, 4103–4106; d) Y. Murata, L. E. Overman, *Heterocycles* **1996**, *42*, 549–553.

[8] For iodide-promoted allenyl acyliminium ion cyclization reactions, see: a) W. G. Beyersbergen van Henegouwen, R. M. Fieseler, F. P. J. T. Rutjes, H. Hiemstra, *Angew. Chem.* **1999**, *111*, 2351–2355; *Angew. Chem. Int. Ed.* **1999**, *38*, 2214–2217; b) W. G. Beyersbergen van Henegouwen, R. M. Fieseler, F. P. J. T. Rutjes, H. Hiemstra, *J. Org. Chem.* **2000**, *65*, 8317–8325.

[9] For reviews on the multicomponent synthesis of heterocycles, see: a) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; b) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101–4111; c) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108.

[10] a) H. Tsukamoto, T. Ueno, Y. Kondo, *J. Am. Chem. Soc.* **2006**, *128*, 1406–1407; b) H. Tsukamoto, T. Ueno, Y. Kondo, *Org. Lett.* **2007**, *9*, 3033–3036; c) H. Tsukamoto, T. Matsumoto, Y. Kondo, *J. Am. Chem. Soc.* **2008**, *130*, 388–389.

[11] Route D is quite different from Pd^0-catalyzed tetrahydropyridine syntheses based on the carbocyclization of a 3,4-pentadie-

nylamine with an organic halide to form both a carbon–carbon bond at C5 and a C6–N1 bond. The products of the latter reactions are often contaminated by the corresponding 2-alkenyl azetidine and 2,3-dihydropyrrole as by-products: a) F. P. J. T. Rutjes, K. C. M. F. Tjen, L. B. Wolf, W. F. J. Karstens, H. E. Schoemaker, *Org. Lett.* **1999**, *1*, 717 – 720; b) S.-K. Kang, T.-G. Baik, A. N. Kulak, *Synlett* **1999**, 324 – 326; c) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904 – 4914; d) S. Ma, F. Yu, J. Li, W. Gao, *Chem. Eur. J.* **2007**, *13*, 247 – 254.

[12] A wide variety of starting materials **9** and **10** can be prepared by two-component coupling reactions, that is, the nucleophilic substitution of the methanesulfonate of a 3-butyn-1-ol or 2,3-butadien-1-ol with a primary amine, or the reductive amination of an aldehyde with a primary 3-butynylamine or 2,3-butadienylamine.

[13] Paraformaldehyde is not suitable as a source of formaldinium ion.

[14] We observed that the use of aryl boronic esters also leads to an increase in product yields; thus, the acid moiety of electron-deficient aryl boronic acids appears to hamper the reaction.

[15] In contrast to the cyclization developed by Overman and co-workers,[7] neither alkynyl amines with internal alkyne groups nor 4-pentynylamines undergo cyclization.

