ORGANIC LETTERS

2012
Vol. 14, No. 23
6076–6079

1,2- and 1,4-Additions of 2-Alkynylcyclohexadienimines with Aromatic Amines To Access 4-Amino-*N*-arylindoles and -azepinoindoles

Li Zhang, Zhiming Li,* and Renhua Fan*

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

rhfan@fudan.edu.cn; zmli@fudan.edu.cn

Received October 28, 2012

ABSTRACT

2-Alkynylcyclohexadienimines, derived from the oxidation of 2-alkynylanilines, react with aromatic amines leading to *N*-arylindoles with a 4-amino substitution. The reaction was metal-controlled, and $Bi(OTf)_3$ proved to be the best catalyst. The resulting 4-amino *N*-arylindoles could be converted to azepino[4,3,2-*cd*]indoles through condensation with aldehydes.

N-Arylindoles appear as central substructures in many pharmaceutical and medicinal compounds.[1] For example, they are potential antipsychotic agents,[2] angiotensin II antagonists,[3] melatonin receptor MT1 agonists,[4] anti HIV-1 agents,[5] and COX-2 inhibitors.[6] Transition-metal-catalyzed C−N cross-coupling of aryl halides with indoles is a straightforward approach to prepare *N*-arylindoles.[7] Recently, a variety of cascade reactions have been developed for the synthesis of *N*-arylindoles.[8] In these elegant tactics, a transition-metal-catalyzed coupling reaction also plays a prominent role (Scheme 1). The development of an alternative method to construct functionalized *N*-arylindoles is still desirable.

(1) (a) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658. (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (c) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148. (d) Smart, B. P.; Oslund, R. C.; Walsh, L. A.; Gelb, M. H. *J. Med. Chem.* **2006**, *49*, 2858.

(2) Andersen, K.; Liljefors, T.; Hyttel, J.; Perregaard, J. *J. Med. Chem.* **1996**, *39*, 3723.

(3) Jahangir Stabler, S. R. *Synth. Commun.* **1994**, *24*, 123.

(4) Spadoni, G.; Balsamini, C.; Bedini, A.; Diamantini, G.; Di Giacomo, B.; Tontini, A.; Tarzia, G.; Mor, M.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Pannacci, M.; Lucini, V.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **1998**, *41*, 3624.

(5) Xu, H.; Liu, W. Q.; Fan, L. L.; Chen, Y.; Yang, L. M.; Lv, L.; Zheng, Y. T. *Chem. Pharm. Bull.* **2008**, *56*, 720.

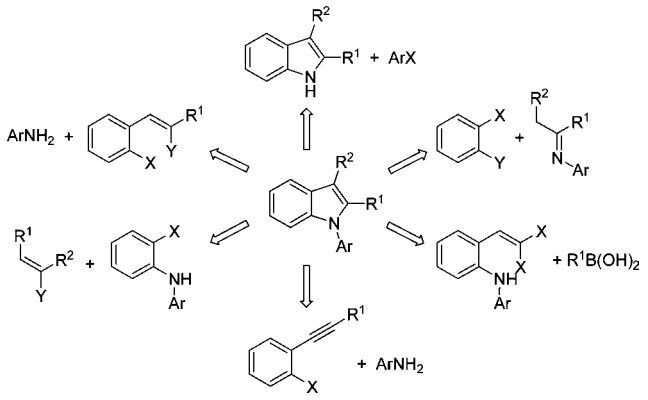
(6) Sano, H.; Noguchi, T.; Tanatani, A.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem.* **2005**, *13*, 3079.

(7) For examples, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Cacchi., S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934. (e) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862. (f) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (g) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (h) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (i) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (j) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766. (k) Martins, A.; Lemouzy, S.; Lautens, M. *Org. Lett.* **2009**, *11*, 181. (l) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337. (m) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332. (n) Ueda, S.; Su, M.-J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 700.

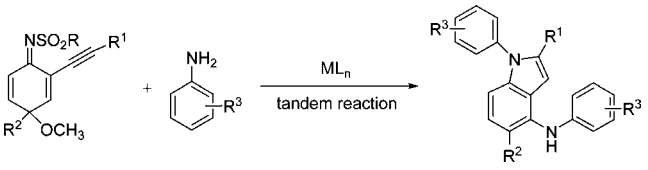
(8) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501. (d) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (e) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (f) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (g) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (h) Tang, Z.-Y.; Hu, Q.-S. *Adv. Synth. Catal.* **2006**, *348*, 846. (i) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764. (j) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529. (k) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (l) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888. (m) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031. (n) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2010**, *16*, 11707. (o) Ackermann, L.; Song, W.; Sandmann, R. *J. Organomet. Chem.* **2011**, *696*, 195.

10.1021/ol3029675
Published on Web 11/27/2012

Scheme 1. Strategies for the Synthesis of *N*-Arylindoles



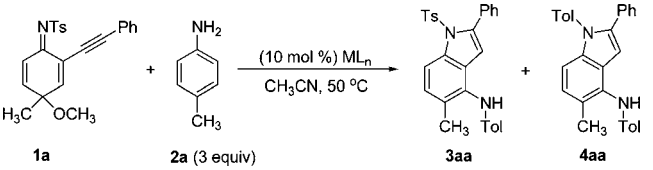
Scheme 2. Our Strategy To Construct 4-Amino-*N*-arylindoles



Some of our recent efforts have been focused on extending the utilization of cyclohexadienimines,[9,10] which are formed from the oxidative dearomatization of aromatic amines.[11] 2-Alkynyl cyclohexadienimines proved to be potential precursors to 4-substituted indoles. Since there are two reaction sites in the α,β-unsaturated imino group, we envisaged that tandem 1,2- and 1,4-additions of aromatic amines to 2-alkynylcyclohexadienimines might provide a path to construct *N*-arylindoles with a 4-amino substitution (Scheme 2). The 4-aminoindole unit is also found in many biologically active compounds, such as (−)-indolactam V,[12] pyrroloazaflavones,[13] and SDZ-216525.[14]

Preliminary investigation revealed that the species of catalyst had a significant influence on the reaction between 2-phenylethynylcyclohexadienimine (**1a**) and *p*-toluidine (**2a**) (Table 1). In the presence of 10 mol % of AuCl, the reaction only provided 4-amino-substituted *N*-Ts indole **3aa** in a 53% yield. When $AuCl_3$ was used instead of AuCl, the desired 4-amino-*N*-arylindole **4aa** was isolated as the major product in 39% yield. When $PdCl_2$ was employed, the yield of *N*-arylindole **4aa** decreased to 7%. For a variety of metal triflates, only AgOTf, $Cu(OTf)_2$, and $Bi(OTf)_3$ exhibited catalytic activities for the generation of *N*-arylindole **4aa**. $Bi(OTf)_3$ proved to be the best catalyst.

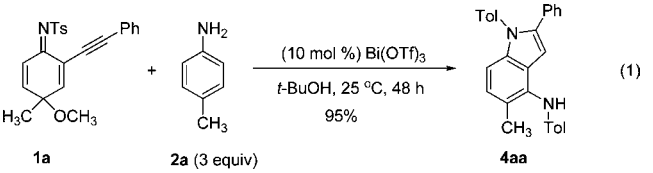
Table 1. Evaluation of Catalysts



entry	catalyst	**3aa** (%)[a]	**4aa** (%)[a]
1	AuCl	53	0
2	$AuCl_3$	11	39
3	$PdCl_2$	64	7
4	$Zn(OTf)_2$	0	0
5	$Ni(OTf)_2$	0	0
6	$Fe(OTf)_2$	0	0
7	$Dy(OTf)_3$	0	0
8	$Sc(OTf)_3$	0	0
9	$Yb(OTf)_3$	0	0
10	$In(OTf)_3$	0	0
11	AgOTf	47	36
12	$Cu(OTf)_2$	7	35
13	$Bi(OTf)_3$	7	62

[a] Reported yields are of the isolated product based on compound **1a**.

To improve the yield of compound **4aa**, various solvents, temperatures, and ratios of cyclohexadienimine and *p*-toluidine were examined. The best yield was obtained when the reaction was conducted in *t*-BuOH with 3 equiv of *p*-toluidine at room temperature for 48 h (eq 1).



(1)

With the optimized reaction conditions in hand, the scope of this reaction was investigated. To simplify the reaction procedure, the crude oxidative dearomatization products were directly used in the $Bi(OTf)_3$-catalyzed reactions (Table 2). For 4-substituted 2-alkynylanilines with a range of different substitutions, the two-step reactions proceeded smoothly leading to the corresponding 4-amino-*N*-arylindoles in good to excellent yields (Table 2, entries 1−7). When 2-ethynyl-4-methylbenzenamine (**5h**)

(9) (a) Wang, L.; Han, Z.; Fan, R. *Adv. Synth. Catal.* **2010**, *352*, 3230. (b) Wang, L.; Fan, R. *Org. Lett.* **2012**, *13*, 3596.

(10) (a) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325. (b) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215. (c) Quideau, S.; Pouységu, L.; Ozanne, A.; Gagnepain, J. *Molecules* **2005**, *10*, 201. (d) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (e) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629. (f) Giroux, M.-A.; Guérard, K. C.; Beaulieu, M.-A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871.

(11) For reviews on dearomatization, see: (a) Quideau, S.; Pouységu, L. *Org. Prep. Proced. Int.* **1999**, *31*, 617. (b) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (c) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (d) López Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andújar Sánchez, C. M.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580. (e) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (f) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (g) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

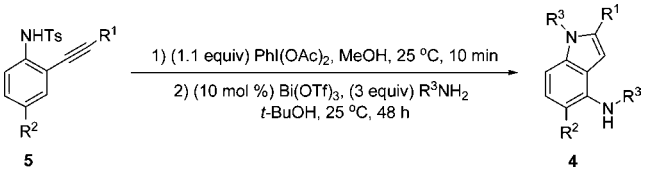
(12) Chen, S.; Borowiak, M.; Fox, J. L.; Maehr, R.; Osafune, K.; Davidow, L.; Lam, K.; Peng, L. F.; Schreiber, S. L.; Rubin, L. L.; Melton, D. *Nat. Chem. Biol.* **2009**, *5*, 258.

(13) Ferlin, M. G.; Chiarelotto, G.; Gasparotto, V.; Barzon, L.; Palu, G.; Castagliuolo, I. *J. Med. Chem.* **2005**, *48*, 3417.

(14) Schoeffter, P.; Floyd, J. R.; Stoll, A.; Siegl, H.; Seiler, M. P.; Hoyer, D. *Eur. J. Pharmacol.* **1993**, *244*, 251.

was used as substrate, the reaction was complex. No desired product **4ha** was obtained (entry 8). With respect to other aromatic amines, both electron-rich and electron-poor anilines are suitable partners for this process (Table 2, entries 9–15). For example, the reaction of 4-methoxybenzenamine (**2b**) gave rise to product **4ab** in a 95% yield (Table 2, entry 9), while the reaction of fluoro- or chloro-substituted aniline **2g** or **2h** afforded compound **4ag** or **4ah** in a 68 or a 75% yield, respectively (Table 2, entries 14 and 15). The reaction of 5-amino-1,3-dimethyl-1*H*-pyrazole or 4-aminopyridine was very complex, and product **4ai** or **4aj** was not isolated (Table 2, entries 16 and 17).

Table 2. Scope Investigation



5 **4**

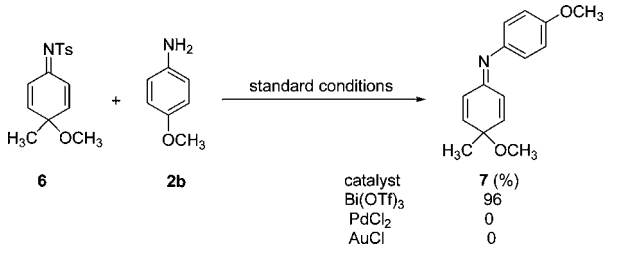
entry	R^1	R^2	R^3	**4** (%)[a]
1	C_6H_5	Me	4-MeC_6H_4	**4aa** (90)
2	4-MeOC_6H_4	Me	4-MeC_6H_4	**4ba** (73)
3	4-ClC_6H_4	Me	4-MeC_6H_4	**4ca** (68)
4	*n*-Bu	Me	4-MeC_6H_4	**4da** (71)
5	*t*-Bu	Me	4-MeC_6H_4	**4ea** (65)
6	C_6H_5	Et	4-MeC_6H_4	**4fa**(76)
7	C_6H_5	*n*-Bu	4-MeC_6H_4	**4ga** (85)
8	H	Me	4-MeC_6H_4	**4ha** (0)
9	C_6H_5	Me	4-MeOC_6H_4	**4ab** (95)
10	C_6H_5	Me	3,5-$(Me)_2C_6H_3$	**4ac** (92)
11	C_6H_5	Me	4-*i*PrC_6H_4	**4ad** (88)
12	C_6H_5	Me	C_6H_5	**4ae** (64)
13	C_6H_5	Me	4-BrC_6H_4	**4af** (73)
14	C_6H_5	Me	4-ClC_6H_4	**4ag** (68)
15	C_6H_5	Me	4-FC_6H_4	**4ah** (75)
16	C_6H_5	Me	4-pyridyl	**4ai** (0)
17	C_6H_5	Me	1,3-$(CH_3)_2$-1H-pyrazol-5-yl	**4aj** (0)

[a] Reported yields are of the isolated product based on compound **5**.

When 4-amino-*N*-Ts-indole **3aa** was treated with *p*-toluidine and $Bi(OTf)_3$, it could not be converted to 4-amino-*N*-arylindole **4aa**. When cyclohexadienimine **6** was used instead of 2-alkynylcyclohexadienimines to react with 4-methoxybenzenamine under the standard conditions, the $Bi(OTf)_3$-catalyzed reaction provided *N*-(4-methoxyphenyl)cyclohexadienimine (**7**) in a 96% yield. No reaction was observed with $PdCl_2$ or AuCl as catalyst (Scheme 3).

To shed some light on the reaction pathway, a primary DFT calculation was performed using Gaussian 09 package.[15] We located the ground states of the intermediates formed from the metal catalyst activation of 2-alkynyl cyclohexadienimine **1a**. As a matter of convenience, the counteranion is not considered. The results indicated that, when bismuth salt was used as catalyst, the direct coordination with the nitrogen atom of imine is most stable (Figure 1, intermediate **I**). When palladium was used, the activation of the triple bond leading to intermediate **II** was most favored. On the basis of the NBO (natural bond orbital) analysis, the C-3 position of 2-alkynylcyclohexadienimine is more positively charged compared with the C-5 position in both intermediates (Figure 1), which is in line with our experimental results.

Scheme 3



6 **2b**

catalyst	**7** (%)
$Bi(OTf)_3$	96
$PdCl_2$	0
AuCl	0

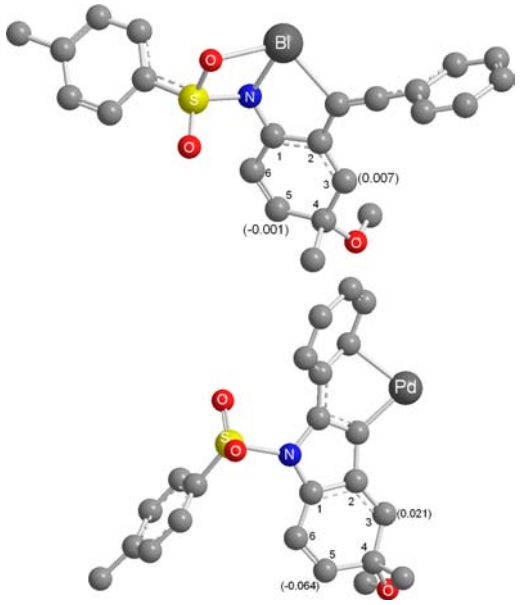
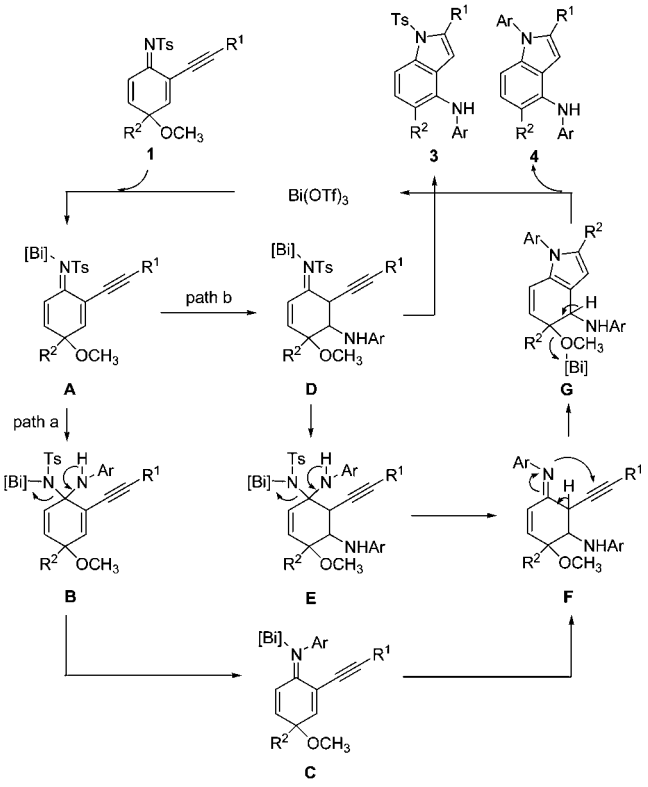


Figure 1. Optimized structures of intermediate **I** with Bi(III) as catalyst (upper) and intermediate **II** with Pd(II) as catalyst (down). The number in parentheses is NBO charges on atoms.

(15) Gaussian 09, Revision A.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford, CT, 2009.

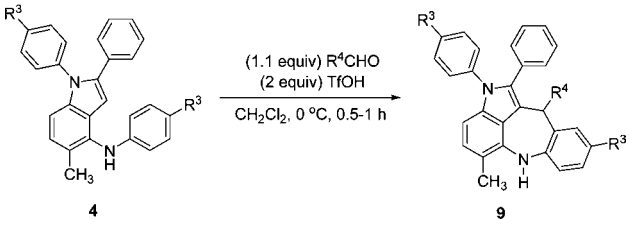
Scheme 4. Plausible Reaction Pathway



As illustrated in Scheme 4, when a suitable Lewis acid such as $Bi(OTf)_3$ was used, the coordination with the carbon−nitrogen double bond promotes 1,2- and 1,4-additions simultaneously.[16] In path a, the 1,2 addition with aromatic amines follows by elimination of $TsNH_2$ to form *N*-aryl 2-alkynylcyclohexadienimine **C**. With the aid of $Bi(OTf)_3$, this intermediate undergoes 1,4-addition to generate intermediate **F**. In path b, the 1,4 addition generates intermediate **D**. Its direct cyclization leads to 4-amino *N*-Ts indole **3**. When the 1,2-addition takes place before the cyclization, intermediate **D** is converted to intermediate **E**, followed by elimination of $TsNH_2$ to afford intermediate **F**. After cyclization and aromatization, 4-amino-*N*-arylindole **4** is formed.

It is noteworthy that, compared with 4-amino-*N*-Ts-indole **3**, 4-amino-*N*-arylindole **4** has a more electron-rich indole ring. This property makes it useful in the synthesis of azepinoindole derivatives.[17] As shown in Table 3, in the presence of 2 equiv of trifluoromethanesulfonic acid (TfOH), treatment of 4-amino-*N*-arylindoles with aldehydes in dichloromethane at 0 °C led to azepino[4,3,2-*cd*]indoles **9**. Various aldehydes including aromatic aldehydes bearing an electron-withdrawing or an electron-donating group, heteroaromatic aldehydes, cinnamaldehyde, 2-phenylacetaldehyde, and butyraldehyde were suitable substrates for this reaction. The corresponding azepino[4,3,2-*cd*]indoles were formed in good to excellent yields. When 4-amino-*N*-arylindoles bearing an electron-withdrawing substituent were used, the corresponding products were formed in moderated yields. The structure of compound **9** was confirmed by single-crystal diffraction analysis of compound **9aak**.

Table 3. Synthesis of Azepino[4,3,2-*cd*]indoles[a]



entry	R^3	R^4	**9**[b] (%)
1	Me	4-$NO_2C_6H_4$	**9aaa** (99)
2	Me	4-$CF_3C_6H_4$	**9aab** (92)
3	Me	4-FC_6H_4	**9aac** (98)
4	Me	4-ClC_6H_4	**9aad** (98)
5	Me	4-BrC_6H_4	**9aae** (97)
6	Me	4-CNC_6H_4	**9aaf** (95)
7	Me	C_6H_5	**9aag** (94)
8	Me	4-$MeOC_6H_4$	**9aah** (85)
9	Me	4-HOC_6H_4	**9aai** (85)
10	Me	2-thiophyl	**9aaj** (90)
11	Me	2-furyl	**9aak** (97)
12	Me	$C_6H_5CH{=}CH$	**9aal** (80)
13	Me	$C_6H_5CH_2$	**9aam** (98)
14	Me	*n*-Pr	**9aan** (91)
15	Br	4-$NO_2C_6H_4$	**9afa** (74)
16	Cl	4-$NO_2C_6H_4$	**9aga** (73)
17	F	4-$NO_2C_6H_4$	**9aha** (70)

[a] Freshly distilled trifluoromethanesulfonic acid was used. [b] Isolated yield based on compound **4**.

In summary, a new strategy for accessing 4-amino--arylindoles through dearomatization and $Bi(OTf)_3$-catalyzed tandem reaction has been developed. 4-Amino-*N*-arylindoles could be converted to azepino[4,3,2-*cd*]indoles. Work is currently ongoing to extend its scope by exploring its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

Acknowledgment. Financial support from the National Natural Science Foundation of China (Nos. 21072033 and 21102019) is gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H NMR and ^{13}C NMR of new compounds, computational details, X-ray crystal structure, and crystallographic data of compound **9aak** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679.

(17) (a) Hester, J. B., Jr. *J. Org. Chem.* **1967**, *32*, 3804. (b) Hester, J. B., Jr. *J. Org. Chem.* **1967**, *32*, 4095. (c) Hester, J. B., Jr.; Tang, A. H.; Keasling, H. H.; Veldkamp, W. *J. Med. Chem.* **1968**, *11*, 101. (d) Sharma, V.; Lansdell, T. A.; Jin, G.; Tepe, J. J. *J. Med. Chem.* **2004**, *47*, 3700.