RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

The facile synthesis of 2-bromoindoles *via* Cs_2CO_3-promoted intramolecular cyclization of 2-(*gem*-dibromovinyl)anilines under transition-metal-free conditions†

Cite this: *RSC Advances*, 2013, **3**, 73

Received 15th September 2012,
Accepted 29th October 2012

DOI: 10.1039/c2ra22172a

www.rsc.org/advances

Pinhua Li,[a] Yong Ji,[b] Wei Chen,[a] Xiuli Zhang[b] and Lei Wang*[ac]

2-Bromoindoles were readily prepared through a facile Cs_2CO_3-promoted intramolecular cyclization of 2-(*gem*-bromovinyl)-*N*-methylsulfonylanilines in excellent yields under transition-metal-free conditions. This methodology could be extended to the synthesis of corresponding 2-chloroindoles. The reaction mechanism suggested that cyclization occurs through a key intermediate, phenylethynyl bromide, followed by cyclization in one-pot.

Introduction

The indole nucleus is an important structural motif frequently found in natural products, materials, and therapeutic agents, such as antibiotic, anticancer and anti HIV activity.[1] Indole derivatives are also used as the starting materials for the synthesis of a large number of alkaloids. Many halogenated indoles are also found in nature, and several brominated indole natural products have been isolated.[2] They are also present in biologically active compounds, for example, **I** (Convolutindole A, isolated from the marine bryozoan *Amathia convolute*, a very potent nematocide),[2e] and **II**, **III** and **IV** (isolated from the marine blue-green alga *Riuularia firma*) (Fig. 1).[2f,g]

Because of the electron-rich character of indoles, the synthesis of brominated indoles is a challenging project. The most straightforward method is electrophilic bromination, and 3-bromoindoles are obtained, along with oxidation side-products.[3] While unprotected 2-bromoindoles are useful for numerous applications,[4] their syntheses are rare and difficult. Although the synthesis of 2-bromoindole based on lithiation of the free indole, then bromination was reported, extension of its derivatives was less well investigated owing to the limitations of regioselectivity and functional group tolerance.[5]

Gem-Dihaloolefins, as an important kind of synthetic intermediate due to their high reactivity and easy availability, have attracted considerable attention in recent years.[6] Most importantly, the preparation of various substituted indoles from 2-(*gem*-dibromovinyl)anilines and 2-(*gem*-dibromovinyl)(*N*-substituted) anilines *via* transition-metal-catalyzed tandem cross-coupling strategies, such as C–N/C–C,[7] C–N/C–N,[8] C–N/C–P,[7a] C–N/C–H,[9] C–N/carbonylation,[10] and C–N/carbonylation/C–C reactions[11] have been developed. Recently, an elegant method for the synthesis of 2-bromoindoles was developed by Lautens *et al. via* Pd/P*t*Bu_3-catalyzed intramolecular reactions of 2-(*gem*-dibromovinyl)anilines.[12]

In continuing our efforts on the organic reactions of *gem*-dihaloolefins under metal-free conditions,[13] herein we describe an efficient Cs_2CO_3-promoted intramolecular cyclization of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines[14] for the facile synthesis of 2-bromoindoles and 2-bromo-*N*-methylsulfonylindoles by controlling the amount of Cs_2CO_3 under transition-metal-free, fluoride-free, mild and environmentally friendly reaction conditions in excellent yields. In addition, this methodology can also be extended to the synthesis of 2-chloroindole derivatives (Scheme 1).

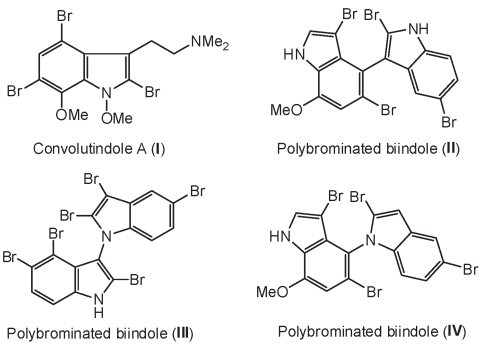


Fig. 1 Representative biologically active 2-bromoindoles.

[a]*Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P. R. China. E-mail: leiwang@chnu.edu.cn; Fax: +86-561-309-0518; Tel: +86-561-380-2069*

[b]*Department of Chemistry, Anhui Agricultural University, Hefei, Anhui 230062, P. R. China*

[c]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China*

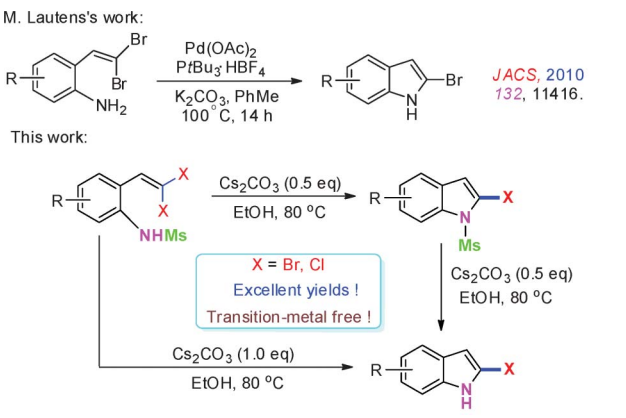
† Electronic supplementary information (ESI) available: Detailed procedures, analytical data, and ^1H, ^{13}C NMR and HRMS spectra of all intermediates and products or other electronic format. See DOI: 10.1039/c2ra22172a

Results and discussion

In our initial attempt to prepare 2-bromoindole (**8a**) from 2-(*gem*-dibromovinyl)aniline (**1a**) in the presence of Cs_2CO_3 (1 equiv.) in EtOH at 80 °C, however, no **8a** was obtained (Table 1, entry 1). When *N*-substituted derivatives **2a–5a** were used as substrates, there was also no desired **8a** detected (Table 1, entries 2–5). To our delight, a 91% yield of **8a** was obtained when 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**6a**) was used (Table 1, entry 6). 2-(*gem*-Dibromovinyl)-*N*-(*p*-tolylsulfonyl)aniline (**7a**) was inferior and gave **8a** in 70% yield (Table 1, entry 7). This result indicated that the cyclization depends on the nitrogen substituents of substrates. When the amine is activated by a strong electron-withdrawing substituent such as sulfonyl, the tandem reaction can proceed efficiently in one-pot. The sulfonyl group acts as a traceless dual-activating group to accomplish indole cyclization, and after indole formation, the sulfonyl group is deprotected *via* N–S bond cleavage.

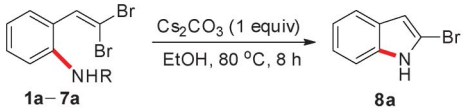
To further optimize the reaction conditions for the synthesis of 2-bromoindole (**8a**) through a base-mediated intramolecular reaction of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**6a**), a variety of bases were examined. As can be seen from Table 2, Cs_2CO_3 exhibited the highest reactivity in EtOH among the bases tested. *t*-BuOK, K_2CO_3, K_3PO_4, BuOLi, Na_2CO_3, KF and CsF were less effective (Table 2, entries 1–8). DBU, DIPEA, Et_3N, DABCO and pyridine were ineffective (Table 2, entries 9–13). The solvent also played an important role in the reaction. EtOH was found to be the best medium for the reaction when Cs_2CO_3 was used as a promoter. Other solvents, DMSO, DMF, THF, MeCN, toluene and dioxane were less effective, and 18–85% yields of **8a** were obtained (Table 2, entries 14–19). However, the reaction did not occur in H_2O (Table 2, entry 20). When the reaction was performed in the presence of Cs_2CO_3 in EtOH at a temperature less than 50 °C, no reaction was observed. The temperature of 80 °C was found to be optimal (Table 2, entries 21–23). With respect to the amount of Cs_2CO_3 used in the reaction, 1.0 equiv. Cs_2CO_3 was found to be the best choice (Table 2, entry 24).

Having optimized the reaction conditions, the generality of this transformation was investigated and the results are listed in Table 3. A variety of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines containing substituents on the benzene rings were examined. The results indicated that a number of functional groups, including both electron-withdrawing and electron-donating ones were tolerated, and the corresponding 2-bromoindoles were obtained in good to excellent yields (Table 3, **8a–r**). The reaction proceeded



Scheme 1 Preparation of 2-bromo(chloro)indoles.

Table 1 Cs_2CO_3-promoted intramolecular cyclization of 2-(*gem*-dibromovinyl) anilines (**1a–7a**)[a]

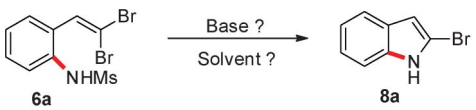


1a–7a 8a

Entry	Substrate, *R*	Yield (%)[b]
1	**1a**, H	0
2	**2a**, $CH_2C_6H_5$	0
3	**3a**, $CO_2C(CH_3)_3$	0
4	**4a**, $COCH_3$	0
5	**5a**, $COCF_3$	0
6	**6a**, SO_2CH_3	91
7	**7a**, $SO_2C_6H_4(p\text{-}CH_3)$	70

[a] Reaction conditions: 2-(*gem*-dibromovinyl)aniline (**1a–7a**, 0.50 mmol), Cs_2CO_3 (0.50 mmol), EtOH (2.0 mL) at 80 °C for 8 h. [b] Isolated yields.

Table 2 Screening of bases and solvents for the intramolecular cyclization of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**6a**)[a]



6a 8a

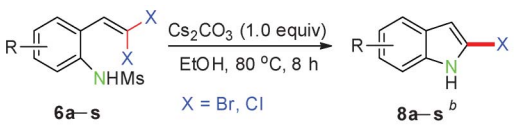
Entry	Base	Solvent/*T* (°C)	Yield (%)[b]
1	Cs_2CO_3	EtOH/80	91
2	*t*-BuOK	EtOH/80	80
3	K_2CO_3	EtOH/80	51
4	K_3PO_4	EtOH/80	35
5	*t*-BuOLi	EtOH/80	24
6	Na_2CO_3	EtOH/80	18
7	KF	EtOH/80	15
8	CsF	EtOH/80	13
9	DBU	EtOH/80	NR
10	DIPEA	EtOH/80	NR
11	Et_3N	EtOH/80	NR
12	DABCO	EtOH/80	NR
13	Pyridine	EtOH/80	NR
14	Cs_2CO_3	DMSO/80	85
15	Cs_2CO_3	DMF/80	73
16	Cs_2CO_3	THF/70	67
17	Cs_2CO_3	MeCN/80	62
18	Cs_2CO_3	Toluene/80	22
19	Cs_2CO_3	Dioxane/80	18
20	Cs_2CO_3	H_2O/80	NR
21	Cs_2CO_3	EtOH/50	NR
22	Cs_2CO_3	EtOH/60	12
23	Cs_2CO_3	EtOH/70	53
24	Cs_2CO_3	EtOH/80	92[c]

[a] Reaction conditions: 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**6a**, 0.50 mmol), base (0.50 mmol), solvent (2.0 mL) at the temperature indicated in Table 2 for 8 h. [b] Isolated yields. [c] Cs_2CO_3 (1.0 mmol) was used.

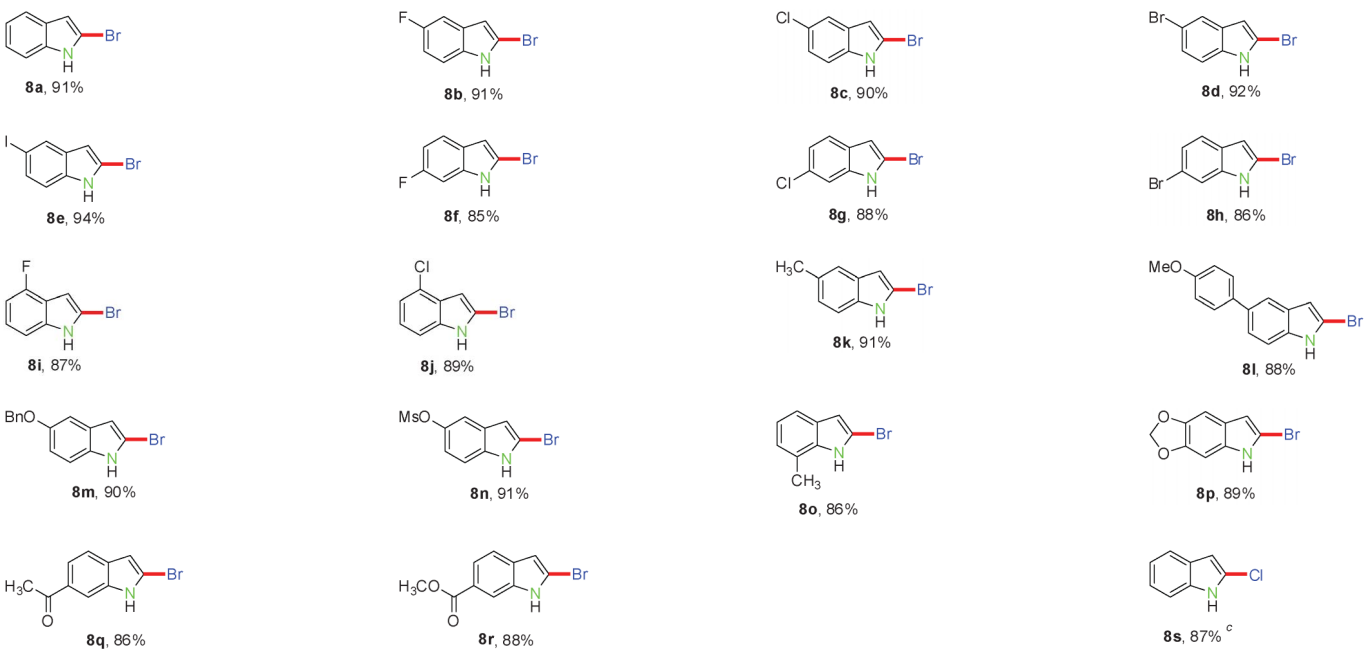
very well with halogen substituents F, Cl, Br and I on the *para*-, or *meta*-positions of anilines (**6b–j**) and afforded high yields of indoles **8b–j**, which are potential synthetic intermediates in organic synthesis and could provide further transformation *via* transition-metal-catalyzed cross-coupling reactions. The product yields of substrates derived from *para*-haloanilines were superior to those from *meta*-haloanilines (Table 3, **8b–e** *vs.* **8f–j**). 2-(*gem*-Dibromovinyl)-*N*-methylsulfonylanilines with an electron-donating functionality, such as CH_3, *p*-$CH_3OC_6H_4$, $C_6H_5CH_2O$, CH_3SO_2O and OCH_2O, on the anilines also underwent the tandem cyclization smoothly to generate the corresponding products **8k–p** in 86–91% yields. It should be noted that the reaction could tolerate an *ortho*-substituted group (**8o**). Substrates, **6q** and **6r**, with electron-withdrawing substituents CH_3OCO and CH_3CO also gave the corresponding products **8q** and **8r** in 86 and 88% yields, respectively. A more remarkable observation was that the reaction also proceeded with 2-(*gem*-dichlorovinyl)-*N*-methylsulfonylaniline (**6s**) to afford 2-chloroindole (**8s**) in good yield.

Sulfonamide is one of the most stable nitrogen protective groups. Generally, most sulfonamides are stable to alkaline hydrolysis, as well as to catalytic reduction. This property prompted us to prepare 2-bromo-*N*-methylsulfonylindoles from the corresponding 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines. Although a facile synthesis of 2-bromo-*N*-methylsulfonylindoles *via* CuI-catalyzed intramolecular cross-coupling of *gem*-dibromoolefins was described,[15] it is desirable to develop an efficient and practical method for their preparation under transition-metal-free conditions, which can overcome the drawbacks of its expensive, poisonous, and air-sensitive properties.[16] During the investigation of the reaction of **6a** under Cs_2CO_3/C_2H_5OH conditions, we were delighted to find that in the reaction of **6a** in the presence of Cs_2CO_3 (0.50 equiv.) in EtOH at 80 °C, 2-bromo-*N*-methylsulfonylindole (**9a**) was isolated in 94% yield and no further deprotection product **6a** was found. Then, a number of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines were examined to explore the generality of the reaction under Cs_2CO_3 (0.50 equiv.) in EtOH conditions. Satisfactorily, as shown in Table 4, substrates with both electron-withdrawing and electron-donating groups on the aromatic rings underwent the intramolecular tandem cyclization very cleanly to generate the corresponding 2-bromo-*N*-methylsulfonylindoles (**9a–r**) in excellent yields by controlling Cs_2CO_3 with 0.50 equiv. It is obvious that the yields of **9a–r** are superior to the corresponding **8a–r**, which are the further transformation products of **9a–r** *via* a deprecation process. Compared with the reaction of **6a–r** to **8a–r**, the similar steric and electronic effects of the substitutions on the anilines were also

Table 3 Synthesis of 2-bromoindoles and 2-chloroindole through Cs_2CO_3-promoted intramolecular cyclization of **6**[a]

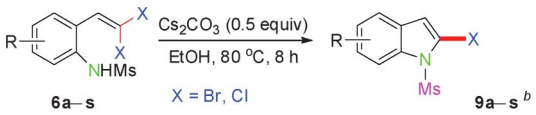


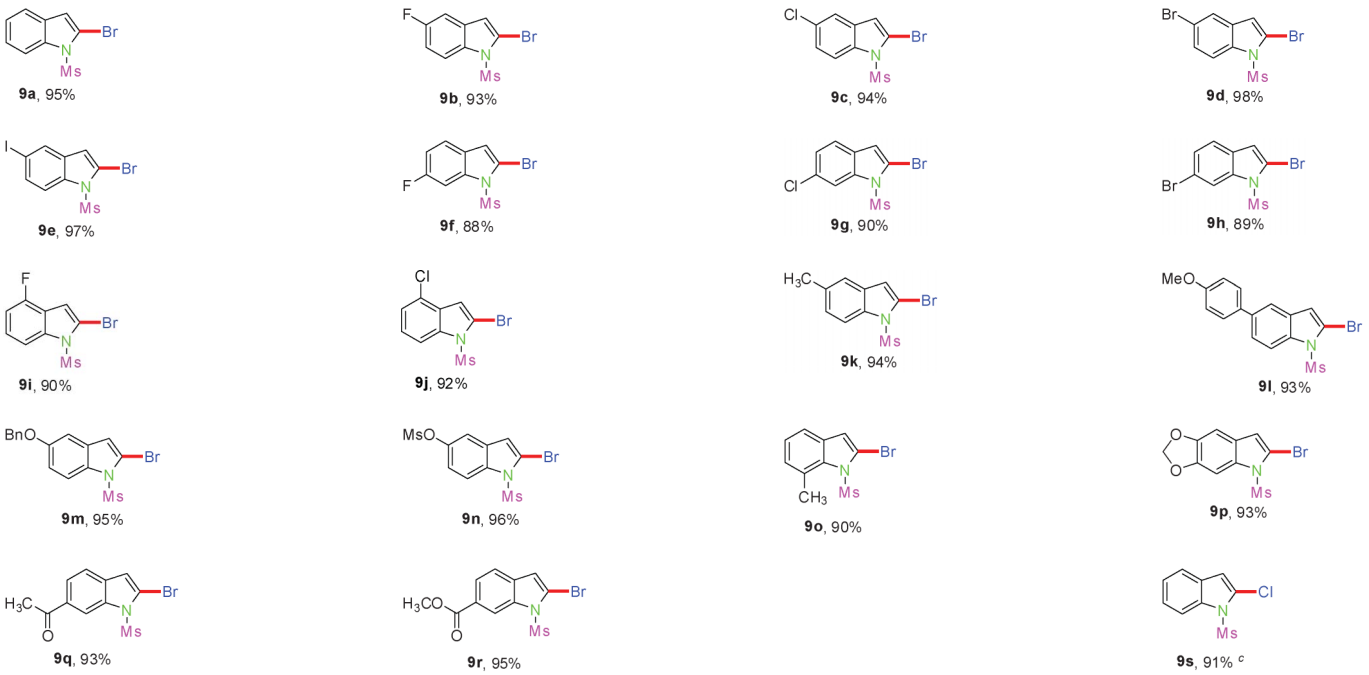
6a–s **8a–s**[b]



[a] Reaction conditions: **6** (0.50 mmol), Cs_2CO_3 (0.50 mmol), EtOH (2.0 mL), at 80 °C for 8 h. [b] Isolated yields. [c] DMF (2.0 mL), 110 °C for 8 h. Ms = CH_3SO_2, Bn = $C_6H_5CH_2$.

Table 4 Synthesis of **9** through Cs_2CO_3-promoted intramolecular cyclization of **6**[a]





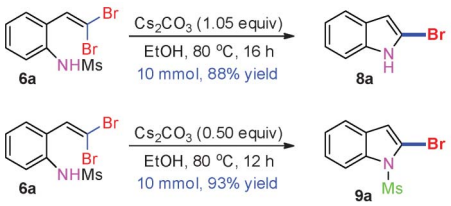
[a] Reaction conditions: **6** (0.50 mmol), Cs_2CO_3 (0.25 mmol), EtOH (2.0 mL), at 80 °C for 8 h. [b] Isolated yields. [c] DMF (2.0 mL), 110 °C for 8 h. Ms = CH_3SO_2, Bn = $C_6H_5CH_2$.

found in the reaction of **6a–r** to **9a–r**. It is noteworthy that **6s** also could undergo the tandem reaction to generate the corresponding 2-chloro-*N*-methylsulfonyindole (**9s**) with good yield in DMF at 110 °C.

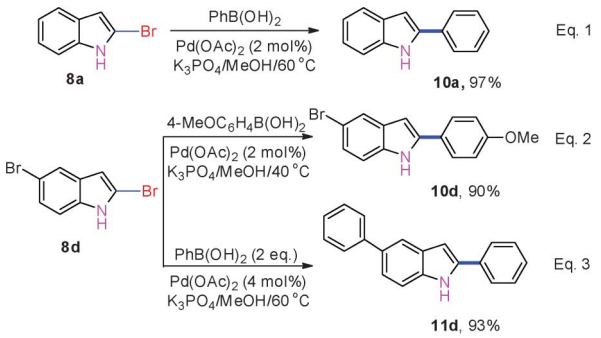
When the reaction scale was increased up to 10 mmol using Cs_2CO_3 and EtOH, 88% and 93% isolated yields of **8a** and **9a** were isolated from the starting material **6a**, respectively, by increasing the reaction time to ensure completion (Scheme 2).

2-Arylindoles exhibit good biological activities, such as antiestrogen, h5-HT_{2A} antagonism, anti-inflammatory properties, and cytotoxicity.[17] Palladium-catalyzed cross-coupling of 2-haloindoles with arylmetal species is a powerful method for preparing them,[18] however, this application has been limited owing to the inaccessibility of 2-haloindoles.[19] With the prepared 2-bromoindoles in our hands, converting them into the corresponding 2-arylindoles was investigated *via* palladium-catalyzed cross-coupling with boronic acids (Scheme 3). The results indicated that the corresponding products were obtained in excellent yields under Suzuki reaction conditions *in the absence of ligand* (Scheme 3). In the analogous studies, an essential ligand such as dppf, S-Phos, or P*t*Bu_3 is needed.[7a,b,e] In addition, **10d** or **11d** was obtained in a high yield while the reaction of **8d** with 4-$MeOC_6H_4B(OH)_2$ or $PhB(OH)_2$ under controlled coupling conditions (Scheme 3, eqn (2) and (3)). This also implies that the reactivity of the 2-position C–Br bond of 2,5-dibromoindole (**8d**) is superior to its 5-position one towards palladium-catalyzed-coupling reactions.[12]

To investigate the reaction mechanism, obtained **9a** was further converted into 2-bromoindole (**8a**) in the presence of Cs_2CO_3 (0.5 equiv.), providing 95% yield (Scheme 4, eqn (1)). Meanwhile, 2-(*gem*-dibromovinyl)-*N*-(*tert*-butoxycarbonyl)aniline (**3a**) only afforded the corresponding phenylethynyl bromide intermediate **A** under Cs_2CO_3 (1.0 equiv.) conditions (Scheme 4, eqn (2)). When the reaction of 2-(1′-methyl-2′,2′-dichlorovinyl)-

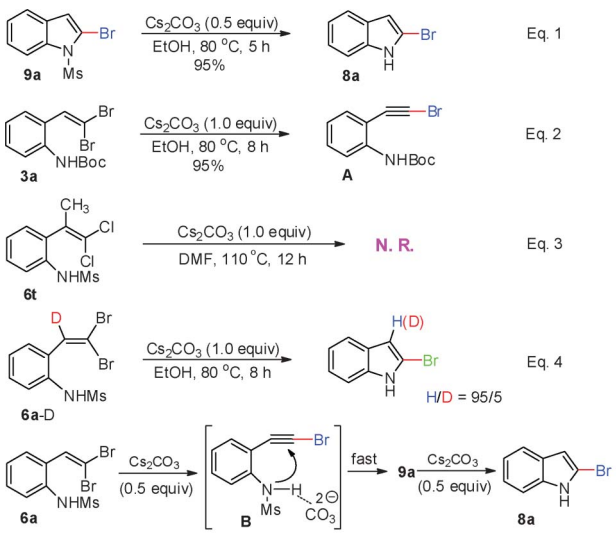


Scheme 2 10 mmol scale reactions of **6a**.



Scheme 3 Suzuki coupling of **8a** and **8d** with boronic acids.

N-methylsulfonylanilines (**6t**) was performed in Cs_2CO_3/DMF, no product was detected and **6t** was recovered in 98% yield (Scheme 4, eqn (3)). In addition, further isotope experiments indicated that when the reaction of deuterium-labeled **6a**-D was performed under the present reaction conditions, 95% of the D-enriched element was lost in the product (Scheme 4, eqn (4)). These results suggested that the intramolecular tandem cyclization of **6a** is through an intermediate phenylethynyl bromide,[20] although it can not be obtained because of the fast reaction of **B** to **9a**. The reaction pathway for the generation of 2-bromoindole (**8a**) was also shown in Scheme 4. Initially, an elimination of HBr from **6a** to intermediate **B** proceeded smoothly in the presence of Cs_2CO_3, followed by an intramolecular nucleophilic addition of the nitrogen to the carbon–carbon triple bond of **B**, affording 2-bromo-*N*-methylsulfonylindole (**9a**) with the assistance of the carbonate anion. The as-obtained **9a** then underwent a cleavage of the sulfonamide linkage to afford deprotection product 2-bromoindole (**8a**) under Cs_2CO_3 conditions.



Scheme 4 Possible reaction pathway and related experiments.

Conclusion

In conclusion, we have developed a novel, efficient, economical, and facile Cs_2CO_3-promoted intramolecular cyclization of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines for the synthesis of 2-bromoindoles and 2-bromo-*N*-methylsulfonylindoles, respectively, under transition-metal-free conditions by controlling the amount of Cs_2CO_3 used in EtOH reaction media.[21] Notably, this methodology can also be readily extended to the synthesis of 2-chloroindoles. The reaction mechanism investigation indicated that the tandem cyclization proceeds through a key intermediate phenylethynyl bromide, followed by the cyclization processes. The sulfonyl group acts as a traceless dual-activating group to undergo indole cyclization and easy deprotection in the presence of Cs_2CO_3. In addition, the further transformation of 2-bromoindoles *via* palladium-catalyzed Suzuki cross-coupling could be carried out *in the absence of ligand*. A detailed mechanistic study and further investigation on transition-metal-free reactions are currently underway in our laboratory.

Acknowledgements

This work was financially supported by the National Science Foundation of China (Nos. 21172092, 20972057).

References

1 For selected reviews, see: (*a*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (*b*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; (*c*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73; (*d*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278; (*e*) G. Collin and H. Höke, "Indole" *In Ullmann's Encyclopedia of Industrial Chemistry*, 2002, Wiley-VCH, Weinheim; (*f*) *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, New York, 1996, vol. 2, p 259. For selected examples, see; (*g*) L. Berrade, B. Aisa, M. Ramirez, S. Galiano, S. Guccione, L. R. Moltzau, F. O. Levy, F. Nicoletti, G. Battaglia, G. Molinaro, I. Aldana, A. Monge and S. Perez-Silandes, *J. Med. Chem.*, 2011, **54**, 3086; (*h*) K. Krajewski, Y. Zhang, D. Parrish, J. Deschamps, P. P. Rollera and V. K. Pathak, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3034; (*i*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5970; (*j*) J. F. Payack, E. Vazquez, L. Matty, M. H. Kress and J. McNamara, *J. Org. Chem.*, 2005, **70**, 175.

2 For selected reviews, see: (*a*) C. K. Narkowicz, A. J. Blackman, E. Lacey, J. H. Gill and K. Heiland, *J. Nat. Prod.*, 2002, **65**, 938; (*b*) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1*, 2000, 1045; (*c*) G. W. Gribble, *J. Nat. Prod.*, 1992, **55**, 1353; (*d*) *Indoles*, ed. R. J. Sundberg, Academic Press, San Diego, 1996. For selected examples, see; (*e*) C. C. Hughes, A. Prieto-Davo, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 629; (*f*) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth and W. Lobin, *J. Am. Chem. Soc.*, 2001, **123**, 2703; (*g*) R. S. Norton and R. J. Wells, *J. Am. Chem. Soc.*, 1982, **104**, 3628.

3 (*a*) J. C. Powers, in *The Chemistry of Heterocyclic Compounds*, ed. Houlihan, W. J., J. Wiley and Sons, New York, 1972, vol. **25**, part 2, p. 128; (*b*) W. C. Frank, Y. C. Kim and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2947.

4 (*a*) M. G. Bursavicha, N. Brooijmans, L. Feldberg, I. Hollander, S. Kim, S. Lombardi, K. Park, R. Mallon and A. M.Gilbert,

Bioorg. Med. Chem. Lett., 2010, **20**, 2586; (*b*) M. S. Techenor, J. D. Trzupek, D. B. Kastrinsky, F. Shiga, I. Hwang and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 15683; (*c*) J. M. Herbert, *Tetrahedron Lett.*, 2004, **45**, 817; (*d*) K. Dinnell, G. G. Chicchi, M. J. Dhar, J. M. Elliott, G. J. Hollingworth, M. M. Kurtz, M. P. Ridgill, W. Rycroft, K.-L. Tsao, A. R. Williams and C. J. Swaina, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1237; (*e*) Y. Liu and G. W. Gribble, *Tetrahedron Lett.*, 2000, **41**, 8717.

5 (*a*) J. Bergman and L. Venemalm, *J. Org. Chem.*, 1992, **57**, 2495.

6 For recent reviews, see: (*a*) G. Chelucci, *Chem. Rev.*, 2012, **112**, 1344; (*b*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641; (*c*) F. Legrand, K. Jouvin and G. Evano, *Isr. J. Chem.*, 2010, **50**, 588; (*d*) J.-R. Wang and K. Manabe, *Synthesis*, 2009, 1405.

7 (*a*) S. Thielges, E. Meddah, P. Bisseret and J. Eustache, *Tetrahedron Lett.*, 2004, **45**, 907; (*b*) Y.-Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538; (*c*) Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2005, **7**, 3549; (*d*) A. Fayol, Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 4203; (*e*) M. Nagamochi, Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2007, **9**, 2955; (*f*) Y.-Q. Fang, J. Yuen and M. Lautens, *J. Org. Chem.*, 2007, **72**, 5152; (*g*) Y.-Q. Fang, R. Karisch and M. Lautens, *J. Org. Chem.*, 2007, **72**, 1341.

8 (*a*) J. Yuen, Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 653.

9 (*a*) C. S. Bryan and M. Lautens, *Org. Lett.*, 2008, **10**, 4633; (*b*) Z.-J. Wang, J.-G. Yang, F. Yang and W. Bao, *Org. Lett.*, 2010, **12**, 3034; (*c*) Z.-J. Wang, F. Yang, X. Lv and W. Bao, *J. Org. Chem.*, 2011, **76**, 967; (*d*) X.-R. Qin, X.-F. Cong, D.-B. Zhao, J.-S. You and J.-B. Lan, *Chem. Commun.*, 2011, **47**, 5611; (*e*) W. Chen, M. Wang, P. Li and L. Wang, *Tetrahedron*, 2011, **67**, 5913.

10 (*a*) T. O. Vieira, L. A. Meaney, Y.-L. Shi and H. Alper, *Org. Lett.*, 2008, **10**, 4899.

11 (*a*) M. Arthuis, R. Pontikis and J.-C. Florent, *Org. Lett.*, 2009, **11**, 4608.

12 (*a*) S. G. Newman and M. Lautens, *J. Am. Chem. Soc.*, 2010, **132**, 11416; (*b*) S. G. Newman, V. Aureggi, C. S. Bryan and M. Lautens, *Chem. Commun.*, 2009, 5236.

13 (*a*) W. Chen, Y. Zhang, L. Zhang, M. Wang and L. Wang, *Chem. Commun.*, 2011, **47**, 10476; (*b*) T. He, H. Li, P. Li and L. Wang, *Chem. Commun.*, 2011, **47**, 8946; (*c*) T. He, L. Yu, L. Zhang, L. Wang and M. Wang, *Org. Lett.*, 2011, **13**, 5016; (*d*) X. Zhang and L. Wang, *Green Chem.*, 2012, **14**, 2141.

14 (*a*) H.-C. Zhang, H. Ye, A. F. Moretto, K. K. Brumfield and B. E. Maryanoff, *Org. Lett.*, 2000, **2**, 89; (*b*) H.-C. Zhang, H. Ye, K. B. White and B. E. Maryanoff, *Tetrahedron Lett.*, 2001, **42**, 4751.

15 (*a*) B. Jiang, K. Tao, W. Shen and J. Zhang, *Tetrahedron Lett.*, 2010, **51**, 6342.

16 (*a*) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, **2**, 1044; (*b*) E. Shirakawa, K. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537; (*c*) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737; (*d*) J. Zhao, Y. Zhao and H. Fu, *Angew. Chem., Int. Ed.*, 2011, **50**, 3769.

17 (*a*) E. von Angerer, N. Knebel, M. Kager and B. Ganss, *J. Med. Chem.*, 1990, **33**, 2635; (*b*) C. Biberger and E. von Angerer, *J. Steroid Biochem. Mol. Biol.*, 1998, **64**, 277; (*c*) M. Medarde, A. C. Ramos, E. Caballero, R. P.-L. De Clairac, J. L. Lopez, D. G. Gravalos and A. S. Feliciano, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2303; (*d*) G. I. Stevenson, A. L. Smith, S. Lewis, S. G. Michie, J. G. Neduvelil, S. Patel, R. Marwood, S. Patel and J. L. Castro, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2697.

18 (*a*) L. Chu, M. H. Fisher, M. T. Goulet and M. J. Wyvratt, *Tetrahedron Lett.*, 1997, **38**, 3871; (*b*) C. A. Merlic and D. M. McInnes, *Tetrahedron Lett.*, 1997, **38**, 7661; (*c*) A. L. Smith, G. I. Stevenson, S. Lewis, S. Patel and J. L. Castro, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2693.

19 (*a*) R. L. Hudkins, J. L. Diebold and F. D. Marsh, *J. Org. Chem.*, 1995, **60**, 6218; (*b*) M. Amat, S. Hadida, G. Pshenichnyi and J. Bosch, *J. Org. Chem.*, 1997, **62**, 3158; (*c*) C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen and T. Gallagher, *Synlett*, 1998, 1025.

20 (*a*) H. Xu, S. Gu, W. Chen, D. Li and J. Dou, *J. Org. Chem.*, 2011, **76**, 2448; (*b*) J. Liu, W. Chen, Y. Ji and L. Wang, *Adv. Synth. Catal.*, 2012, **354**, 1585; (*c*) M. Okutani and Y. Mori, *J. Org. Chem.*, 2009, **74**, 442.

21 Cs_2CO_3 (99.995%) was purchased from Aldrich and contains Cu (0.30 ppm) and Pd (0.01 ppm); other elements including: Ni, Co, Fe, Ru, and Rh were not detected (ICP-MS determination data).

