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Communication

Microwave irradiated synthesis of 2-bromo(chloro)indoles via intramolecular cyclization of 2-(*gem*-dibromo(chloro)vinyl)anilines in the presence of TBAF under metal-free conditions

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2-Bromo(chloro)indoles were readily and efficiently prepared through TBAF-promoted intramolecular cyclization of 2-(*gem*-dibromo(chloro)vinyl)anilines in excellent yields under metal-free and microwave irradiation conditions.

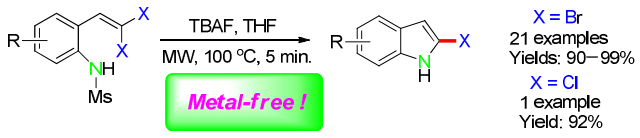
Introduction

The indole skeleton is one of the important structural motifs widely found in dyes, natural products, materials, and pharmaceutically active compounds, such as antibiotic, anticancer and anti HIV agents.[1] In addition, the indole derivatives are also used as starting materials for the synthesis of large number of alkaloids. Many halogenated indole derivatives are also found in nature, and several brominated indole natural products have been isolated.[2] They are also present in biologically active compounds, such as Convolutindole A,[2d] and polybrominated bisindoles.[2e,f]

Due to the electron-rich nature of indoles, the preparation of brominated indoles is still a challenge. The most straightforward method is electrophilic bromination of indoles, and 3-bromoindoles are obtained, along with the by-products.[3] While unprotected 2-bromoindoles are useful for numerous applications,[4] their preparation is often difficult. Although the synthesis of 2-bromoindole based on lithiation of unsubstituted indole, followed by bromination was developed, the extension of its derivatives was less investigated owing to the limitation of regioselectivity and functional group tolerance on lithiation.[5]

gem-Dihaloolefins, as one of the important synthetic intermediates for their higher reactivity and easy availability have been attracted much attention in recent years.[6] Especially, the construction of various functionalized indole derivatives from 2-(2,2-dibromovinyl)anilines and 2-(2,2-dibromovinyl)(*N*-substituted)anilines through the transition-metal-catalyzed cross-coupling methodologies, such as carbon-nitrogen/carbon-carbon,[7] carbon-nitrogen/carbon-nitrogen,[8] carbon-nitrogen/carbon-phosphine,[7a] carbon-nitrogen/carbon-hydrogen,[9] carbon-nitrogen/carbonylation,[10] and carbon-nitrogen/carbonylation/carbon-carbon tandem reactions[11] has been reported. Recently, Lautens et al developed an efficient method for the synthesis of 2-bromoindoles via Pd/P*t*Bu$_3$-catalyzed intramolecular reactions of 2-(*gem*-dibromovinyl)anilines.[12]

Microwave heating is an attractive tool that has recently been used in organic synthesis. And it presents a powerful and green alternative to conventional synthesis, which helps the chemical process more economic and soft.[13] In continuing our efforts on the organic transformations of *gem*-dihaloolefins under metal-free conditions[14a-c] and the solid-phase construction of indole derivatives based on a traceless, activating sulfonyl linker by Zhang,[14d] herein we developed a *tetra*-butylammonium fluoride (TBAF)-promoted intramolecular cyclization of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines[15] for the synthesis of 2-bromoindoles under microwave irradiation conditions. The reactions generated unprotected 2-bromoindoles under metal-free and mild reaction conditions in nearly quantitatively yields. In addition, this methodology can also be extended to synthesis of 2-chloroindoles (Scheme 1).



Scheme 1. Microwave irradiated synthesis of 2-bromo(chloro)indoles.

In our initial attempt to obtain 2-bromoindole from the corresponding 2-(*gem*-dibromovinyl)aniline in the presence of TBAF in THF at 80 °C for 8 h, a complicated mixture of compounds was obtained, but no desired 2-bromoindole was observed. When *N*-substituted derivatives of 2-(*gem*-dibromovinyl)aniline, such as *N*-benzyl, *N*-acetyl, and *N*-

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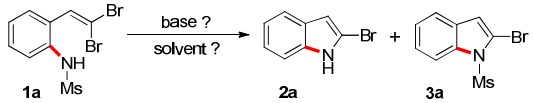
trifluoroacetyl were used as substrates, however, no desired 2-bromoindole was detected and a complicated mixture of compounds was generated. While 2-(*gem*-dibromovinyl)-*N*-*tert*-butoxycarbonylaniline was used, 2-(bromoethynyl)-*N*-*tert*-butoxycarbonylaniline was isolated in 91% yield. To our delight, 94% yield of 2-bromoindole was obtained when 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline was used as substrate. However, 2-(*gem*-dibromovinyl)-*N*-(*p*-tolylsulfonyl)aniline was inferior and generated 2-bromoindole in 76% yield. The results indicated that this cyclization depends on the nitrogen substituents of substrates. When the amine is activated by a strong electron-withdrawing group such as sulfonyl, the tandem reaction can occur efficiently in one pot. The *N*-sulfonyl linker serves as a dual-activating group to undergo 2-bromoindoles formation. After first-step cyclization, the sulfonamide linkage proceeds nitrogen-sulfur bond cleavage to remove sulfonyl group.

Table 1. Screening of base and solvent for the intramolecular cyclization of **1a**[a]



1a **2a** **3a**

Entry	Base	Solvent	Yield [%][b]	
			2a	**3a**
1	TBAF	THF	94	0
2	TBAC	THF	0	0
3	TBAB	THF	0	0
4	TBAI	THF	0	0
5	TBA•HSO_4	THF	0	0
6	TBA•OH	THF	0	35
7	TBA•OAc	THF	0	72
8	KF	THF	0	0
9	CsF	THF	0	0
10	Et_3N	THF	0	0
11	DABCO	THF	0	0
12	K_2CO_3	THF	0	18
13	K_3PO_4	THF	22	27
14	^{t}BuOK	THF	36	51
15	TBAF	DMF	91	trace
16	TBAF	CH_3CN	78	trace
17	TBAF	H_2O	67	trace
18	TBAF	DMSO	52	trace
19	TBAF	Dioxane	27	16
20	TBAF	Toluene	25	0
21	TBAF	C_2H_5OH	19	23
22	TBAF	–	43	trace
23[c]	TBAF	THF	57	10
24[d]	TBAF	THF	99	0
25[e]	TBAF	THF	99	0
26[f]	TBAF	THF	72	0
27[g]	–	THF	<5	–
28[h]	–	THF	<5	–
29[i]	–	THF	<5	–

[a] Reaction conditions: 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**1a**, 0.50 mmol), base (1.0 mmol), solvent (2.0 mL) at 80 °C for 8 h. [b] Isolated yields. [c] The reaction was irradiated at 100 W and 80 °C for 20 min. [d] The reaction was irradiated at 100 W and 100 °C for 20 min. [e] The reaction was irradiated at 100 W and 100 °C for 5 min. [f] The reaction was irradiated at 100 W and 100 °C for 2 min. [g] Pd(OAc) (5.0 ppm in THF) was added. [h] Pd(OAc) (10.0 ppm in THF) was added. [i] CuI (50.0 ppm in THF) was added.

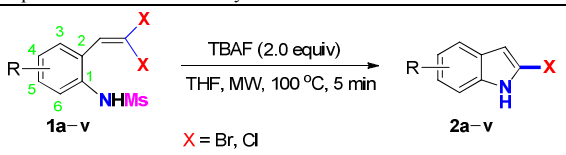
To further optimize the reaction conditions for the synthesis of 2-bromoindole (**2a**) from 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**1a**) through a base-promoted intramolecular cyclization, a variety of bases were examined. The results were summarized in Table 1. As the analogues of TBAF, TBAC (*tetra*-butylammonium chloride), TBAB (*tetra*-butylammonium bromide), TBAI (*tetra*-butylammonium iodide), or TBA•HSO_4 (*tetra*-butylammonium hydrogen sulfate) was used instead of TBAF, no product was detected and starting material was unchanged and recovered (Table 1, entries 2–5). Meanwhile, TBA•OH (*tetra*-butylammonium hydroxide) and TBA•OAc (*tetra*-butylammonium acetate) generated 2-bromo-*N*-methylsulfonylindole (**3a**) in 35 and 72% yields, and no **2a** was obtained (Table 1, entries 6 and 7). Other bases, KF, CsF, Et_3N, and DABCO were ineffective promoters to the reaction (Table 1, entries 8–11). However, K_2CO_3, K_3PO_4, and ^{t}BuOK gave **3a** or a mixture of **2a** and **3a** in inferior yields (Table 1, entries 12–14). With respect to TBAF loading, 2 equiv of TBAF was found to be optimal. On the other hand, the influence of solvent on the reaction was also examined, and the results indicated that THF was the best one among the solvents tested. Other solvents, DMF, CH_3CN, H_2O, DMSO, dioxane, toluene, and C_2H_5OH were inferior (Table 1, entries 15–21). However, only 43% yield of **2a** was obtained in the absence of solvent (Table 1, entry 22). The further investigation indicated that the reaction was completed at 80 °C in 8 h. Gratifyingly, the reaction was completed under microwave irradiation conditions at 100 W and 100 °C in 5 min and 99% yield of **2a** was obtained (Table 1, entries 23–26).

Organic reactions performed in the absence of transition metal have received much attention, because they can overcome the drawbacks of the expensive, poisonous, and air-sensitive properties of metals or organometallics, and metal-free reaction is one of the best choices in the pharmaceutical industry due to the avoidance of metal contamination.[16] However, some reactions turned out to be actually catalyzed by a trace amount of Pd or Cu contamination, not really "transition-metal-free".[17] In order to figure out whether the model reaction completed in the presence of trace amount of transition metal or not, additional trace amount of Pd (5.0–10.0 ppm) or Cu (50.0 ppm) was added to the reaction of **1a** in THF under microwave irradiation condition without TBAF, providing less than 5% yield of **2a** (Table 1, entries 27–29).[14c,17e,f] This result indicated that TBAF plays an important role in the intramolecular cyclization reaction of **1a**.

On the basis of the optimized reaction conditions (in the presence of TBAF under microwave irradiation at 100 W and 100 °C for 5 min), the scope of this transformation was investigated and the results were summarized in Table 2. A variety of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines bearing substituents on the benzene rings were examined. The results showed that a number of functional groups, including electron-withdrawing and electron-donating ones were tolerated, and the corresponding 2-bromoindoles were generated in excellent yields (Table 2, entries 1–21). Halogen substituents, such as F, Cl, Br and I, on the 4-, 5-, or 3-position of substrates (**1b**–**j**) underwent the intramolecular cyclization very smoothly and afforded the excellent yields of the corresponding di-halogenated indoles **2b**–**j** (Table 2, entries 2–10), which could provide the further transformation via transition-metal-catalyzed cross-coupling reactions. 2-(*gem*-

Dibromovinyl)-*N*-methylsulfonylanilines with an electron-donating functionality, such as CH_3, CH_3O, $C_6H_5CH_2O$, CH_3SO_2O, *p*-$CH_3OC_6H_4$ or OCH_2O on the anilines also underwent the cyclization very well to generate the corresponding products **2k**–**q** in 90–96% yields (Table 2, entries 11–17). It should be noted that the reaction could tolerate *ortho*-substituted group (**2q**). Under the present reaction conditions, 1-(*gem*-dibromovinyl)-2-naphthylamine (**1r**) also underwent the reaction very well to generate the desired product **2r** in 96% yield. Substrates (**1s**–**u**) with electron-withdrawing groups, CH_3OCO, and CH_3CO on the 4-, and 3-position of anilines also gave the corresponding products **2s**–**u** in 90–93% yields. More remarkable observation was that 2-(*gem*-dichlorovinyl)-*N*-methylsulfonylaniline (**1v**) also could proceed the reaction to generate 2-chloroindole (**2v**) with high yield in DMF at 110 °C under microwave irradiation (Table 2, entry 22). It is important to note that the reaction scale was increased up to 10 mmol under TBAF/THF conditions for 10 min, 94% isolated yield of **2a** was obtained from **1a** (Scheme 2).

Table 2. Microwave irradiated synthesis of 2-bromo(chloro)indoles through TBAF-promoted intramolecular cyclization of **1**[a]

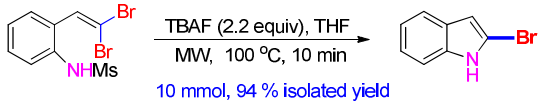


1a–**v** **2a**–**v**

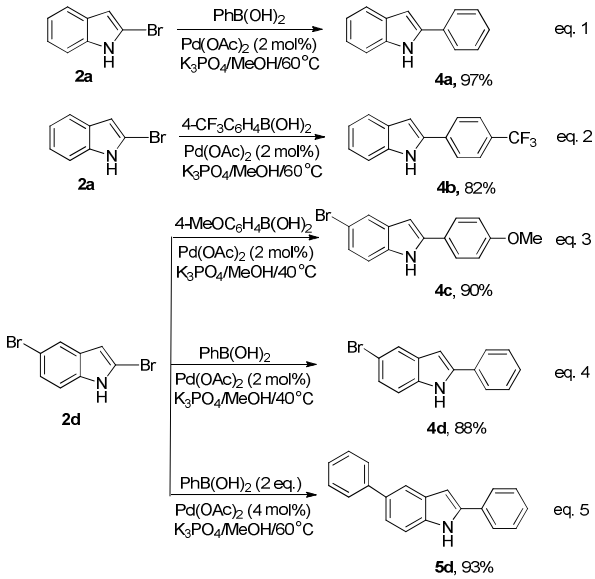
Entry	**1**, R	X	**2**	Yield [%][b]
1	**1a**, H	Br	**2a**	99
2	**1b**, 4-F	Br	**2b**	97
3	**1c**, 4-Cl	Br	**2c**	96
4	**1d**, 4-Br	Br	**2d**	97
5	**1e**, 4-I	Br	**2e**	94
6	**1f**, 5-F	Br	**2f**	91
7	**1g**, 5-Cl	Br	**2g**	93
8	**1h**, 5-Br	Br	**2h**	91
9	**1i**, 3-F	Br	**2i**	92
10	**1j**, 3-Cl	Br	**2j**	91
11	**1k**, 4-CH_3	Br	**2k**	95
12	**1l**, 4-CH_3O	Br	**2l**	93
13	**1m**, 4-$C_6H_4CH_2O$	Br	**2m**	92
14	**1n**, 4-CH_3SO_2O	Br	**2n**	94
15	**1o**, 4-(*p*-CH_3O)C_6H_4	Br	**2o**	96
16	**1p**, 4,5-(OCH_2O)	Br	**2p**	91
17	**1q**, 6-CH_3	Br	**2q**	90
18	**1r**, 5,6-benzo	Br	**2r**	96
19	**1s**, 4-CH_3OCO	Br	**2s**	91
20	**1t**, 5-CH_3OCO	Br	**2t**	93
21	**1u**, 5-CH_3CO	Br	**2u**	90
22	**1v**, H	Cl	**2v**	91[c]

[a] Reaction conditions: **1** (0.50 mmol), TBAF (1.0 mmol), THF (2.0 mL) and the reaction mixture was irradiated at 100 W and 100 °C for 5 min. [b] Isolated yields. [c] DMF (2.0 mL), the reaction mixture was irradiated at 100 W and 110 °C for 10 min.

2-Arylindoles exhibit high biological activities, such as antiestrogen, h5-HT_{2A} antagonism, anti-inflammatory, and cytotoxicity.[18] Palladium-catalyzed cross-coupling of 2-haloindoles with an arylmetal species is one of the useful strategies for the synthesis of 2-arylindoles,[19] but this application has been limited by the inaccessibility of the 2-haloindoles.[20] With the prepared 2-bromoindoles in our hands, transformation of them into the corresponding 2-arylindoles was investigated via palladium-catalyzed cross-coupling with arylboronic acids (Scheme 3). The results indicated that the corresponding products were obtained in high yields under the Suzuki reaction conditions (Scheme 3, eq. 1 and 2). In the analogy studies, a special ligand such as dppf, S-Phos, or P(*t*-Bu)$_3$ is essential.[7a,b,e] Futhermore, only **4c**, **4d** or **5d** was obtained in high yield during the reaction of **2d** with 4-$MeOC_6H_4B(OH)_2$ or $PhB(OH)_2$ by controlling Suzuki coupling conditions (Scheme 3, eq. 3, 4 and 5).

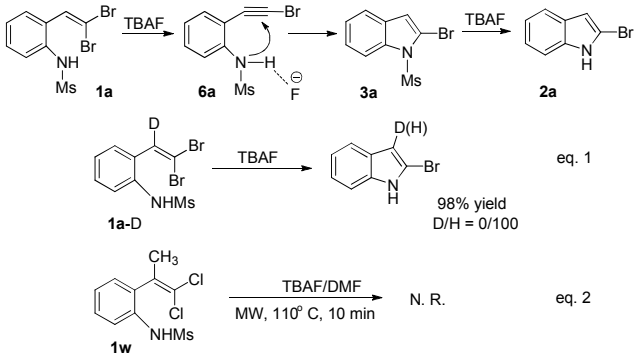


Scheme 2. Synthesis of 2-bromoindole in 10 mmol scale.



Scheme 3. The Suzuki coupling of **2a** and **2d** with arylboronic acids.

A reaction mechanism for the generation of 2-bromoindole (**2a**) was proposed in Scheme 4. Initially, an elimination of HBr from **1a** to intermediate **6a** proceeded smoothly in the presence of TBAF,[14a,b] followed by an intramolecular nucleophilic addition of nitrogen to carbon-carbon triple bond of **6a** to afford a cyclization product **3a** with the assistance of fluoride anion. Finally, the obtained **3a** underwent a cleavage of the sulfonamide linkage to afford the desired product **2a** under TBAF conditions.[14d,21]



Scheme 4. Possible reaction mechanism and the controlled experiments.

To verify the formation of intermediates **6a** and **3a** in the reaction, control experiments of **1a** and its isotope investigation were conducted. When **1a** was carried out in the presence of TBAF (1.0 equiv) under microwave irradiation at 100 W and 100 °C for 5 min, **3a** was isolated in 61% yield, and **2a** was obtained in 15% yield. On the other hand, when deuterium-labeled **1a**-D was carried out under the present reaction conditions, **2a** was obtained in 98% yield, and no 2-bromo-3-D-indole was detected (Scheme 4, eq. 1). It also supports that the reaction was through an alkynyl bromide intermediate **6a**. We also tried the reaction of 2-(1'-methyl-2',2'-dichlorovinyl)-*N*-methylsulfonylaniline (**1w**) in the presence of TBAF in DMF under present reaction conditions, however, no product was isolated and **1w** was recovered in 98% yield (Scheme 4, eq. 2). In addition, ICP analysis indicated that Cu and Pd in the reaction mixture were 0.27 and 0.03 ppm, respectively.[22]

In summary, we have developed an efficient and facile TBAF-promoted intramolecular cyclization of 2-(*gem*-dibromo(chloro)vinyl)anilines for the synthesis of 2-bromo(chloro)indoles under microwave irradiation conditions. The reactions were carried out in THF in the absence of metal, and generated the corresponding products in excellent yields. It is important to note that when the amine is activated by a strong electron-withdrawing group such as sulfonyl, the tandem reaction can occur efficiently in one pot. The reaction mechanism investigation indicated that the sulfonyl linker serves as a dual-activating group to undergo indole cyclization. And after indole formation, it is activated and subsequently proceeds nitrogen-sulfur bond cleavage to remove sulfonyl group promoted by TBAF. Moreover, further transformation of 2-bromoindoles via palladium-catalyzed cross-coupling can be carried out.

Experimental Section

General remarks

All reagents were purchased from commercial suppliers and used without further purification. 2-(*gem*-Dibromovinyl)-*N*-methylsulfonylanilines were prepared according to the literature.[7b] All TBAF (*tetra*-*n*-butylammonium fluoride)-promoted intramolecular cyclization reactions of *gem*-dibromoolefins were carried out under microwave irradiation conditions and air atmosphere. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance NMR spectrometer (400 MHz or 100 MHz, respectively) with $CDCl_3$ as solvent and recorded in ppm relative to internal tetramethylsilane standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT instrument. All MW reactions were carried out in a Discover SP (CEM) microwave reactor.

Typical procedure for the synthesis of 2-bromoindole (2a) via microwave irradiated intramolecular cyclization of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (1a) in the presence of TBAF

In a 10 mL of sealable reaction tube with a Teflon-coated screw cap equipped with a magnetic stir bar was charged with 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**1a**, 0.50 mmol), TBAF (THF solution, 1.0 mol/L, 1.0 mL, 1.0 mmol) and THF (2.0 mL). The reaction vessel was placed in a Discover SP (CEM) microwave reactor, and the reaction mixture was irradiated at 100W and 100 °C for 5 min. Then it was cooled to room temperature, extracted twice with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was further purified by flash chromatography on silica gel (eluant: hexane/ethyl acetate) to give the desired product 2-bromoindole (**2a**).

Acknowledgements

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Notes and references

1 For selected reviews, see: (*a*) S. Cacchi and G. Fabrizi, *Chem. Rev.,* 2005, **105**, 2873; (*b*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.,* 2006, **106**, 2875; (*c*) M. Somei and F. Yamada, *Nat. Prod. Rep.,* 2004, **21**, 278; (*d*) M. Somei and F. Yamada, *Nat. Prod. Rep.,* 2005, **22**, 73; For selected examples, see: (*e*) J. F. Payack, E. Vazquez, L. Matty, M. H. Kress and J. McNamara, *J. Org. Chem.,* 2005, **70**, 175; (*f*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.,* 2005, **127**, 5970.

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

3 (*a*) J. C. Powers, In *The Chemistry of Heterocyclic Compounds;* W. J. Houlihan, Ed.; 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. S. Techenor, J. D. Trzupek, D. B. Kastrinsky, F. Shiga, I. Hwang and D. L. Boger, *J. Am. Chem. Soc.,* 2006, **128**, 15683; (*b*) J.

M. Herbert, *Tetrahedron Lett.,* 2004, **45**, 817; (*c*) 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; (*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; For the preparation of indoles regarding the cyclisations of alkynylanilines, see: (*b*) H.-C. Zhang, K. K. Brumfield and B. E. Maryanoff, *Tetrahedron Lett.,* 1997, **38**, 2439; (*c*) R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.,* 1991, **113**, 6689; (*d*) H.-C. Zhang, K. K. Brumfield, L. Jaroskova and B. E. Maryanoff, *Tetrahedron Lett.,* 1998, **39**, 4449; (*e*) M. D. Collini and J. W. Ellingboe, *Tetrahedron Lett.,* 1997, **38**, 7963; (*f*) M. C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli and A. Bedeschi, *Tetrahedron Lett.,* 1997, **38**, 2307; (*g*) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles,* 1988, **27**, 2225; (*h*) A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.,* 1992, **33**, 3915; (*i*) M. C. Yasuhara, Y. Kanamori, M. Kaeko, A. Numata, Y. Kondo and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1,* 1999, 529.

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; (e) *Handbook of Organopalladium Chemistry for Organic Synthesis*; E., Ed. Negishi,; Wiley-Interscience: New York, 2002; p 650.

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

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

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

13 (*a*) C. O. Kappe and A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, 2005; (*b*) A. Loupy, *Microwaves in Organic Synthesis*, 2nd ed., Wiley-VCH: Weinheim, 2006; (*c*) C. O. Kappe, D. Dallinger and S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*, Wiley-VCH, Weinheim, 2009; (*d*) J. D. Moseley and C. O. Kappe, *Green Chem.,* 2011, **13**, 794.

14 (*a*) W. Chen, Y. Zhang, L. Zhang, M. Wang and L. Wang, *Chem. Commun.,* 2011, **47**, 10476; (*b*) M. Okutani; Y. Mori, *J. Org. Chem.,* 2009, **74**, 442; (*c*) P. Li, Y. Ji, W. Chen, X. Zhang and L. Wang, *RSC Advances,* 2013, **3**, 73; (*d*) H.-C. Zhang, H. Ye, A. F. Moretto, K. K. Brumfield and B. E. Maryanoff, *Org. Lett.,* 2000, **2**, 89.

15 B. Jiang, K. Tao, W. Shen and J. Zhang, *Tetrahedron Lett.,* 2010, **50**, 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.-W. Lei, *J. Am. Chem. Soc.,* 2010, **132**, 16737; (*d*) J. Zhao, Y. Zhao and H. Fu, *Angew. Chem., Int. Ed.,* 2011, **50**, 3769.

17 For recent reviews, see: (*a*) I. Thomé, A. Nijs and C. Bolm, *Chem. Soc. Rev.,* 2012, **41**, 979; (*b*) R. H. Crabtree, *Chem. Rev.,* 2012, **112**, 1536; (*c*) A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.,* 2012, **41**, 3140. For selected examples, see: (*d*) N. Leadbeater and M. Marco, *Angew. Chem., Int. Ed.,* 2003, **42**, 1407; (*e*) R. Arvela, N. Leadbeater, M. Sangi, V. Williams, P. Granados and R. Singer, *J. Org. Chem.,* 2005, **70**, 161; (*f*) R. K. Arvela and N. E. Leadbeater, *J. Org. Chem.*, 2005, **70**, 1786; (*g*) S. Buchwald and C. Bolm, *Angew. Chem., Int. Ed.,* 2009, **48**, 5586; (*h*) N. Leadbeater, *Nat. Chem.,* 2010, **2**, 1007; (*i*) Z. Gonda, G. L. Tolnai and Z. Novák, *Chem.–Eur. J.,* 2010, **16**, 11822; (*j*) J. Bonnamour, M. Piedrafita and C. Bolm, *Adv. Synth. Catal.,* 2010, **352**, 1577; (*k*) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.,* 2011, **50**, 5018; (*l*) Y. Ji, P. Li, X. Zhang and L. Wang, *Org. Biomol. Chem.,* 2013, **11**, 4095.

18 (*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, P.-L. R. 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.

19 (*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.

20 (*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.

21 H.-C. Zhang, H. Ye, K. B. White and B. E. Maryanoff, *Tetrahedron Lett.,* 2001, **42**, 4751.

22 The reaction solution was analysis by ICP-MS, and the determination data indicated that Cu and Fe are less than 0.27 ppm, and Pd, Sn, Ni, Co, Ru and Rh are less than 0.03 ppm.