ACES Asian Chemical Editorial Society

DOI: 10.1002/asia.201600420

CHEMISTRY AN ASIAN JOURNAL Communication

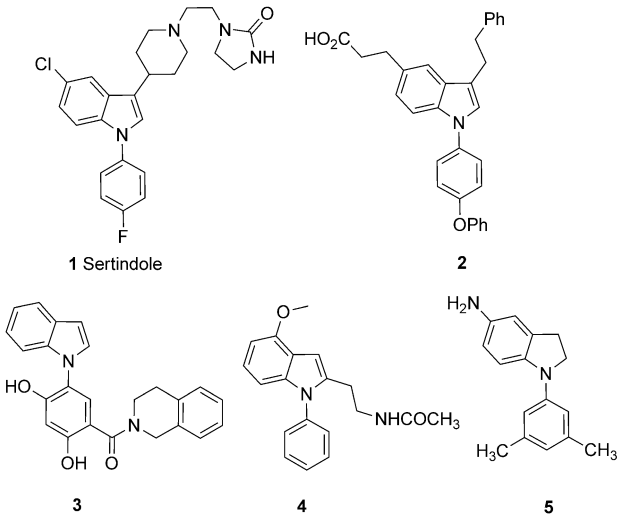
Arylindoles

Brønsted Acid-Catalyzed Synthesis of *N*-Arylindoles from 2-Vinylanilines and Quinones

Han-Ming Zhang, Zhong-Hua Gao, Liang Yi, and Song Ye*[a]

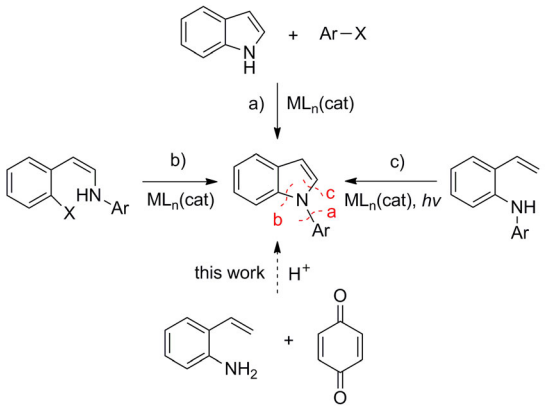
Abstract: In the presence of a quinone, Brønsted acid-catalyzed intramolecular C–N bond formation of *o*-vinylanilines by electrophilic cyclization was developed, giving the corresponding *N*-arylindoles in good to high yields. The reaction worked well for *o*-vinylanilines with terminal and internal C=C double bonds.

Since its discovery,[1] indole has been well recognized as a privileged structure in organic and medical chemistry.[2] Many pharmacological and bioactive compounds contain an *N*-arylindole structural motif. Such as, *N*-(4-fluorophenyl)indole **1** (sertindole) is an efficient antipsychotic agent (Scheme 1),[3] *N*-(4-*p*henoxyphenyl)-1*H*-indole **2** is a designed cytosolic phospholipase inhibitor,[4] compound **3** is a heat shock protein 90 (HSP90) inhibitor,[5] *N*-phenylindole **4** is a potential melatonin receptor MT1 agonists,[6] and *N*-arylindole **5** is a good cyclooxygenase-2 inhibitor .[7]



Scheme 1. Pharmacological and bioactive *N*-arylindoles.

The preparation of indoles has been intensively pursued by many chemists,[8] and various methods have been developed for the synthesis of *N*-arylindoles (Scheme 2). The predominant strategy relies on the transition-metal-catalyzed coupling of an



Scheme 2. Typical routes and our strategy for the synthesis of *N*-arylindoles.

indole and haloarenes (Scheme 2, route a).[9] In addition, the metal-catalyzed intramolecular C–N bond forming of *N*-(2-halostyryl)aniline has also been well established (Scheme 2, route b).[10] In 2012, Zheng et al. reported a pioneering visible-light-mediated ruthenium-catalyzed synthesis of *N*-arylindoles from styryl aniline by an oxidative coupling of C–H and N–H bonds (Scheme 2, route c).[11] In this paper, we communicate a metal-free synthesis of *N*-arylindoles by a Brønsted acid-catalyzed C–N bond formation from C(sp^2)–H of *o*-vinylanilines and in situ generated quinone imines.[12]

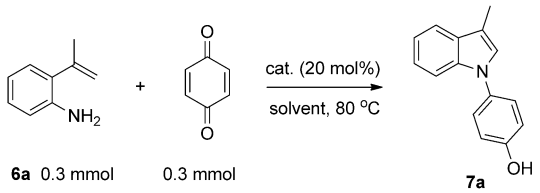
The model reaction of 2-vinylaniline **6a** with 1,4-benzoquinone was carried out in the presence of various Brønsted acids (Table 1). We were happy to find that the reaction catalyzed by 20 mol% of *p*-toluenesulfonic acid gave the desired *N*-arylindole **7a** in 66% yield (entry 1). The reaction using benzoic acid as the catalyst afforded the product in 64% yield (entry 2). However, further exploring of carboxylic acids, such as 4-nitrobenzoic acid, 2-phenylacetic acid, and formic acid, led to no improvement (entries 3–5). Phenol could also catalyze the reaction but with low yield (entry 6). Better yield was achieved when the reaction was carried out in 1,4-dioxane than in THF (entries 7 and 8).

With the optimized reaction condition in hand, the Brønsted acid-catalyzed synthesis of *N*-arylindoles was then explored

[a] *H.-M. Zhang, Z.-H. Gao, L. Yi, Prof. S. Ye*
Beijing National Laboratory for Molecular Sciences
Key Laboratory of Molecular Recognition and Function
Institute of Chemistry, Chinese Academy of Sciences
Beijing 100190 (China)
E-mail: songye@iccas.ac.cn

Supporting information for this article can be found under http://dx.doi.org/10.1002/asia.201600420.

Table 1. Optimization of reaction conditions.

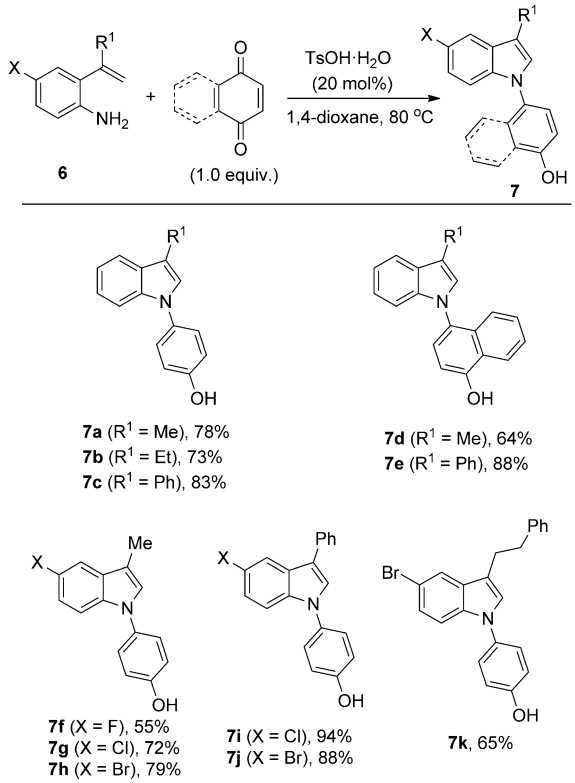


6a 0.3 mmol 0.3 mmol **7a**

Entry	Brønsted acid	Solvent	Yield [%][a]
1	$TsOH·H_2O$	THF	66
2	$C_6H_5CO_2H$	THF	64
3	$4\text{-}NO_2C_6H_4CO_2H$	THF	47
4	$C_6H_5CH_2CO_2H$	THF	42
5	HCO_2H	THF	38
6	phenol	THF	36
7	$C_6H_5CO_2H$	1,4-dioxane	70
8	$TsOH·H_2O$	1,4-dioxane	78

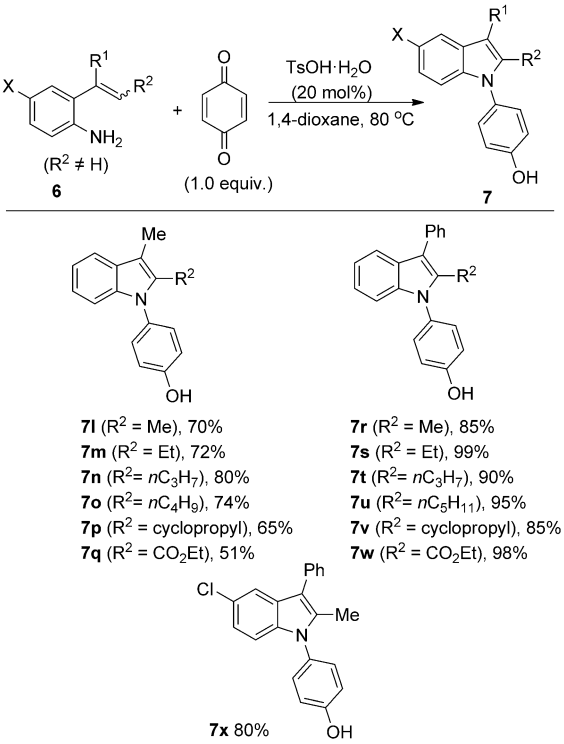
[a] Isolated yields.

with various anilines with *ortho*-terminal alkene substituents (Scheme 3). It was found that the reaction went well for all *ortho*-vinylanilines with different alkyl and aryl substituents (R^1 = Me, Et, Ph), and the one with aryl group resulted better yields than that with the alkyl groups (**7a** and **7b** versus **7c**). The reaction with naphthalene-1,4-dione proceeded as well (**7d** and **7e**). Anilines with the *para*-substituents (4-F, 4-Cl, 4-Br) were well tolerated (**7f**–**7k**).



Scheme 3. Reaction of anilines with terminal alkenes.

To further explore the scope of the reaction, anilines with internal alkenes were investigated for the synthesis of 2,3-disubstituted *N*-arylindoles (Scheme 4). We were satisfied to find that all the anilines with internal alkenes (R^2 = Me, Et, *n*-C_3H_7, *n*-



Scheme 4. Reaction of anilines with internal alkenes.

C_4H_9) worked well to give the *n*-arylindoles **7l**–**7o** in good yields. In addition, branched alkyl (R^2 = cyclopropyl) and ester groups ($R^2 = CO_2Et$) were well tolerated in spite of some decrease in the yields (**7p** and **7q**). Once again, the anilines with α-aryl worked better than with α-alkyl (**7r**–**7w** versus **7l**–**7q**). The example of 2,3,5-trisubstituted *N*-arylindole **7x** could be obtained in 80% yield.

The structure of *N*-arylindole **7w** was established by the X-ray analysis of its single crystal (Figure 1).[13]

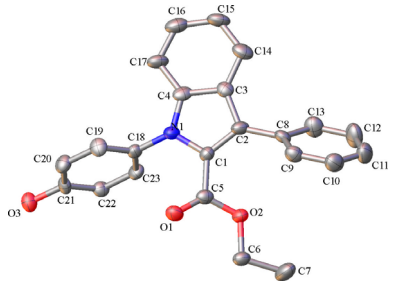
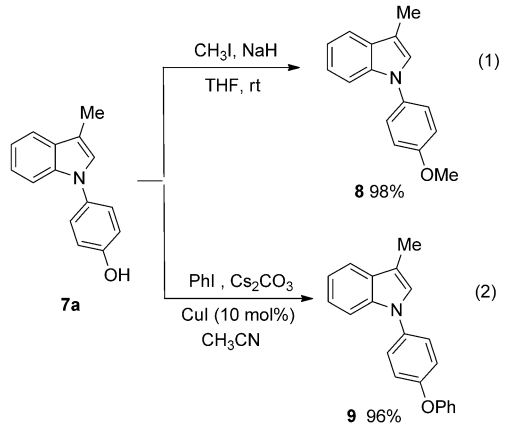


Figure 1. X-ray structure of *N*-arylindole **7w**, hydrogen is omitted for clarity.

The hydroxyl group in *N*-arylindole **7a** could be methylated under basic conditions [Eq. (1)], and phenylated in the presence of CuI as the catalyst [Eq. (2)].[14]



A plausible catalytic cycle is depicted in Figure 2. The protonation of the quinone with the catalytic acid facilitates the formation of the imine with aniline **6**. An intramolecular electrophilic cyclization of alkenes with the protonated quinone imine **II** generates indoline cation **III**. The removal of the proton by the quinone affords the *N*-arylindole and furnishes the catalytic cycle.

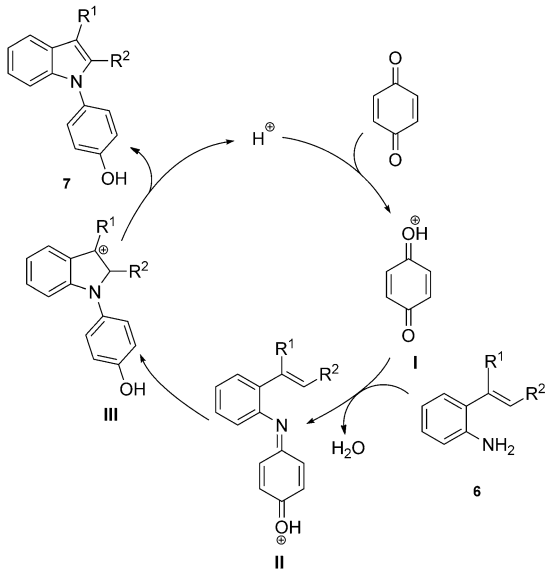


Figure 2. Proposed catalytic cycle.

To identify a possible reaction intermediate, the mass spectrum of the reaction mixture was tested before full consumption of the starting materials, and a species with 224.1070 *m/z* was observed, which is accorded with the molecular weight of intermediate **II** or **III** ($C_{15}H_{14}ON$).[15] The observed better performance of 2-vinylanilines with α-aryl (R^1 = aryl) than with α-alkyl (R^1 = alkyl; Scheme 3 and 4) can also be rationalized by better stability of the carbon cation **III** when α-aryl is present.

In summary, the Brønsted acid-catalyzed synthesis of *N*-arylindoles from 2-vinyl anilines and quinones was developed. The reaction worked well for both anilines with terminal and internal alkenes, giving the corresponding multisubstituted *N*-arylindoles in good yields. The indoline carbon cation, generated by the electrophilic cyclization of alkenes with the protonated quinone imine, is proposed as the key intermediate for the reaction. Related reactions involving the Brønsted acid-catalyzed generation of carbon cations are underway in our laboratory.

Experimental Section

Acid-catalyzed synthesis of *N*-arylindoles

To a 25 mL reaction tube equipped with a stir bar was charged with 2-vinylanilines **6** (0.3 mmol), quinone (0.3 mmol), $TsOH{\cdot}H_2O$ (11.4 mg, 0.06 mmol). To this mixture was added distilled 1,4-dioxane (2 mL). The reaction mixture was stirred at 80 °C until the reaction was completed, typically for 10–18 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether, typically 1/12) to give the desired product.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 21425207 and 21521002) and the Chinese Academy of Sciences is greatly acknowledged.

Keywords: aniline · Brønsted acid · carbocation · C–N bond formation · synthetic methods

[1] a) A. Baeyer, *Justus Liebigs Ann. Chem.* **1866**, *140*, 295–313; b) A. Baeyer, A. Emmerling, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 679–682.
[2] a) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489–4497; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73–103; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761–793; d) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278–311; e) S. Hibino, T. Choshi, *Nat. Prod. Rep.* **2002**, *19*, 148–180; f) B. P. Smart, R. C. Oslund, L. A. Walsh, M. H. Gelb, *J. Med. Chem.* **2006**, *49*, 2858–2860; g) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175–191.
[3] a) K. Andersen, T. Liljefors, J. Hyttel, J. Perregaard, *J. Med. Chem.* **1996**, *39*, 3723–3738; b) J. Perregaard, E. K. Moltzen, E. Meier, C. Sánchez, *J. Med. Chem.* **1995**, *38*, 1998–2008.
[4] T. Tomoo, T. Nakatsuka, T. Katayama, Y. Hayashi, Y. Fujieda, M. Terakawa, K. Nagahira, *J. Med. Chem.* **2014**, *57*, 7244–7262.
[5] J. Ren, J. Li, Y. Wang, W. Chen, A. Shen, H. Liu, D. Chen, D. Cao, Y. Li, N. Zhang, Y. Xu, M. Geng, J. He, B. Xiong, J. Shen, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2525–2529.
[6] G. Spadoni, C. Balsamini, A. Bedini, G. Diamantini, B. D. Giacomo, A. Tontini, G. Tarzia, *J. Med. Chem.* **1998**, *41*, 3624–3634.
[7] H. Sano, T. Noguchi, A. Tanatani, Y. Hashimoto, H. Miyachi, *Bioorg. Med. Chem.* **2005**, *13*, 3079–3091.
[8] a) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29–41; b) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442; c) L. Ackermann, *Synlett* **2007**, 0507–0526; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; e) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508–3549; f) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929–3968; g) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; *Angew. Chem.* **2009**, *121*, 9786–9824; h) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; i) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309.
[9] a) H. Wang, Y. Li, F. Sun, Y. Feng, K. Jin, X. Wang, *J. Org. Chem.* **2008**, *73*, 8639–8642; b) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem. Int. Ed.* **2007**, *46*, 934–936; *Angew. Chem.* **2007**, *119*, 952–954; c) N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, B. M. Bhanage, *Tetrahedron Lett.* **2007**, *48*,

6573 – 6576; d) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164 – 5173; e) C. J. Smith, M. W. S. Tsang, A. B. Holmes, R. L. Danheiser, J. W. Tester, *Org. Biomol. Chem.* **2005**, *3*, 3767 – 3781; f) L. Shi, M. Wang, C. A. Fan, F. M. Zhang, Y. Q. Tu, *Org. Lett.* **2003**, *5*, 3515 – 3517; g) G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.* **2001**, *66*, 7729 – 7737; h) G. Mann, J. F. Hartwig, M. S. Driver, C. F. Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827 – 828.

[10] a) J. A. Brown, *Tetrahedron Lett.* **2000**, *41*, 1623 – 1626; b) R. C. Hodgkinson, J. Schulzb, M. C. Willis, *Org. Biomol. Chem.* **2009**, *7*, 432 – 434; c) M. C. Willis, G. N. Brace, T. J. K. Findlay, I. P. Holmes, *Adv. Synth. Catal.* **2006**, *348*, 851 – 856; d) L. Ackermann, *Org. Lett.* **2005**, *7*, 439 – 442; e) M. Beller, C. Breindl, T. H. Riermeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403 – 1412.

[11] S. Maity, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 9562 – 9566; *Angew. Chem.* **2012**, *124*, 9700 – 9704.

[12] For related examples of Brønsted -catalyzed reactions, see: a) B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 8737 – 8740; *Angew. Chem.* **2014**, *126*, 8882 – 8885; b) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986 – 990.

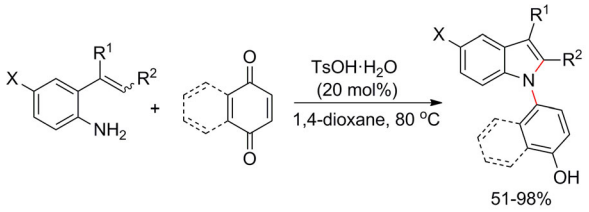
[13] CCDC 1470773 (**7w**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[14] The cleavage of C–O bond of the aryl ethers was reported: P. Álvarez-Bercedo, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 17352.

[15] See the Supporting Information for details.

Manuscript received: March 28, 2016
Accepted Article published: May 4, 2016
Final Article published: ■■ ▮▮, 0000

COMMUNICATION



Simple and efficient! In the presence of a quinone, Brønsted acid-catalyzed intramolecular C–N bond formation of *o*-vinylanilines by electrophilic cyclization was developed, giving the corresponding *N*-arylindoles in good to high yields (see scheme).

Arylindoles

*Han-Ming Zhang, Zhong-Hua Gao, Liang Yi, Song Ye**

■■ – ■■

Brønsted Acid-Catalyzed Synthesis of *N*-Arylindoles from 2-Vinylanilines and Quinones