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Brønsted acid-catalyzed synthesis of carbazoles from 2-substituted indoles†‡

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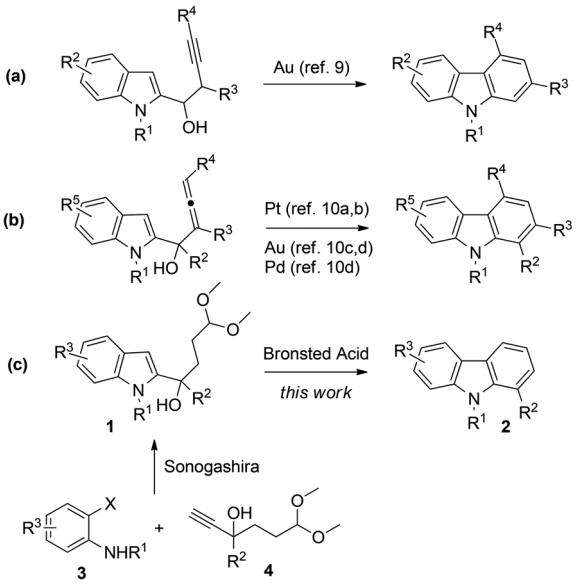
A simple and efficient method for the synthesis of disubstituted carbazoles has been developed. In this approach, carbazoles are synthesized from *o*-haloanilines and terminal alkynes using a two-step strategy, namely, Sonogashira coupling and intramolecular cyclization to provide indoles, which are followed by a *p*-TSA·H_2O-catalyzed carbazole formation.

The tricyclic carbazole nucleus is one of the most important heterocycles since it is not only found in many natural products and bioactive molecules[1] but also broadly serves as a building block for potential electroluminescent materials[2] due to its special thermal[3] and electrical[4] properties, as well as a host material for triplet emitters in organic light-emitting diodes.[5] Accordingly, a variety of well-documented traditional and modern methods have been developed for the construction of carbazoles and their derivatives.[6,7] These synthetic methods are mainly classified into two broad categories: one is the formation of the pyrrole core from biphenyls, and the other is the formation of a benzene ring from indoles. However, these literature methods have suffered from some drawbacks such as harsh reaction conditions, low yields, and poor atom economy. Therefore it is still of interest to uncover new synthetic methods for the realisation of these important molecules.

Synthetic pathways towards carbazoles from indoles have drawn a great deal of attention because indole substances abundantly exist.[8] For example, Ma and coworkers reported a Au-catalyzed cyclization of 1-(indol-2-yl)-3-alkyn-1-ols for the synthesis of carbazoles (Scheme 1a).[9] Cyclization reaction of 1-(indol-2-yl)-2,3-allenols involving Pt,[10a,b] Au,[10c,d] and Pd[10d]-catalysis was also achieved by Ma and Alcaide, respectively (Scheme 1b). Knölker also reported many applications of iron-mediated[10k–q] and palladium-catalysed[10e–j] approaches for the synthesis of carbazole derivatives. In 1995, Mahboobi reported carbazole synthesis from l-(*N*-benzylindol-2-y1)-3-(l,3-dioxolan-2-yl)-propan-1-ol in the presence of HCl, but only one example was recorded.[11] In this paper, we report herein our preliminary results on the synthesis of disubstituted carbazoles using a two-step procedure from *o*-haloanilines **3** and terminal alkynes **4** (Scheme 1c).



Scheme 1 Carbazole synthesis from indoles.

In order to introduce different substitutes on the indole ring, the starting materials, **1a–j**, are prepared mainly through a Sonogashira[12] coupling reaction and then with an intramolecular cyclization, starting from *o*-haloanilines **3** and terminal alkynes **4**. We initiated our studies by examining different protecting groups of **3** with terminal alkyne **4a** under classical Sonogashira conditions. When R was H, Me, or Ac, indole products were not obtained, but only the direct Sonogashira coupling product **5** was generated. However, a Ts protecting

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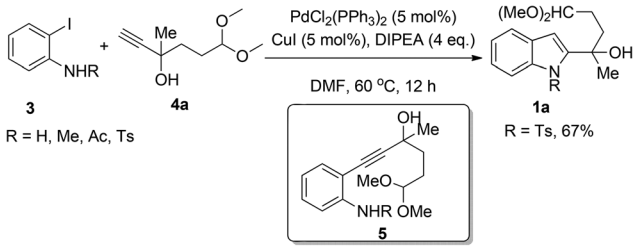
† This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday.
‡ Electronic supplementary information (ESI) available: Experimental procedures and the characterization data of new compounds. See DOI: 10.1039/c4qo00242c



Scheme 2 Protecting group's effect on **3** to form indole **1**.

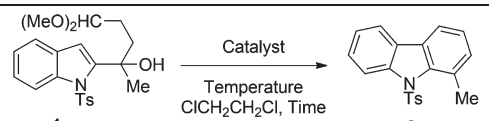
group was found to give the desired indole product **1a** with an acceptable yield of 67% (Scheme 2).

After determining the optimal protecting group, we turned our attention to the optimization of the carbazole formation reaction conditions. 5,5-Dimethoxy-2-(1-tosyl-1*H*-indol-2-yl)-pentan-2-ol **1a** was employed as a model substrate. A variety of reaction conditions (catalyst, temperature) were examined and some of the representative results are shown in Table 1. It was found that *p*-TSA·H_2O was more effective than the other acids, such as Amberlyst 15, albeit capable of promoting the reaction but with lower yields (entries 1 and 2). When the reaction was conducted at a higher temperature (40 °C), it rapidly gave the carbazole product in 95% yield within 1.5 h (entry 3). Decreasing the amount of catalyst to 20 mol% and prolonging the reaction time to 3 h led to the best result (entry 4).

With the optimized conditions in hand, we next investigated the substrate scope of this reaction. As illustrated in Scheme 3, the transformation was found to be very general. Various substituted indoles can successfully give the corresponding carbazole derivatives (**2a–2h**). However, the electron-withdrawing groups (F, NO_2, and CF_3) on indoles slowed down the reaction, and needed a higher temperature (60 °C), but the products were still isolated in moderate to good yields (56%–85%) (**2f–2h**). Moreover, R^2 could also be an aryl group (**2i**), or H (**2j**).

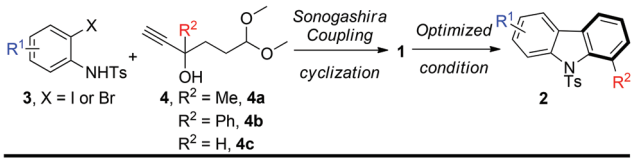
A plausible mechanism for the annulation of 5,5-dimethoxy-2-(1-tosyl-1*H*-indol-2-yl)pentan-2-ol **1a** catalyzed by *p*-TSA·H_2O is presented in Scheme 4. The intermediate acetal **6** is formed through the elimination of MeOH from indole **1a** in the presence of *p*-TSA·H_2O, which was also isolated as diastereoisomers in a nearly 1 : 1 ratio. Then the successive elimination of water/MeOH from intermediates **7** and/or **8** gave carbazole product **2a**.[13]

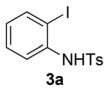
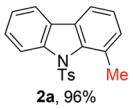
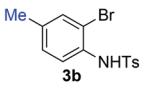
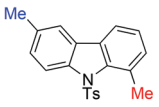
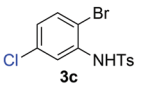
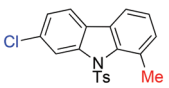
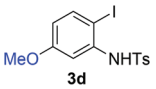
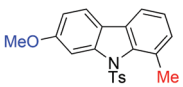
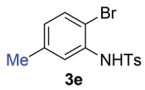
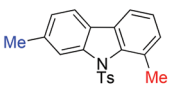
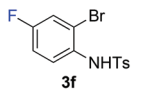
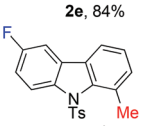
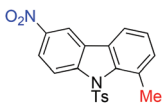
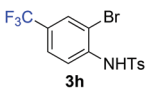
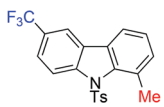
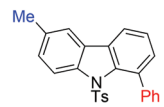
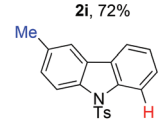
Table 1 Reaction optimization[a]



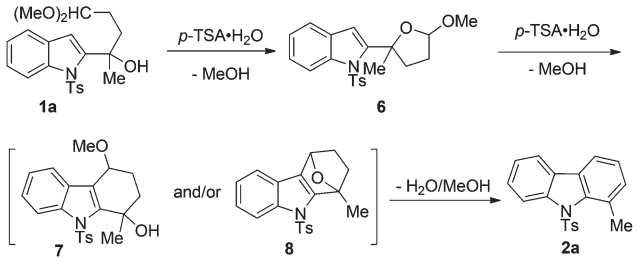
Entry	Catalyst (eq.)	Temperature (°C)	Time (h)	Yield[b] (%)
1	Amberlyst 15 (2)	40	14	69
2	*p*-TSA·H_2O (2)	23	48	93
3	*p*-TSA·H_2O (2)	40	1.5	95
4	***p*-TSA·H_2O (0.2)**	**40**	**3**	**96**

[a] Reaction conditions: **1a** (0.2 mmol), catalyst, in $ClCH_2CH_2Cl$ (2 mL). [b] Isolated yield.



entry	3	4	1	2
1	 **3a**	**4a**	**1a**, 67%	 **2a**, 96%
2	 **3b**	**4a**	**1b**, 75%	 **2b**, 98%
3	 **3c**	**4a**	**1c**, 66%	 **2c**, 76%
4	 **3d**	**4a**	**1d**, 49%	 **2d**, 64%
5	 **3e**	**4a**	**1e**, 64%	 **2e**, 84%
6	 **3f**	**4a**	**1f**, 92%	 **2f**, 85%[b]
7	 **3g**	**4a**	**1g**, 48%	 **2g**, 56%[b]
8	 **3h**	**4a**	**1h**, 69%	 **2h**, 77%[b]
9	**3b**	**4b**	**1i**, 77%	 **2i**, 72%
10	**3b**	**4c**	**1j**, 62%	 **2j**, 79%

Scheme 3 Sonogashira coupling for indole synthesis and *p*-TSA·H_2O-catalyzed carbazole synthesis.[a] [a] Indole synthesis conditions: **3** (0.8 mmol), **4** (0.88 mmol), $PdCl_2(PPh_3)_2$ (0.04 mmol), CuI (0.04 mmol), *N*,*N*-diisopropylethylamine (3.2 mmol), DMF (2 mL), at 60 °C for 12 h, isolated yield. Carbazole synthesis conditions: **1** (0.2 mmol), *p*-TSA·H_2O (0.04 mmol), $ClCH_2CH_2Cl$ (2 mL), at 40 °C for 3 h, isolated yield. [b] At 60 °C.



Scheme 4 A plausible mechanism.

Conclusions

In summary, we have developed a simple and efficient two-step approach (Sonogashira/intramolecular cyclization for indole synthesis and *p*-TSA·H_2O-catalyzed carbazole synthesis) for the synthesis of diversified substituted carbazoles from *o*-haloanilines **3** and terminal alkynes **4** in good isolated yields under mild conditions. Because of the ready availability of the starting materials and the potential of the products, this method should be useful in organic synthesis and medicinal chemistry. Further studies on the synthetic applications of this reaction are in progress in our laboratory.

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Notes and references

1 (*a*) R. S. Kapil, in *The Alkaloids*, ed. R. H. F. Manske, Academic Press, New York, 1971, vol. 13, p. 273; (*b*) H. P. Husson, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1985, vol. 26, p. 1; (*c*) P. Bhattacharyya and D. P. Chakraborty, in *Progress in the Chemistry of Organic Natural Products*, ed. W. Herz and H. Grisebach and G. W. Kirby, Springer, Wien, 1987, Vol. 52, p. 159; (*d*) D. P. Chakraborty, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1993, vol. 44, p. 257; (*e*) H.-J. Knölker, *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, JAI, Greenwich, 1995, vol. 1, p. 173; (*f*) C. Ito, M. Itoigawa, A. Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino and H. Furukawa, *J. Nat. Prod.*, 2004, **67**, 1488; (*g*) H.-J. Knölker, *Chem. Lett.*, 2009, **38**, 8; (*h*) I. Bauer and H.-J. Knölker, *Top. Curr. Chem.*, 2012, **309**, 203; (*i*) Y. Qiu, D. Ma, C. Fu and S. Ma, *Org. Biomol. Chem.*, 2013, **11**, 1666.

2 (*a*) J. K. R. Thomas, J. T. Lin, Y.-T. Tao and C.-W. Ko, *J. Am. Chem. Soc.*, 2001, **123**, 9404; (*b*) J. Huang, Y. Niu, W. Yang, Y. Mo, M. Yuan and Y. Cao, *Macromolecules*, 2002, **35**, 6080.

3 M. Haussler, J. Liu, R. Zheng, J. W. Y. Lam, A. Qin and B. Z. Tang, *Macromolecules*, 2007, **40**, 1914.

4 F. Sanda, T. Nakai, N. Kobayashi and T. Masuda, *Macromolecules*, 2004, **37**, 2703.

5 (*a*) A. Dijken, J. J. A. M. Bastiaansen, N. M. M. Kiggen, B. M. W. Langeveld, C. Rothe, A. Monkman, I. Bach, P. Stössel and K. Brunner, *J. Am. Chem. Soc.*, 2004, **126**, 7718; (*b*) W.-Y. Wong, L. Liu, D. Cui, L. M. Leung, C.-F. Kwong, T.-H. Lee and H.-F. Ng, *Macromolecules*, 2005, **38**, 4970; (*c*) R. M. Adhikari and D. C. Neckers, *J. Org. Chem.*, 2009, **74**, 3341.

6 For reviews on carbazole synthesis, see: (*a*) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (*b*) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193.

7 For select recent examples for carbazole syntheses, see: (*a*) W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560; (*b*) B. Witulski and C. Alayrac, *Angew. Chem., Int. Ed.*, 2002, **41**, 3281; (*c*) L.-C. Campeau, P. Thansandote and K. Fagnou, *Org. Lett.*, 2005, **7**, 1857; (*d*) S. H. Cho, J. Yoon and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996; (*e*) V. P. Kumar, K. K. Gruner, O. Kataeva and H.-J. Knölker, *Angew. Chem., Int. Ed.*, 2013, **52**, 11073; (*f*) A. C. Hernandez-Perez and S. K. Collins, *Angew. Chem., Int. Ed.*, 2013, **52**, 12696; (*g*) L. Ackermann and A. Althammer, *Angew. Chem., Int. Ed.*, 2007, **46**, 1627; (*h*) Z. Liu and R. C. Larock, *Org. Lett.*, 2004, **6**, 3739; (*i*) B.-Y. Lim, M.-K. Choi and C.-G. Cho, *Tetrahedron Lett.*, 2011, **52**, 6015; (*j*) R. B. Bedford and M. Betham, *J. Org. Chem.*, 2006, **71**, 9403; (*k*) R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2002, 2310; (*l*) R. Forke, M. P. Krahl, T. Krause, G. Schlechtingen and H.-J. Knölker, *Synlett*, 2007, 268; (*m*) Y. Ou and N. Jiao, *Chem. Commun.*, 2013, **49**, 3473; (*n*) H. Hagelin, J. D. Oslob and B. Åkermark, *Chem. – Eur. J.*, 1999, **5**, 2413; (*o*) D. J. S. Jean Jr., S. F. Poon and J. L. Schwarzbach, *Org. Lett.*, 2007, **9**, 4893; (*p*) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H.-Z. Tang, M. Fujiki, S. Yamaguchi and K. Tamao, *Angew. Chem., Int. Ed.*, 2003, **42**, 2051; (*q*) T. Kitawaki, Y. Hayashi, A. Ueno and N. Chida, *Tetrahedron*, 2006, **62**, 6792; (*r*) A. Kuwahara, K. Nakano and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413; (*s*) A. Kumar, A. Yadav, A. Verma, S. Jana, M. Sattar, S. Kumar, C. D. Prasad and S. Kumar, *Chem. Commun.*, 2014, **50**, 9481.

8 (*a*) D. Shu, G. N. Winston-McPherson, W. Song and W. Tang, *Org. Lett.*, 2013, **15**, 4162; (*b*) S. Tu, C. Ding, W. Hu, F. Li, Q. Yao and A. Zhang, *Mol. Diversity*, 2011, **15**, 91; (*c*) K. Ozaki, H. Zhang, H. Ito, A. Lei and K. Itami,

Chem. Sci., 2013, **4**, 3416; (*d*) C. Zhu and S. Ma, *Org. Lett.*, 2014, **16**, 1542.

9 Y. Qiu, W. Kong, C. Fu and S. Ma, *Org. Lett.*, 2012, **14**, 6198.

10 For Pt-catalyzed: (*a*) W. Kong, C. Fu and S. Ma, *Chem. Commun.*, 2009, 4572; (*b*) W. Kong, C. Fu and S. Ma, *Org. Biomol. Chem.*, 2012, **10**, 2164. For Au-catalyzed: (*c*) W. Kong, C. Fu and S. Ma, *Chem. – Eur. J.*, 2011, **17**, 13134; (*d*) B. Alcaide, P. Almendros, J. Alonso, M. T. Quirós and P. Gadziński, *Adv. Synth. Catal.*, 2011, **353**, 1871. For palladium-catalyzed route to carbazoles: ref. 10*d* and (*e*) R. Forke, A. Jäger and H.-J. Knölker, *Org. Biomol. Chem.*, 2008, **6**, 2481; (*f*) R. Forke, M. P. Krahl, F. Däbritz, A. Jäger and H.-J. Knölker, *Synlett*, 2008, 1870; (*g*) M. Schmidt and H.-J. Knölker, *Synlett*, 2009, 2421; (*h*) C. Börger, O. KataevA and H.-J. Knölker, *Org. Biomol. Chem.*, 2012, **10**, 7269; (*i*) R. Hesse, K. K. Gruner, O. Kataeva, A. W. Schmidt and H.-J. Knölker, *Chem. – Eur. J.*, 2013, **19**, 14098; (*j*) R. Hesse, A. Jäger, A. W. Schmidt and H.-J. Knölker, *Org. Biomol. Chem.*, 2014, **12**, 3866. For iron-mediated synthesis of carbazoles: (*k*) H.-J. Knölker and M. Bauermeister, *J. Chem. Soc., Chem. Commun.*, 1989, 1468; (*l*) H.-J. Knölker, M. Bauermeister and J.-B. Pannek, *Chem. Ber.*, 1992, **125**, 2783; (*m*) H.-J. Knölker and M. Wolpert, *Tetrahedron*, 2003, **59**, 5317; (*n*) O. Kataeva, M. P. Krahl and H.-J. Knölker, *Org. Biomol. Chem.*, 2005, **3**, 3099; (*o*) R. Czerwonka, K. R. Reddy, E. Baum and H.-J. Knölker, *Chem. Commun.*, 2006, 711; (*p*) K. E. Knott, S. Auschill, A. Jäger and H.-J. Knölker, *Chem. Commun.*, 2009, 1467; (*q*) K. K. Gruner, T. Hopfmann, K. Matsumoto, A. Jäger, T. Katsuki and H.-J. Knölker, *Org. Biomol. Chem.*, 2011, **9**, 2057.

11 S. Mahboobi and S. Kuhr, *Arch. Pharm.*, 1995, **328**, 45.

12 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.

13 S. M. Rafiq, R. Sivasakthikumaran and A. K. Mohanakrishnan, *Org. Lett.*, 2014, **16**, 2720.

