DOI: 10.1002/adsc.200900880

Gold-Catalyzed Intramolecular Alkyne Cycloisomerization Cascade: Direct Synthesis of Aryl-Annulated[*a*]carbazoles from Aniline-Substituted Diethynylarenes

Kimio Hirano,[a] Yusuke Inaba,[a] Toshiaki Watanabe,[a] Shinya Oishi,[a] Nobutaka Fujii,[a,*] and Hiroaki Ohno[a,*]

[a] Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan
Fax: (+81)-75-753-4570; e-mail: hohno@pharm.kyoto-u.ac.jpnfujii@pharm.kyoto-u.ac.jp

Received: December 18, 2009; Published online: February 9, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900880.

Abstract: Aniline-substituted diethynylarenes, which are readily synthesized through Sonogashira coupling reactions from commercially available 1,2-dihaloarenes, directly produce aryl- and heteroaryl-annulated[*a*]carbazoles by the gold-catalyzed intramolecular cascade hydroamination/cycloisomerization without producing theoretical by-products. This new atom-economical route is easily applicable to various aryl-annulated[*a*]carbazoles containing an alkyl, aryl or ester substituent.

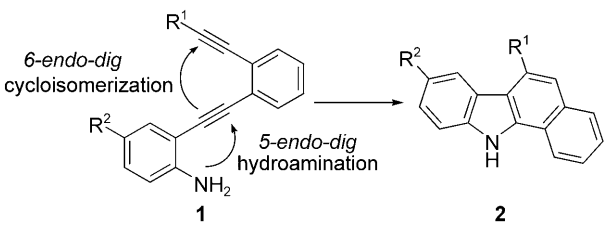
Keywords: alkynes; carbazoles; cascade reactions; gold catalysis; heterocycle synthesis

Catalytic cascade reactions are becoming increasingly important for the direct construction of target molecules and for reducing waste product formation.[1] Among them, the catalytic cycloisomerization cascade would have undeniable benefits from both atom-economical and environmental points of view. In recent years, gold catalysts have emerged as effective tools for various transformations. Based on the versatile reactivity of gold catalysts, several gold-catalyzed cascade transformations were recently reported.[2]

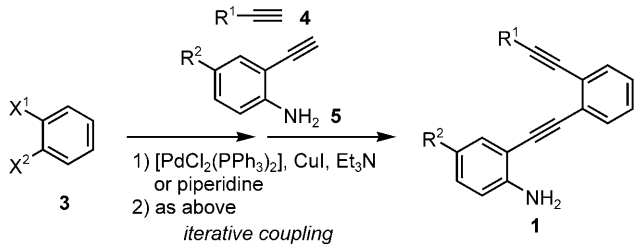
Currently, aryl-annulated carbazoles with diverse biological activity have attracted considerable attention in organic chemistry.[3] In particular, aryl- and heteroaryl-annulated[*a*]carbazoles exhibit a broad range of biological activities such as antitumor[4] and antimicrobial,[5] and are also utilized in the field of materials chemistry as light-emitting diodes[6] and fluorescence reagents.[7] However, most of the reported synthetic methods for this class of compounds require multistep conversions,[3] which restricts efficient structure optimization and their application. Therefore, development of a concise and reliable methodology to obtain substituted aryl- and heteroaryl-annulated[*a*]carbazoles is highly desirable.

Our ongoing program is directed towards the construction of heterocyclic frameworks by multi-bond forming processes.[8] As part of this, we designed a cascade reaction strategy for the assembly of a benzo[*a*]carbazole scaffold based on gold-catalyzed *5-endo-dig* hydroamination[9] followed by *6-endo-dig* cycloisomerization[10] of aniline-substituted diethynylarenes **1** (Scheme 1). Although base-promoted intramolecular cascade reactions of related diyne derivatives have been reported by Wu and co-workers,[11] a catalytic cycloisomerization cascade of diyne derivatives directly giving aryl-annulated[*a*]carbazoles without producing theoretical by-products, is unprecedented.[12] Herein we present a concise synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles by a gold-catalyzed intramolecular hydroamination-cycloisomerization cascade of aniline-substituted diethynylarene derivatives.

The substrates **1** required for the designed cascade reaction were readily prepared starting from commercially available 1,2-dihaloarenes. The representative



Scheme 1. Hydroamination-cycloisomerization cascade.



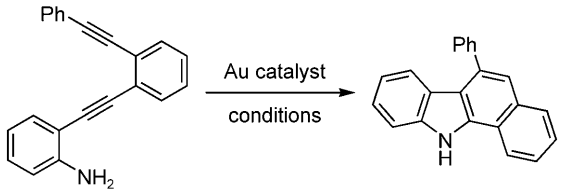
Scheme 2. Representative preparation of substrates **1**.

preparation of substrates **1** is shown in Scheme 2. The iterative Sonogashira reactions of 1,2-dihalobenzenes **3** with substituted acetylenes **4** and ethynylanilines **5** (the order depending on the substrate) gave the aniline-substituted diethynylanilines **1** without producing undesirable indoles. Other heterocyclic congeners were also prepared in the same manner, using 1,2-dihaloheteroarenes.

Initially, screening of gold catalysts for the cascade reaction was carried out using the aniline derivative **1a** by treatment with 20 mol% gold catalyst for 16 h (Table 1, entries 1–10). Whereas Ph_3PAuCl was ineffective in producing **2a** (entry 1), the reaction using AuCl and $AuCl_3$ as a ligand-free gold catalyst gave the desired carbazole **2a** in 33% and 42% yield, respectively, accompanied by formation of unidentified high polar compounds on TLC (entries 2 and 3). The use of the gold-oxo complex $[(Ph_3PAu)_3O]BF_4$ resulted in a 21% yield of **2a**, with 71% recovery of the starting material **1a** (entry 4). To our delight, treatment of aniline **1a** with $NaAuCl_4 \cdot 2H_2O$ afforded **2a** in good yield (64%, entry 5). Although activation of AuCl with AgOTf gave several side products (entry 6), a combination of Ph_3PAuCl and a silver salt generally gave better results (70–80%, entries 7–10). Of the four silver salts tested ($AgBF_4$, $AgSbF_6$, $AgNTf_2$, and AgOTf), AgOTf has proven to be the most promising additive (80%, entry 10). Next, we optimized the reaction conditions (reaction temperature, time, and solvent) using Ph_3PAuCl/AgOTf. The cascade reaction at room temperature required 7 h to reach completion affording a 70% yield of **2a** (entry 11), which was inferior to that obtained at 80 °C (81% within 1.5 h, entry 12). Investigation of the catalyst loading and reaction solvent (entries 13–16) revealed that 5 mol% Ph_3PAuCl/AgOTf in MeCN most effectively produced **2a** in 80% yield (entry 13).

With the conditions optimized (Table 1, entries 12 and 13), we then investigated the cascade reaction

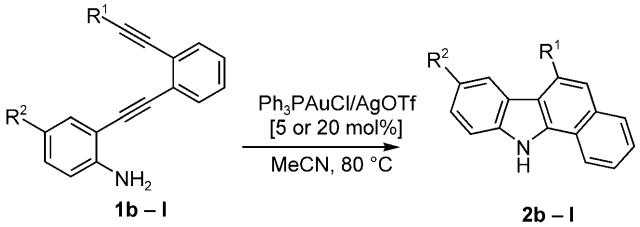
Table 1. Optimization of reaction conditions using **1a**.



Entry	Au catalyst [mol%]	Solvent	T [°C]	t [h]	Yield [%][a]
1	Ph_3PAuCl [20]	MeCN	80	16	n.r.[b]
2	AuCl [20]	MeCN	80	16	33
3	$AuCl_3$ [20]	MeCN	80	16	42
4	$[(Ph_3PAu)_3O]BF_4$ [20]	MeCN	80	16	21
5	$NaAuCl_4 \cdot 2H_2O$ [20]	MeCN	80	16	64
6	AuCl/AgOTf [20]	MeCN	80	16	n.d.[c]
7	$Ph_3PAuCl/AgBF_4$ [20]	MeCN	80	16	73
8	$Ph_3PAuCl/AgSbF_6$ [20]	MeCN	80	16	74
9	$Ph_3PAuCl/AgNTf_2$ [20]	MeCN	80	16	70
10	Ph_3PAuCl/AgOTf [20]	MeCN	80	16	80
11	Ph_3PAuCl/AgOTf [20]	MeCN	r.t.	7.0	70
12	Ph_3PAuCl/AgOTf [20]	MeCN	80	1.5	81
13	Ph_3PAuCl/AgOTf [5]	MeCN	80	1.5	80
14	Ph_3PAuCl/AgOTf [5]	EtOH	80	1.5	71
15	Ph_3PAuCl/AgOTf [5]	DCE[d]	80	3.0	73
16	Ph_3PAuCl/AgOTf [5]	Tol[e]	80	8.0	33

[a] Yields of isolated **2a**.
[b] n.r. = no reaction.
[c] n.d. = not detected.
[d] DCE = 1,2-dichloroethane.
[e] Tol = toluene.

Table 2. Reaction of various aniline derivatives.[a]



1b – l 2b – l

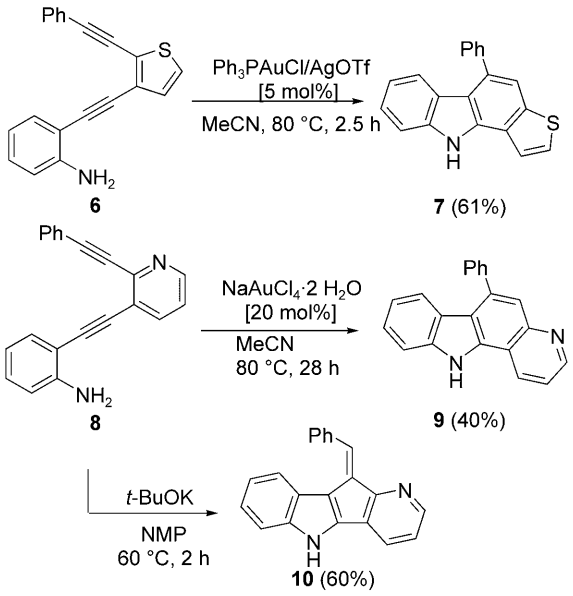
Entry	1	R^1	R^2	*t* [h][c]	2	Yield [%][b,c]
1	**1b**	*n*-Pr	H	0.75	**2b**	87
2	**1c**	*c*-Hex	H	0.75	**2c**	82
3	**1d**	*t*-Bu	H	24	**2d**	19
4	**1e**	*p*-MeC_6H_4	H	3.5 (0.83)	**2e**	42 (65)
5	**1f**	*p*-$MeOC_6H_4$	H	4.0 (1.5)	**2f**	29 (45)
6	**1g**	*p*-$F_3CC_6H_4$	H	0.50	**2g**	84
7	**1h**	*p*-NCC_6H_4	H	1.0	**2h**	78
8	**1i**	*p*-ClC_6H_4	H	0.75	**2i**	81
9	**1j**	Ph	CO_2Me	2.0 (2.0)	**2j**	35 (44)
10	**1k**	Ph	CF_3	5.5 (1.0)	**2k**	52 (88)
11	**1l**	Ph	Me	2.0 (0.83)	**2l**	29 (78)

[a] Unless otherwise stated, all the reactions were carried out with $Ph_3PAuCl/AgOTf$ [5 mol%] in MeCN at 80 °C.
[b] Yields of isolated products.
[c] Reaction times and yields in parentheses indicate those with 20 mol% of the catalyst.

using various substrates. First, substituent R^1 on the alkyne terminus was evaluated (Table 2, entries 1–8). Anilines **1b** and **1c** with an *n*-propyl or cyclohexyl group were good substrates for the gold-catalyzed cascade cyclization (entries 1 and 2). However, **1d** bearing a *tert*-butyl group afforded **2d** in only 19% yield (entry 3), presumably due to steric repulsion of the *tert*-butyl group and the gold complex on the second cyclization, as well as the formation of a sterically congested product. Reaction of **1e** or **1f**, which have electron-rich aryl groups (*p*-MeC_6H_4 or *p*-$MeOC_6H_4$) as the R^1 substituents, with 5 mol% of the catalyst gave **2e** and **2f** in relatively low yields (42% and 29%, respectively). Yields were improved to 65% and 45%, respectively (entries 4 and 5), with increased loading of the catalyst (20 mol%). In contrast, the reactions of **1g** and **1h** bearing an electron-deficient aryl group (*p*-$F_3CC_6H_4$ or *p*-NCC_6H_4) with 5 mol% of the catalyst resulted in **2g** or **2h** in good yields (84% and 78%, entries 6 and 7). The versatility of the reaction can be seen by the cascade cyclization of aniline **1i** containing a chlorophenyl group to produce the corresponding 6-(*p*-chlorophenyl)benzo[*a*]carbazole **2i** in 81% yield (entry 8). From these observations, many substituent types on the alkyne terminus are tolerated for the cascade cyclization, while a *tert*-butyl group and electron-rich aryl substituents on the alkyne terminus decrease the reactivity of the substrates.

We next applied the gold-catalyzed cascade cyclization to anilines **1j–l** having a substituent R^2 at the *para*-position to the amino group (Table 2, entries 9–11). With 5 mol% $Ph_3PAuCl/AgOTf$, these anilines gave moderate yields of the desired carbazoles **2j–l** regardless of the electronic properties of the substituent R^2 (29–52% yield, entries 9–11). Although the use of 20 mol% catalyst in the reaction of **1j** only slightly increased the yield of **2j** (44%, entry 9),[13] it efficiently improved the reactivity of **1k** and **1l** to give **2k** and **2l** in 88% and 78% yield, respectively (entries 10 and 11). The decreased nucleophilicity of aniline **1j** bearing a methoxycarbonyl group would be less appropriate for the gold-catalyzed hydroamination-cycloisomerization reaction.

Finally, we investigated the cascade cyclization of heterocyclic congeners **6** and **8**. A diethynylthiophene derivative **6**, which has a five-membered heterocycle connecting to two alkynes, can be used for this cascade reaction to give the corresponding thienocarbazole **7** in 61% yield (Scheme 3). Unfortunately, the cascade cyclizaion of the aniline **8** involving a pyridine moiety did not afford the desired pyridocarbazole **9** by treatment with 20 mol% $Ph_3PAuCl/AgOTf$. However, the more electrophilic $NaAuCl_4 \cdot 2H_2O$ (20 mol%) produced **9** in 40% yield (Scheme 3). Interestingly, the base-promoted reaction of the same aniline **8** dramatically changed the cyclization mode leading to the formation of isomeric product **10**[14] in 60% yield, through cascade *5-endo-dig*/*5-exo-dig* cyclization. These results demonstrate that the isomeric annulated carbazoles can be selectively synthesized



Scheme 3. Cascade cyclizations of heterocyclic congeners.

from the single substrates by simply changing the reaction conditions.

In conclusion, we have developed a novel gold-catalyzed intramolecular cascade cyclization for the synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles. This reaction is applicable to various aryl-annulated[*a*]carbazoles containing an alkyl or aryl substituent. It provides potent methodology for the fields of drug discovery and materials chemistry.

Experimental Section

Representative Procedure for Synthesis of Aryl- and Heteroaryl-annulated[*a*]carbazoles. Synthesis of 6-Phenyl-11*H*-benzo[*a*]carbazole (2a) (Table 1, Entry 13)

A mixture of Ph_3PAuCl (2.9 mg, 5.9 μmol) and AgOTf (1.5 mg, 5.9 μmol) in acetonitrile (0.59 mL) was stirred at room temperature under argon. After 2-{[2-(phenylethynyl)-phenyl]ethynyl}aniline (**1a**) (34 mg, 0.12 mmol) was added, the mixture was stirred at 80 °C for 1.5 h. The reaction mixture was deluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (Chromatorex® NH) with *n*-hexane/EtOAc (3:1) to afford **2a** as a yellow solid; yield: 29 mg (80% yield); mp 164–165 °C; IR (neat): $\nu = 3429\ cm^{-1}$ (NH); ^1H NMR (500 MHz, C_6D_6): $\delta = 7.04$ (ddd, $J = 8.0$, 6.9, 1.2 Hz, 1H, 8-H), 7.23 (d, $J = 8.0$ Hz, 1H, 10-H), 7.24–7.33 (m, 4H, 9-H and Ph), 7.35–7.40 (m, 2H, 2-H and 3-H), 7.48 (s, 1H, 5-H), 7.63–7.67 (m, 3H, 1-H and Ph), 7.78 (d, $J =$ 8.0 Hz, 1H, 7-H), 7.81–7.83 (m, 1H, 4-H), 7.95 (br s, 1H, NH); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 111.9$, 117.9, 120.6, 121.4, 121.6, 122.0, 123.2, 125.0, 125.4, 125.8, 126.3, 128.9, 129.2 (2C), 129.8, 130.4 (2C), 133.3, 136.3, 137.8, 139.8, 142.5; HR-MS (FAB): $m/z = 293.1208$, calcd. for $C_{22}H_{15}N$ [M^+]: 293.1204.

Acknowledgements

This work was supported in part by Kaken Pharmaceutical Co., Ltd., a Grant-in-Aid for Encouragement of Young Scientists (A) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Targeted Proteins Research Program, and the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO). T.W. is grateful to Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

References

[1] For recent reviews on cascade reactions, see; a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; c) S. F. Kirsch, *Synthesis* **2008**, 3183–3204.

[2] For recent reviews on gold catalysis: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; d) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442.

[3] For reviews, see: a) G. H. Kirsch, *Curr. Org. Chem.* **2001**, *5*, 507–518; b) H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427; c) F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213–7256.

[4] a) E. Lescot, G. Muzard, J. Markovits, J. Belleney, B. P. Roques, J.-B. Le Pecq, *J. Med. Chem.* **1986**, *29*, 1731–1737; b) C. M. Cavazos, S. T. Keir, T. Yoshinari, D. D. Bigner, H. S. Friedman, *Cancer Chemother. Pharmacol.* **2001**, *48*, 250–254.

[5] T. A. Choi, R. Czerwonka, W. Fröhner, M. P. Krahl, K. R. Reddy, S. G. Franzblau, H.-J. Knölker, *ChemMedChem* **2006**, *1*, 812–815.

[6] J. P. Chen, H. Tanabe, X.-C. Li, T. Thoms, Y. Okamura, K. Ueno, *Synth. Met.* **2003**, *132*, 173–176.

[7] J. You, W. Zhao, L. Liu, X. Zhao, Y. Suo, H. Wang, Y. Li, C. Ding, *Talanta* **2007**, *72*, 914–925.

[8] a) H. Ohno, Y. Ohta, S. Oishi, N. Fujii, *Angew. Chem.* **2007**, *119*, 2345–2348; *Angew. Chem. Int. Ed.* **2007**, *46*, 2295–2298; b) T. Watanabe, S. Ueda, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2007**, 4516–4518; c) H. Ohno, M. Iuchi, N. Fujii, T. Tanaka, *Org. Lett.* **2007**, *9*, 4813–4815; d) Y. Ohta, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2008**, 835–837; e) H. Ohno, A. Okano, S. Kosaka, K. Tsukamoto, M. Ohata, K. Ishihara, H. Maeda, T. Tanaka, N. Fujii, *Org. Lett.* **2008**, *10*, 1171–1174; f) Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 3535–3538; g) A. Okano,

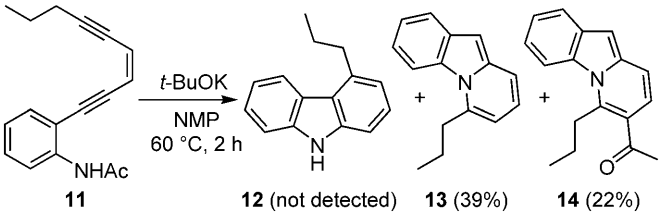
T. Mizutani, S. Oishi, T. Tanaka, H. Ohno, N. Fujii, *Chem. Commun.* **2008**, 3534–3536; h) S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 5239–5242; i) Y. Ohta, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2009**, *11*, 1979–1982; j) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2009**, *74*, 4720–4726.

[9] For alkyne hydroamination to give indoles, see: a) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610–618; b) M. Alfonsi, A. Arcadi, M. Aschi, G. Bianchi, F. Marinelli, *J. Org. Chem.* **2005**, *70*, 2265–2273; c) Y. Miyazaki, S. Kobayashi, *J. Comb. Chem.* **2008**, *10*, 355–357; d) C. Praveen, Y. W. Sagayaraj, P. T. Perumal, *Tetrahedron Lett.* **2009**, *50*, 644–647.

[10] For gold-catalyzed electrophilic activation of alkynes toward intramolecular nucleophilic attack at the C-3 position of indoles, see: a) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123–1127; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358–1373; c) R. Sanz, D. Miguel, F. Rodríguez, *Angew. Chem.* **2008**, *120*, 7464–7467; *Angew. Chem. Int. Ed.* **2008**, *47*, 7354–7357; d) Y. Lu, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 1517–1522.

[11] For related base-mediated reactions, see: a) M.-J. Wu, C.-Y. Lee, C.-F. Lin, *Angew. Chem.* **2002**, *114*, 4251–4253; *Angew. Chem. Int. Ed.* **2002**, *41*, 4077–4079; b) C.-Y. Lee, C.-F. Lin, J.-L. Lee, C.-C. Chiu, W.-D. Lu, M.-J. Wu, *J. Org. Chem.* **2004**, *69*, 2106–2110.

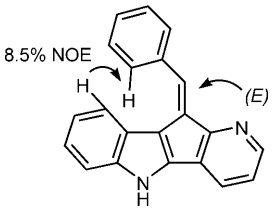
[12] In 2004, Wu reported base-promoted cascade cyclization of aniline-substituted (*Z*)-endiyne derivatives of type **11** to form carbazoles of type **12**. However, our detailed reinvestigation of the reactions have proven that these reactions provide pyrido[1,2-*a*]indole derivatives, not carbazoles. For example, the reaction of **11** under the reported conditions (*t*-BuOK, NMP, 60 °C) gave the indole **13** (39%) and its acetylated product **14** (22%), without formation of the carbazole **12**. Spectral data of **13** including ^{1}H NMR in $CDCl_3$, which apparently show 3-H of the indole nucleus, are in good agreement with those reported by Wu (assigned as the carbazole **12**). The unambiguous structure assignment for **13** was made by HMQC and HMBC analyses, see the Supporting Information.



11 **12** (not detected) **13** (39%) **14** (22%)

[13] Microwave-assisted conditions (23 W, 100 °C, 20 min) were also ineffective for improvement of the yield of **2j** (45%).

[14] The NOE analysis indicates that **10** has the *E*-configuration.



10

