Advanced Synthesis & Catalysis

Accepted Article

Title: Palladium-Catalyzed Regioselective Synthesis of 1-Hydroxycarbazoles Under Aerobic Conditions

Authors: So Won Youn, Young Ho Kim, and Yoon Hyung Jo

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801265

Link to VoR: http://dx.doi.org/10.1002/adsc.201801265

10.1002/adsc.201801265

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Palladium-Catalyzed Regioselective Synthesis of 1-Hydroxycarbazoles Under Aerobic Conditions

So Won Youn,[a,*] Young Ho Kim,[a] and Yoon Hyung Jo[a]

[a] Center for New Directions in Organic Synthesis, Department of Chemistry and Research Institute for Natural Sciences, Hanyang University, Seoul 04763, Korea
Fax: (+82)-2-2298-0319; e-mail: sowony73@hanyang.ac.kr

Dedicated to Professor Yong Hae Kim on the occasion of his 80th birthday

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. A palladium-catalyzed aerobic C−H amidation of *N*-Ts-2-amino-3'-hydroxylbiaryls has been developed to afford a diverse range of 1-hydroxycarbazoles with high regioselectivity and efficiency. This protocol benefits from operational simplicity, robustness, and sustainability with the use of ambient air as the sole terminal oxidant. Further elaboration of the products obtained from this process provides facile access to various carbazole alkaloids including carbazolequinones and biscarbazoles. A mechanism involving dual directing group-assisted regioselective C–H activation at the more sterically hindered C2'-position of 2-amino-3'-hydroxylbiaryls is proposed.

Keywords: carbazoles; C-H activation; palladium catalysis; regioselectivity

1-Oxygenated carbazoles[1] and carbazolequinones[2] are ubiquitous structural motifs found in a wide range of natural products, and they are known to exhibit various biological activities (Figure 1).[3] Thus, efficient and regioselective synthesis of, in particular, 1-oxygenated carbazoles is highly desirable.

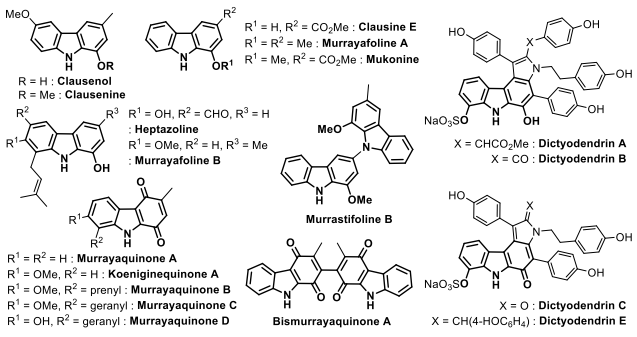
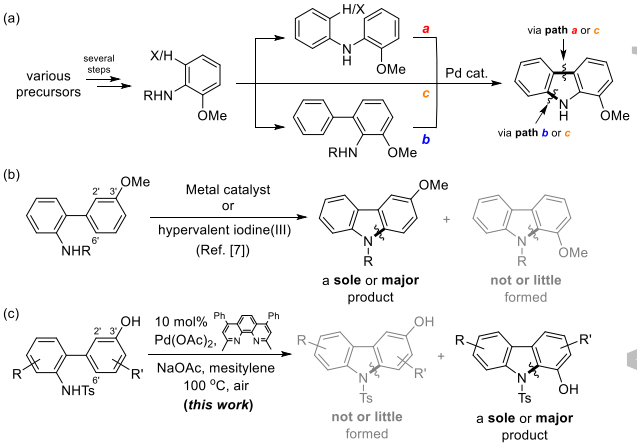


Figure 1. Naturally occurring bioactive 1-oxygenated carbazoles and carbazolequinones.

One of the more common and straightforward synthetic strategies for carbazole synthesis is construction of the pyrrole nucleus through metal-mediated C-C and/or C-N bond formation starting from aniline derivatives bearing appropriate functionality. In general, 1-oxygenated carbazoles (e.g., 1-methoxycarbazoles) have been formed by 1) oxidative cyclization of *N*-aryl-2-methoxyanilines through a C–C bond formation (path a, Scheme 1a)[4]; 2) oxidative C-H amin(d)ation of 2-amino-3-methoxybiaryls through C–N bond formation (path b)[5]; or 3) one-pot sequential Pd-catalyzed Buchwald−Hartwig amination and cyclization of 2-methoxyanilines with halogenated arenes through simultaneous C–N and C–C bond formation (path c).[6]



Scheme 1. Synthesis of 1-oxygenated carbazoles.

All of these methods require 2-methoxyaniline derivatives as a starting material, which are generally prepared in tedious and often lengthy sequences of steps from commercially available reagents. Due to limited availability of diversely substituted 2-

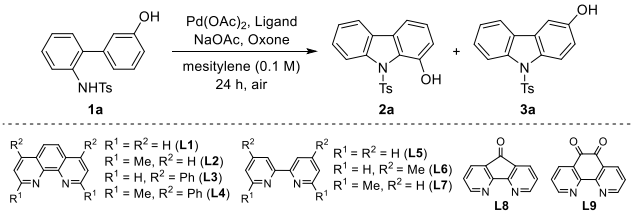
10.1002/adsc.201801265

methoxyanilines, alternative protocols such as oxidative C−H amin(d)ation of 2-amino-3'-methoxybiaryls, which can be readily prepared from 2-bromoanilines and 3-methoxyphenylboronic acids or 3-bromoanisoles, would be a new, complementary and more efficient route to this scaffold through an alternative C–N bond formation (Scheme 1b). However, it is well precedented in the literature that 3-methoxycarbazoles are generally obtained as the sole or major product through C-H activation at the less sterically hindered C6'-position rather than the C2'-position (Scheme 1b).[7-9] Thus, regioselective synthesis of 1-oxygenated carbazoles from this type of C3'-substituted substrate remains an unresolved challenge. In view of their prevalence in bioactive molecules[1] and their utility for further transformation into carbazolequinones, biscarbazoles, and other alkaloids,[3, 10-12] development of such a synthetic method is of great importance to provide straightforward access to a diverse range of 1-oxygenated carbazoles.

Inspired by the seminal work of Miura and Rawal on hydroxyl-directed C-H functionalization under Pd catalysis,[13-14] we have devised a strategy to synthesize 1-hydroxycarbazoles via oxidative C-H amidation of 2-amino-3'-hydroxylbiaryls taking advantage of the free hydroxyl moiety as a potential secondary directing group[15] for regiocontrolled C-H activation (Scheme 1c). Instead of installation of O-containing directing groups such as esters, carbamates, or ethers, use of the free hydroxyl moiety as a directing group would be more straightforward and atom-/step-economical. Therefore, realization of our proposed method would provide an attractive and potentially powerful route for the expedient synthesis of a wide range of 1-oxygenated carbazoles via a C-N bond forming cyclization. However, the direct and regioselective oxidative C-H amidation of free phenol derivatives constitutes a challenge for several reasons: 1) In addition to aforementioned regiochemistry issues,[7-9] in general, functionalization of phenols preferentially provides the *p*-isomer or inseparable mixtures with low selectivity. 2) Strong oxidants such as $PhI(OAc)_2$ often employed in oxidative C−H amin(d)ation[16] could affect the compatibility of free phenols, which are well-known to be sensitive toward oxidative decomposition.[17] 3) While significant progress has been made in transition-metal-catalyzed C-H functionalization of free phenols using a phenoxy group as a directing group,[18-19] all precedented methods lead to the formation of C-C and/or C-O bonds, and synthetic methods for new C-N bond formation via regioselective C-H amin(d)ation have yet to be realized.[20]

Herein we report a Pd-catalyzed aerobic C−H amidation for the synthesis of 1-hydroxycarbazoles with high efficiency and regioselectivity. This process involves a C–H activation at the more sterically hindered C2'-position of *N*-Ts-2-amino-3'-hydroxylbiaryls with the aid of a dual directing group,[21] leading to formation of 1-oxygenated carbazoles (Scheme 1c), which are not the regioisomers preferentially obtained by oxidative C−H amin(d)ation of the corresponding C3'-substituted 2-aminobiaryls.

Table 1. Optimization studies.



Entry	Pd cat. [mol%]	Ligand [mol%]	NaOAc [equiv]	Oxone [equiv]	*T* [ºC]	**2a** [%][a]	**3a** [%][a]
1	20	-	0.5	1	80	(44)	9
2	20	**L1** (20)	0.5	1	80	10	10
3	20	**L2** (20)	0.5	1	80	37	11
4	20	**L3** (20)	0.5	1	80	0	60
5	20	**L4** (20)	0.5	1	80	(70)	(11)
6	20	**L5** (20)	0.5	1	80	12	7
7	20	**L6** (20)	0.5	1	80	7	5
8	20	**L7** (20)	0.5	1	80	(40)	(41)
9	20	**L8** (20)	0.5	1	80	19	0
10	20	**L9** (20)	0.5	1	80	6	8
11	10	**L4** (10)	0.5	1	80	30	7
12	10	**L4** (10)	0.5	1	100	(68)	(18)
13	10	**L4** (10)	1	1	80	(66)	(19)
14[b]	**10**	**L4 (10)**	**1**	**1**	**100**	**(75)**	**(22)**
15	-	**L4** (10)	1	1	100	0	0
16	10	-	1	1	100	(24)	(8)
17	10	**L4** (10)	-	1	100	(30)	(1
18[b]	**10**	**L4 (10)**	**1**	**-**	**100**	**(74)**	**(18)**
19[c]	10	**L4** (10)	1	1	100	(18)	(7)
20[c]	10	**L4** (10)	1	-	100	(10)	trac
21[b,d]	10	**L4** (10)	1	-	100	(77)	(15)

[a] Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. Values in parentheses indicate isolated yields. [b] For 12 h. [c] Under argon atmosphere. [d] Under O_2 (1 atm).

In light of our recent success in the synthesis of carbazoles using *N*-Ts-2-aminobiaryl derivatives,[7e] we initially attempted the proposed reaction using **1a** as the test substrate under our previously reported conditions (5 mol% $Pd(OAc)_2$, Oxone, *p*TsOH in PivOH/DMF at 25 ºC). Both the desired product **2a** and the regioisomer **3a** were obtained in low yields and selectivity (**2a**: 15%, **3a**: 18%).[21] After scrupulous examination of the reaction parameters, we discovered that both yields and selectivity could be improved when mesitylene and NaOAc were used as the solvent and additive, respectively (Table 1, entry 1). Considering several reports on the positive effect of nitrogen ligands in various Pd-catalyzed aerobic oxidation reactions,[22] we next extended our investigation to a variety of nitrogen ligands (entries 2-10).[21] Much to our delight, bathocuproine (**L4**) was identified as an effective ligand resulting in further improvements of both reactivity and

10.1002/adsc.201801265

regioselectivity (**2a**: 70%, **3a**: 11%, entry 5). Further optimization of the reaction conditions secured a good yield of **2a** with lower catalyst loading at higher temperature after a shorter reaction time (entries 11-14; entries 5 vs 14).

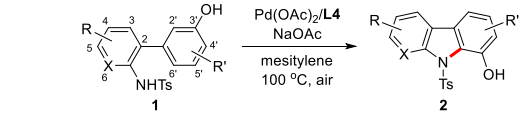
Control experiments showed that all reaction parameters ($Pd(OAc)_2$ catalyst, **L4** ligand, NaOAc additive, air oxidant) except Oxone as an oxidant were indispensable for this transformation (entries 15-20), while a comparable yield of **2a** was obtained in the absence of Oxone (entries 14 vs 18). In addition, reaction of **1a** under an argon atmosphere irrespective of the presence of Oxone resulted in a drastically decreased conversion (entries 19-20), while reaction under O_2 (1 atm) had only a marginal effect (entry 21). These results suggested that ambient air was the sole effective oxidant in this transformation.[23]

Very intriguingly, as proposed, C-H activation and cyclization occurred predominantly at the more sterically encumbered C2'-position between the two possible sites to afford 1-hydroxycarbazole **2a** as the major isomer along with a small amount of 3-hydroxycarbazole **3a**. This uncommon regioselectivity could be attributed to the presence of the hydroxyl group at the C3'-position of **1a**, which acts as a secondary directing group, leading to C-N bond formation at the more congested C2'-position between the two substituents.[21] The influence of the hydroxyl group could be ascertained by the fact that cyclization of *O*-Me-**1a** took place exclusively at the less sterically hindered C6'-position to afford the corresponding 3-methoxycarbazole (*O*-Me-**3a**) in 83% yield under the optimized reaction conditions (Scheme 2a). Furthermore, to showcase the effectiveness of free hydroxyl group, other potential secondary directing groups (e.g., -NHTs, -NHAc, -O(2-Py), -OSi(OH)*t*Bu$_2$) have been examined under the optimized reaction conditions.[21] However, all reactions formed the corresponding 3-substituted carbazoles as the sole or major product through C-H activation at the less sterically hindered C6'-position, clearly indicating the superiority of free hydroxyl group as a secondary directing group.

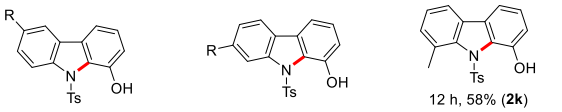
Notably, subjecting **1a** to the previously reported C-H amin(d)ation protocols for carbazole synthesis[5, 7, 9] resulted in decomposition or very low conversion favoring **3a**,[21] demonstrating the remarkable regiochemical selectivity of the method presented herein. To the best of our knowledge, this represents the first example in which a phenoxy group was used as a directing group for a Pd-catalyzed oxidative C-N bond formation at the more sterically hindered position, favoring formation of the less common 1-hydroxycarbazole.

Having determined the optimized conditions as entry 15 in Table 1, we set out to explore the scope of this process (Table 2). A variety of substituents on both aromatic rings of substrate **1** were well tolerated irrespective of their positions and electronic properties, leading to the formation of 1-hydroxycarbazoles **2** as a single or major product in good to high yields. Heteroaromatic motifs such as pyridine could also be incorporated to afford 8-hydroxy-α-carboline **2y**, a key motif present in various bioactive molecules.[24] *N*,*N*′-Bistosyl-2,2"-diamino-5'-hydroxy-[1,1';3',1"]terphen-

Table 2. Reaction of various arenediazonium salts and styrenes.[a]



***a. Substituent R of the aniline moiety* (R' = H)**



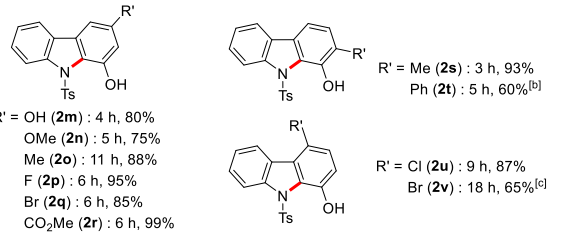
R = H (**2a**) : 12 h, 74%
OMe (**2b**) : 5 h, 77%
Me (**2c**) : 7 h, 74%
Cl (**2d**) : 9 h, 76%
CO_2Me (**2e**) : 6 h, 68%
NO_2 (**2f**) : 8 h, 58%

R = OMe (**2g**) : 5 h, 60%
Me (**2h**) : 11 h, 75%
Cl (**2i**) : 9 h, 75%
NO_2 (**2j**) : 11 h, 76%

12 h, 58% (**2k**)

8 h, 70% (**2l**)

***b. Substituent R' of the 2-aryl moiety* (R = H)**

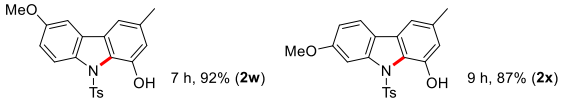


R' = OH (**2m**) : 4 h, 80%
OMe (**2n**) : 5 h, 75%
Me (**2o**) : 11 h, 88%
F (**2p**) : 6 h, 95%
Br (**2q**) : 6 h, 85%
CO_2Me (**2r**) : 6 h, 99%

R' = Me (**2s**) : 3 h, 93%
Ph (**2t**) : 5 h, 60%[b]

R' = Cl (**2u**) : 9 h, 87%
Br (**2v**) : 18 h, 65%[c]

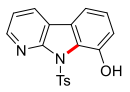
c. Substituents R and R'



7 h, 92% (**2w**)

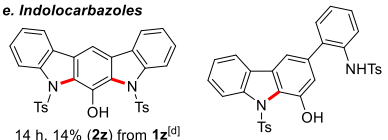
9 h, 87% (**2x**)

d. Pyridoindoles



24 h, 64% (**2y**)[b]

e. Indolocarbazoles

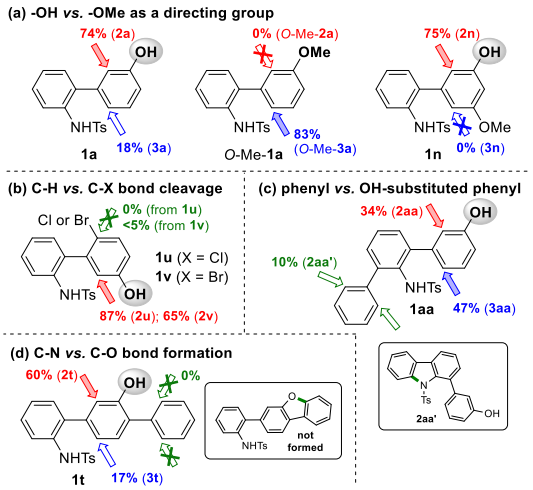


14 h, 14% (**2z**) from **1z**[d]
2 h, 20% (**2z**) from **2z'**

14 h, 52% (**2z'**)[d]

[a] Reaction conditions: **1** (1 equiv), $Pd(OAc)_2$ (10 mol%), **L4** (10 mol%), and NaOAc (1 equiv) in mesitylene (0.1 M) at 100 °C under aerobic conditions. Isolated yields are provided. Other regioisomers (e.g., **3a**) were obtained in 0-25% yields. [b] In mesitylene and 1,2-dichlorobenzene (1:2, 0.1 M). [c] Debrominated product **2a** was obtained in 9% yield. [d] After 12 h, another 10 mol% $Pd(OAc)_2$ and **L4** were added.

10.1002/adsc.201801265



Scheme 2.

yl **1z** provided predominantly a mono cyclized product **2z'** in 52% yield along with the fused pentacyclic indolo[2,3-*b*]carbazol-6-ol **2z** in 14% yield. Resubjecting **2z'** to the standard reaction conditions still gave only 20% yield of **2z** together with mostly recovered **2z'**; however, particularly noteworthy is the regioselective formation of both C-N bonds at two *ortho* positions to a hydroxyl group leading to only **2z** without detectable formation of the other regioisomer.

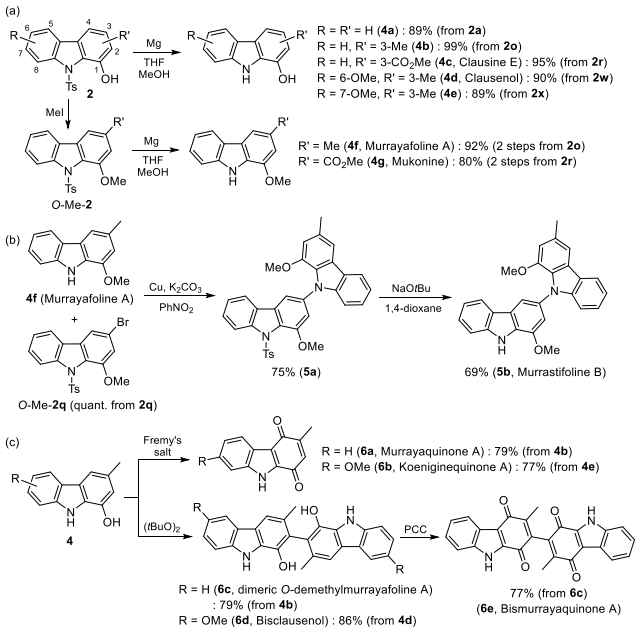
Mild reaction conditions and the use of air as the sole sustainable oxidant in the absence of additional strong oxidant ensure the hydroxyl group remains intact as well as good functional-group tolerance. Notably, exclusive or predominant formation of **2u** and **2v** from C2'-chlorinated and brominated substrates **1u** and **1v**, respectively, demonstrates this new protocol is complementary to the Pd-catalyzed Buchwald–Hartwig amination/cyclization, and the remaining halide would be a useful handle for further transformations (Scheme 2b).

Although an ester moiety at the C5'-position of **1r** is a potential secondary directing group, **2r** was obtained as the sole product, showing a non-directing effect of the ester moiety of **1r** in this reaction. As the aforementioned outcome of *O*-Me-**1a**, when there are both methoxy and hydroxyl substituents at the two *meta* positions as in substrate **1n**, C-H functionalization took place selectively at the position *ortho* to the hydroxyl and *para* to the methoxy group, providing **2n** as the only product (Scheme 2a). Furthermore, in the case of substrate **1aa**, C-N bond formation occurred predominantly at the hydroxyl-substituted benzene ring (**2aa**/**3aa**) rather than the non-substituted benzene ring (**2aa'**), although the regioselectivity for **2aa** and **3aa** decreased probably due to steric hindrance (i.e., proximal 3 substituents, Ts, OH, and Ph in **2aa**) (Scheme 2c). All of these findings suggest that a free hydroxyl group at the C3'-position of **1** as a secondary directing group plays a crucial role in the high reactivity and regioselectivity for **2**.

Finally, the compatibility of this method with the previous C-H etherification[17b-c, 19f] was examined. **1t** was selectively converted to 1- and 3-hydroxy-2-phenylcarbazole **2t**/**3t** in 77% overall yield with no formation of dibenzofurans (Scheme 2d). This result indicates that the hydroxyl group itself is not a sufficient primary directing group to promote C-O bond formation favorably over C-N bond formation, and thus the present method is complementary to prior methods for dibenzofuran synthesis from 2-arylphenols.

To highlight the synthetic utility of this reaction, some reactions were carried out on a larger scale (up to 2 mmol). Compared to reactions generally performed at the 0.1-0.2 mmol scale, to our delight, comparable or only marginally decreased yields were obtained.[21] Moreover, further derivatization of the 1-hydroxycarbazoles obtained from this process has been undertaken. As illustrated in Scheme 3a, deprotection of the *N*-Ts group and methylation of the hydroxyl group proceeded smoothly to give various 1-hydroxy and 1-methoxy NH-free carbazoles **4** including naturally occurring clausine E (**4c**), clausenol (**4d**), murrayafoline A (**4f**), and mukonine (**4g**). Given an intact bromo substituent in **2q** as well as easy deprotection and methylation, we envisioned the coupling reaction of *O*-methylated **2q** (*O*-Me-**2q**) with murrayafoline A (**4f**) for swift access to murrastifoline B (**5b**). In the literature, there is only one known example of the synthetic route to **5b** based on the path a strategy in Scheme 1, C-C bond formation using a superstoichiometric amount of $Pd(OAc)_2$ to construct the lower carbazole ring and a two-fold Buchwald–Hartwig coupling for the upper carbazole ring.[4a] Gratifyingly, rapid synthesis of the target molecule **5b** was successfully achieved through Ullmann-type coupling followed by removal of the *N*-Ts group (Scheme 3b). In addition, oxidation and oxidative dimerization were readily accomplished to afford the natural and non-natural carbazolequinones **6a-b**, biscarbazoles **6c-d**, and biscarbazolequinone **6e** in good yields (Scheme 3c).[10-11]

10.1002/adsc.201801265



Scheme 3. Synthetic application.

In summary, we have developed a new Pd-catalyzed aerobic intramolecular C−H amidation of *N*-Ts-2-amino-3'-hydroxylbiaryls. We have demonstrated that a dual directing group strategy allows for regioselective functionalization of the sterically more encumbered C–H bond, leading to the facile formation of 1-hydroxycarbazoles. The synthetic utility of this method in the synthesis of various carbazole alkaloids including carbazolequinones and biscarbazoles was also demonstrated. The salient features of this protocol are broad substrate scope, good functional group tolerance, high and uncommon regioselectivity, high sustainability and practicality using ambient air as a green and safe oxidant under mild conditions.

Experimental Section

General Procedure for the Pd-Catalyzed Regioselective Synthesis of 1-Hydroxy-carbazoles 2. Substrate **1** (0.1~0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.01~0.02 mmol, 10 mol%), bathocuproine (0.01~0.02 mmol, 10 mol%), and NaOAc (0.1~0.2 mmol, 1 equiv) were dissolved in mesitylene (1~2 mL, 0.1 M). The resulting mixture was stirred at 100 °C in an oil bath under aerobic conditions (in a closed vial with a screw cap). After the reaction was completed, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding 1-hydroxycarbazole product **2**. Other regioisomers (e.g., **3a**) were separable from **2** and obtained in 0-25% yields. All reactions were carried out 3-5 times repetitively and the average values of chemical yields are given.

Acknowledgements

This work was supported by both Basic Science Research Program and Nano·Material Technology Department Program through the National Research Foundation of Korea (NRF) funded by the Korea government (MSIP) (Nos. 2012M3A7B4049644, 2014-011165, 2015R1A2A2A01002559, and 2018R1A2A2A05018392).

References

[1] a) K. Liu, S. Zhang, *ACS Med. Chem. Lett.* **2015**, *6*, 894; b) Y. Hieda, M. Anraku, T. Choshi, H. Tomida, H. Fujioka, N. Hatae, O. Hori, J. Hirose, S. Hibino, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3530; c) W.-R. Chao, D. Yean, K. Amin, C. Green, L. Jong, *J. Med. Chem.* **2007**, *50*, 3412.

[2] a) I. Sieveking, P. Thomas, J. C. Estévez, N. Quiñones, M. A. Cuéllar, J. Villena, C. Espinosa-Bustos, A. Fierro, R. A. Tapia, J. D. Maya, R. López-Muñoz, B. K. Cassels, R. J. Estévez, C. O. Salas, *Bioorg. Med. Chem.* **2014**, *22*, 4609; b) P. H. Bernardo, C. L. L. Chai, G. A. Heath, P. J. Mahon, G. D. Smith, P. Waring, B. A. Wilkes, *J. Med. Chem.* **2004**, *47*, 4958.

[3] a) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193; b) J. Roy, A. K. Jana, D. Mal, *Tetrahedron* **2012**, *68*, 6099; c) C. Sànchez, C. Mèndez, J. A. Salas, *Nat. Prod. Rep.* **2006**, *23*, 1007; d) J.-F. Morin, M. Leclerc, D. Adès, A. Siove, *Macromol. Rapid Commun.* **2005**, *26*, 761; e) J. V. Grazulevicius, P. Strohriegl, J. Pielichowski, K. Pielichowski, *Prog. Polym. Sci.* **2003**, *28*, 1297; f) J. Cheng, K. Kamiya, I. Kodama, *Cardiovasc. Drug Rev.* **2001**, *19*, 152.

[4] Selected recent examples: a) C. Börger, A. W. Schmidt, H.-J. Knölker, *Synlett* **2014**, *25*, 1381; b) C. Börger, H.-J. Knölker, *Tetrahedron* **2012**, *68*, 6727; c) V. Sridharan, M. A. Martín, J. C. Menéndez, *Eur. J. Org. Chem.* **2009**, 4614; d) J. K. Laha, P. Petrou, G. D. Cuny, *J. Org. Chem.* **2009**, *74*, 3152; e) S. Hostyn, G. V. Baelen, G. L. F. Lemière, B. U. W. Maes, *Adv. Synth. Catal.* **2008**, *350*, 2653; f) B. Liegault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022; g) P. Bernal, J. Tamariz, *Helv. Chim. Acta* **2007**, *90*, 1449.

[5] a) V. Elumalai, C. Gambarotti, H.-R. Bjørsvik, *Eur. J. Org. Chem.* **2018**, 1984; b) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603.

[6] a) L. Ackermann, A. Althammer, P. Mayer, *Synthesis* **2009**, 3493; b) L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627; *Angew. Chem.* **2007**, *119*, 1652; c) one-pot domino reaction of 2-chloroaniline with 2-bromoanilsole derivatives: R. B. Bedford, J. G. Bowen, A. L. Weeks, *Tetrahedron* **2013**, *69*, 4389; d) one-pot domino reaction of 2-iodo-6-methoxyaniline with silylaryl triflates: Z. Liu, R. C. Larock, *Tetrahedron* **2007**, *63*, 347.

[7] a) Y. Monguchi, H. Okami, T. Ichikawa, K. Nozaki, T. Maejima, Y. Oumi, Y. Sawama, H. Sajiki, *Adv. Synth. Catal.* **2016**, *358*, 3145; b) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2015**, *17*, 1597; c) Q. Jiang, D. Duan-Mu, W. Zhong, H. Chen, H. Yan, *Chem. Eur. J.* **2013**, *19*, 1903; d) S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996; e) S. W. Youn, J. H. Bihn, B. S. Kim, *Org. Lett.* **2011**, *13*, 3738; f) D.

Kajiyama, K. Inoue, Y. Ishikawa, S. Nishiyama, *Tetrahedron* **2010**, *66*, 9779; g) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184; h) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560 and Ref. [5].

[8] Using the corresponding 2-azido- or 2-nitro-3'-methoxybiaryls instead of 2-amino-3'-methoxybiaryls: a) L. Yang, Y. Zhang, X. Zou, H. Lu, G. Li, *Green Chem.* **2018**, *20*, 1362; b) I. T. Alt, B. Plietker, *Angew. Chem. Int. Ed.* **2016**, *55*, 1519; *Angew. Chem.* **2016**, *128*, 1542; c) H. Gao, Q.-L. Xu, M. Yousufuddin, D. H. Ess, L. Kürti, *Angew. Chem. Int. Ed.* **2014**, *53*, 2701; *Angew. Chem.* **2014**, *126*, 2739; d) B. J. Stokes, B. Jovanović, H. Dong, K. J. Richert, R. D. Riell, T. G. Driver, *J. Org. Chem.* **2009**, *74*, 3225.

[9] Using the substrates containing other substituents instead of OMe at the C3'-position: a) L. Yang, H. Li, H. Zhang, H. Lu, *Eur. J. Org. Chem.* **2016**, 5611; b) L. L. Chng, J. Yang, Y. Wei, J. Y. Ying, *Chem. Commun.* **2014**, *50*, 9049; c) K. Takamatsu, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 2892; d) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; *Angew. Chem.* **2011**, *123*, 8764.

[10] Oxidation to carbazolequinones: a) F. Ji, H. Huang, M. Li, Y. Guo, C. Song, J. Chang, *Synthesis* **2018**, *50*, 3921; b) G. Bringmann, S. Tasler, *Tetrahedron* **2001**, *57*, 331; c) G. Bringmann, A. Ledermann, M. Stahl, K.-P. Gulden, *Tetrahedron* **1995**, *51*, 9353; d) T. Martin, C. J. Moody. *J. Chem. Soc. Perkin Trans 1* **1988**, 235 and Ref. [5a].

[11] Dimerization/coupling to biscarbazoles: a) C. Brütting, R. F. Fritsche, S. K. Kutz, C. Börger, A. W. Schmidt, O. Kataeva, H.-J. Knölker, *Chem. Eur. J.* **2018**, *24*, 458; b) C. Börger, O. Kataeva, H.-J. Knölker, *Org. Biomol. Chem.* **2012**, *10*, 7269; c) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth, W. Lobin, *J. Am. Chem. Soc.* **2001**, *123*, 2703; d) G. Lin, A. Zhang, *Tetrahedron* **2000**, *56*, 7163; e) G. Lin, A. Zhang, *Tetrahedron Lett.* **1999**, *40*, 341; f) G. Bringmann, A. Ledermann, G. Francois, *Heterocycles* **1995**, *40*, 293 and Refs. [4a] and [10a-b].

[12] Y. Liu, Y. Guo, F. Ji, D. Gao, C. Song, J. Chang, *J. Org. Chem.* **2016**, *81*, 4310.

[13] a) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740; *Angew. Chem.* **1997**, *109*, 1820; b) D. D. Hennings, S. Iwasa, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 2; c) D. D. Hennings, S. Iwasa, V. H. Rawal, *Tetrahedron Lett.* **1997**, *38*, 6379.

[14] Selected examples of transition-metal-catalyzed hydroxyl-directed C–H functionalization: a) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; b) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967; c) X. Wang, Y. Lu, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12203; d) Y. Lu, D.-H. Wang, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 5916.

[15] Examples of C–H activation at the more congested *ortho* position of *meta*-substituted arenes using a secondary directing group a) C.-H. Yeh, W.-C. Chen, P. Gandeepan, Y.-C. Hong, C.-H. Shih, C.-H. Cheng, *Org. Biomol. Chem.* **2014**, *12*, 9105; b) S. Ueda, H. Nagasawa, *J. Org. Chem.* **2009**, *74*, 4272.

[16] Selected reviews: a) Y. N. Timsina, B. F. Gupton, K. C. Ellis, *ACS Catal.* **2018**, *8*, 5732; b) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247; c) J. Jiao, K. Murakami, K. Itami, *ACS Catal.* **2016**, *6*, 610; d) J. Yuan, C. Liu, A. Lei, *Chem. Commun.* **2015**, *51*, 1394; e) W. A. Nack, G. Chen, *Synlett* **2015**, *26*, 2505; f) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901; g) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061.

[17] a) V. P. Reddy, G. K. S. Prakash, In *The Chemistry of Phenols*; Z. Rappoport, Ed. John Wiley & Sons, Ltd: Chichester, **2003**; b) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 9250; c) J. Zhao, Y. Wang, Y. He, L. Liu, Q. Zhu, *Org. Lett.* **2012**, *14*, 1078.

[18] Selected recent examples on C-C bond formation at the *ortho* position of phenols: a) J.-L. Dai, N.-Q. Shao, J. Zhang, R.-P. Jia, D.-H. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 12390; b) F. Zhu, Y. Li, Z. Wang, X.-F. Wu, *Angew. Chem. Int. Ed.* **2016**, *55*, 14151; *Angew. Chem.* **2016**, *128*, 14357; c) N. Battini, S. Battula, Q. N. Ahmed, *Eur. J. Org. Chem.* **2016**, 658; d) J. C. Lewis, J. Wu, R. G. Bergman, J. A. Ellman, *Organometallics* **2005**, *24*, 5737; e) R. B. Bedford, S. J. Coles, M. B Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112; *Angew. Chem.* **2003**, *115*, 116 and Refs [13b-c] and [15a].

[19] Selected recent examples on C-C/C-O bond formation at the C2'-position of 2-arylphenols: a) T. Zhou, B. Li, B. Wang, *Chem. Commun.* **2017**, *53*, 6343; b) S. Duan, Y. Xu, X. Zhang, X. Fan, *Chem. Commun.* **2016**, *52*, 10529; c) P. Finkbeiner, U. Kloeckner, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2015**, *54*, 4949; *Angew. Chem.* **2015**, *127*, 5033; d) J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 17306; e) K. Inamoto, J. Kadokawa, Y. Kondo, *Org. Lett.* **2013**, *15*, 3962; f) Y. Wei, N. Yoshikai, *Org. Lett.* **2011**, *13*, 5504 and Refs. [13a] and [17b-c]. C-C bond formation at the *peri* position of 1-naphthols: g) V. S. Thirunavukkarasu, M. Donati, L. Ackermann, *Org. Lett.* **2012**, *14*, 3416; h) S. Mochida, M. Shimizu, K. Hirano, T. Satoh, M. Miura, *Chem.- Asian J.* **2010**, *5*, 847.

[20] Selected recent examples on *ortho*-amination of free phenols involving radical mechanism or organocatalysis: a) Y. Zhao, B. Huang, C. Yang, W. Xia, *Org. Lett.* **2016**, *18*, 3326; b) M.-L. Louillat-Habermeyer, R. W. Jin, F. W. Patureau, *Angew. Chem. Int. Ed.* **2015**, *54*, 4102; *Angew. Chem.* **2015**, *127*, 4175; c) S.-G. Wang, Q. Yin, C.-X. Zhuo, S.-L. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 647; *Angew. Chem.* **2015**, *127*, 657; d) S. Brandes, M. Bella, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1147; *Angew. Chem.* **2006**, *118*, 1165.

[21] For details on optimization studies, effect of other secondary directing groups, mechanistic studies, proposed mechanism, and full list of related references, see the Supporting Information.

[22] For example, see: a) S. W. Youn, T. Y. Ko, Y. H. Jang, *Angew. Chem. Int. Ed.* **2017**, *56*, 6636; *Angew. Chem.* **2017**, *129*, 6736; b) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072; c) M. M. S. Andappan, P. Nilsson, M. Larhed, *Chem. Commun.* **2004**, 218 and Ref. [17b].

[23] Reviews: a) N. Gulzar, B. Schweitzer-Chaput, M. Klussmann, *Catal. Sci. Technol.* **2014**, *4*, 2778; b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234; c) Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381; d) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851; e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; *Angew. Chem.* **2011**, *123*, 11256.

[24] a) F. Liger, F. Popowycz, T. Besson, L. Picot, C. M. Galmarini, B. Joseph, *Bioorg. Med. Chem.* **2007**, *15*, 5615; b) K. Ueshima, H. Akihisa-Umeno, A. Nagayoshi, S. Takakura, M. Matsuo, S. Mutoh, *Biol. Pharm. Bull.* **2005**, *28*, 247; c) M. Shiomi, T. Ito, *Eur. J. Pharmacol.* **2001**, *431*, 127.

10.1002/adsc.201801265

COMMUNICATION

Palladium-Catalyzed Regioselective Synthesis of 1-Hydroxycarbazoles Under Aerobic Conditions

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

So Won Youn,* Young Ho Kim, and Yoon Hyung Jo