Advanced Synthesis & Catalysis

Accepted Article

Title: tert-Butoxide-Mediated Synthesis of 3,4'-Biquinolines from 2-Aminochalcones

Authors: JIYE JEON, So Young Lee, and Cheol-Hong Cheon

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900029

Link to VoR: http://dx.doi.org/10.1002/adsc.201900029

10.1002/adsc.201900029

UPDATE

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

tert-Butoxide-Mediated Synthesis of 3,4'-Biquinolines from 2-Aminochalcones

Jiye Jeon,[a,†] So Young Lee,[a,†] and Cheol-Hong Cheon[a,*]

[a] Department of Chemistry, Korea University, 145 Anam-ro, Seoungbuk-gu, Seoul 02841
Tel: (+82)-2-3290-3147; Fax: (+82)-2-3290-3121; E-mail: cheon@korea.ac.kr
[†] These authors contributed equally to this work.

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######.((Please delete if not appropriate))

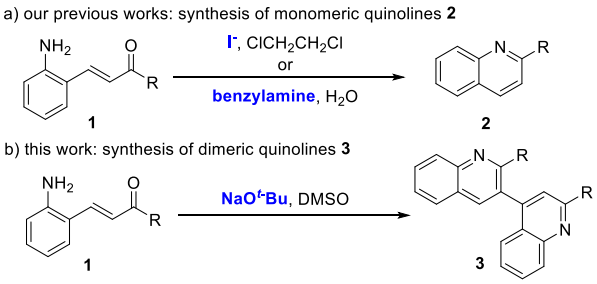
Abstract. A novel protocol to synthesize 3,4'-biquinolines from 2-aminochalcones in the presence of a stoichiometric amount of sodium *tert*-butoxide as the nucleophilic promotor was developed. Conjugate addition of *tert*-butoxide to 2-aminochalcones provided the corresponding enolates, which underwent Michael addition to another molecule of 2-aminochalcone to afford a dimeric species of 2-aminochalcones. Subsequent cyclization between the amino and carbonyl groups followed by aromatization provides 3,4'-biquinoline products. Various 2-aminochalcones were submitted to this protocol and the desired 3,4'-biquinoline products were obtained in good to high yields in a short reaction time.

Keywords: Biquinolines; 2-Aminochalcones; Nucleophilic Catalyst; tert-Butoxide; Dimerization

Biquinolines, in which two quinoline units are linked by a single bond between the two heterocyclic scaffolds, have received considerable attention due to their potential applications in medicinal chemistry and materials science: they could exhibit not only important properties of the monomeric quinoline scaffold but also potential synergic effects arising from the dimeric quinoline structure.[1,2] Consequently, several synthetic protocols for producing biquinoline derivatives have been reported.[3-6] However, these previously reported methods have been applicable to a very limited scope of biquinoline derivatives,[7] and thus the actual applications of such biquinoline compounds in medicinal chemistry and materials science have not been fully explored yet.

Our group has commenced a research program to develop novel protocols to access quinoline derivatives from readily available starting materials.[8-10] In this regard, we recently developed highly efficient protocols for the synthesis of 2-substituted quinolines **2** from 2-aminochalcones **1** using a nucleophile as the catalyst (Scheme 1a). For example, iodide was found to be an efficient catalyst for the transformation of 2-aminochalcones **1** to quinolines **2** in an organic solvent.[9a] Soon after, we also developed the on-water synthesis of quinolines **2** from the same starting materials **1** with benzylamine as the nucleophilic catalyst using water as the sole solvent.[9b]

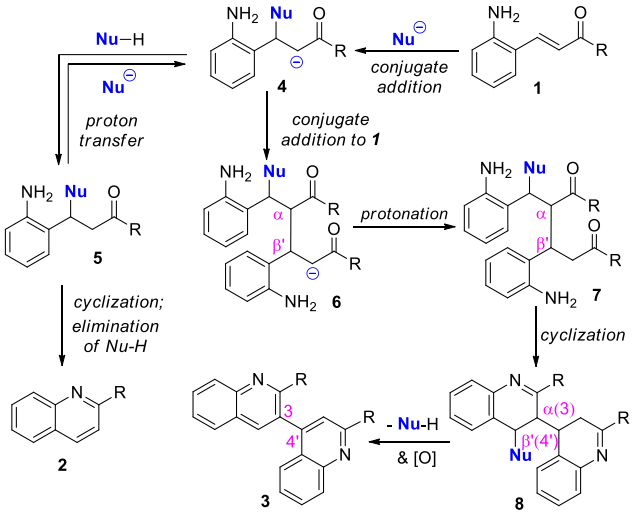
As continuing effort for the development of an efficient protocol for the synthesis of quinoline derivatives, herein, we present a new method to generate 3,4'-biquinolines **3** from 2-aminochalcones **1** using *tert*-butoxide as a nucleophilic promotor (Scheme 1b). This protocol was applied to various 2-aminochalcones **1**, leading to the desired 3,4'-biquinolines **3** in good to high yields under mild reaction conditions in short reaction times (generally less than 60 min).



Scheme 1. Nucleophile-Controlled Divergent Syntheses of Quinolines **2** and 3,4'-Biquinolines **3** from 2-Aminochalones **1**

In our previously reported synthesis of quinolines **2** from 2-aminochalcones **1** with a nucleophilic catalyst, the nucleophile undergoes conjugate addition to 2-aminochalcones **1** to give the corresponding enolates **4**, which subsequently abstract a proton to form the saturated ketones **5** bearing the nucleophile at the β-position. Condensation between the amino and carbonyl groups in **5** followed by elimination of the nucleophile would provide the desired quinoline products **2** (Scheme 2).[9,11] Based on the reaction mechanism for the synthesis of quinolines **2** from 2-aminochalcones **1**, we hypothesized that if enolates **4** underwent Michael addition to another molecule of 2-

aminochalcones **1** instead of the proton abstraction, dimeric intermediates **7** of 2-aminochalcones, connected through the C_{α}-$C_{\beta'}$ bond, would be generated after protonation. Subsequent condensations between each pair of the amino and carbonyl groups in the adjacent position would furnish partially reduced 3,4'-biquinolines **8**. Final aromatization of **8** would yield the desired 3,4'-biquinolines **3**.[12,13]

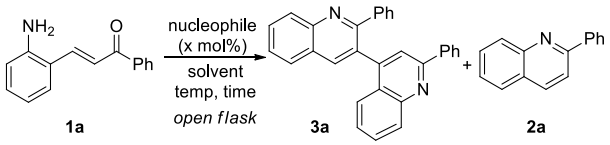


Scheme 2. Working Hypothesis for Synthesis of 3,4'-Biquinolines **3** from 2-Aminochalcones **1**

Based on this working hypothesis, we first investigated several different nucleophiles for the formation of 3,4'-biquinolines **3** over quinolines **2** from 2-aminochalcones **1** (Table 1). In particular, since the concentration of enolates **4** should be kept as high as possible to favor the conjugate addition to 2-aminochalcones **1** over proton abstraction, we first explored a nucleophile possessing relatively strong basicity as a potential catalyst in this transformation with an expectation of regeneration of enolates **4** from ketones **5** through deprotonation.[14] Interestingly, the choice of a nucleophile has a dramatic influence on the efficiency of this transformation (entries 1-4). The reactions of 2-aminochalcone **1a** with a stoichiometric amount of NaOH, NaOMe, or NaOEt in 1,2-dichloroethane (DCE) at 80 °C provided biquinoline **3a** in little or no yield (entries 1-3), while the reaction with NaOt-Bu provided a mixture of biquinoline **3a** and its 3',4'-dihydrobiquinoline analogue **3a-H$_2$** in 74% combined yield along with quinoline **2a** in 12% yield (entry 4). Next, we investigated the effect of reaction media in this transformation (entries 4-9). Interestingly, the choice of the solvent was found to exert a considerable influence on the efficiency of this transformation; a reaction in a protic solvent led to the exclusive formation of quinoline **2a** (entry 7), while those in aprotic media provided **3a** along with **2a** in a variable ratio (entries 4-6, 8-9). Among the solvents tested, the reaction in DMSO provided **3a** in the best yield without any formation of **3a-H$_2$** (entry 6), and thus DMSO was chosen as the optimal solvent for further investigation.

Next, the amount of sodium *tert*-butoxide was further examined (entries 6, 10-12). Although sodium *tert*-butoxide could be reduced to sub-stoichiometric amounts without any significant loss in the efficiency of this transformation (entry 11), we decided to use one equivalent of sodium *tert*-butoxide as the optimal amount of the nucleophile. Then, the lowering reaction temperature was observed to exert beneficial influence on the formation of **3a** over **2a**, and thus, 40 °C was chosen as the optimal reaction temperature for this transformation (entry 13). Then, we investigated the effect of the reaction atmosphere. When the reaction was performed in an argon atmosphere, biquinoline **3a** was obtained in low yield and unoxidized intermediates including **3a-H$_2$** were obtained along with unreacting starting material **1a** (entry 14). Furthermore, the effect of a counter cation in *tert*-butoxide was investigated. It was found that a counter cation in the nucleophile had little influence on the efficiency of this transformation; when potassium *tert*-butoxide was used instead of sodium *tert*-butoxide as the nucleophilic promotor, the desired product **3a** was obtained in a similar efficiency (entry 15). Although potassium *tert*-butoxide afforded **3a** in a similar yield as sodium *tert*-butoxide, sodium *tert*-butoxide was chosen as the optimal nucleophilic promotor in this transformation.

Table 1. Optimization of Reaction Parameters

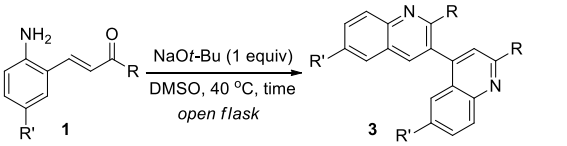


entry	nucleophile (x mol%)	solvent	temp (°C)	time (min)	yield (%)[a] 3a	2a
1	NaOH (100)	1,2-DCE	80	120	N.D.[b]	N.D.[b]
2	NaOMe (100)	1,2-DCE	80	120	18	N.D.[b]
3	NaOEt (100)	1,2-DCE	80	120	N.D.[b]	N.D.[b]
4	NaOt-Bu (100)	1,2-DCE	80	120	74[c]	12
5	NaOt-Bu (100)	DMF	80	10	54	26
6	NaOt-Bu (100)	DMSO	80	10	74	22
7	NaOt-Bu (100)	ethanol	80	10	N.D.[b]	99
8	NaOt-Bu (100)	THF	80	540	53	30
9	NaOt-Bu (100)	CH_3CN	80	30	66	26
10	NaOt-Bu (10)	DMSO	80	540	2	8
11	NaOt-Bu (50)	DMSO	80	10	72	23
12	NaOt-Bu (200)	DMSO	80	10	80	17
13	NaOt-Bu (100)	DMSO	40	30	87 (86)[d]	11
14[e]	NaOt-Bu (100)	DMSO	40	540	20	trace
15	KOt-Bu (100)	DMSO	40	30	85	10

[a] Yield was determined by ^{1}H NMR analysis of the crude mixture. [b] Not detected. [c] Combined yield of **3a** and **3a-H$_2$**. [d] Isolated yield of **3a**. [e] Under a nitrogen atmosphere.

Under these optimized reaction conditions (NaOt-Bu (100 mol%), DMSO, 40 °C, open flask), we further investigated the substrate scope of 2-aminochalcones **1** in this synthesis (Table 2). 2-Aminochalcones **1** carrying a different substituent on the phenyl ring could be applicable to this protocol and biquinolines **3** were obtained in good to high yields regardless of the position and electronic nature of the substituent (entries 1-9). Furthermore, 2-aminochalcones **1** bearing heteroaromatic and fused aromatic scaffolds also provided biquinolines **3** without any loss in the efficiency (entries 10-13). Next, the effect of a substituent on the 2-aminophenyl ring in 2-aminochalcones **1** was explored (entries 14-17). The substituent on the 2-aminophenyl ring had little influence on the efficiency of this transformation and biquinolines **3** were obtained in high yields.

Table 2. Substrate Scope of 2-Aminochalcones **1**[a]

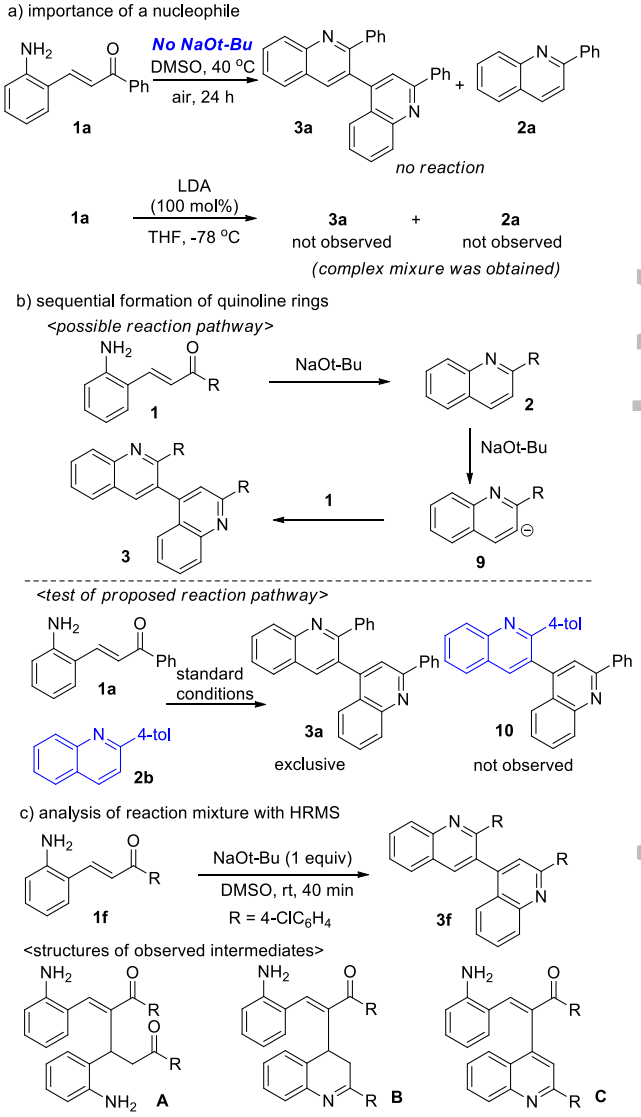


entry	biquinoline (**3**)	R	R'	time (min)	yield (%)[b]
1	**3a**	C_6H_5	H	30	86
2	**3b**	4-$MeOC_6H_4$	H	30	70
3[c]	**3c**	4-MeC_6H_4	H	10	68
4	**3d**	3-MeC_6H_4	H	30	79
5	**3e**	2-MeC_6H_4	H	30	83
6[c]	**3f**	4-ClC_6H_4	H	90	64
7	**3g**	4-BrC_6H_4	H	10	72
8	**3h**	3-BrC_6H_4	H	10	80
9	**3i**	2-BrC_6H_4	H	10	65
10	**3j**	2-furyl	H	30	82
11	**3k**	2-thienyl	H	10	85
12	**3l**	1-naphthyl	H	10	76
13	**3m**	2-naphthyl	H	10	81
14[c]	**3n**	C_6H_5	OMe	45	75
15	**3o**	C_6H_5	F	10	81
16	**3p**	C_6H_5	Cl	30	77
17[c]	**3q**	C_6H_5	Br	10	80
18	**3r**	Me	H	10	-[d]
19	**3s**	i-Pr	H	120	45
20	**3t**	t-Bu	H	30	99

[a] Reaction conditions: **1** (0.20 mmol) and NaOt-Bu (0.20 mmol) in DMSO (2.0 mL) at 40 °C in an open flask. [b] Isolated yield of **3**. [c] Reaction was carried out at 80 °C. [d] A complex mixture was obtained.

In addition, we further investigated substrates **1** bearing an alkyl group connected to the carbonyl group (entries 18-20). Unlike the aryl ketones, the structure of the alkyl group played a critical role in determining the efficiency of this transformation. In particular, ketones **1** possessing an acidic α-proton were not applicable to this protocol. For instance, methyl ketone **1r** and isopropyl ketone **1s** provided the desired products **3** in no yield and a moderate yield, respectively (entries 18 and 19). On the other hand, *tert*-butyl ketone **1t**, bearing no acidic α-proton, afforded biquinoline **3t** in a quantitative yield (entry 20).

With these results in hand, we carried out several control experiments to gain information about the reaction mechanism (Scheme 3). First, we explored the importance of the nucleophilicity of the catalyst in this transformation. When this transformation was carried out in the absence of a nucleophilic catalyst, no reaction was observed and the starting material **1a** remained intact in the reaction mixure. Furthermore, when lithium diisopropyl amide (LDA), a sterically very hindered base with little nucleophilicity, was used in place of sodium *tert*-butoxide, neither biquinoline **3a** nor quinoline **2a** was formed; instead, a complex mixture of unidentifiable products was obtained (Scheme 3a). This result suggested that the catalyst should possess a suitable nucleophilicity to promote this transformation.

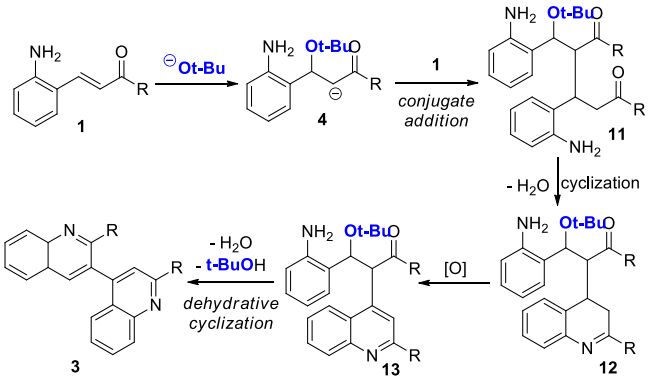


Scheme 3. Control Experiments

Next, we explored the possibility of the formation of biquinolines **3** through sequential production of quinolines **2** followed by the second quinoline ring formation at the C-3 position. Under this scenario, 2-aminochalcone **1** initially undergoes dehydrative cyclization to generate quinoline **2**. Deprotonation of the initially formed quinoline **2** with *tert*-butoxide at the C-3 position would generate 3-quinolinyl anion **9**, which would act as the nucleophilic catalyst for the second quinoline formation with 2-aminochalcone **1** leading to biquinoline **3**. To test this reaction pathway, we subjected a mixture of **1a** and **2b** to the standard reaction conditions. Under these conditions, only **3a** was observed without any formation of mixed biquinoline **10**. Based on this result, we could rule out this reaction pathway (Scheme 3b).

Furthermore, we attempted to analyze the reaction mixture by high resolution mass spectrometry (HRMS) before the reaction went to the completion (Scheme 3c). When **1f** was subjected to the standard conditions at room temperature, we did observe several compounds **A**, **B**, and **C** from HRMS analysis, which could be generated from their *tert*-butoxide adducts **11**, **12**, and **13** via elimination of *tert*-butanol during the ionization.[15,16]

Based on these experimental results, we proposed a plausible reaction mechanism for this transformation (Scheme 4). As expected, *tert*-butoxide would undergo conjugate addition to 2-aminochalcones **1** to afford enolates **4**. Conjugate addition of **4** to another molecule of **1** would afford 1,5-dicarbonyl intermediates **11**. Subsequent dehydrative cyclization between the amino and carbonyl groups would lead to intermediates **12**, which would undergo oxidation to form 2-aminochalcone derivatives **13**, bearing a quinoline ring and tert-butoxide at the α and β-positions, respectively.[17] Final dehydrative cyclization of intermediates **13** would provide the desired 3,4'-biquinolines **3**.



Scheme 4. Plausible Reaction Mechanism for the Synthesis of 3,4'-Biquinolines **3** from 2-Aminochalcones **1**

In conclusion, we developed a novel protocol for the synthesis of 3,4'-biquinoline derivatives from 2-aminochalcones using *tert*-butoxide as a nucleophilic promotor. The conjugate addition of *tert*-butoxide to 2-aminochalcones generated the corresponding enolates, which underwent conjugate addition to another molecule of the 2-aminochalcones affording dimers of the 2-aminochalcones connected through C_{α}-$C_{\beta'}$ bond. Condensation of each pair of the amino and carbonyl groups in the adjacent position followed by aromatization provided the desired 3,4'-biquinoline products. Various 2-aminochalcones could be applicable to this protocol and the desired biquinolines were obtained in good to high yields. Further application of the resulting 3,4'-biquinolines and the development of a novel protocol using a nucleophile are currently underway in our laboratory and will be reported in due course.

Experimental Section

General procedure for the synthesis of 3,4'-biquinolines 3 from 2-aminochalcones 1 (Table 2): To a solution of (*E*)-2-aminochalcone **1** (0.20 mmol) in dimethyl sulfoxide (2.0 mL) was added sodium *tert*-butoxide (19.2 mg, 0.20 mmol) at room temperature. The reaction mixture was allowed to stir at 40 °C in an open flask and monitored by TLC. After complete consumption of compound **1**, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then the crude reaction mixture was extracted with a mixture of water and ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by short flash column chromatography on silica to provide the desired biquinoline product **3**.

Acknowledgements

This work was supported by National Research Foundation of Korea (NRF) grants funded by the Korean Government (NRF-2018R1D1A1A02086110 and NRF-2014-011165, Center for New Directions in Organic Synthesis). J.J. acknowledges the financial support from an NRF-2018-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program funded by the Korean Government.

References

[1] For a review of biquinolines, see: P. J. Still, Aromatic Biheterocycles: Syntheses, Structures, and Properties. In *Advances in Heterocyclic Chemistry*; A. R. Katritzky, Ed.; Elsevier; 1996, Vol. 67, 1-117.

[2] 2,2'-Biquinolines have been used as chelating ligands and analytical reagents for copper. For recent selected examples, see: a) A. Gaál, G. Orgován, V. C. Mihucz, I. Pape, D. Ingerle, C. Streli, N. Szoboszlai, *J. Trace Elem. Med. Biol.* **2018**, *47*, 79; b) A. Kyziot, A. Cierniak, J. Gubernator, A. Markkowski, M. Jeżowska-Bojczuk, U. K. Komarnicka, *Dalton Trans.* **2018**, *47*, 1981; c) L. Wang, H. Yin, P. Cui, M. Hetu, C. Wang, S. Monro, R. D. Schaller, C. G. Cameron, B. Liu, S. Kilina, S. A. McFarland, W. Sun, *Dalton Trans.* **2017**, *46*, 8091, and references therein.

[3] For a classical example of synthesizing biquinolines via Friedlander reactions, see: R. P. Thummel, F. Lefoulon, *J. Org. Chem.* **1985**, *50*, 666.

[4] For examples of synthesis of biquinolines via the Vilsmeier–Haack reaction, see: a) T. P. Glushenko, V. I. Goncharov, A. V. Aksenov, *Chem. Heterocycl. Com.* **2008**, *44*, 973; b) A. S. Lyakhovenenko, V. V. Trifonov, V. I. Goncharov, A. V. Aksenov, *Chem. Heterocycl. Com.* **2006**, *46*, 1205.

[5] For selected examples of the synthesis of biquinolines via a homo-coupling reaction, see: a) R. Rahil, S. Sengmany, E. L. Gall, E. Léonel, *Synthesis* **2018**, *50*, 146; b) X.-W. Chen, H. Zhao, B. Xiong, H.-F. Jiang, P. H. Dixneuf, M. Zhang, *Org. Biomol. Chem.* **2017**, *15*, 6093; c) D. E. Stephens, J. Lakey-Beitia, J. E. Burch, H. D. Arman, O. V. Larionov, *Chem. Commun.* **2016**, *52*, 9945; d) W.-W. Xie, Y. Liu, R. Yuan, D. Zhao, T.-Z. Yu, J. Zhang, C.-S. Da, *Adv. Synth. Catal.* **2016**, *358*, 994, and references therein

[6] For selected examples of the synthesis of biquinolines via a cross-coupling reaction, see: a) L.-Y. Liao, X.-R. Kong, X.-F. Duan, *J. Org. Chem.* **2014**, *79*, 777; b) M. Kuriyama, S. Matsuo, M. Shinozawa, O. Onomaru, *Org. Lett.* **2013**, *15*, 2716; c) G. Verniest, X. Wang, N. D. Kimpe, A. Padwa, *J. Org. Chem*. **2010**, *75*, 424, and references therein.

[7] Most previous syntheses of biquinolines have not been designed for the preparation of biquinolines. Instead, the biquinolines were included as one of the representative examples of the protocols developed.

[8] S. H. Kwon, H.-A. Seo, C.-H. Cheon, *Org. Lett.* **2016**, *18*, 5280.

[9] a) S. Y. Lee, J. Jeon, C.-H. Cheon, *J. Org. Chem.* **2018**, *83*, 5177; b) S. Y. Lee, C.-H. Cheon, *J. Org. Chem.* **2018**, *83*, 13036.

[10] D. Y. Park, S. Y. Lee, J. Jeon, C.-H. Cheon, *J. Org. Chem.* **2018**, *83*, 12486.

[11] The Hintermann group reported a conceptually similar protocol for the synthesis of coumarins from (*E*)-2-hydroxycinnamates, see: F. Boeck, M. Blazejak, M. R. Anneser, L. Hintermann, *Beilstein J. Org. Chem.* **2012,** *8*, 1630.

[12] For biological properties of 3,4'-biquinolines, see: N. K. Shah, N. M. Shah, M. P. Patel, R. G. Patel, *J. Serb. Chem. Soc.* **2012**, *77*, 279; b) N. M. Shah, M. P. Patel, R. G. Patel, *J. Chem. Sci.* **2012**, *124*, 669.

[13] There has been only one reported protocol for the synthesis of 3,4'-biquinolines. See: M. Kuriyama, S. Matsuo, M. Shinozawa, O. Onomaru, *Org. Lett.* **2013**, *15*, 2716.

[14] Reactions with less basic nucleophiles such as pyridine and phosphines did not provide any desired biquinoline product **3a** and 2-aminochalcone **1a** remained in the reaction mixture.

[15] For details, see Supporting Information.

[16] Although fragmentations seldom occur during ionization with electron spray ionization (ESI), we could consider **A**, **B**, and **C** as possible intermediates in this transformation. Under this scenario, *tert*-buoxide should be eliminated before the cyclization, and then add to the enone moiety for the second quinoline formation. However, since this mechanism seems to be far less efficient than one shown in Scheme 4, we excluded this pathway and consider compounds **11**, **12**, and **13** as possible intermediates.

[17] In our previous studies for the synthesis of quinolines **2** from 2-aminochalcones **1**, we found that α-substituted 2-aminochalcones were also applicable to this protocol (see ref 9). Thus, we believed that the reaction mechanism proposed in Scheme 4 would be consistent with our previous results.

10.1002/adsc.201900029

UPDATE

tert-Butoxide-Mediated Synthesis of 3,4'-Biquinolines from 2-Aminochalcones

Adv. Synth. Catal. **2019**, *Volume*, Page – Page

Jiye Jeon,[a,†] So Young Lee,[a,†] and Cheol-Hong Cheon[a,*]