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Synthesis of 2-Amino-2′-hydroxy-1,1′-biaryls via Cascade Benzannulation and C−N Bond Cleavage Sequence

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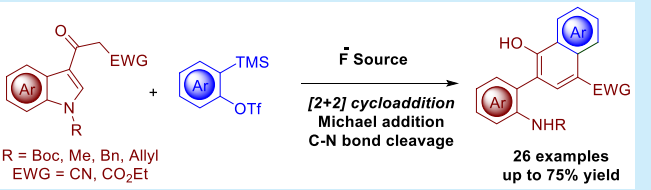
ABSTRACT: A serendipitous synthesis of N-substituted 2-amino-2′-hydroxy-1,1′-biaryls through an aryne annulation with indolyl β-ketonitrile/ester in a cascade manner is demonstrated. The reaction sequence involves benzyne-mediated [2 + 2] Stoltz-type cycloaddition−cleavage and intramolecular Michael addition followed by C−N bond cleavage under transition-metal-free reaction conditions. Interestingly, while [4 + 2] Diels−Alder reaction is a possible pathway, no traces of the regioisomer was isolated.



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Functionalized biaryl structural motifs are found in a variety of natural products including bioactives and catalysts. They have a wide range of applications in pharmaceuticals, agrochemicals, and novel organic materials such as liquid crystals and conducting polymers.[1] The presence of hindered C−C bond rotation in biaryl compounds (e.g., BINAP, BINOL, NOBIN, and their derivatives, etc.) imparts them the property of becoming excellent ligands in asymmetric catalysis and chiral drugs (Figure 1) such as TMC-95A, (*R*)-streptonigrin, etc.[2] Most of the axially chiral biaryls have naphthalene rings connected by a rotationally restricted bond or naphthalene/indole ring connected to a substituted benzene ring with rotational restriction.

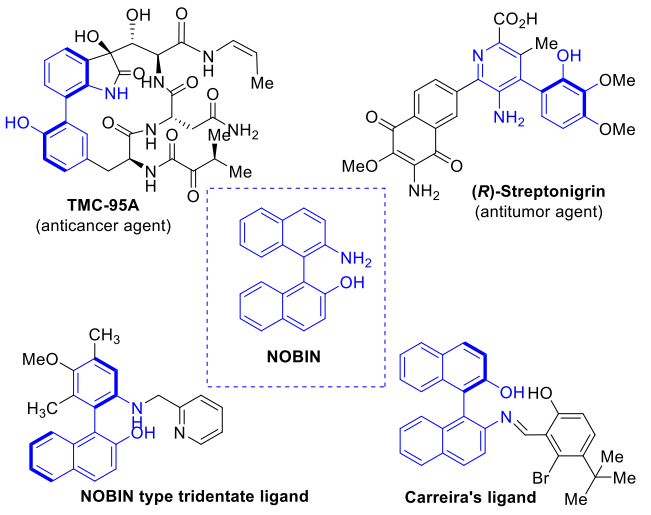

Figure 1. Representative examples of biaryl motif ligands and bioactive compounds.

The methods for the synthesis of this class of compounds include transition-metal-catalyzed cross couplings (e.g., Mizoroki−Heck, Suzuki−Miyaura, etc.), C−H oxidative direct arylation, acid-mediated reactions, etc. with the use of a naphthalene core as one of the partners.[3−5] The naphthalene partner is usually obtained from coal tar or by annulation of benzyne through a cycloaddition process.[6−8] Recently, Shu et al. have demonstrated the use of a multicomponent reaction to initiate Stoltz's β-keto ester insertion to benzyne, followed by cycloaddition to generate a substituted naphthalene skeleton (Scheme 1a).[9] Dubrovskiy and Larock were able to synthesize chromanones and flavanones via an aryne insertion/annulation strategy (Scheme 1b).[10] Our research group has been engaged in developing new applications for Stoltz's β-keto ester insertion onto arynes.[11] Toward this end, we envisaged that β-keto ester/nitrile appended onto the indole ring allowing the insertion−Michael addition−aromatize deamination (C−N bond cleavage)[12] reaction sequence to provide 2-amino-2′-hydroxy-1,1′-biaryl skeleton **3** under transition-metal-free catalysis (path A) (Scheme 1c). The formation of biaryl skeleton **3′** is also possible if the reaction goes through [4 + 2] cycloaddition followed by aromatization via C−N bond cleavage[13] (path B) (Scheme 1c). Pleasantly, we encountered the formation of biaryl **3** exclusively, indicating that Stoltz's β-

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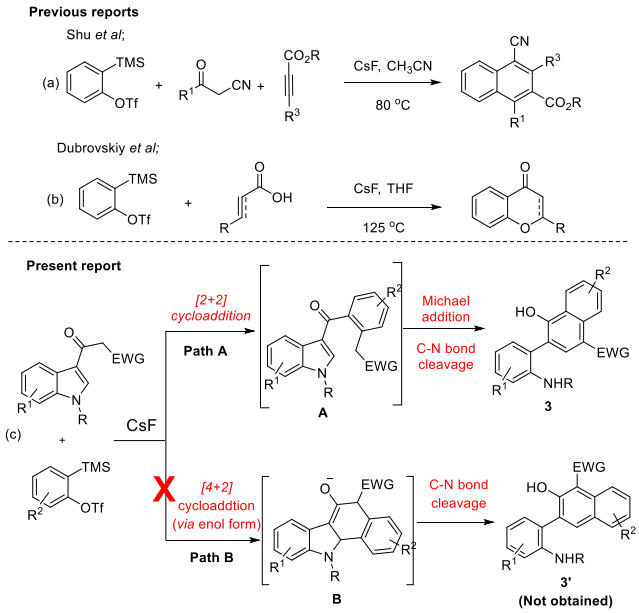
Scheme 1. Previous and Present Aryne Insertion/Annulation

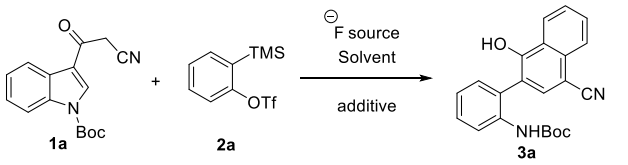


keto ester/nitrile insertion onto arynes is dominating against the inverse Diels−Alder reaction in the present annulation reaction conditions. The product thus obtained has an electron-withdrawing group and electron-donating phenol group para to each other instead of ortho to each other if the reaction has to operate by [4 + 2] cycloaddition. The details are presented herein.

Initially, the cascade aryne annulation reaction of in situ generated benzyne from **2a** with *N*-Boc indole *β*-ketonitrile **1a** was carried out in THF as solvent using 3.0 equiv of CsF as a fluoride source at 60 °C. To our delight, the desired product **3a** was obtained in 68% yield (Table 1, entry 1). The optimization of conditions was attempted to improve the yield. The yield of the product **3a** slightly increased with the addition of 18-crown-6 to reaction mixture (Table 1, entry 2). We did not observe any improvement of yield with 1.5 equiv of benzyne precursor **2a** (Table 1, entry 3). However, the reaction with different fluoride sources such as KF and TBAF failed to improve the yield (Table 1, entries 4−6). Screening of solvents such as acetonitrile, 1,4-dioxane, and toluene were found to be inefficient to increase the product yield when compared to the THF (Table 1, entries 7−9). Increasing the reaction temperature led to a decrease in the product yield (Table 1, entry 10). Control experiments revealed that temperatures higher than ambient and CsF were needed for the present cascade aryne annulation reaction (Table 1, entries 11−13). Overall, a combination of *N*-Boc indole *β*-ketonitrile **1a** (1.0 equiv), aryl triflate **2a** (1.2 equiv), CsF (3.0 equiv), and 18-crown-6 (3.0 equiv) in THF at 60 °C for 16 h were found to be the optimum reaction conditions.

With the optimized conditions in hand, we then examined the scope of present cascade reaction with a variety of substitution patterns. As summarized in Table 2, the annulation of *N*-Boc indole *β*-ketonitrile **1** with arynes proceeded smoothly, irrespective of substitution patterns on both substrates. The reaction with dimethyl-substituted aryne participated in the aryne annulation reaction smoothly to provide the desired compound **3b** in 56% yield. Moreover,

Table 1. Optimization of Reaction Conditions[a]



entry	fluoride source	additive[b]	solvent	yield[c] (%)
1	CsF		THF	68
2	CsF	18-crown-6	THF	72
3[d]	CsF	18-crown-6	THF	72
4	KF		THF	56
5	KF	18-crown-6	THF	63
6	TBAF		THF	[e]
7	CsF		CH_3CN	64
8	CsF		1,4-dioxane	58
9	CsF		Toluene	48
10[f]	CsF	18-crown-6	THF	51
11[g]	CsF	18-crown-6	THF	20
12[h]	CsF	18-crown-6	THF	
13[i]			THF	

[a]Standard reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), and fluoride source (3.0 equiv) in solvent (0.1 M) at 60 °C for 16 h. [b]3.0 equiv used. [c]Yield of isolated product. [d]1.5 equiv of **2a** used. [e]Complex mixture. [f]Reaction performed at 80 °C. [g]Reaction time 3 h. [h]Reaction performed at room temperature. [i]Without CsF.

methoxy-substituted arynes also tolerated the reaction conditions well to produce the corresponding compounds **3c** and **3d** in good yields. The electron-poor difluoro-substituted aryne gave slightly lower yield (Table 2, entry **3e**). Further, we turned our attention to examine the substitutions on phenyl ring in *N*-Boc indole *β*-ketonitrile **1**. The halogen-substituted indoles **1** (6-Cl, 5-Br and 4-Br), also underwent the reaction, without any electronic effect, to deliver the required compounds **3f−3n** in good yields (59−72%). The compound with an electron-donating group on indole **1** (5-OMe) also participated in the reaction very well to provide the desired compound in good yield (Table 2, entry **3o**). Notably, 2-methyl-substituted indole **1** delivered the corresponding product **3p** in 58% yield without any steric hindrance. The reaction of unsymmetrical aryne precursors such as 3-methoxy aryl triflate, 3-methoxy-5-methyl aryl triflate, and naphthyl triflate provided the regioisomeric products that are consistent with the literature reports.[14] The molecular structure of a representative compound **3a** was confirmed by single-crystal X-ray crystallography (Table 2).

To expand further the scope of the present annulation, reaction of *N*-alkyl indole *β*-ketonitrile **1** with benzyne precursors **2** were investigated. Under optimized reaction conditions, *N*-methyl indole *β*-ketonitrile **1g** with benzyne precursor **2a** resulted in a mixture of the insertion product **5** and arylation product **6** (Scheme 2a). The reason might be the less electrophilic nature of C-2 position in *N*-methyl indole compared to *N*-Boc indole due to the inductive effect of corresponding groups. To overcome this problem, reaction temperature was increased to 105 °C and 1,4-dioxane was used as a solvent, which furnished the desired product **3q** in good yield (Scheme 2b). Next, we investigated the generality of the reaction with respect to diversely substituted alkyl indoles (Table 3). The substitutions such as methyl, benzyl, and allyl groups on indole nitrogen were well tolerated and afforded the

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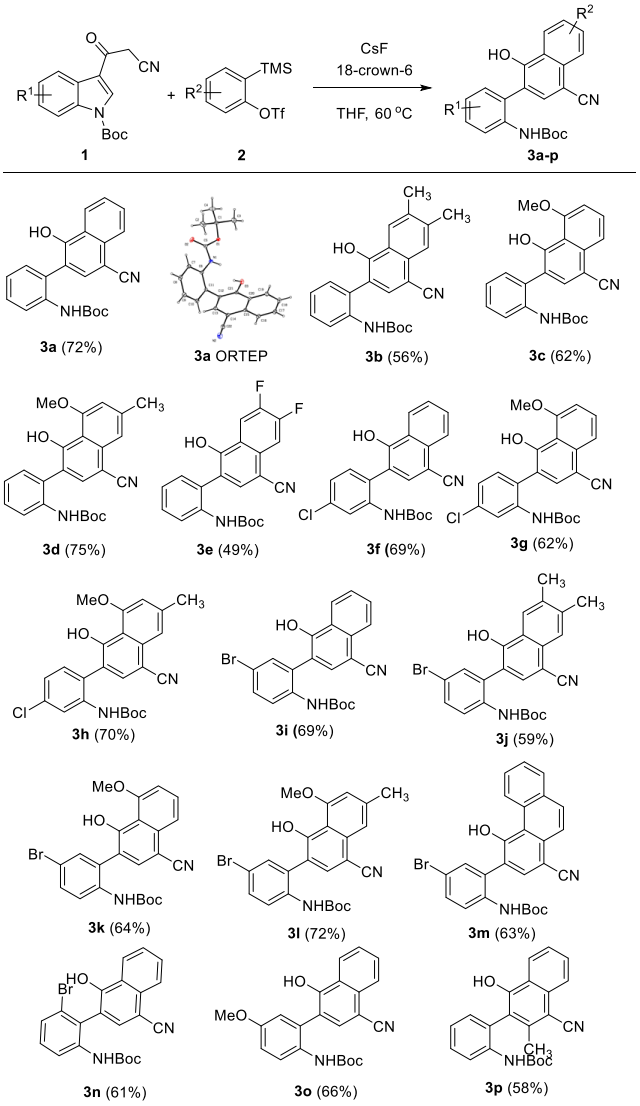
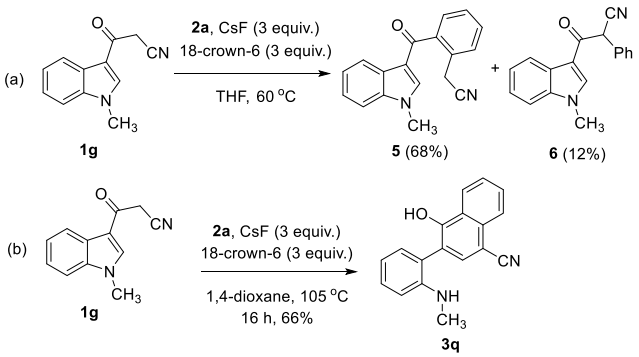
Table 2. Substrate Scope of *N*-Boc-indole (1) and Benzyne Precursors (2)[a,b]



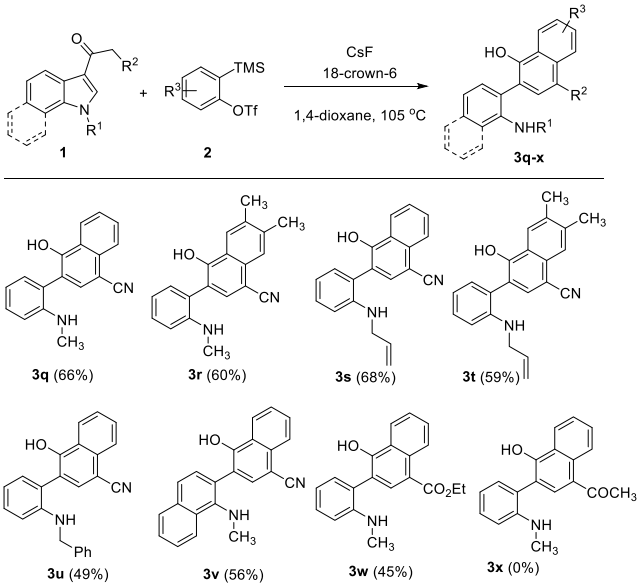
[a]Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), CsF (3.0 equiv), and 18-crown-6 (3.0 equiv) in THF (0.1 M) at 60 °C for 16 h. [b]Yield of isolated product.

Scheme 2. Reaction of *N*-Methylindole (1g) and Aryl Triflate (2a)



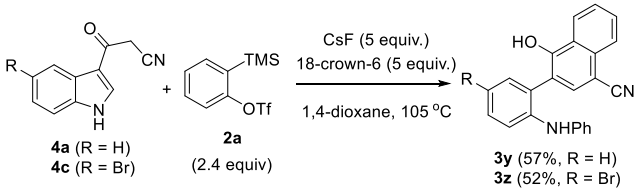
corresponding biaryls **3q**–**3u** in good yields (49–68%). The benzo[*g*]indole *β*-ketonitrile involved in aryl annulation provided the binaphthyl product **3v** in 56% yield. The indole having a *β*-ketoester also participated well and gave the desired product **3w** in 45% yield, while the indole having 1,3-diketone failed to produce the desired product **3x**.[15] It is worth mentioning that when the reaction was performed with indole *β*-ketonitrile **4** without *N*-protection in the presence of excess benzyne precursor **2a**, the desired biaryl products with *N*-arylation **3y** and **3z** were observed in 57% and 52% yields, respectively (Scheme 3).

Table 3. Substrate Scope of *N*-Alkylindole (1) and Benzyne Precursors (2)[a,b]



[a]Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), CsF (3.0 equiv), and 18-crown-6 (3.0 equiv) in 1,4-dioxane (0.1 M) at 105 °C for 16 h. [b]Yield of isolated product.

Scheme 3. Reaction of Indole (4) and Aryl Triflate (2a)



A gram-scale synthesis of compound **3a** was also demonstrated in Scheme 4a. To see the distribution of deuterium atoms in the product, a control experiment was performed using 2 equiv of D_2O in the reaction mixture, and no deuterium incorporation was found in the product (Scheme 4b). Further, an aryne insertion intermediate **5** was converted to compound **3q** under standard conditions in 81% yield (Scheme 4c). It clearly indicated that the reaction is going through *β*-ketonitrile insertion onto arynes. Based on the outcome of above experiment (Scheme 4c) and known literature,[6,8] a plausible reaction mechanism was proposed (Scheme 5). The mechanism involves the [2 + 2] cycloaddition of transient benzyne **A**, generated in situ from *o*-silyl aryl triflate **2a** and *N*-Boc indole *β*-ketonitrile **1a** to give a strained four membered ring intermediate, **B**. The ring opening of intermediate **B** generates the insertion product **C**, which would further undergo intramolecular Michael addition to give tetracyclic intermediate **D**, followed by aromatization via C–N

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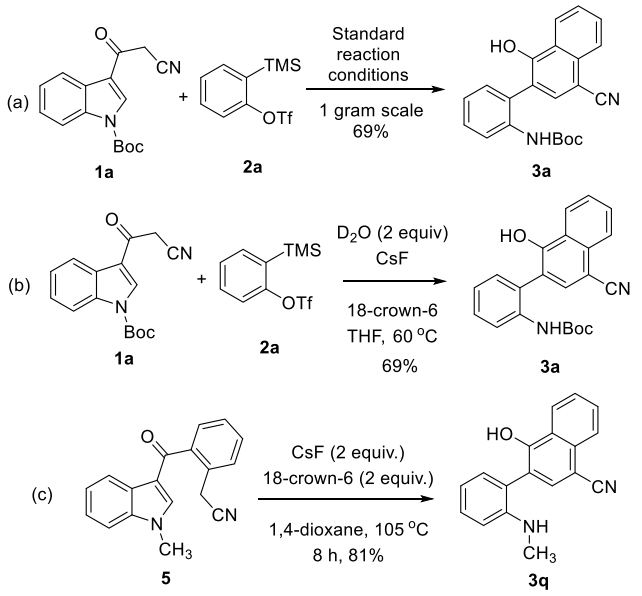
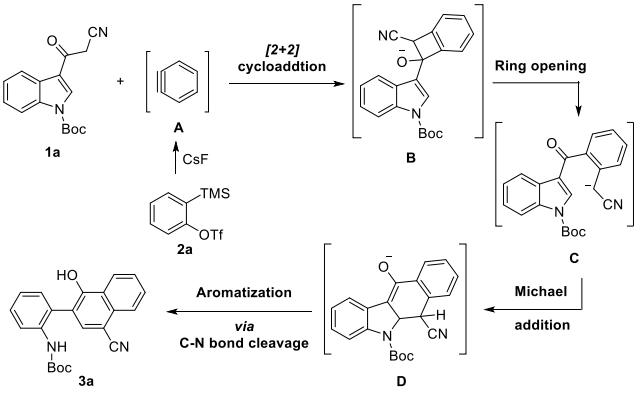
Scheme 4. Gram-Scale Synthesis and Control Experiments



Scheme 5. Plausible Mechanism



bond cleavage leads to *N*-Boc-2-amino-2′-hydroxy-1,1′-biaryl **3a**.

In summary, we have developed a simple protocol for the synthesis of *N*- substituted-2-amino-2′-hydroxy-1,1′-biaryls using a one pot aryne annulation strategy. Intramolecular Michael addition and subsequent C−N bond cleavage are key reactions in this annulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02749.

Experimental procedures, characterization details, ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2009564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coord. Chem. Rev.* **2016**, *308*, 131. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (c) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) (a) Lu, S.; Ng, S. V. H.; Lovato, K.; Ong, J.-Y.; Poh, S. B.; Ng, X. Q.; Kürti, L.; Zhao, Y. *Nat. Commun.* **2019**, *10*, 3061. (b) Lebedev, Y.; Polishchuk, I.; Maity, B.; Guerreiro, M. D. V.; Cavallo, L.; Rueping, M. *J. Am. Chem. Soc.* **2019**, *141*, 19415. (c) Uraguchi, D.; Nakashima, D.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7242. (d) Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 8716. (e) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (f) Ding, K.; Li, X.; Ji, B.; Guo, H.; Kitamura, M. *Curr. Org. Synth.* **2005**, *2*, 499.

https://dx.doi.org/10.1021/acs.orglett.0c02749
Org. Lett. XXXX, XXX, XXX−XXX

(g) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213.

(3) Selected reviews on biaryl syntheses: (a) Zhang, Y.-F.; Shi, Z.-J. *Acc. Chem. Res.* **2019**, *52*, 161. (b) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977; *Angew. Chem.* **1990**, *102*, 1006.

(4) (a) Zhu, S.; Chen, Y.-H.; Wang, Y.-B.; Yu, P.; Li, S.-Y.; Xiang, S.-H.; Wang, J.-Q.; Xiao, J.; Tan, B. *Nat. Commun.* **2019**, *10*, 4268. (b) Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L.; Xu, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5202. (c) Cheng, D.-J.; Yan, L.; Tian, S.-K.; Wu, M.-Y.; Wang, L.-X.; Fan, Z.-L.; Zheng, S.-C.; Liu, X.-Y.; Tan, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 3684; *Angew. Chem.* **2014**, *126*, 3758.

(5) Selective references for the synthesis of NOBIN and its derivatives: (a) Yuan, H.; Du, Y.; Liu, F.; Guo, L.; Sun, Q.; Feng, L.; Gao, H. *Chem. Commun.* **2020**, *56*, 8226. (b) Guo, L.; Liu, F.; Wang, L.; Yuan, H.; Feng, L.; Lu, H.; Gao, H. *Org. Chem. Front.* **2020**, *7*, 1077. (c) Ding, W.-Y.; Yu, P.; An, Q.-J.; Bay, K. L.; Xiang, S.-H.; Li, S.; Chen, Y.; Houk, K. N.; Tan, B. *Chem.* **2020**, *6*, 2046. (d) Guo, L.; Liu, F.; Wang, L.; Yuan, H.; Feng, L.; Kürti, L.; Gao, H. *Org. Lett.* **2019**, *21*, 2894. (e) Qi, L.-W.; Li, S.; Xiang, S.-H.; Wang, J.; Tan, B. *Nat. Catal.* **2019**, *2*, 314. (f) Yang, G.; Guo, D.; Meng, D.; Wang, J. *Nat. Commun.* **2019**, *10*, 3062. (g) Chang, X.; Zhang, Q.; Guo, C. *Org. Lett.* **2019**, *21*, 4915. (h) Forkosh, H.; Vershinin, V.; Reiss, H.; Pappo, D. *Org. Lett.* **2018**, *20*, 2459. (i) Chen, Y.-H.; Qi, L.-W.; Fang, F.; Tan, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 16308; *Angew. Chem.* **2017**, *129*, 16526. (j) Gao, H.; Xu, Q.-L; Keene, C.; Yousufuddin, M.; Ess, D. H.; Kürti, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 566; *Angew. Chem.* **2016**, *128*, 576. (k) Berkessa, S. C.; Clarke, Z. J. F.; Fotie, J.; Bohle, D. S.; Grimm, C. C. *Tetrahedron Lett.* **2016**, *57*, 1613. (l) Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11041; *Angew. Chem.* **2014**, *126*, 11221. (m) Shirakawa, S.; Wu, X.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 14200; *Angew. Chem.* **2013**, *125*, 14450. (n) Gao, H.; Ess, D. H.; Yousufuddin, M.; Kürti, L. *J. Am. Chem. Soc.* **2013**, *135*, 7086. (o) Chandrasekharam, M.; Chiranjeevi, B.; Gupta, K. S. V.; Sridhar, B. *J. Org. Chem.* **2011**, *76*, 10229. (p) Singer, R. A.; Brock, J. R.; Carreira, E. M. *Helv. Chim. Acta* **2003**, *86*, 1040. (q) Korber, K.; Tang, W.; Hu, X.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 7163. (r) Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. - Eur. J.* **1999**, *5*, 1734. (s) Smrcina, M.; Vyskocil, S.; Polivkova, J.; Polakova, J.; Kocovsky, P. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1520.

(6) Selected references for aryne review: (a) Roy, T.; Biju, A. T. *Chem. Commun.* **2018**, *54*, 2580. (b) Bhojgude, S. S.; Bhunia, A.; Biju, A. T. *Acc. Chem. Res.* **2016**, *49*, 1658. (c) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520; *Angew. Chem.* **2012**, *124*, 1550. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (e) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (f) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (g) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (h) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502; *Angew. Chem.* **2003**, *115*, 518. (i) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.

(7) Selected references for aryne annulation: (a) John, J.; Omanakuttan, V. K.; Aneeja, T.; Suresh, C. H.; Jones, P. G.; Hopf, H. *J. Org. Chem.* **2019**, *84*, 5957. (b) Singh, R.; Nagesh, K.; Yugandhar, D.; Prasanthi, A. V. G. *Org. Lett.* **2018**, *20*, 4848. (c) Neog, K.; Das, B.; Gogoi, P. *Org. Biomol. Chem.* **2018**, *16*, 3138. (d) Gouthami, P.; Chavan, L. N.; Chegondi, R.; Chandrasekhar, S. *J. Org. Chem.* **2018**, *83*, 3325. (e) Thangaraj, M.; Bhojgude, S. S.; Jain, S.; Gonnade, R. G.; Biju, A. T. *J. Org. Chem.* **2016**, *81*, 8604. (f) Gesu, A.; Pozzoli, C.; Torre, E.; Aprile, S.; Pirali, T. *Org. Lett.* **2016**, *18*, 1992. (g) Shu, W.-M.; Zheng, K.-L.; Ma, J.-R.; Wu, A.-X. *Org. Lett.* **2016**, *18*, 3762. (h) Shu, W.-M.; Ma, J.-R.; Zheng, K.-L.; Wu, A.-X. *Org. Lett.* **2016**, *18*, 196. (i) Bhunia, A.; Kaicharla, T.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2014**, *50*, 11389. (j) Liu, F.-L.; Chen, J.-R.; Zou, Y.-Q.; Wei, Q.; Xiao, W.-J. *Org. Lett.* **2014**, *16*, 3768. (k) Ma, Z.-X.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 2742. (l) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488; *Angew. Chem.* **2011**, *123*, 4580. (m) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525. (n) Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, *2008*, 1159. (o) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

(8) Selected references for aryne insertion−annulation: (a) Singh, S.; Samineni, R.; Pabbaraja, S.; Mehta, G. *Tetrahedron* **2019**, *75*, 2923. (b) Ghotekar, G. S.; Shaikh, A. C.; Muthukrishnan, M. *J. Org. Chem.* **2019**, *84*, 2269. (c) Hu, W.; Zhang, C.; Huang, J.; Guo, Y.; Fu, Z.; Huang, W. *Org. Lett.* **2019**, *21*, 941. (d) Welin, E. R.; Ngamnithiporn, A.; Klatte, M.; Lapointe, G.; Pototschnig, G. M.; McDermott, M. S. J.; Conklin, D.; Gilmore, C. D.; Tadross, P. M.; Haley, C. K.; Negoro, K.; Glibstrup, E.; Grünanger, C. U.; Allan, K. M.; Virgil, S. C.; Slamon, D. J.; Stoltz, B. M. *Science* **2019**, *363*, 270. (e) Takikawa, H.; Nishii, A.; Suzuki, K. *Synthesis* **2016**, *48*, 3331. (f) Kranthikumar, R.; Chegondi, R.; Chandrasekhar, S. *J. Org. Chem.* **2016**, *81*, 2451. (g) Okuma, K.; Horigami, K.; Nagahora, N.; Shioj, K. *Synthesis* **2015**, *47*, 2937. (h) Okuma, K.; Hirano, K.; Tanabe, Y.; Itoyama, R.; Miura, A.; Nagahora, N.; Shioji, K. *Chem. Lett.* **2014**, *43*, 492. (i) Okuma, K.; Itoyama, R.; Sou, A.; Nagahora, N.; Shioj, K. *Chem. Commun.* **2012**, *48*, 11145. (j) Allan, K. M.; Hong, B. D.; Stoltz, B. M. *Org. Biomol. Chem.* **2009**, *7*, 4960. (k) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (l) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.

(9) Shu, W.-M.; Liu, S.; He, J.-X.; Wang, S.; Wu, A.-X. *J. Org. Chem.* **2018**, *83*, 9156.

(10) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

(11) Kallepu, S.; Sanjeev, K.; Chegondi, R.; Mainkar, P. S.; Chandrasekhar, S. *Org. Lett.* **2018**, *20*, 7121.

(12) Selected references for indole C−N bond cleavage: (a) Uruvakili, A.; Swamy, K. C. K. *Org. Biomol. Chem.* **2019**, *17*, 3275. (b) Lvov, A. G.; Shirinian, V. Z.; Zakharov, A. V.; Krayushkin, M. M.; Kachala, V. V.; Zavarzin, I. V. *J. Org. Chem.* **2015**, *80*, 11491.

(13) One example of [4 + 2] cycloaddition followed by aromatization via indole C−N bond cleavage has been reported; see: Tao, Y.; Zhang, F.; Tang, C.-Y.; Wu, X.-Y.; Sha, F. *Asian J. Org. Chem.* **2014**, *3*, 1292.

(14) (a) Mirzaei, S.; Khosravi, H. *Tetrahedron Lett.* **2017**, *58*, 3362. (b) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(15) Reaction of arynes with aroylacetones leads to formation of 4-aryl-2-naphthols and 3-aryl-1-naphthols via aryne insertion followed by an intramolecular aldol reaction and dehydration; see: Okuma, K.; Itoyama, R.; Sou, A.; Nagahora, N.; Shioj, K. *Chem. Commun.* **2012**, *48*, 11145.

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