ACES Asian Chemical Editorial Society

doi.org/10.1002/asia.202100710

CHEMISTRY AN ASIAN JOURNAL Communication

I_2-Promoted Intramolecular Oxidative Cyclization of Butenyl Anilines: A Facile Route to Benzo[*b*]azepines

Zhenyu An[+],[a] Yi Ren[+],[a] Yafeng Liu,[b] and Rulong Yan*[a]

Abstract: A metal-free approach for the synthesis of seven-membered *N*-heterocycles has been developed by the I_2-promoted intramolecular cross-coupling/annulation of butenyl anilines. This cyclization reaction involves C–H activation and C–C bond formation and exhibits good functional group tolerance. A series of benzo[*b*]azepine derivatives are obtained in moderate to good yields.

Azepines, as valuable seven-membered *N*-heterocycles, are important structural motifs embedded in bioactive molecules, pharmaceuticals, and natural products.[1] In particular, benzo[*b*]azepine derivatives exhibit various bioactive and pharmaceutical properties (Figure 1),[2] such as antiparasitic activity (**I**),[3] antitumor activity (**II**),[4] nonpeptidic vasopressin V2 receptor agonist (**III**),[5] and respiratory syncytial virus inhibitor (**IV**).[6] In addition, 1-propyl-1-benzazepines (**V**) exhibit potent CCR5 antagonistic activity, which is selected as promising anti-HIV-1 agent.[7]

Due to the wide applications, continuous efforts have been focused on efficient strategies to afford benzo[*b*]azepine skeletons.[8] Recent years, a series of [*m*+*n*] cycloadditions have emerged as versatile methods to access various benzo[*b*]azepines.[9] Besides these methods, benzo[*b*]azepine skeletons could be assembled through intramolecular cross-coupling reactions,[10a–d] photocatalytic radical reactions,[10e] ring expansion reactions,[10f–g] and others.[10h–k] For instance, Wang[11] developed a method for the construction of benzo[*b*]azepines via copper-catalyzed oxidative C(sp^3)–H/C(sp^2)–H cross-coupling (Scheme 1a). Kim[12] reported the Lewis acid catalyzed synthesis of ring-fused 1-benzazepine derivatives from 2-(aryl) cyclopropane 1,1-diesters via [1,5]-hydride shift/cyclization sequences (Scheme 1b). In 2018, Shi[13] disclosed a Ni-catalyzed method for the preparation of benzo[*b*]naphtho[1,2-*d*]azepines via intramolecular cyclization of alkyl bromide-tethered alkylidenecyclopropanes (Scheme 1c). Although some approaches have been established to provide benzo[*b*]azepines, the majority of them have significant limitations, such as transition metal catalysts, multiple reaction steps, harsh conditions, and complex substrates. Thus, a facile strategy to benzo[*b*]azepines under mild conditions is still desirable.

Molecular iodine, an inexpensive and low-toxic oxidant, shows a remarkable ability to promote the oxidative cross-coupling reaction to form C–X (X = C, N, O, or S) bond.[14] In particular, I_2-mediated oxidative C–C bond formation has been proved to be an efficient method for the synthesis of heterocyclic compounds.[15] For example, Larock[16a] and Liang[16b] achieved intramolecular oxidative cross-coupling/annulation reactions through the formation of C–C bond in the presence of molecular iodine, respectively. Inspired by these

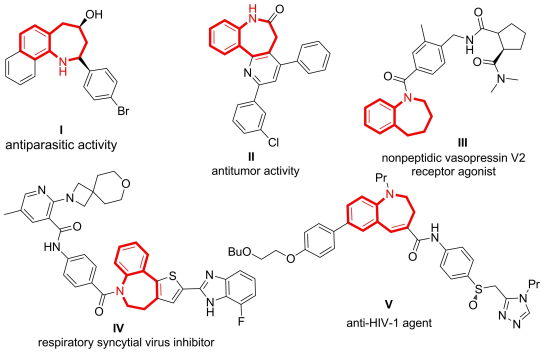
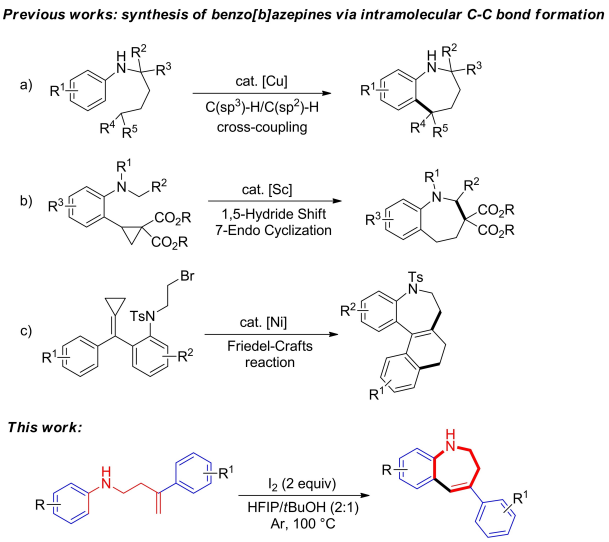


Figure 1. Bioactive compounds containing benzo[*b*]azepine core.



Scheme 1. Approaches for the synthesis of benzo[*b*]azepines.

[a] *Z. An,[+] Y. Ren,[+] Prof. Dr. R. Yan*
State Key Laboratory of Applied Organic Chemistry
Key laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province
College of Chemistry and Chemical Engineering
Lanzhou University
Lanzhou 730000 (P. R. China)
E-mail: yanrl@lzu.edu.cn

[b] *Y. Liu*
Chemical Science and Engineering College
North Minzu University
Yinchuan 750000 (P. R. China)

[+] *These authors contribute equally to this work.*

Supporting information for this article is available on the WWW under https://doi.org/10.1002/asia.202100710

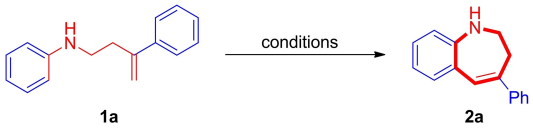
works, we report a facile approach for the synthesis of benzo[*b*] azepine derivatives from butenyl anilines through I_2-promoted intramolecular cross-coupling of two C(sp^2)–H bonds.

Initially, we attempted to optimize the reaction conditions for this I_2-promoted intramolecular cross-coupling/cyclization of *N*-(3-phenylbut-3-en-1-yl)aniline **1a**. As shown in Table 1, the reaction was conducted in the presence of I_2 (1.0 equiv) in DCE at 100 °C for 12 h under argon atmosphere. Pleasingly, the reaction proceeded smoothly to afford the desired product **2a** in 35% yield (Table 1, entry 1). The structure of **2a** was determined by X-ray diffraction analysis (see the Supporting Information for details). Next, the product **2a** was obtained in 30–48% in THF, HFIP, and CH_3CN, but no product was formed in DMF (Table 1, entries 2–5). Furthermore, some mixture solvents were screened, and the yield was increased to 60% using the mixture of HFIP/*t*BuOH (2:1) as the solvent (Table 1, entries 6–9). Either decreasing or increasing the temperature failed to improve the yield of **2a** (Table 1, entries 10–11). The reaction was unable to occur in the absence of I_2 (Table 1, entry 12), indicating that molecular iodine was essential for this reaction. Subsequently, we investigated the effect of the amount of iodine and found that when the dosage of I_2 was increased to 2.0 equiv, the yield of product **2a** was increased to 71% (Table 1, entries 13–14). However, further increase in the amount of I_2 did not lead to significant difference in the yield (Table 1, entry 15). A series of acids were screened as additives, but none of them gave a better result (Table 1, entries 16–18). Finally, the reaction was also carried out with 2.0 equiv. of I_2 in HFIP, and the product **2a** was isolated in 53% yield (Table 1, entry 19). So the optimized reaction conditions were established as Table 1, entry 14.

Based on the optimal reaction conditions, we investigated the substituent scope of this protocol by the synthesis of a variety of benzo[*b*]azepines. As shown in Scheme 2, substrates **1** with electron-donating or electron-withdrawing groups on aniline moiety performed smoothly and gave the desired products in moderate yields. These results illustrate that the electronic effect of substituents on the aniline moiety have a slight influence on the reaction. For example, substrate **1h** bearing strong electron-withdrawing group CF_3 gave the product **2h** in 46% yield. Furthermore, substrates **1i**–**1q** derived from *meta*- and *ortho*-substituted anilines produced the corresponding products **2i**–**2q** in 52–62% yields, indicating that the steric effect was negligible. Notably, disubstituted substrates **1r**–**1s** were also tolerated to afford **2r**–**2s** in moderate yields.

Encouraged by the above results, we next investigated the scope of R^2 moieties of substrates **1**, and the results are shown in Scheme 3. Under the optimized reaction conditions, substrates **1t**–**1z** with different groups on the *para*-position of the benzene ring of R^2 moieties were compatible with this transformation and generated the desired products **2t**–**2z** in moderate yields. Among them, the yields of R^2 moieties with electron-withdrawing groups were slightly higher than those with electron-donating groups. Moreover, the substrates **1aa**–**1af** with groups on both aniline moieties and R^2 moieties were also suitable for this transformation, generating desired products in 49–75% yields. Unfortunately, this method was not compatible with naphthyl substrate **1ag** and only a trace amount of **2ag** was detected.

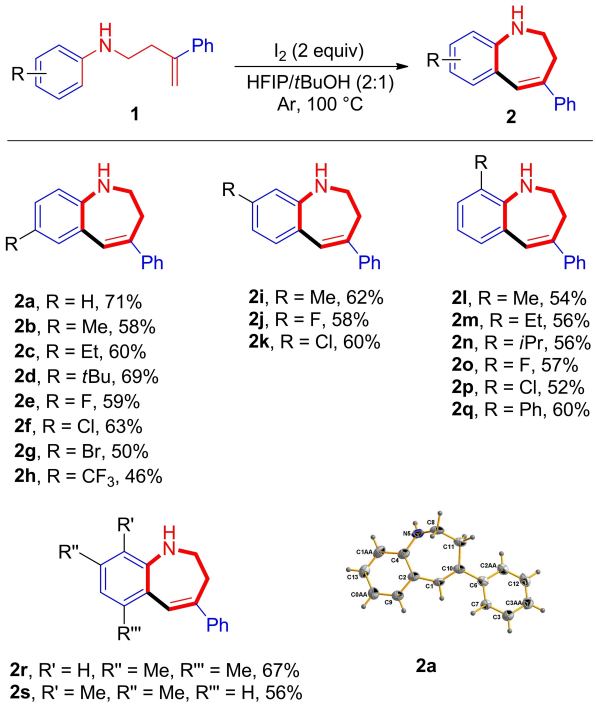
Table 1. Optimization of the reaction conditions.[a]



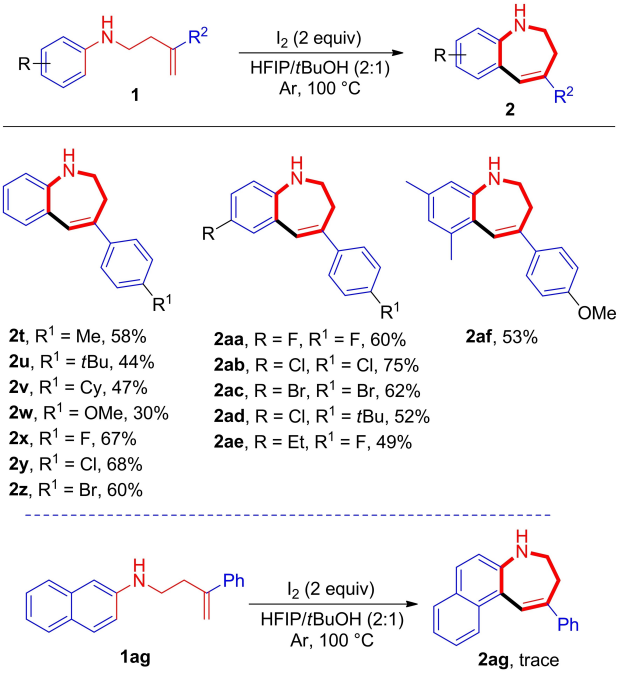
1a **2a**

Entry	I_2 [eq.]	Additive	Solvent	Temp. [°C]	Yield[b] [%]
1	1.0	–	DCE	100	35
2	1.0	–	THF	100	30
3	1.0	–	DMF	100	0
4	1.0	–	HFIP	100	48
5	1.0	–	CH_3CN	100	32
6	1.0	–	HFIP/DCE (1:1)	100	47
7	1.0	–	HFIP/THF (1:1)	100	44
8	1.0	–	HFIP/*t*BuOH (1:1)	100	55
9	1.0	–	HFIP/*t*BuOH (2:1)	100	60
10	1.0	–	HFIP/*t*BuOH (2:1)	80	54
11	1.0	–	HFIP/*t*BuOH (2:1)	120	40
12	–		HFIP/*t*BuOH (2:1)	100	0
13	1.5	–	HFIP/*t*BuOH (2:1)	100	66
14	**2.0**	**–**	**HFIP/*t*BuOH (2:1)**	**100**	**71**
15	2.5	–	HFIP/*t*BuOH (2:1)	100	69
16	2.0	CF_3COOH	HFIP/*t*BuOH (2:1)	100	43
17	2.0	$BF_3 \cdot OEt_2$	HFIP/*t*BuOH (2:1)	100	63
18	2.0	$FeCl_3$	HFIP/*t*BuOH (2:1)	100	61
19	2.0	–	HFIP	100	53

[a] Reaction conditions: **1a** (0.2 mmol), I_2, and solvent (3 mL) for 12 h under argon. [b] Isolated yield. Entry in bold highlights optimized reaction conditions, and the reaction time was monitored by TLC.

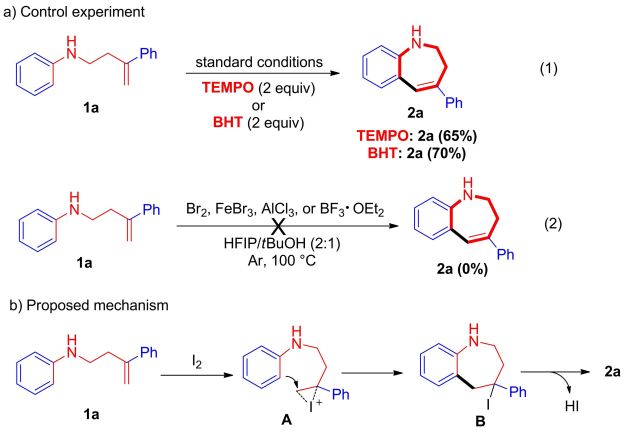


Scheme 2. Scope of substrates **1**. Reaction conditions: **1** (0.2 mmol), I_2 (0.4 mmol) in HFIP/*t*BuOH (2 mL/1 mL) at 100 °C for 12 h under argon.



Scheme 3. Scope of substrates **1**. Reaction conditions: **1** (0.2 mmol), I_2 (0.4 mmol) in HFIP/*t*BuOH (2 mL/1 mL) at 100 °C for 12 h under argon.

To verify the mechanism of this novel transformation, radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methyl phenol (BHT) were added under the standard conditions, the generation of **2a** was not suppressed (Scheme 4a-1). It can be inferred that a radical process is impossible in this transformation. When the reaction was carried out using Br_2, $FeBr_3$, $AlCl_3$, or $BF_3{\cdot}OEt$ instead of I_2 as additive, it was found that no desired product was obtained (Scheme 4a-2). This result indicated that iodine was crucial for this process. On the basis of the above results and previous reports,[16–17] a possible mechanism is outlined in Scheme 4b. Initially, iodonium intermediate **A** is generated through the coordination of C=C bond of substrate **1a** with iodine cation. Then, the aromatic ring of the aniline moiety attacks the activated double bond to form intermediate **B**. Finally, the elimination of HI produces the desired product **2a**.



Scheme 4. Radical inhibition experiment and proposed mechanism.

In conclusion, we have developed an I_2-mediated intramolecular oxidative cyclization reaction, which includes functionalization of C(sp^2)–H bond and construction of C–C bond. This atom-economical and metal-free approach provides facile access to a variety of benzo[*b*]azepine derivatives from butenyl anilines.

Acknowledgements

This work was supported by National Natural Science Foundation of China (21672086).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Butenyl anilines · Benzo[*b*]azepines · I_2-promoted · Intramolecular annulation · Metal-free

[1] a) H. Tabata, T. Yoneda, T. Oshitari, H. Takahashi, H. Natsugari, *J. Med. Chem.* **2017**, *60*, 4503–4509; b) J. A. Lowe, D. L. Hageman, S. E. Drozda, S. McLean, D. K. Bryce, R. T. Crawford, S. Zorn, J. Morrone, J. Bordner, *J. Med. Chem.* **1994**, *37*, 3789–3811; c) K. Kondo, H. Ogawa, T. Shinohara, M. Kurimura, Y. Tanada, K. Kan, H. Yamashita, S. Nakamura, T. Hirano, Y. Yamamura, T. Mori, M. Tominaga, A. Itai, *J. Med. Chem.* **2000**, *43*, 4388–4397; d) S. Loison, M. Cottet, H. Orcel, H. Adihou, R. Rahmeh, L.

Lamarque, E. Trinquet, E. Kellenberger, M. Hibert, T. Durroux, B. Mouillac, D. Bonnet, *J. Med. Chem.* **2012**, *55*, 8588–8602; e) H. Ahmed, A. Haider, J. Varisco, M. Stankovic, R. Wallimann, S. Gruber, I. Iten, S. Hane, A. M. Herde, C. Keller, R. Schibli, D. Schepmann, L. Mu, B. Wünsch, S. M. Ametamey, *J. Med. Chem.* **2019**, *62*, 9450–9470.

[2] a) J. Ryczak, M. Papini, A. Lader, A. Nasereddin, D. Kopelyanskiy, L. Preu, C. L. Jaffe, C. Kunick, *Eur. J. Med. Chem.* **2013**, *64*, 396–400; b) A. K. Singh, V. Raj, S. Saha, *Eur. J. Med. Chem.* **2017**, *142*, 244–265; c) S. G. Ayala, J. A. Castrillón, A. Palma, S. M. Leal, P. Escobar, A. Bahsas, *Bioorg. Med. Chem.* **2010**, *18*, 4721–4739; d) D. Boeglin, D. Bonnet, M. Hibert, *J. Comb. Chem.* **2007**, *9*, 487–500; e) Y. Murakami, H. Hara, T. Okada, H. Hashizume, M. Kii, Y. Ishihara, M. Ishikawa, M. Shimamura, S. Mihara, G. Kato, K. Hanasaki, S. Hagishita, M. Fujimoto, *J. Med. Chem.* **1999**, *42*, 2621–2632.

[3] A. Palma, A. F. Yépes, S. M. Leal, C. A. Coronado, P. Escobar, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2360–2363.

[4] A. Link, C. Kunic, *J. Med. Chem.* **1998**, *41*, 1299–1305.

[5] C. M. Yea, C. E. Allan, D. M. Ashworth, J. Barnett, A. J. Baxter, J. D. Broadbridge, R. J. Franklin, S. L. Hampton, P. Hudson, J. A. Horton, P. D. Jenkins, A. M. Penson, G. R. W. Pitt, P. Riviere, P. A. Robson, D. P. Rooker, G. Semple, A. Sheppard, R. M. Haigh, M. B. Roe, *J. Med. Chem.* **2008**, *51*, 8124–8134.

[6] E. A. Fordyce, D. W. Brookes, C. Lise-Ciana, M. S. Coates, S. F. Hunt, K. Ito, J. K. Underwood, S. T. Onions, G. F. Parra, G. Rapeport, V. Sherbukhin, J. A. Stockwell, P. Strong, J. C. Thomas, J. Murray, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2201–2206.

[7] a) M. Seto, N. Miyamoto, K. Aikawa, Y. Aramaki, N. Kanzaki, Y. Iizawa, M. Baba, M. Shiraishi, *Bioorg. Med. Chem.* **2005**, *13*, 363–386; b) M. Seto, K. Aikawa, N. Miyamoto, Y. Aramaki, N. Kanzaki, K. Takashima, Y. Kuze, Y. Iizawa, M. Baba, M. Shiraishi, *J. Med. Chem.* **2006**, *49*, 2037–2048.

[8] a) Z. Zuo, J. Liu, J. Nan, L. Fan, W. Sun, Y. Wang, X. Luan, *Angew. Chem. Int. Ed.* **2015**, *54*, 15385–15389; *Angew. Chem.* **2015**, *127*, 15605–15609; b) Y. Li, M. Hu, J.-H. Li, *ACS Catal.* **2017**, *7*, 6757–6761; c) F. Ling, Z. Xie, J. Chen, C. Ai, H. Shen, Z. Wang, X. Yi, W. Zhong, *Adv. Synth. Catal.* **2019**, *361*, 3094–3101; d) P. A. Wender, T. M. Pedersen, M. J. C. Scanio, *J. Am. Chem. Soc.* **2002**, *124*, 15154–15155; e) V. V. Pagar, R.-S. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4923–4926; *Angew. Chem.* **2015**, *127*, 5005–5008.

[9] a) J.-J. Feng, T.-Y. Lin, C.-Z. Zhu, H. Wang, H.-H. Wu, J. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 2178–2181; b) B. Cendon, N. Casanova, C. Comanescu, R. García-Fandiño, A. Seoane, M. Gulías, J. L. Mascareñas, *Org. Lett.* **2017**, *19*, 1674–1677; c) J. Chen, Z. Yin, Y. Huang, *Org. Lett.* **2019**, *21*, 7060–7064; d) K. Zhang, L. Cai, S. Hong, O. Kwon, *Org. Lett.* **2019**, *21*, 5143–5146; e) K. Nagaraju, R. Gurubrahamam, K. Chen, *J. Org. Chem.* **2020**, *85*, 7060–7067.

[10] a) S. Jalal, K. Bera, S. Sarkar, K. Paul, U. Jana, *Org. Biomol. Chem.* **2014**, *12*, 1759–1770; b) D. B. Ramachary, V. V. Narayana, *Eur. J. Org. Chem.* **2011**, 3514–3522; c) C.-Y. Sie, C.-P. Chuang, *Org. Biomol. Chem.* **2018**, *16*, 5483–5491; d) D. Li, Y. Park, J. Yun, *Org. Lett.* **2018**, *20*, 7526–7529; e) Y. Zhao, J.-R. Chen, W.-J. Xiao, *Org. Lett.* **2018**, *20*, 224–227; f) S. Wang, X.-D. An, S.-S. Li, X. Liu, Q. Liu, J. Xiao, *Chem. Commun.* **2018**, *54*, 13833–13836; g) S. Stockerl, T. Danelzik, D. G. Piekarski, O. G. Mancheño, *Org. Lett.* **2019**, *21*, 4535–4539; h) C. Guo, M. Fleige, D. J. Muller, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 7840–7843; i) L. Wu, Y. Meng, J. Ferguson, L. Wang, F. Zeng, *J. Org. Chem.* **2017**, *82*, 4121–4128; j) H. Qiao, S. Zhang, K. Li, Z. Cao, F. Zeng, *J. Org. Chem.* **2019**, *84*, 10843–10851; k) Y. Wang, S. Jia, E.-Q. Li, Z. Duan, *J. Org. Chem.* **2019**, *84*, 15323–15330.

[11] R. Wang, R.-X. Jin, Z.-Y. Qin, K.-J. Bian, X.-S. Wang, *Chem. Commun.* **2017**, *53*, 12229–12232.

[12] C. W. Suh, S. J. Kwon, D. Y. Kim, *Org. Lett.* **2017**, *19*, 1334–1337.

[13] B. Jiang, J.-X. Liu, Y. Wei, M. Shi, *Org. Lett.* **2018**, *20*, 6229–6233.

[14] a) P. T. Parvatkar, P. S. Parameswaran, S. G. Tilve, *Chem. Eur. J.* **2012**, *18*, 5460–5489; b) Y.-M. Ren, C. Cai, R.-C. Yang, *RSC Adv.* **2013**, *3*, 7182–7204; c) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702–711; d) W.-C. Gao, F. Hu, Y.-M. Huo, H.-H. Chang, X. Li, W.-L. Wei, *Org. Lett.* **2015**, *17*, 3914–3917; e) S. Ma, X. Hao, X. Huang, *Org. Lett.* **2003**, *5*, 1217–1219.

[15] a) Z. Lv, B. Wang, Z. Hu, Y. Zhou, W. Yu, J. Chang, *J. Org. Chem.* **2016**, *81*, 9924–9930; b) Q.-F. Yu, Y.-H. Zhang, Q. Yin, B.-X. Tang, R.-Y. Tang, P. Zhong, J.-H. Li, *J. Org. Chem.* **2008**, *73*, 3658–3661; c) X. Wu, X. Geng, P. Zhao, J. Zhang, X. Gong, Y.-D. Wu, A.-X. Wu, *Org. Lett.* **2017**, *19*, 1550–1553; d) Q. Gao, X. Wu, S. Liu, A.-X. Wu, *Org. Lett.* **2014**, *16*, 1732–1735.

[16] a) X. Zhang, M. A. Campo, T. Yao, R. C. Larock, *Org. Lett.* **2005**, *7*, 763–766; b) H.-T. Zhu, K.-G. Ji, F. Yang, L.-J. Wang, S.-C. Zhao, S. Ali, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2011**, *13*, 684–687.

[17] a) J. Barluenga, D. Palomas, E. Rubio, J. M. Gonzalez, *Org. Lett.* **2007**, *9*, 2823–2826; b) A.-Y. Peng, Y.-X. Ding, *Org. Lett.* **2004**, *6*, 1119–1121.

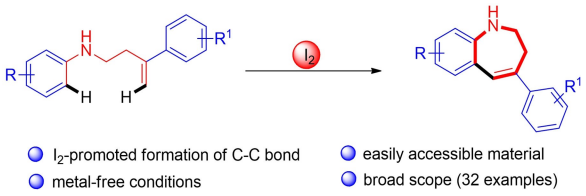
[18] For the synthesis of substrates 1 in the Supporting Information, please see: a) J. Wang, Y. Wang, D. Liu, W. Zhang, *Adv. Synth. Catal.* **2015**, *357*, 3262–3272; b) B. Yang, K. Chansaenpak, H. Wu, L. Zhu, M. Wang, Z. Li, H. Lu, *Chem. Commun.* **2017**, *53*, 3497–3500.

Manuscript received: June 28, 2021
Revised manuscript received: July 11, 2021
Version of record online: ■■, ■■■

ACES Asian Chemical Editorial Society

CHEMISTRY
AN ASIAN JOURNAL
Communication

COMMUNICATION



*Z. An, Y. Ren, Y. Liu, Prof. Dr. R. Yan**

An efficient strategy for the synthesis of benzo[*b*]azepine derivatives has been developed by the I_2-promoted intramolecular cross-coupling/annulation of butenyl anilines. This cyclization reaction involves C–H activation and C–C bond formation. A series of benzo[*b*]azepine derivatives are obtained in moderate to good yields.