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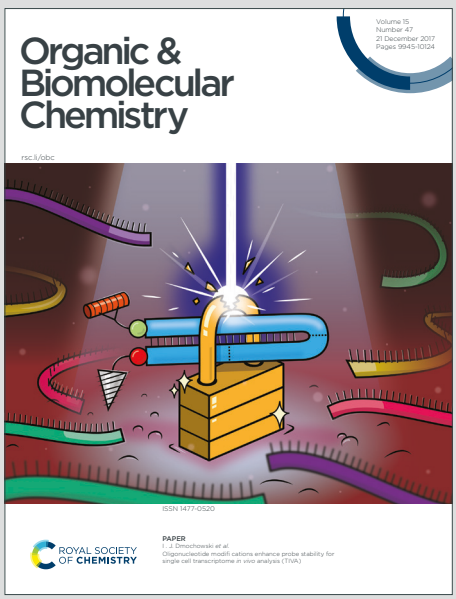

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COMMUNICATION

Copper-Catalyzed Radical Cascade Cyclization for Synthesis of CF_3-Containing Tetracyclic Benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-ones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Here, a general copper-catalyzed radical cascade carbocyclization reaction with 2-arylbenzoimidazoles and a Togni reagent was realized. Structurally diverse CF_3-containing tetracyclic core benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones were obtained in moderate to good yields. The wide substrate scope, good functional group tolerance, and ease of scale-up of this method are expected to promote its potential applications in pharmacy and biotechnology.

Organofluorine compounds display unique physical properties that make them indispensible for applications such as agrochemicals, pharmaceuticals, polymers, and organic materials.[1] Incorporating trifluoromethyl groups into organic molecules can dramatically alter many of the physical properties of such compounds, including lipophilicity, metabolic stability, and conformational behavior.[2] As a consequence, the development of general methods for introducing CF_3 groups into organic molecules has been a subject of intense research.[3] On the other hand, structurally diverse benzimidazole[2,1-*a*]isoquinolines, containing fused five-membered and six-membered rings, are privileged structural elements in chemical biology and material sciences.[4] However, many established methods are heavily dependent on multi-step condensation reactions with pre-functionalized starting materials, with limited functional group tolerability and low overall yields.[5] Therefore, the development of new and general methods, especially one-pot strategies, for producing these polycyclic structures from readily available starting materials is highly desirable.

A strategy involving radical-based cascade carbocyclization initiated by intermolecular addition of a carbon-centered radical to a π system has been used to conveniently and rapidly construct these polycyclic frameworks with high levels of atom and step economy.[6] In the very recent past few years, Yu,[7] Song,[8] Li,[9] He,[10] and their colleagues as well as our group[11] have independently developed efficient radical cascade carbocyclization reactions that were used to access some structurally diverse benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones. Besides, a few reports on the synthesis of CF_3-containing isoquinolinediones, enabled by peroxidate, electrochemical technique or others, were disclosed.[12] However, the practical methods for the synthesis of CF_3-containing tetracyclic core benzimidazole[2,1-*a*]isoquinolines, is still highly appealing. In view of the considerable progress that has been made in the development of transition metal-mediated/-catalyzed trifluoromethylation reactions for introducing CF_3 groups into organic molecules,[13] we reasoned that similar CF_3-containing tetracyclic core benzimidazole[2,1-*a*]isoquinolines, each with a proper catalytic system and trifluoromethyl radical precursor, might be realized by deploying a radical-based cascade carbocyclization strategy. Herein, we developed a copper-catalyzed radical cascade cyclization for the purpose of synthesizing structurally diverse CF_3-containing tetracyclic core benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-ones, some of which are expected to find use in synthetic chemistry, pharmaceuticals and organic electronics.

To find suitable reaction conditions for this cascade reaction, various metal catalysts, trifluoromethyl radical precursors, and solvents were screened (Table 1). Here, *N*-methacryloyl-2-phenylbenzoimidazole **1a** was chosen as the model substrate to access the target product **3a**. The *N*-methacryloyl-2-phenylbenzoimidazole **1a** was initially treated for 12 h with CF_3SO_2Na in one experiment (entry 1) and $TMSCF_3$ in another (entry 2), in each case combined with (diacetoxyiodo)benzene (PIDA), to form the desired **3a**, respectively, only 33% and 16% yields. When **1a** was treated instead with just Togni I (CAS: 887144-97-0) in one experiment (entry 3) and Togni II (CAS: 887144-94-7) in another (entry 4), these two reactions furnished product **3a** in 39% and 47% yields, respectively. Previous reports demonstrated the potential of using copper salts as catalysts for activating Togni reagents;[14] therefore, CuCl, CuBr, CuI and $Cu(OAc)_2$ were each also included in tests. Pleasingly, in this screening, the presence of each of these copper salts was associated with an improvement in the reaction

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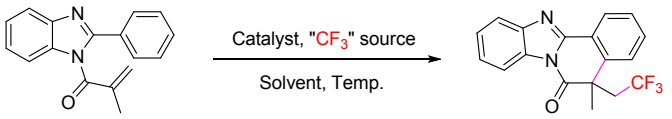
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of reaction conditions[a]



1a 3a

entry	catalyst	"CF_3" source	oxidant	solvent	Yield (%)[b]
1	no	CF_3SO_2Na	PIDA	DCE	33
2	no	$TMSCF_3$	PIDA	DCE	16
3	no	Togni I	no	DCE	39
4	no	Togni II	no	DCE	47
5	CuCl	Togni II	no	DCE	55
6	CuBr	Togni II	no	DCE	54
7	CuI	Togni II	no	DCE	75
8	$Cu(OAc)_2$	Togni II	no	DCE	68
9	CuI	Togni II	no	DCE	51[c]
10	CuI	Togni II	no	DCE	50[d]
11	CuI	Togni II	no	PhCl	37
12	CuI	Togni II	no	EtOAc	45
13	CuI	Togni II	no	DCM	48
14	CuI	Togni II	no	DMSO	50
15	CuI	Togni II	no	DMF	47
16	CuI	Togni II	no	DCE	74[e]
17	CuI	Togni II	no	DCE	51[f]
18	CuI	Togni II	no	DCE	48[g]
19	I_2	Togni II	no	DCE	40
20	KI	Togni II	no	DCE	47
20	NaI	Togni II	no	DCE	46
22	nBu_4NI	Togni II	no	DCE	43

[a] Reaction conditions: **1a** (0.2 mmol), "CF_3" source (0.4 mmol), copper salt (10 mol%) and oxidant (0.4 mmol) in solvent (2.0 mL) at 120 °C for 12 h under air. [b] Yield of the isolated product. [c] 5% CuI was added. [d] 1% CuI was added. [d] Reaction performed at 120 °C for 0.5 h. [e] Reaction performed at 90 °C for 12 h. [g] Reaction performed at 60 °C for 12 h.

(entries 5-8), and when CuI was included, the yield of product **3a** was 75% (entry 7). When the amount of copper salt was 5 mol%, the yield of **3a** was significantly reduced to 51%; While when 1% CuI was added, the yield of **3a** was 50% (entries 9 and 10). A series of solvents including PhCl, EtOAc, DCM, DMSO and DMF were each also tested, but they were not as efficient as DCE (Table 1, entries 11-15). Additionally, control experiments revealed that a 74% yield of **3a** was obtained when the reaction was performed for 0.5 h (entry 16), while decreases in the yield were observed when the reaction temperature was decreased to 90 °C and 60 °C (entries 17 and 18). In order to further improve the yield of **3a**, the role of some other iodide reagents, such as I_2, KI, NaI and nBu_4NI were added in place of CuI, however, the reaction efficiency did not improve obviously (entries 19-22). Therefore, the optimized conditions are as follows: CuI (10 mol%) as the catalyst, Togni II (2.0 equiv) as the CF_3 source, and DCE (2.0 mL) as the solvent, carrying out at 120 °C for 0.5 h.

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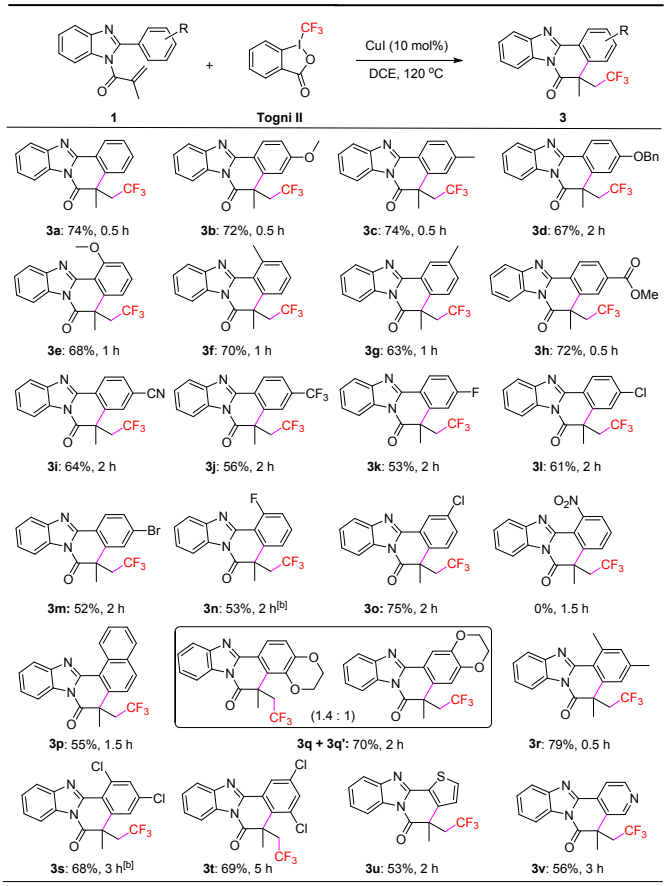
We next set out to investigate the scope of the *N*-methacryloyl-2-phenylbenzoimidazole substrate **1** in reactions with Togni II (Table 2). Both compounds containing electron-donating substituents and

Table 2. Substrate scope[a]



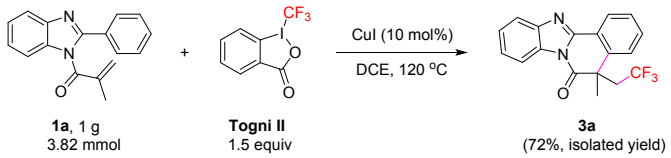
[a] Reaction conditions: **1** (0.3 mmol), Togni II (2.0 equiv), CuI (10 mol%), DCE (2.0 mL), 120 °C. Isolated yields are shown. [b] CuI (30 mol%) was used.

those containing electron-withdrawing substituents readily underwent the radical cascade reactions smoothly, providing the desired benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-ones **3** in moderate to good yields (**3b**–**3o**). The experiments showed that the established conditions can bear a variety of functional groups, including –Me, -OMe, -OBn, -COOMe, -CN, -CF_3, -F, -Cl and -Br, (**3b**–**3o**, 52–75% yields). While when *ortho*-NO_2 substituted substrate was tested, no desired parduct was detected. Substrates bearing multiple substituents on the benzene ring also reacted well to give the corresponding products **3p**–**3t** in satisfactory yields (55–79%). Notably, when 1-(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-benzo[*d*]imidazol-1-yl)prop-2-en-1-one **1q** was deployed under the standard conditions, two isomerically related products denoted as **3q** and **3q'** were obtained, with a 1.4:1 molar ratio of **3q** to **3q'**. We unexpectedly yet fortunately delivered the thiophene-containing and pyridine-containing heteroaryl products **3u** and **3v** in moderate 53% and 56% yields, respectively, which might broaden the opportunity for further application. Further substrate test found when acrylamide was used as substrate, no radical cascade cyclization occurred, with all substrate recovered, which indicated

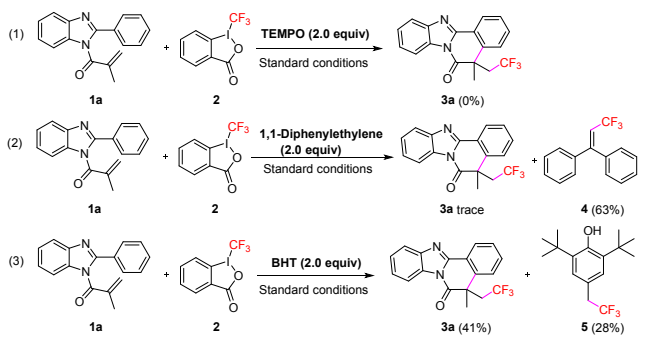
that the methyl group attached to the double bond is important for cyclization process.

To illustrate the synthetic utility of this radical cascade cyclization protocol, we also investigated the ability to scale up this reaction. Conducting the reaction with substrate **1a** on a gram scale provided **3a** in a satisfactory 72% yield; While when 1% CuI was added, the yield of 3a was 43%. (Scheme 1, detailed procedure provided in ESI).

Scheme 1. The gram-scale synthesis of **3a**

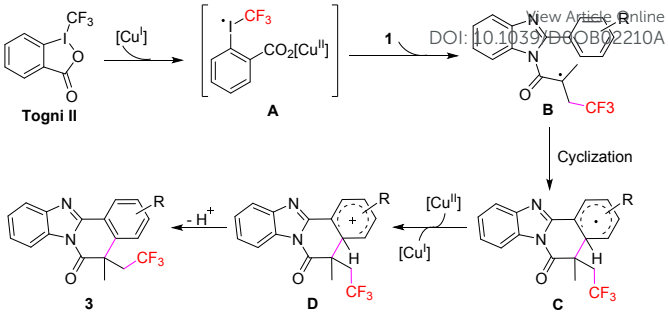


In each of two control experiments involving adding stoichiometric amounts of a radical inhibitor, in one experiment 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv, equation 1) and in the other 1,1-diphenylethylene (2.0 equiv, equation 2), the reaction of **1a** with Togni II to form **3a** was completely suppressed. Meanwhile, an obvious decrease in the yield was observed when butylated hydroxytoluene (BHT, 2.0 equiv) was added (equation 3). Notably, the products **4** and **5** did form from Togni II with 1,1-diphenylethylene and BHT (equations 2 and 3). These results suggested that this radical cascade carbocyclization is in general initiated by the formation of a CF_3 radical from Togni II.



On the basis of the present results and previous reports,[6,13] a mechanism for this radical cascade carbocyclization reaction was derived, and is shown in Scheme 2. Initially, according to this proposed mechanism, decomposition of Togni II occurs to deliver the CF_3 radical with the assistance of CuI under heating and release of the Cu^{II} species **A**. Then, the addition of the CF_3 radical to a C-C double bond in an *N*-methacryloyl-2-phenylbenzoimidazole **1** produces the radical intermediate **B**, which then undergoes intramolecular cyclization to afford the radical intermediate **C**. Subsequent reaction of intermediate **C** with the Cu^{II} species **A** leads to the cationic intermediate **D**. And finally according to the proposed mechanism, loss of a proton from **D** affords the desired product **3**.

Scheme 2. Proposed reaction mechanism



Conclusions

In conclusion, a practical copper-catalyzed radical cascade carbocyclization reaction was developed for the preparation of a variety of structurally diverse CF_3-containing tetracyclic core benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones. This simple radical cascade strategy features easy-handling, a wide substrate scope, and good functional group compatibility, and is easily scaled up. The developed understanding of the mechanism of this type of reaction and the potential applications of its products might garner more research interest in this area. Research and development of bioactive products are currently in progress in our group.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21801007).

Notes and references

1 (a) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303–319; (b) S. Z. Zard, *Current Fluoroorganic Chemistry*, 2007, Chapter 2, pp 25–38; (c) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (d) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (e) A. Harsanyi and G. Sandford, *Green Chem.*, 2015, **17**, 2081–2086; (f) M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640; (g) S. Caron, *Org. Process Res. Dev.*, 2020, **24**, 470–480; (h) X. Wang, J. Lei, G.-F. Li, J.-P. Meng, C. Li, J.-Z. Li and K. Sun, 2020, DOI: 10.1039/D0OB02168G.

2 (a) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (b) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (c) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (d) L.-L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513–1522.

3 (a) X. Dong, R. Sang, Q. Wang, X.-Y. Tang and M. Shi, *Chem. Eur. J.*, 2013, **19**, 16910–16915; (b) L. Ling, K. Liu, X.-Q. Li and Y.-X. Li, *ACS Catal.*, 2015, **5**, 2458–2468; (c) S.-M. Wang, J.-B. Han, C.-P. Zhang, H.-L. Qin and J.-C. Xiao. *Tetrahedron*, 2015, **71**, 7949–7976. (d) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.

4 (a) L. W. Deady and T. Rodemann, *Aust. J. Chem.*, 2001, **54**, 529–534; (b) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442; (c) X.-X. Guo, D.-W. Gu, Z.-X. Wu and W.-B. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651; (d) F. Pan, C. Shu and L.-W. Ye, *Org. Biomol. Chem.*, 2016, **14**, 9456–9465; (e) K. Alam, S. W. Hong, K. H. Oh and J. K. Park, *Angew. Chem., Int. Ed.*, 2017, **56**, 13572–13576.

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DOI: 10.1039/D0OB02210A

5 (a) G. Meng, H.-Y. Niu, G.-R. Qu, J. S. Fossey, J.-P. Li and H.-M. Guo, *Chem. Commun.*, 2012, **48**, 9601−9603; (b) V. O. Iaroshenko, D. Ostrovskyi, M. Miliutina, A. Maalik, A. Villinger, A. Tolmachev, D. M. Volochnyuk and P. Langer, *Adv. Synth. Catal.*, 2012, **354**, 2495−2503; (c) X. Sun, Y. Hu, S.-Z. Nie, Y.-Y. Yan, X.-J. Zhang and M. Yan, *Adv. Synth. Catal.*, 2013, **355**, 2179−2184; (d) X. Sun, X.-H. Lv, L.-M. Ye, Y. Hu, Y.-Y. Chen, X.-J. Zhang and M. Yan, *Org. Biomol. Chem.*, 2015, **13**, 7381−7383; (e) Y. G. Liu, G.-Q. Chen, C.-W. Tse, X. G. Guan, Z.-J. Xu, J.-S. Huang and C.-M. Che, *Chem.−Asian J.*, 2015, **10**, 100−105*;* (f) T. B. Nguyen, L. Ermolenkoa and A. Al-Mourabit, *Chem. Commun.*, 2016, **52**, 4914−4917 and references therein.

6 (a) U. Wille, *Chem. Rev.*, 2013, **113**, 813−853; (b) D. Liu, C. Liu and A.-W. Lei, *Chem. Asian J.*, 2015, **10**, 2040−2054; (c) K. Sun, X. Wang, C. Li, H. Wang and L. Li, *Org. Chem. Front.*, 2020, **7**, 3100−3119; (d) K. Sun, J. Lei, Y.-J. Liu, B. Liu and N. Chen, *Adv. Synth. Catal.*, 2020, **362**, 3709−3726; (e) Z.-G. Zhang, X.-Q. Song, G.-F. Li, X. Li, D. Zheng, X.-N. Zhao, H.-R. Miao, G.-S. Zhang, L.-T. Liu, *Chin. Chem. Lett*., 2020. DOI: 10.1016/j.cclet.2020.11.001; (f) Z. Gan, G. Li, X. Yang, Q. Yan, G. Xu, G. Li, Y.-Y. Jiang and D. Yang. *Sci China Chem*., 2020, **63**, 1652−1658.

7 (a) K. Sun, S.-J. Li, X.-L. Chen, Y. Liu, X.-Q. Huang, D.-H. Wei, L.-B. Qu, Y.-F. Zhao and B. Yu, *Chem. Commun.*, 2019, **55**, 2861−2864; (b) F.-L. Zeng, K. Sun, X.-L. Chen, X.-Y. Yuan, S.-Q. He, Y. Liu, Y.-Y. Peng, L.-B. Qu, Q.-Y. Lv and B. Yu, *Adv. Synth. Catal*., 2019, **361**, 5176−5181.

8 S.-S. Jiang, Y.-T. Xiao, Y.-C. Wu, S.-Z. Luo, R.-J. Song and J.-H. Li, *Org. Biomol. Chem.*, 2020, **18**, 4843−4847.

9 B. Wang, L. Zou, L. Wang, M.-M. Sun and P.-H. Li, *Chin. Chem. Lett.*, 2020, DOI: 10.1016/j.cclet.2020.08.013.

10 L. Liu, D.-Y. Yang, Y.-H. He and Z. Guan, *J. Org. Chem.*, 2020, **85**, 11892−11901.

11 K. Sun, G.-F. Li, Y.-Y. Li, J. Yu, Q. Zhao, Z.-G. Zhang and G.-S. Zhang, *Adv. Synth. Catal.*, 2020, **362**, 1947−1954.

12 (a) W.-Q. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem*., *Int. Ed*., 2013, **52**, 13086 –13090; (b) D.-Q. Liang, Q.-S. Dong, P.-H. Xu, Y. Dong, W.-L. Li and Y.-H. Ma, *J. Org. Chem*., 2018, **83**, 11978−11986; (c) Z.-X. Zhang, L. Zhang, Y. Cao, F. Li, G.-C. Bai, G.-Q. Liu, Y. Yang and F.-Y. Mo, *Org. Lett*., 2019, **21**, 762−766; (d) J.-C. Wang, K. Sun, X.-L. Chen, T. Chen, Y. Liu, L.-B. Qu, Y.-F. Zhao and B. Yu, *Org. Lett*., 2019, **21**, 1863−1867.

13 (a) W.-J. Fu, F.-J. Xu, Y.-Q. Fu, C. Xu, S.-H. Li and D.-P. Zou, *Eur. J. Org. Chem.*, 2014, **2014**, 709−712; (b) V. Krishnamurti, S. B. Munoz, X. Ispizua-Rodriguez, J. Vickerman, T. Mathew and G. K. Surya Prakash, *Chem. Commun.*, 2018, **54**, 10574−10577; (c) X.-C. Liu, G.-J. Mao, J.-Y. Qiao, C.-Z. Xu, H. Liu, J.-J. Ma, Z.-Z. Sun and W.-Y. Chu, *Org. Chem. Front.*, 2019, **6**, 1189−1193; (d) S.-J. Han, X.-Y. Gao, Q.-S. Wu, J.-Y. Li, D.-P. Zou, Y.-J. Wu and Y.-S. Wu, *Adv. Synth. Catal.*, 2019, **361**, 1559-1563, (e) Z.-Z. Han and C.-P. Zhang, *Adv. Synth. Catal.*, 2020, DOI: 10.1002/adsc.202000750.

14 (a) G. Han, Y. Liu and Q. Wang, *Org. Lett.*, 2014, **16**, 3188−3191; (b) G.-F. Han, Q. Wang, L.-W. Chen, Y.-X. Liu and Q.-M. Wang, *Adv. Synth. Catal.*, 2016, **358**, 561−566; (c) J. Zheng, Z.-Y. Deng, Y. Zhang and S.-L. Cui, *Adv. Synth. Catal.*, 2016, **358**, 746−751.

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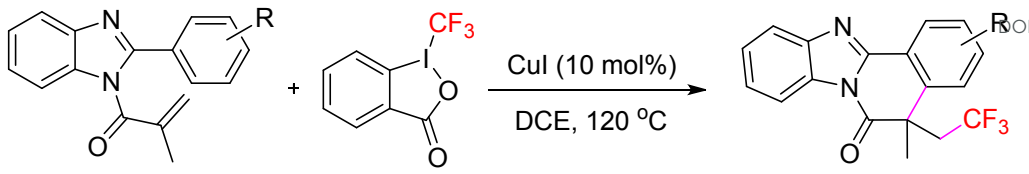

+ Multistep radicals relay + Privileged structural motifs + Ease scale up operation

A practical copper-catalyzed radical cascade carbocyclization reaction was developed for the preparation of a variety of structurally diverse CF_3-containing tetracyclic core benzimidazo[2,1-*a*]isoquinoline-6(5*H*)-ones.