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IODINE-PROMOTED CYCLIZATION OF ALKYLIDENE BARBITURATES IN WATER: FACILE SYNTHESIS OF DIHYDROFURYL SPIROBARBITURATES

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Abstract – An efficient and environmentally benign method *via* iodine-promoted bimolecular annulation of alkylidene barbiturates in water has been developed, affording a variety of significant spirobarbiturate derivatives in good to excellent yields. All products were directly obtained by filtration and following recrystallization. The present protocol exhibits its advantages in terms of simple operation, high efficiency, good functional group tolerance and feasibility for large-scale synthesis.

Barbiturate core is a vital scaffold found in numerous bioactive compounds and natural products.[1] In particular, many commercially available drugs are derived from barbiturate motifs.[2] Spirobarbiturates, a kind of important barbiturate derivatives, are also present in many bioactive compounds, such as anticonvulsant agent,[3] anticancer agent,[4] MMP-13 inhibitor[5] and TACE inhibitor.[6] Thus, their synthesis has drawn a great deal of attention, and numerous synthetic approaches to access functionalized spirobarbiturates have been developed.[7,8]

On the other hand, the development of clean and economical chemical processes has given rise to considerable attention in modern synthetic chemistry due to the increasing awareness of environmental problems. Performing the organic reactions in water has proven to be a greener and attractive protocol,[9] since it can reduce the use of detrimental organic solvents and simplify the product separation procedure. Meanwhile, molecular iodine was frequently used as an environmentally friendly and highly efficient reagent in the construction of heterocyclic compounds because of its low cost, low toxicity and abundant availability.[10,11] On the basis of these points and our sustained interest in halogen-promoted synthesis of structurally diverse heterocycles,[12] herein we present a novel and environmentally benign

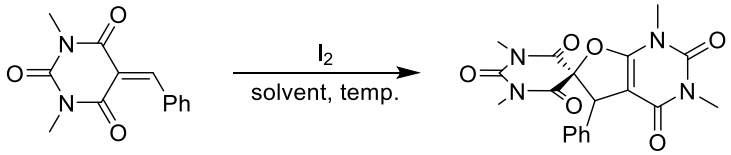
iodine-promoted synthesis of dihydrofuryl spirobarbiturates with water as the solvent. Although such spirocyclic frameworks have been reported,[13] the method *via* bimolecular cyclization of alkylidene barbiturates and C–C bond cleavage has not been investigated.

In our initial design, we attempted to synthesize an imidazolinyl spirobarbiturate *via* NIS-promoted tandem reaction of unsaturated barbiturate (**1a**) and amidine in a ball mill.[12d] It was found that an unexpected compound along with the desired product were simultaneously generated. The NMR spectral analysis revealed that this unanticipated product was a dihydrofuryl spirobarbiturate (**2a**), and amidine did not participate in this transformation. Some preliminary experiments showed that the liquid-phase reaction and I_2 instead of NIS as the promoter could deliver **2a** in higher yield. To the best of our knowledge, this is a new organic reaction to access such significant spirocyclic scaffold, thus we decided to investigate this transformation in more details.

At first, a reaction of a mixture of **1a** (0.6 mmol) and I_2 (0.6 mmol) in several common organic solvents at 80 ^oC was carried out (Table 1, entries 1–6), and the results demonstrated that MeCN as the solvent was optimal to give product **2a** in a moderate yield. It should be pointed out that a side product benzaldehyde was obviously observed by thin-layer chromatography in these cases. Further experiments indicated that the water from solvent was indispensable to this transformation, because **2a** was obtained in a similar yield as we performed the reaction under N_2 atmosphere (Table 1, entry 7), while **2a** could be hardly generated when anhydrous MeCN was employed as the solvent (Table 1, entry 8). Next, we attempted a mixed solvent of MeCN and water (1:1, v/v) to improve the product yield (Table 1, entry 9). To our great delight, **2a** was obtained in nearly quantitative yield (96%), along with 63% of benzaldehyde. As to benzaldehyde isolated in a low yield, the reason may attribute to the weight loss during evaporation and drying procedures. Subsequently, the effect of the amount of I_2 was examined. It was found that 1.0 equiv. of I_2 was optimal to provide **2a** in high yield (Table 1, entry 9 *vs.* entries 10–12). Considering a co-product HI was generated during the transformation, thus we performed the reaction in the presence of aq. HI (57%) to verify whether HI could affect the reaction efficiency. As 1.0 equiv. of HI instead of I_2 as the promoter, no product **2a** was detected (Table 1, entry 13). In addition, a slightly decreased yield (92%) was obtained when the reaction was carried out with both 1.0 equiv. of I_2 and HI (Table 1, entry 14). These results demonstrated that HI could not facilitate the formation of **2a**. Furthermore, temperature screening revealed that the reaction performed at 80 ^oC was the best choice (Table 1, entry 9 *vs.* entries 15–17). In order to develop a more clean and economical method to construct such spirocyclic motif, we then carried out this reaction in pure water instead of the mixed solvent (Table 1, entry 18). It is worthy to mention that a lot of solid was formed during the reaction, and spirobarbiturate **2a** was isolated in 88% yield after filtration and recrystallization from ethanol. Although the yield is slightly lower than that from the column chromatography, this protocol is more convenient and environmentally friendly, thus we adopt

this condition to further study the cyclization of alkylidene barbiturates. The effect of the amount of water on product yield was finally examined, and comparable yields were also delivered (Table 1, entries 19 and 20).

Table 1. Optimization of the reaction conditions[a]

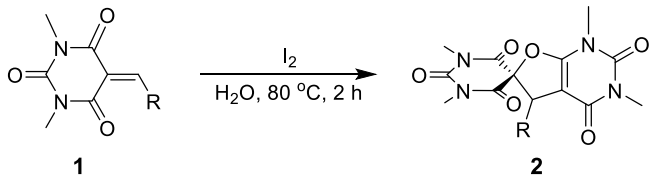


1a **2a**

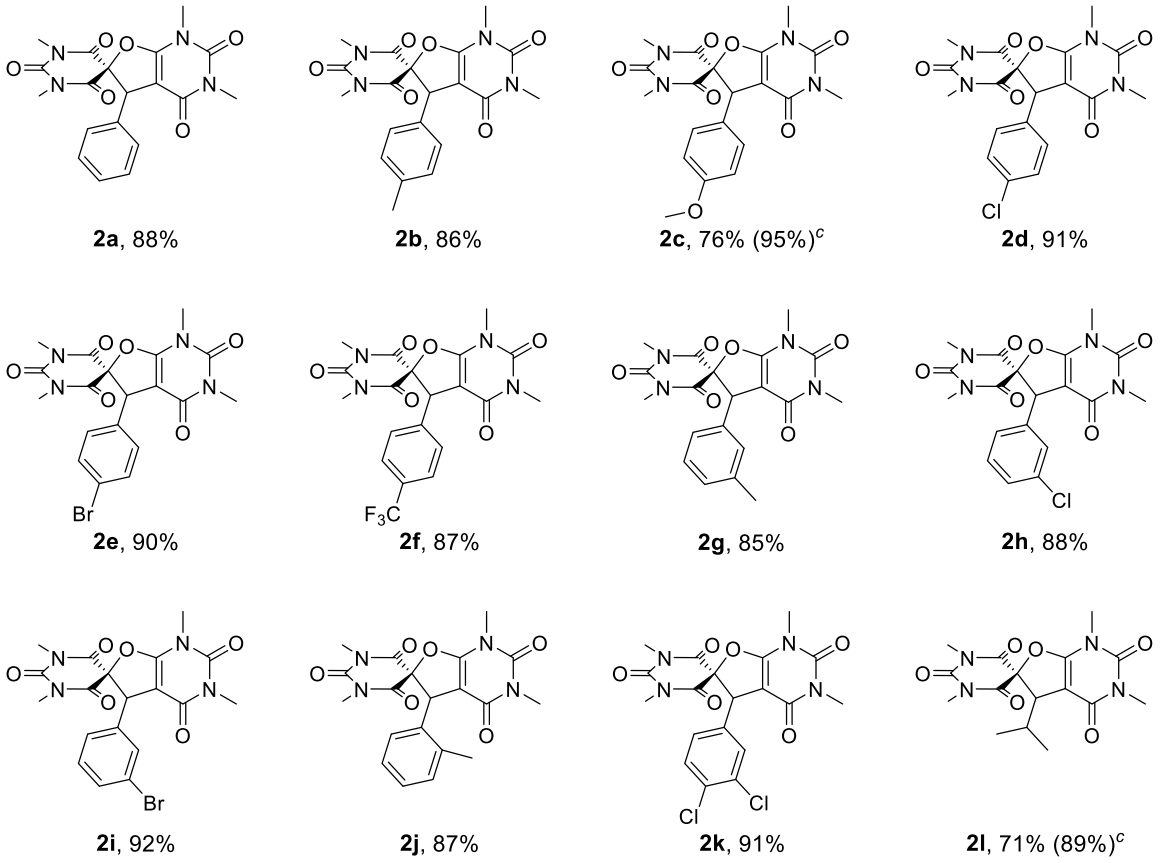
Entry	Solvent	I_2 (equiv.)	Temp. (°C)	Time (h)	Yield[b] (%)
1	DCE	1.0	80	3	41
2	EtOH	1.0	80	5	26
3	MeCN	1.0	80	3	47
4	toluene	1.0	80	3	37
5	DMF	1.0	80	5	22
6	DMSO	1.0	80	5	19
7[c]	MeCN	1.0	80	3	44
8[d]	MeCN	1.0	80	3	trace
9	MeCN/H_2O (1:1)	1.0	80	2	96 (63)[e]
10	MeCN/H_2O (1:1)	1.2	80	2	96
11	MeCN/H_2O (1:1)	0.8	80	3	72
12	MeCN/H_2O (1:1)	–	80	3	0
13[f]	MeCN/H_2O (1:1)	–	80	2	0
14[f]	MeCN/H_2O (1:1)	1.0	80	2	92
15	MeCN/H_2O (1:1)	1.0	100	2	95
16	MeCN/H_2O (1:1)	1.0	60	3	91
17	MeCN/H_2O (1:1)	1.0	40	8	83
18[g]	H_2O	1.0	80	2	88
19[g,h]	H_2O	1.0	80	2	87
20[g,i]	H_2O	1.0	80	2	88

[a] Reaction conditions: a mixture of **1a** (0.6 mmol) and I_2 was stirred in a solvent (4 mL) at the designated temperature. [b] Isolated yield. [c] Under N_2 atmosphere. [d] Dry MeCN as the solvent. [e] Value in parentheses was yield of PhCHO. [f] 1.0 equiv. of aq. HI (57%) was used. [g] The resulting precipitate was filtered and further purified by recrystallization from EtOH. [h] 2 mL of water was employed as the solvent. [i] 6 mL of water was employed as the solvent.

Table 2. Iodine-promoted synthesis of dihydrofuryl barbiturates **2** in water



1 **2**



2a, 88% **2b**, 86% **2c**, 76% (95%)[c] **2d**, 91%

2e, 90% **2f**, 87% **2g**, 85% **2h**, 88%

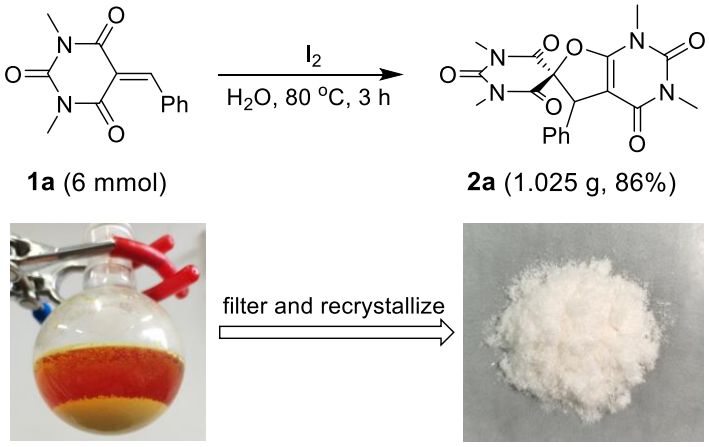
2i, 92% **2j**, 87% **2k**, 91% **2l**, 71% (89%)[c]

[a] Reaction conditions: a mixture of **1** (0.6 mmol) and I_2 (0.6 mmol) in water (4 mL) was stirred at 80 °C for 2 h. [b] Isolated yields by recrystallization from EtOH. [c] The reaction was performed in a mixed solvent of MeCN/water (1:1, v/v) and subsequently purified by column chromatography.

With the optimized rection conditions in hand, we then examined the generality of this bimolecular cyclization. First, a series of *para*-substituted electron-donating or electron-withdrawing groups on the phenyl group in R were investigated, and the results demonstrated that both electron-donating and electron-withdrawing groups substituted unsaturated barbiturates reacted smoothly under the standard conditions to give product **2b**–**f** in yields of 76–91%. Among them, methoxy-substituted spirobarbiturate **2c** was obtained in a lower yield. The reason may be attributed to its solubility in water and ethanol. Notably, product **2c** could be obtained in 95% yield when the reaction was performed in MeCN/water and then separated by column chromatography. Next, the steric effects of substituents on the phenyl ring in R were examined. It was delightedly found that the either *meta*- or *ortho*-substituted alkylidene barbiturates

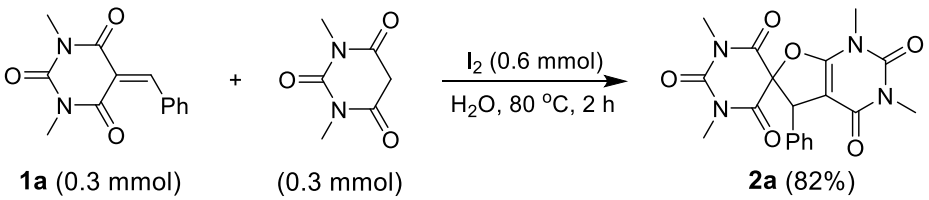
reacted well to provide corresponding spiro products **2g**–**j** in excellent yields of 85–92%, thus indicating that steric hindrance of the substituent did not significantly influence the reaction efficiency. In addition, alkylidene barbiturate **1k** with 3,4-dichloro substituent still exhibited high reactivity under the optimized reaction conditions. Furthermore, an alkyl-substituted barbiturate **1l** was also compatible in this reaction, and the corresponding spirobarbiturates **2l** was delivered in 71% yield under the standard conditions. Alternatively, **2j** could be obtained in an excellent yield (89%) by the column chromatography.

To reveal the practicability of this method, we also performed the reaction on a 6.0 mmol scale for the gram-scale synthesis of **2a**. Gratifyingly, product **2a** was delivered in a comparable yield (86%) as the reaction time was extended to 3 h. This result demonstrated that the present approach could be easily adopted for a large-scale synthesis of spirobarbiturates.



Scheme 1. Gram-scale synthesis of **2a**

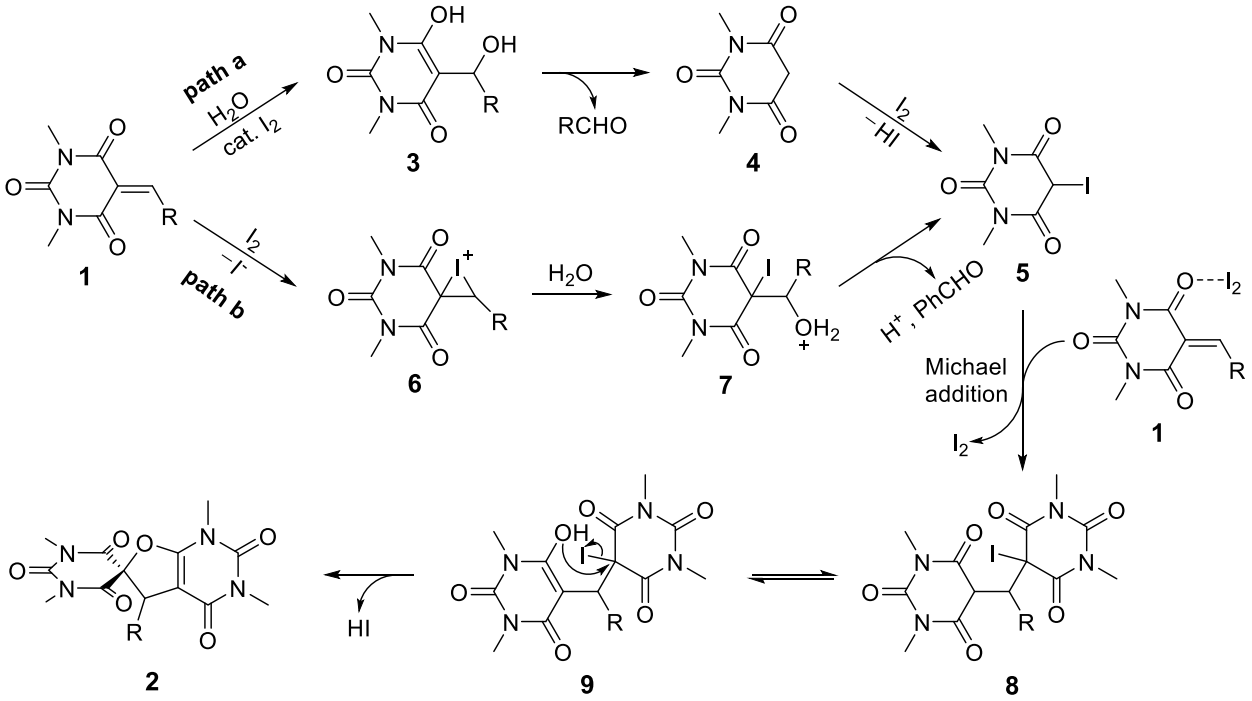
To gain insight into the reaction mechanism, a control experiment was also carried out (Scheme 2). When alkylidene barbiturate**1a** was allowed to react with 1,3-dimethylbarbituric acid in the presence of I_2 under the standard reaction conditions, product **2a** was obtained in a good yield of 82%, indicating that a retro-Knoevenagel reaction and following cyclization may be involved.



Scheme 2. A control experiment

On the basis of the above experimental results and relevant literature, a plausible reaction mechanism is proposed in Scheme 3. At first, an iodine-catalyzed addition of unsaturated olefin **1** with water occurs to produce adduct **3** (path a), which subsequently eliminates aldehyde and affords 1,3-dimethylbarbituric

acid **4**. Then, **4** reacts with iodine to provide iodo-barbiturate **5**. Alternatively, **1** first reacts with iodine to give iodonium intermediate **6** (path b),[14] which is subsequently attacked by water to form oxonium salt **7**. Afterwards, **7** eliminates a molar equivalent aldehyde (detected by TLC) and generates intermediate **5**. Next, a Michael addition takes place between **1** and **5** in the presence of I_2 to afford iodide intermediate **8**,[13a,13b,15] which tautomerizes into enol-form intermediate **9**. Finally, an intramolecular nucleophilic substitution occurs with the elimination of HI to give final product **2**.



Scheme 3. Proposed reaction mechanism

In summary, we have successfully developed a novel method for the facile synthesis of dihydrofuryl spirobarbiturates *via* bimolecular cyclization of alkylidene barbiturates and C–C bond cleavage in water. This protocol features clean reaction conditions, high efficiency, excellent product yields, straightforward work-up procedure and feasibility for large-scale synthesis. These advantages make the present approach a practical and environmentally friendly alternative for the construction of spirodihydrofuran motifs.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on a 400 MHz NMR spectrometer (400 MHz for ^{1}H NMR; 100 MHz for ^{13}C NMR) or 500 MHz NMR spectrometer (500 MHz for ^{1}H NMR; 125 MHz for ^{13}C NMR). ^{1}H NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ at δ 77.16 ppm. Data for ^{1}H NMR and ^{13}C NMR are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). High-resolution mass spectra (HRMS)

were measured with ESI-TOF in a positive mode. All melting points were determined on a XT-4 binocular microscope. IR spectra were recorded on a IRPrestige-21 spectrometer by preparing KBr pellets.

Starting Materials. Alkylidene barbiturates **1** were prepared according to previous reported procedures.[16] All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Products 2. 1,1',3,3'-Tetramethyl-5-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2*H*,2'*H*-spiro[furo[2,3-*d*]-pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(1'*H*,3*H*,3'*H*)-pentaone (2f). A mixture of alkylidene barbiturate **1f** (187.3 mg, 0.6 mmol), I_2 (152.2 mg, 0.6 mmol) and water (4 mL) was introduced into a 25 mL of glass tube. Then the mixture was stirred in an oil bath at 80 ^oC for 2 h. After completion of the reaction, the reaction mixture was filtered and the resulting precipitate was washed with water to afford crude products. Subsequently, the crude products were further purified by recrystallization from EtOH to afford pure dihydrofuryl spirobarbiturate **2f** as a white solid (121.3 mg, 87%), mp 285–287 ^oC; IR (KBr) 1724, 1709, 1701, 1673, 1520, 1438, 1419, 1389, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 4.98 (s, 1H), 3.53 (s, 3H), 3.44 (s, 3H), 3.30 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.0, 162.7, 158.7, 151.2, 149.5, 137.1, 131.8 (q, J = 32.9 Hz), 129.0 (2C), 125.9 (q, J = 3.6 Hz, 2C), 123.7 (q, J = 272.4 Hz), 89.8, 85.2, 58.5, 30.2, 29.7, 28.5, 28.4; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{18}F_3N_4O_6$ $[M + H]^+$ 467.1178, found 467.1182.

Characterization data of other synthesized dihydrofuryl spirobarbiturates and copies of NMR spectra for all products are available in the Supporting Information.

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REFERENCES

1. (a) J. T. Bojarski, J. L. Mokrosz, H. J. Bartoń, and M. H. Paluchowska, *Adv. Heterocycl. Chem.*, 1985, **38**, 229; (b) A. Dömling, W. Wang, and K. Wang, *Chem. Rev.*, 2012, **112**, 3083; (c) V. Estévez, M. Villacampa, and J. C. Menéndez, *Chem. Soc. Rev.*, 2014, **43**, 4633.
2. (a) M. C. Smith and B. J. Riskin, *Drugs*, 1991, **42**, 365; (b) F. Grams, H. Brandstetter, S. D'Alò, D. Gepperd, H.-W. Krell, H. Leinert, V. Livi, E. Menta, A. Oliva, and G. Zimmermann, *Biol. Chem.*, 2001, **382**, 1277; (c) E. Maquoi, N. E. Sounni, L. Devy, F. Olivier, F. Frankenne, H.-W. Krell, F.

Grams, J.-M. Foidart, and A. Noël, *Clin. Cancer Res.*, 2004, **10**, 4038; (d) K. E. Lyons and R. Pahwa, *CNS Drugs*, 2008, **22**, 1037.

3. E. M. Galati, M. T. Monforte, N. Miceli, and E. Raneri, *Il Farmaco*, 2001, **56**, 459.
4. R. K. Bhaskarachar, V. G. Revanasiddappa, S. Hegde, J. P. Balakrishna, and S. Y. Reddy, *Med. Chem. Res.*, 2015, **24**, 3516.
5. S.-H. Kim, A. T. Pudzianowski, K. J. Leavitt, J. Barbosa, P. A. McDonnell, W. J. Metzler, B. M. Rankin, R. Liu, W. Vaccaro, and W. Pitts, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1101.
6. J. J.-W. Duan, L. Chen, Z. Lu, B. Jiang, N. Asakawa, J. E. Sheppeck II, R.-Q. Liu, M. B. Covington, W. Pitts, S.-H. Kim, and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 266.
7. For selected reviews, see: (a) X. Xie, W. Huang, C. Peng, and B. Han, *Adv. Synth. Catal.*, 2018, **360**, 194; (b) C. Segovia, A. Lebrêne, V. Levacher, S. Oudeyer, and J.-F. Brière, *Catalysts*, 2019, **9**, 131; (c) K. Babar, A. F. Zahoor, S. Ahmad, and R. Akhtar, *Mol. Divers.*, 2021, **25**, 2487.
8. For some recent examples, see: (a) H.-W. Zhao, T. Tian, H.-L. Pang, B. Li, X.-Q. Chen, Z. Yang, W. Meng, X.-Q. Song, Y.-D. Zhao, and Y.-Y. Liu, *Adv. Synth. Catal.*, 2016, **358**, 2619; (b) Y. Liu, W. Yang, Y. Wu, B. Mao, X. Gao, H. Liu, Z. Sun, Y. Xiao, and H. Guo, *Adv. Synth. Catal.*, 2016, **358**, 2867; (c) Z. Gao, C. Wang, L. Zhou, C. Yuan, Y. Xiao, and H. Guo, *Org. Lett.*, 2018, **20**, 4302; (d) C.-C. Wang, J. Zhou, Z.-W. Ma, X.-P. Chen, and Y.-J. Chen, *Org. Biomol. Chem.*, 2019, **17**, 9200.
9. C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68.
10. For selected reviews, see: (a) A. N. French, S. Bissmire, and T. Wirth, *Chem. Soc. Rev.*, 2004, **33**, 354; (b) H. Togo and S. Iida, *Synlett*, 2006, 2159; (c) Y.-M. Ren, C. Cai, and R.-C. Yang, *RSC Adv.*, 2013, **3**, 7182; (d) P. T. Parvatkar, P. S. Parameswaran, and S. G. Tilve, *Chem. Eur. J.*, 2012, **18**, 5460.
11. For some recent examples, see: (a) T. Fukuda, M. Komure, G. Onodera, M. Kimura, and M. Iwao, *Heterocycles*, 2018, **97**, 916; (b) K. Kobayashi and D. Fujiwara, *Heterocycles*, 2018, **96**, 1999; (c) J. Feng, T. He, Y. Xie, Y. Yu, J. B. Baell, and F. Huang, *Org. Biomol. Chem.*, 2020, **18**, 9483; (d) A. S. Komendantova, K. A. Lyssenko, I. V. Zavarzin, and Y. A. Volkova, *Org. Chem. Front.*, 2020, **7**, 1640; (e) P. Zhao, Y. Zhou, X.-X. Yu, C. Huang, Y.-D. Wu, G. Yin, and A.-X. Wu, *Org. Lett.*, 2020, **22**, 8528; (f) C. Xu, G. Yin, F.-C. Jia, Y.-D. Wu, and A.-X. Wu, *Org. Lett.*, 2021, **23**, 2559; (g) X.-X. Yu, P. Zhao, Y. Zhou, C. Huang, L.-S. Wang, Y.-D. Wu, and A.-X. Wu, *J. Org. Chem.*, 2021, **86**, 12141.
12. (a) Y. Li, H. Xu, M. Xing, F. Huang, J. Jia, and J. Gao, *Org. Lett.*, 2015, **17**, 3690; (b) H. Xu, H.-W. Liu, H.-S. Lin, and G.-W. Wang, *Chem. Commun.*, 2017, **53**, 12477; (c) H. Xu, H.-W. Liu, K. Chen, and G.-W. Wang, *J. Org. Chem.*, 2018, **83**, 6035; (d) H. Xu, K. Chen, H.-W. Liu, and G.-W. Wang, *Org. Chem. Front.*, 2018, **5**, 2864; (e) H. Xu, F. Yu, R. Huang, M. Weng, H. Chen, and Z. Zhang,

Org. Chem. Front., 2020, **7**, 3368; (f) M.-Y. Weng, H. Xu, H. Chen, and Z. Zhang, *Heterocycles*, 2021, **102**, 114; (g) H. Xu, R. Hong, M.-Y. Weng, R.-L. Huang, G.-W. Wang, and Z. Zhang, *Org. Lett.*, 2021, **23**, 5305.

13. (a) M. N. Elinson, A. N. Vereshchagin, N. O. Stepanov, P. A. Belyakov, and G. I. Nikishin, *Tetrahedron Lett.*, 2010, **51**, 6598; (b) A. N. Vereshchagin, M. N. Elinson, E. O. Dorofeeva, T. A. Zaimovskaya, N. O. Stepanov, S. V. Gorbunov, P. A. Belyakov, and G. I. Nikishin, *Tetrahedron*, 2012, **68**, 1198; (c) M. B. Teimouri, P. Akbari-Moghaddam, and M. Motaghinezhad, *Tetrahedron*, 2013, **69**, 6804.
14. (a) H. Shen, Q. Deng, R. Liu, Y. Feng, C. Zheng, and Y. Xiong, *Org. Chem. Front.*, 2017, **4**, 1806; (b) D. Kour, A. Gupta, K. K. Kapoor, V. K. Gupta, Rajnikant, D. Singh, and P. Das, *Org. Biomol. Chem.*, 2018, **16**, 1330; (c) L. He, Y. Yang, X. Liu, G. Liang, C. Li, D. Wang, and W. Pan, *Synthesis*, 2020, **52**, 459.
15. For selected examples on iodine-catalyzed Michael addition, see: (a) B. K. Banik, M. Fernandez, and C. Alvarez, *Tetrahedron Lett.*, 2005, **46**, 2479; (b) G. Yin, L. Fan, T. Ren, C. Zheng, Q. Tao, A. Wu, and N. She, *Org. Biomol. Chem.*, 2012, **10**, 8877; (c) N. Ahmed and B. V. Babu, *Synth. Commun.*, 2013, **43**, 3044; (d) D. von der Heiden, S. Bozkus, M. Klussmann, and M. Breugst, *J. Org. Chem.*, 2017, **82**, 4037; (e) Y. Takeda, R. Kajihara, N. Kobayashi, K. Noguchi, and A. Saito, *Org. Lett.*, 2017, **19**, 6744.
16. R. Gu, K. Flidrova, and J.-M. Lehn, *J. Am. Chem. Soc.*, 2018, **140**, 5560.