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Cs_2CO_3 catalyzed direct aza-Michael addition of azoles to α,β-unsaturated malonates†

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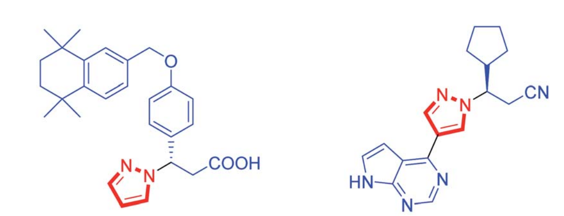
A highly efficient method for the synthesis of azole derivatives *via* a direct aza-Michael addition of azoles to α,β-unsaturated malonates using Cs_2CO_3 as a catalyst, has been successfully developed. A series of azole derivatives have been obtained in up to 94% yield and the reaction could be amplified to gram scale in excellent yield in the presence of 10 mol% of Cs_2CO_3.

Introduction

Azoles and their derivatives are important heterocyclic scaffolds which have been widely found in many natural products, bioactive compounds, and drug candidates.[1,2] Particularly, the pyrazole constitutes the structural core featured in numerous pharmacologically active molecules.[3] For example, the β-pyrazolyl acid **A** has activity toward human GPR40 G-protein coupled receptor (Fig. 1).[4] A prominent example is the Janus kinase (JAK) inhibitor Ruxolitinib (INCB018424), which has been used in the treatment of myelofibrosis (Fig. 1).[5] Therefore, in the past two decades, continuous efforts have been directed towards the development of efficient methods for accessing such pyrazole structures in medicinal chemistry and organic synthesis.[6–11] To date, numerous concise and robust synthetic methods, mainly including *N*-nucleophilic substitutions,[6] C–N cross-couplings[7,8] and aza-Michael additions,[9,10] have been established. Among them, the direct aza-Michael addition of pyrazole has attracted more attention as a highly efficient method for construction of pyrazole derivatives.[10,11]

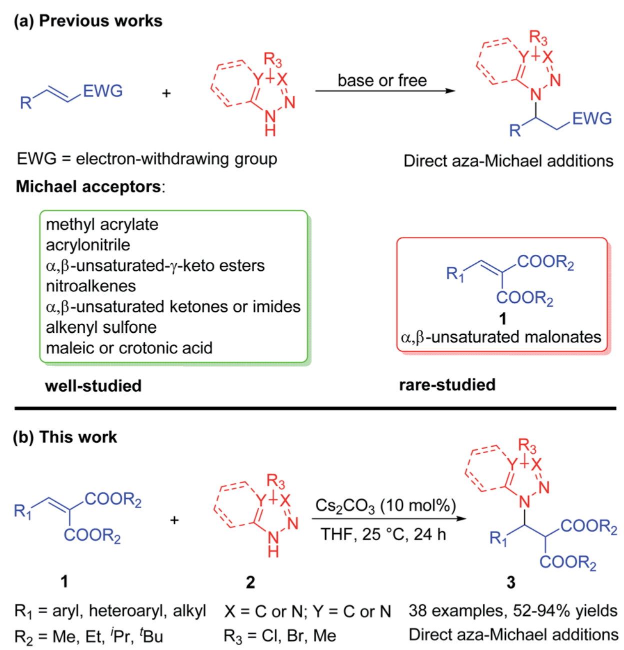


β-pyrazolyl acid **A**
GPR40 G-protein coupled receptor

Ruxolitinib
INCB018424

Fig. 1 Biologically pyrazole compounds.

As we all know, the pyrazoles *via N*-deprotonation generating active *N*-nucleophiles under base-catalysis,[12] could react with all kinds of Michael receptors to afford pyrazole derivatives. These Michael receptors in aza-Michael addition of pyrazole mainly include methyl acrylate,[10c,d,j,k] acrylonitrile,[10c,j] β,γ-unsaturated-α-keto esters,[10f] nitroalkenes,[10e] α,β-unsaturated ketones[10a–c] or imides[10i] and maleic or crotonic acid[10g,h] (Scheme 1a). Specially, several catalytic asymmetric aza-Michael additions of pyrazoles had been successfully realized in which the optically active pyrazole derivatives were obtained.[11] Nevertheless, the development of alternative receptor in aza-Michael addition of azole will be remain as a highly desirable work, owing to their easy accessing other valuable pyrazole derivatives. To the best of our



Scheme 1 Commonly encountered aza-Michael addition of azoles.

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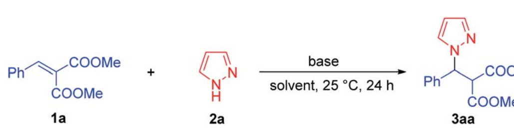
knowledge, the α,β-unsaturated malonates, which had been used as Michael receptors in numerous transformations, had their potential in the construction of azole derivatives *via* direct aza-Michael addition of azoles.[13] Herein, we describe a Cs_2CO_3 catalyzed direct aza-Michael addition of azoles **2** to α,β-unsaturated malonates **1** to afford azole derivatives **3** (Scheme 1b).

Results and discussion

In the initial study, dimethyl 2-benzylidenemalonate **1a** and pyrazole **2a** were chosen as the model substrates for the synthesis of pyrazole derivatives *via* the direct aza-Michael addition. No product was observed without catalyst when stirring in THF at 25 °C for 24 h (Table 1, entry 1). Next, various bases as catalysts were surveyed in THF at 25 °C and trace amount of product **3aa** was observed in the presence of 100 mol% of organic base Et_3N (Table 1, entry 2). Meanwhile, DBU could afford pyrazole derivative **3aa** in lower yield (31%, Table 1, entry 3). When the reaction was performed with 100 mol% of inorganic bases, the acceptable yields of **3aa** were obtained (Table 1, entries 4–7). Comparatively, the Cs_2CO_3 exhibited a slight superiority in reactivity toward this aza-Michael addition compared with $LiOH\cdot H_2O$, $K_3PO_4\cdot 7H_2O$, and K_2CO_3 (Table 1, entries 6 *vs.* 4, 5 and 7). Further optimization of the reaction conditions was then aimed at exploring the efficiency of solvent. Unfortunately, the yield of **3aa** decreased slightly in other types of solvents (CH_3OH, $PhCH_3$, EtOAc, CH_2Cl_2, Table 1, entries 6 *vs.* 8–11), and the THF was still the most suitable solvent for this reaction. The efficiency of temperature was also examined (Table 1, entries 6 and 12–13), and it was found that increasing the temperature to 40 °C had nearly no effect on the yield of **3aa** (Table 1, entry 12) but the yield of **3aa** decreased when reducing the temperature to 0 °C (Table 1, entry 13). Increasing the amount of pyrazole **2a** to 0.3 mmol could further improve the yield of **3aa** to 80% (Table 1, entry 14). We were delighted to find that reducing the amount of Cs_2CO_3 to 10 mol% had no effect on the yield of **3aa** (Table 1, entry 15), while the yield of **3aa** decreased significantly when reducing the amount of Cs_2CO_3 to 1 mol% (Table 1, entry 16). Reducing the amount of solvent THF to 0.20 mL, the yield of **3aa** increased slightly (Table 1, entry 17). The reaction was amplified to 0.50 mmol scale and also proceeded smoothly, affording **3a** in 84% yield (Table 1, entry 18). Therefore, the optimal conditions were identified as 10 mol% of Cs_2CO_3 in THF at 25 °C for 24 h.

Table 1 Optimization of the reaction conditions[a]



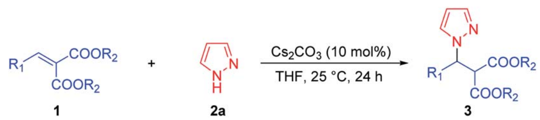
Entry	Base	Solvent	*T* (°C)	Yield[b] (%)
1	—	THF	25	0
2	Et_3N	THF	25	Trace
3	DBU	THF	25	31
4	$LiOH\cdot H_2O$	THF	25	60
5	$K_3PO_4\cdot 7H_2O$	THF	25	58
6	Cs_2CO_3	THF	25	69
7	K_2CO_3	THF	25	53
8	Cs_2CO_3	CH_3OH	25	—
9	Cs_2CO_3	$PhCH_3$	25	62
10	Cs_2CO_3	EtOAc	25	48
11	Cs_2CO_3	CH_2Cl_2	25	61
12	Cs_2CO_3	THF	40	67
13	Cs_2CO_3	THF	0	50
14[c]	Cs_2CO_3	THF	25	80
15[c,d]	Cs_2CO_3	THF	25	79
16[c,e]	Cs_2CO_3	THF	25	55
17[c,e,f]	Cs_2CO_3	THF	25	83
18[g]	Cs_2CO_3	THF	25	84

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), base (100 mol%), solvent (1.0 mL), 24 h. [b] Isolated yield. [c] 0.30 mmol of **2a** was used. [d] 10 mol% of Cs_2CO_3 was used. [e] 1 mol% of Cs_2CO_3 was used. [f] 0.2 mL of THF was used. [g] **1a** (0.50 mmol), **2a** (0.75 mmol), Cs_2CO_3 (10 mol%), THF (0.5 mL), 24 h.

Under the optimal conditions (Table 1, entry 17), various α,β-unsaturated malonates **1** were evaluated, affording the corresponding pyrazole derivatives **3** in moderate to excellent yields (up to 92%). As shown in Table 2, the reactivity of this direct aza-Michael addition was sensitive to the steric hindrance on the ester group of α,β-unsaturated malonates **1**. The substrates **1** containing bulkier ester groups ($-CO_2Et$, $-CO_2{}^iPr$, and $-CO_2{}^tBu$) gave lower yields than its with $-CO_2Me$ group (Table 2, entries 2–4 *vs.* 1). For the effects of substituents in the phenyl ring, the reactivity of the direct aza-Michael addition was sensitive to the steric hindrance rather than to the electronic property of α,β-unsaturated malonates **1**. The substrates **1** with ortho-substituents gave lower yields than those with para or meta ones (Table 2, entries 7 *vs.* 5 and 6, 10 *vs.* 8 and 9, 13 *vs.* 11 and 12, 17 *vs.* 15 and 16, 20 *vs.* 18 and 19). The substrates with 2-F, 2-Cl, 2-Br, 2-Me or 2-OMe substituents on phenyl ring (**1g**, **1j**, **1m**, **1q** and **1t**) were transformed into pyrazole derivatives **3ga**, **3ja**, **3ma**, **3qa** and **3ja** in moderate yields (Table 2, entries 7, 10, 13, 17 and 20). Meanwhile, the fused-ring substrates (**1u** and **1v**) were also tolerable, giving the desired products with 75% and 88% yields, respectively (Table 2, entries 21 and 22). For the thienyl heteroaromatic substrates **1w** and **1x**, the reaction generated the desired products **3wa** and **3xa** in 84% and 88% yield (Table 2, entries 23 and 24), while the 2-furyl heteroaromatic substrate **1y** afforded the desired product **3ya** in 76% yield (Table 2, entry 25). At the same time, the alkyl substituted substrates **1z**, **1α**, **1β** and **1γ** also gave the corresponding pyrazole derivatives **3za**, **3αa**, **3βa** and **3γa** in good yields (60–92%, Table 2, entries 26–29).

Next, the use of this catalytic system for aza-Michael addition of a variety of substituted pyrazoles **2** was explored, and the desired pyrazole derivatives **3** were obtained in moderate to excellent yields (up to 94%). As shown in Table 3, the electronic nature of the substituents in pyrazoles **2** had obvious effect on the efficiency of this reaction (Table 3, **3ab**–**3af**). The substrates **2** with electron-donating Me group gave higher yields than those with electron-withdrawing (Cl or Br) substituents (Table 3, **3ae**, **3af** *vs.* **3ab**, **3ac** and **3ad**). For indazole substrate **2g**, the aza-

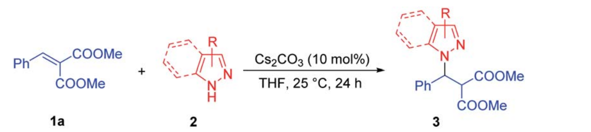
Table 2 Substrate scope of α,β-unsaturated malonates[a]

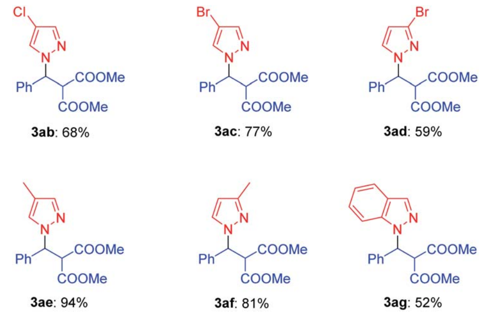


Entry	R_1	R_2	3	Yield[b] (%)
1	Ph	Me	**3aa**	84
2	Ph	Et	**3ba**	68
3	Ph	^{i}Pr	**3ca**	67
4	Ph	^{t}Bu	**3da**	69
5	4-FC_6H_4	Me	**3ea**	84
6	3-FC_6H_4	Me	**3fa**	73
7	2-FC_6H_4	Me	**3ga**	66
8	4-ClC_6H_4	Me	**3ha**	92
9	3-ClC_6H_4	Me	**3ia**	87
10	2-ClC_6H_4	Me	**3ja**	64
11	4-BrC_6H_4	Me	**3ka**	74
12	3-BrC_6H_4	Me	**3la**	71
13	2-BrC_6H_4	Me	**3ma**	52
14	4-$F_3CC_6H_4$	Me	**3na**	81
15	4-MeC_6H_4	Me	**3oa**	63
16	3-MeC_6H_4	Me	**3pa**	91
17	2-MeC_6H_4	Me	**3qa**	55
18	4-$MeOC_6H_4$	Me	**3ra**	77
19	3-$MeOC_6H_4$	Me	**3sa**	87
20	2-$MeOC_6H_4$	Me	**3ta**	65
21	2-Naphthyl	Me	**3ua**	75
22	1-Naphthyl	Me	**3va**	88
23	3-Thienyl	Me	**3wa**	84
24	2-Thienyl	Me	**3xa**	81
25	2-Furyl	Me	**3ya**	76
26	^{n}Pr	Me	**3za**	85
27	^{i}Pr	Me	**3αa**	92
28	^{i}Bu	Me	**3βa**	60
29	$^n C_9H_{19}$	Me	**3γa**	74

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), Cs_2CO_3 (10 mol%), THF (0.5 mL), 25 °C, 24 h. [b] Isolated yield.

Table 3 Substrate scope of azoles.[a,b]





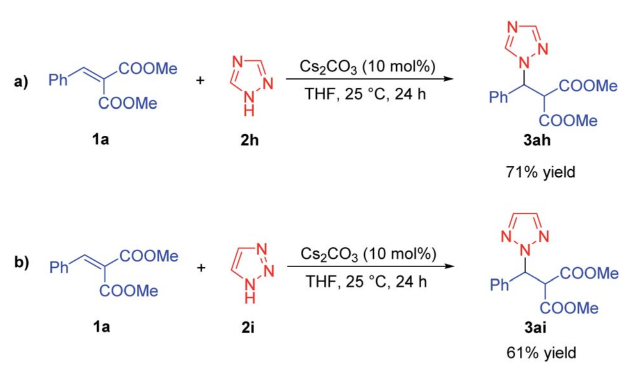
[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), Cs_2CO_3 (10 mol%), THF (0.5 mL), 25 °C, 24 h. [b] Isolated yield.

Michael addition generated the desired product **3ag** in 52% yield (Table 3, entry 7).[14]

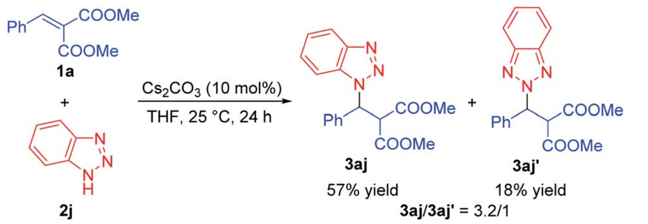
Then, the use of this catalytic system for the direct aza-Michael addition of triazoles **2** to dimethyl 2-benzylidenemalonate **1a** was explored, and the desired *N*1-substituted triazole derivative **3ah** was obtained in 71% yield for the 1,2,4-triazole **2h**, while the *N*2-substituted triazole derivative **3ai** was obtained in 61% yield for the 1,2,3-triazole **2i** (Scheme 2). For the substrate 1*H*-benzotriazole **2j**, the reaction generated triazole derivatives **3aj** and **3aj′** in 57% and 18% yields, simultaneously (**3aj**/**3aj′** = 3.2/1, based on the isolated yields, Scheme 3) under the optimal conditions.[15] Besides, the direct aza-Michael additions of imidazole and pyrrole to dimethyl 2-benzylidene-malonate **1a** were also explored, unfortunately, no desired products were observed under the optimal conditions.

On account of the synthetic potential of this method, the reaction was amplified to gram scale. As shown in Scheme 4, the direct aza-Michael addition of pyrazole **2a** (1.02 g, 15.0 mmol) to methyl dimethyl 2-benzylidenemalonate **1a** (2.20 g, 10.0 mmol) proceeded smoothly under the optimal conditions, affording the pyrazole derivative **3aa** in 75% yield (Scheme 4a). Delightly, the yield of **3aa** could be improved to 94% when the reaction concentration was increased twice as much in the gram scale synthesis (Scheme 4b).

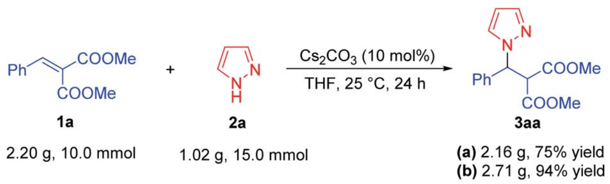
According to the previous studies on the reactive properties of azoles in literatures,[9,12] a reasonable catalytic cycle was proposed in Fig. 2. Because the pK_a value of *N*1–H in azole is less that of H_2CO_3 [pK_a (*N*1–H) = 2.49, pK_{a1} (H_2CO_3) = 6.37], the *N*1-deprotonation of azoles **2** could be promoted by the conjugated base CO_3^{2-}, which had been from the ionization of Cs_2CO_3. First, the active *N*-nucleophiles **I** and HCO_3^- were generated *via* the *N*1-deprotonation of azoles **2**. Then the *N*-nucleophiles **I** attacked the α,β-unsaturated malonates **1** at β-positions, forming the enolate intermediates **II**. Next, the HCO_3^- transferred the H^+ to the enolate oxygen of intermediates **II** due to that the p*K*a value of HCO_3^- is less than that of enolates, providing the enol type azole derivatives **3′**. Meanwhile, the CO_3^{2-} could regenerate and participate in the next round of catalytic cycle.



Scheme 2 Direct aza-Michael addition of triazoles **2h** and **2i** to dimethyl 2-benzylidenemalonate **1a**.



Scheme 3 Direct aza-Michael addition of benzotriazole **2j** to dimethyl 2-benzylidenemalonate **1a**.



Scheme 4 Preparative scale syntheses of selected compound.

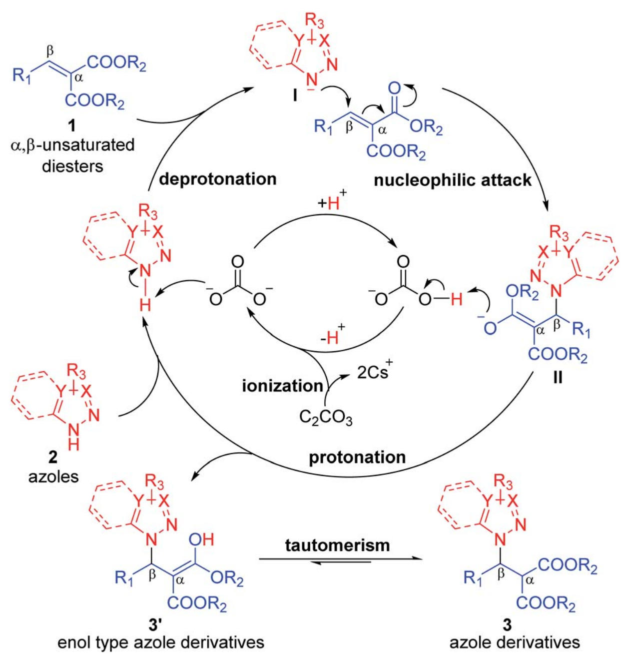


Fig. 2 Proposed catalytic cycle.

Finaly, the azole derivatives **3** were obtained *via* the tautomerism of the enol type azole derivatives **3′**.

Conclusions

We have developed a highly efficient method for the synthesis of azole derivatives *via* a direct aza-Michael addition of azoles to α,β-unsaturated malonates using Cs_2CO_3 as catalyst. A series of azole derivatives (38 examples) have been obtained in up to 94% yield. The reaction could be amplified to gram scale in excellent yield (94%) in the presence of 10 mol% of Cs_2CO_3, which had shown the potential value of the catalytic system for practical synthesis. Further study on an enantioselective version of this direct aza-Michael addition is still in progress.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 For selected reviews, see:(*a*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; (*b*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2015, **57**, 10257; (*c*) R. J. D. Hatley, S. J. F. Macdonald, R. J. Slack, J. Le, S. B. Ludbrook and P. T. Lukey, *Angew. Chem., Int. Ed.*, 2018, **57**, 3298.

2 (*a*) D. Patel, M. Jain, S. R. Shah, R. Bahekar, P. Jadav, B. Darji, Y. Siriki, D. Bandyopadhyay, A. Joharapurkar, S. Kshirsagar, H. Patel, M. Shaikh, K. V. V. M. Sairam and P. Patel, *ChemMedChem*, 2011, **6**, 1011; (*b*) G. Venkatesan, P. Paira, S. L. Cheong, K. Vamsikrishna, S. Federico, K.-N. Klotz, G. Spalluto and G. Pastorin, *Bioorg. Med. Chem.*, 2014, **22**, 1751; (*c*) M. Xin, X. Zhao, W. Huang, Q. Jin, G. Wu, Y. Wang, F. Tang and H. Xiang, *Bioorg. Med. Chem.*, 2015, **23**, 6250; (*d*) G. Venkatesan, P. Paira, S. L. Cheong, S. Federico, K. N. Klotz, G. Spalluto and G. Pastorin, *Eur. J. Med. Chem.*, 2015, **92**, 784; (*e*) Z. S. Cheruvallath, S. L. Gwaltney, M. Sabat, M. Tang, H. Wang, A. Jennings, D. Hosfield, B. Lee, Y. Wu, P. Halkowycz and C. E. Grimshaw, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 2678; (*f*) M. Dawidowski, V. C. Kalel, V. Napolitano, R. Fino, K. Schorpp, L. Emmanouilidis, D. Lenhart, M. Ostertag, M. Kaiser, M. Kolonko, B. Tippler, W. Schliebs, G. Dubin, P. Mäser, I. Tetko, K. Hadian, O. Plettenburg, R. Erdmann, M. Sattler and G. M. Popowicz, *J. Med. Chem.*, 2020, **63**, 847.

3 For selected reports, see:(*a*) J. J. Cui, M. Tran-Dube, H. Shen, M. Nambu, P.-P. Kung, M. Pairish, L. Jia, J. Meng, L. Funk, I. Botrous, M. McTigue, N. Grodsky, K. Ryan, E. Padrique, G. Alton, S. Timofeevski, Y. S. amazaki, Q. Li, H. Zou and J. Christensen, *J. Med. Chem.*, 2011, **54**, 6342; (*b*) M. Andrés, M. Bravo, M. A. Buil, M. Calbet, J. Castro, T. Domènech, P. Eichhorn, M. Ferrer, E. Gómez, M. D. Lehner, I. Moreno, R. S. Roberts and S. Sevilla, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3349; (*c*) S. Fuse, T. Morita, K. Johmoto, H. Uekusa and H. Tanaka, *Chem.–Eur. J.*, 2015, **21**, 14370; (*d*) B. Gopula, Y.-F. Tsai, T.-S. Kuo, P.-Y. Wu, J. P. Henschke and H.-L. Wu, *Org. Lett.*, 2015, **17**, 1142; (*e*) S. Patel, S. F. Harris, P. Gibbons, G. Deshmukh, A. Gustafson, T. Kellar, H. Lin, X. Liu, Y. Liu, Y. Liu, C. Ma, K. Scearce-Levie, A. S. Ghosh, Y. G. Shin, H. Solanoy,

J. Wang, B. Wang, J. Yin, M. Siu and J. W. Lewcock, *J. Med. Chem.*, 2015, **58**, 8182; (*f*) F. A. Romero, J. M. Murray, K. W. Lai, V. Tsui, B. K. Albrecht, L. An, M. H. Beresini, G. de L. Boenig, S. M. Bronner, E. W. Chan, K. X. Chen, Z. Chen, E. F. Choo, K. Clagg, K. Clark, T. D. Crawford, P. Cyr, D. D. A. Nagata, K. E. Gascoigne, J. L. Grogan, G. Hatzivassiliou, W. Huang, T. L. Hunsaker, S. Kaufman, S. G. Koenig, R. Li, Y. Li, X. Liang, J. Liao, W. Ly, J. Q. Liu, J. Maher, C. Masui, M. Merchant, Y. Ran, A. M. Taylor, J. S. Wai, F. Wang, X. Wei, D. Yu, B.-Y. Zhu, X. Zhu and S. R. Magnuson, *J. Med. Chem.*, 2017, **60**, 9162; (*g*) S. Varghese, R. Rahmani, S. Russell, G. S. Deora, L. Ferrins, A. Toynton, A. Jones, M. Sykes, A. Kessler, A. Eufrasio, A. T. Cordeiro, J. Sherman, A. Rodriguez, V. M. Avery, M. Piggott and J. B. Baell, *ACS Med. Chem. Lett.*, 2020, **11**, 278.

4 S. P. Brown, P. Dransfield, J. B. Houze, J. Liu, J. Liu, Z. Ma, J. C. Medina, V. Pattaropond, M. J. Schmitt, R. Sharma and Y. Wang, US Pat. 7687526B2, 2010.

5 R. A. Mesa, U. Yasothan and P. Kirkpatrick, *Nat. Rev. Drug Discovery*, 2012, **11**, 103.

6 For selected reports, see:(*a*) A. Huang, K. Wo, S. Y. C. Lee, N. Kneitschel, J. Chang, K. Zhu, T. Mello, L. Bancroft, N. Norman and S.-L. Zheng, *J. Org. Chem.*, 2017, **82**, 8864; (*b*) C. Pezzetta, D. Bonifazi and R. W. M. Davidson, *Org. Lett.*, 2019, **21**, 8957; (*c*) D. Xu, L. Frank, T. Nguyen, A. Stumpf, D. Russell, R. Angelaud and F. Gosselin, *Synlett*, 2020, **31**, 595.

7 For selected reports, see:(*a*) A. Correa and C. Bolm, *Angew. Chem., Int. Ed.*, 2007, **46**, 8862; (*b*) Y.-C. Teo, F.-F. Yong, C.-Y. Poh, Y.-K. Yana and G.-L. Chua, *Chem. Commun.*, 2009, 6258; (*c*) H. W. Lee, A. S. C. Chan and F. Y. Kwong, *Tetrahedron Lett.*, 2009, **50**, 5868; (*d*) Q. Yang, Y. Wang, D. Lin and M. Zhang, *Tetrahedron Lett.*, 2013, **54**, 1994; (*e*) A. M. Haydl, K. Xu and B. Breit, *Angew. Chem., Int. Ed.*, 2015, **54**, 7149; (*f*) F. Damkaci, A. Alawaed and E. Vik, *Tetrahedron Lett.*, 2016, **57**, 2197; (*g*) C. Yuan, Y. Zhao and L. Zheng, *Synlett*, 2019, **30**, 2173.

8 For selected reports, see:(*a*) M. L. Kantam, T. Ramani and L. Chakrapani, *Synth. Commun.*, 2008, **38**, 626; (*b*) Y.-C. Teo and G.-L. Chua, *Chem.–Eur. J.*, 2009, **15**, 3072; (*c*) Y.-S. Liu, Y. Liu, X.-W. Ma, P. Liu, J.-W. Xie and B. Dai, *Chin. Chem. Lett.*, 2014, **25**, 775; (*d*) T. Niwa, H. Ochiai, Y. Watanabe and T. Hosoya, *J. Am. Chem. Soc.*, 2015, **137**, 14313; (*e*) Q. Zhou, F. Du, Y. Chen, Y. Fu, W. Sun, Y. Wu and G. Chen, *J. Org. Chem.*, 2019, **84**, 8160; (*f*) A. Y. Jiu, H. S. Slocumb, C. S. Yeung, X.-H. Yang and V. M. Dong, *Angew. Chem., Int. Ed.*, 2021, **60**, 19660.

9 For selected review, see: M. G. Vinogradov, O. V. Turova and S. G. Zlotin, *Org. Biomol. Chem.*, 2019, **17**, 3670.

10 For selected reports, see:(*a*) L. Yang, L.-W. Xu, W. Zhou, L. Li and C.-G. Xia, *Tetrahedron Lett.*, 2006, **47**, 7723; (*b*) Y.-J. Wu, *Tetrahedron Lett.*, 2006, **47**, 8459; (*c*) J.-M. Xu, C. Qian, B.-K. Liu, Q. Wu and X.-F. Lin, *Tetrahedron*, 2007, **63**, 986; (*d*) C. Qian, J.-M. Xu, Q. Wu, D.-S. Lv and X.-F. Lin, *Tetrahedron Lett.*, 2007, **48**, 6100; (*e*) Y. Wu, J. Wang, P. Li and F. Y. Kwong, *Synlett*, 2012, **23**, 788; (*f*) J. Wang, P.-F. Li, S. H. Chan, A. S. C. Chan and F. Y. Kwong, *Tetrahedron Lett.*, 2012, **53**, 2887; (*g*) H. N. Khachatryana, S. S. Hayotsyana, K. S. Badalyana, H. S. Attaryana and G. V. Hasratyan, *Russ. J. Gen. Chem.*, 2015, **85**, 1982; (*h*) H. N. Khachatryan, *Russ. J. Gen. Chem.*, 2017, **87**, 572; (*i*) H. Zhou, X. Xiang, B. Ma, G. Wang, Z. Zhang and J. Yang, *Synthesis*, 2019, **51**, 3142; (*j*) K. Kodolitsch, F. Gobec and C. Slugovc, *Eur. J. Org. Chem.*, 2020, **2020**, 2973; (*k*) A. Gupta and M. L. Condakes, *J. Org. Chem.*, 2021, **86**, 17523; (*l*) V. Srinivasulu, M. A. A. Khanfar, H. A. Omar, R. ElAwady, S. M. Sieburth, A. Sebastian, D. M. Zaher, F. A. Marzooq, F. H and T. H. Al-Tel, *J. Org. Chem.*, 2019, **84**, 14476; (*m*) V. Srinivasulu, I. Shehadi, M. A. Khanfar, O. G. Malik, H. Tarazi, I. A. Abu-Yousef, A. Sebastian, N. Baniodeh, M. J. O'Connor and T. H. Al-Tel, *J. Org. Chem.*, 2019, **84**, 934; (*n*) V. Srinivasulu, P. Schilf, S. Ibrahim, M. A. Khanfar, S. M. Sieburth, H. Omar, A. Sebastian, R. A. AlQawasmeh, M. J. O'Connor and T. H. Al-Tel, *Nat. Commun.*, 2018, **9**, 4989.

11 For selected reports, see:(*a*) P. Diner, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983; (*b*) Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu and J. Zhou, *Org. Lett.*, 2009, **11**, 1999; (*c*) J. Zhang, Y. Zhang, X. Liu, J. Guo, W. Cao, L. Lin and X. M Feng, *Adv. Synth. Catal.*, 2014, **356**, 3545; (*d*) P. Li, F. Fang, J. Chen and J. Wang, *Tetrahedron: Asymmetry*, 2014, **25**, 98; (*e*) S.-J. Lee, J.-Y. Bae and C.-W. Cho, *Eur. J. Org. Chem.*, 2015, **2015**, 6495.

12 F. Chevallier, Y. S. Halauko, C. Pecceu, I. F. Nassar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevichd and F. Mongin, *Org. Biomol. Chem.*, 2011, **9**, 4671.

13 For selected reports, see:(*a*) I. Meskini, L. Toupet, M. Daoudi, A. Kerbal, B. Bennani, P. H. Dixneuf, Z. H. Chohan, A. C. L. Leite and T. B. Hadda, *J. Braz. Chem. Soc.*, 2010, **21**, 1129; (*b*) I. Meskini, L. Toupet, M. Daoudi, A. Kerbal, M. Akkurt, Z. H. Chohan and T. B. Hadda, *J. Chem. Crystallogr.*, 2010, **40**, 812; (*c*) L. Patalag, J. A. Ulrichs, P. G. Jones and D. B. Werz, *Org. Lett.*, 2017, **19**, 2090.

14 For selected reports, see:(*a*) F. Zigheimat, M. R. Islami and F. Nourmohammadian, *Synlett*, 2014, **25**, 229; (*b*) J. Yang, Y. Bao, H. Zhou, T. Li, N. Li and Z. Li, *Synthesis*, 2016, **48**, 1139.

15 For selected reports on the aza-Michael addition of 1*H*-benzotriazole, see:(*a*) G. Luo, S. Zhang, W. Duan and W. Wang, *Synthesis*, 2009, **9**, 1564; (*b*) J. Lv, H. Wu and Y. Wang, *Eur. J. Org. Chem.*, 2010, **2010**, 2073; (*c*) J. Wang, W. Wang, X. Liu, Z. Hou, L. Lin and X. M. Feng, *Eur. J. Org. Chem.*, 2011, **2011**, 2039; (*d*) S.-L. Xie, Y.-H. Hui, X.-J. Long, C.-C. Wang and Z.-F. Xie, *Chin. Chem. Lett.*, 2013, **24**, 28; (*e*) S.-W. Chen, G.-C. Zhang, Q.-X. Lou, W. Cui, S.-S. Zhang, W.-H. Hu and J.-L. Zhao, *ChemCatChem*, 2015, **7**, 1935; (*f*) Z. Li, T. Li, R. Fu and J. Yang, *Heterocycl. Commun.*, 2017, **23**, 287.

