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Brønsted acid mediated intramolecular cyclopropane ring expansion/[4 + 2]-cycloaddition†

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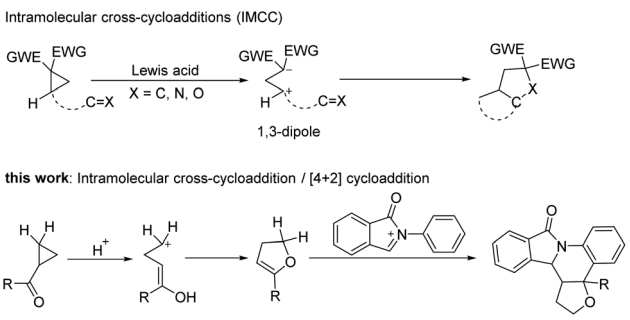
A cascade reaction of 3-hydroxy-2-phenylisoindolin-1-one and cyclopropyl ketone has been developed *via* a BrØnsted acid-promoted ring-opening/intramolecular cross-cycloaddition/[4 + 2]-cycloaddition process. The developed methodology provides straightforward access to pentacyclic isoindolin-1-one derivatives under simple reaction conditions.

Cyclopropane derivatives have received immense attention in organic synthesis due to their versatile activity.[1] In particular, upon activation by a Lewis acid, the donor–acceptor cyclopropanes could generate 1,3-zwitterions through the heterolytic cleavage of the central C–C bond between the donating and the electron-withdrawing moieties, which were trapped easily by different double bonds, such as C=C, C=N, and C=O.[2] This is one of the most commonly used strategies for the construction of different cycles through ring expansion reactions as the electron-donating or -accepting substituents make polar processes more favorable.[3] Thus, a number of very brilliant examples related to intermolecular cycloadditions and intramolecular cross-cycloadditions have been reported (IMCC; Scheme 1).[4] Generally, cyclopropanes involved in synthetically useful reactions contain two activating groups, and monoactivated cyclopropane derivatives such as cyclopropyl ketones are sluggish because of their low activities.[5] To date, few methods for the ring-opening reactions of cyclopropyl ketones have been published and these methods showed severe disadvantages such as harsh reaction conditions (strong Lewis acids[6] or nucleophiles[7]) and limited substrate scope (β-effect of the silicon atom of a trimethylsilyl group[8]). Hence, the exploration of new efficient methods for ring-opening coupling/intramolecular cross-cycloaddition reactions of cyclopropyl ketones is a highly demanding goal.

Recently, we reported a copper-catalyzed cascade reaction of 2-formylbenzonitrile, cyclopropyl ketones, and diaryliodonium salts *via* the expansion of cyclopropane/formation of *N*-acyliminium/the [4 + 2]-cycloaddition process.[9] We envisioned that dihydrofuran derivatives were produced from the ring-opening coupling reaction of cyclopropyl ketones catalyzed by copper salts. A natural extension of the work is to explore the possibility of replacing the copper salts with other non-metallic catalysts. Herein, we report a BrØnsted acid-promoted ring-opening coupling reaction of cyclopropyl ketones with 3-hydroxy-2-phenylisoindolin-1-one for the facile synthesis of substituted pentacyclic isoindolin-1-one,[10] which usually represents an important class of pharmaceutical compounds due to their various medicinal properties.

Inspired by our previous work,[9] we chose 3-hydroxy-2-phenylisoindolin-1-one **1a** as the 4π diene in the hetero-D–A reaction as the hydroxyl group was easily removed by using catalysts. Initially, the reaction conditions for the ring-opening coupling/[4 + 2]-cycloaddition reaction from 3-hydroxy-2-phenylisoindolin-1-one **1a**[11] and (4-chlorophenyl)(cyclopropyl) methanone **2a** were optimized in a sealed tube (Table 1). The catalyst-free reaction of **1a** (0.3 mmol) with **2a** (0.45 mmol) in 1,2-dichloroethane (DCE) at 110 °C for 30 min did not provide



Scheme 1 Synthetic strategies of acridines with anthranils.

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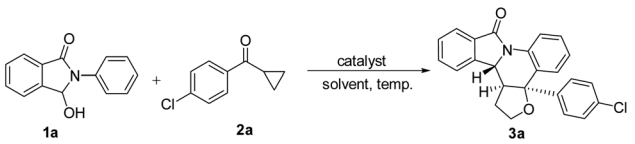
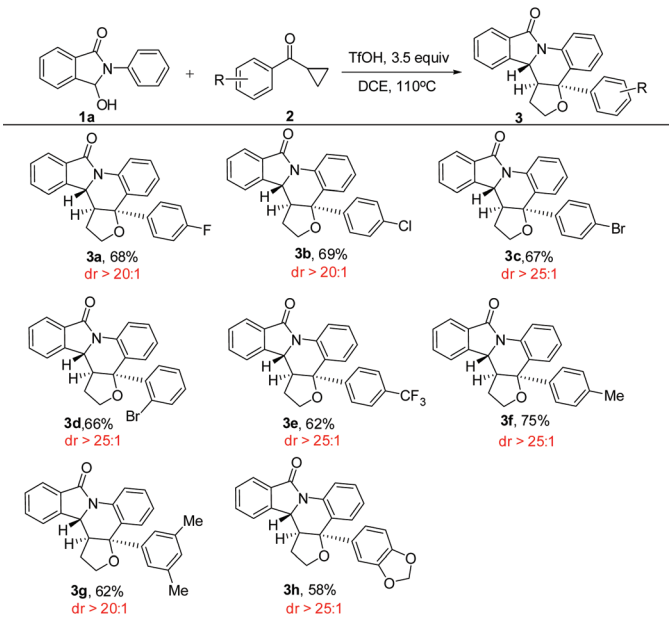
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Temperature (°C)	Solvent	Yield[b] (%)
1	—	110	DCE	—
2	$BF_3{\cdot}Et_2O$	110	DCE	23
3	Benzoic acid	110	DCE	Trace
4	TsOH	110	DCE	25
5	HOAc	110	DCE	Trace
6	TfOH	110	DCE	58
7[c]	TfOH	110	DCE	48
8[d]	TfOH	110	DCE	52
9	TfOH	110	Toluene	21
10	TfOH	110	THF	20
11	TfOH	110	MeCN	22
12	TfOH	110	DMF	—
13	TfOH	110	1,4-Dioxane	21
14	TfOH	r.t.	DCE	—
15	TfOH	80	DCE	35
16	TfOH	130	DCE	50
17[e]	TfOH	110	DCE	65
18[f]	TfOH	110	DCE	67
19[g]	**TfOH**	**110**	**DCE**	**69**
20[h]	TfOH	110	DCE	65

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), catalyst (1.5 equiv.) in solvent (2 mL), 30 min. [b] Isolated yield. [c] 15 min. [d] 60 min. [e] TfOH (2.5 equiv.). [f] TfOH (3 equiv.). [g] TfOH (3.5 equiv.). [h] TfOH (5 equiv.).

Table 2 Cyclopropyl(phenyl)methanone **2** scope[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol) and TfOH (3.5 equiv.) in 1,2-dichloroethane (DCE) (2 mL), 110 °C, 30 min. [b] Isolated yield. The diastereomeric ratio was determined by the ^{1}H NMR analysis of products.

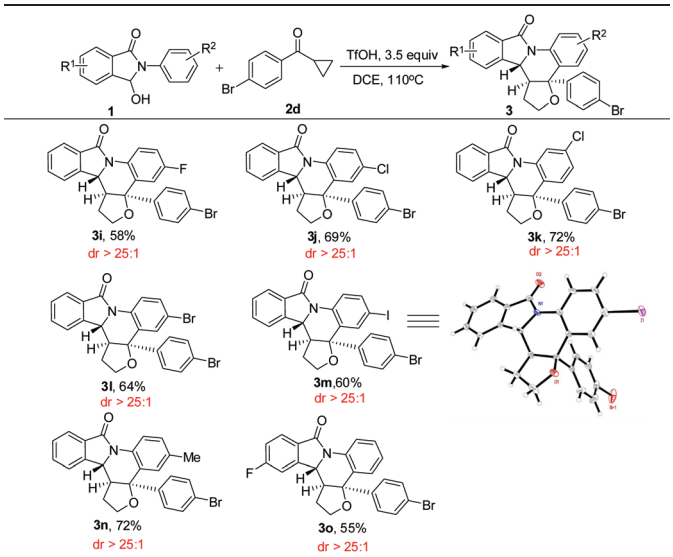
any products (entry 1). To our satisfaction, when $BF_3{\cdot}Et_2O$ was used as a Lewis acid catalyst, the annulation reaction occurred at 110 °C in DCE, and the expected product **3a** was obtained in 23% yield. To increase the yield, some BrØnsted acids, such as TsOH, HOAc and TfOH, were employed (entries 3–6). TfOH was the most efficient catalyst for this reaction and the desired product **3a** as a single diastereoisomer (dr > 20 : 1) was formed in 58% yield. After shortening or elongating the reaction time, the isolated yields of **3a** were not improved (48% and 55%, entries 7 and 8). Subsequently, a survey of other solvents was carried out with TfOH. We found that a change in the solvent has a significant effect on the reaction outcome. Among the solvents tested, DCE appeared to be the most suitable reaction medium. To a large extent, the temperature affected the reaction rate and the yield of **3a** was only 35% at 80 °C, while the yield was decreased to 50% at 130 °C. Gratifyingly, the reaction can be further promoted when the loading of TfOH was increased, and a more favorable outcome of 69% yield was observed in the presence of 3.5 equiv. of TfOH (entry 19). Thus, the optimum reaction conditions for the transformation were as follows: 3.5 equiv. TfOH and DCE (untreated), at 110 °C for 30 min.

The results of the experiments run under the optimized reaction conditions to probe the scope of the tandem reaction are summarized in Table 2. To our delight, all cyclopropyl (phenyl)methanone **2**, including electron-donating (methyl, dimethyl) and electron-deficient (trifluoromethyl) at the 4-position, afforded 3a-phenyl-1,2,13b,13c-tetrahydrofuro[3,2-*c*] isoindolo[2,1-*a*]quinolin-9(3aH)-ones **3a–3h** in 58–75% isolated yields and excellent diastereoselectivity (Table 2). For example, cyclopropyl(phenyl)methanones bearing halogen groups such as Cl, F and Br were compatible in this methodology to give the halogen-containing products **3a–3c** in moderate yields (67–69%). Interestingly, the cascade reaction can override the *ortho*-effect that (2-bromophenyl)(cyclopropyl)methanone shows giving product **3d** in 66% yield. Disubstituted substrates also afforded the corresponding pentacyclic isoindolin-1-one product **3g** in an acceptable yield.

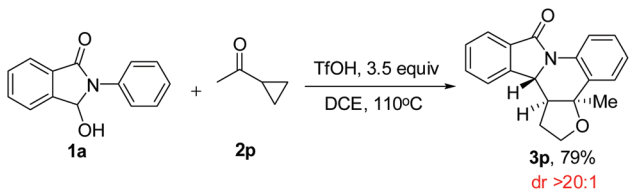
Subsequently, the cascade reaction was carried out with differently substituted 3-hydroxy-2-phenylisoindolin-1-one **1** under the optimized conditions (Table 3). The results also show that variation of the aromatic electronic properties of the substituent at either R^1 or R^2 of the 3-hydroxy-2-phenylisoindolin-1-one **1** was tolerated, furnishing the corresponding products in 55–72% yields (**3i–3o**). Notably, a *meta*-chloro substituent was also tolerated to afford the desired products **3k** in 72% yield and excellent diastereoselectivity. The structure of **3m** was confirmed by single-crystal X-ray diffraction. Encouraged by the above success, we then turned our attention to apply this methodology to other cyclopropyl ketones. Remarkably, the catalytic system is applicable for the cascade reaction of 3-hydroxy-2-phenylisoindolin-1-one **1a** with 1-cyclopropylethan-1-one **2p** to afford the methyl product **3p** in 79% yield (Scheme 2).

In order to figure out the reaction mechanism, control experiments were carried out (Scheme 3). To confirm whether

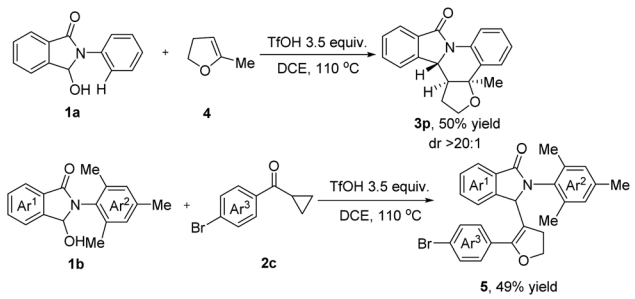
Table 3 3-Hydroxy-2-phenylisoindolin-1-one **1** scope[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2d** (0.45 mmol) and TfOH (3.5 equiv.) in 1,2-dichloroethane (DCE) (2 mL), 110 °C, 30 min. [b] Isolated yield. The diastereomeric ratio was determined by the ^{1}H NMR analysis of products.



Scheme 2 Using the 1-cyclopropylethan-1-one **2p** as the substrate.



Scheme 3 Experiments for mechanistic understanding.

the ring-opening/intramolecular cross-cycloaddition process of cyclopropyl ketone **2** is a crucial step, we performed the reaction of 3-hydroxy-2-phenylisoindolin-1-one **1a** with 5-methyl-2,3-dihydrofuran **4** under the standard reaction conditions, resulting in the formation of product **3p** in 50% yield. In addition, the dihydrofuran intermediate can be detected with GC-MS in the reaction. This result indicates that the dihydrofuran might be the crucial intermediate, which was delivered from substrate **2** firstly.[12] Next, treatment of (4-bromophenyl)

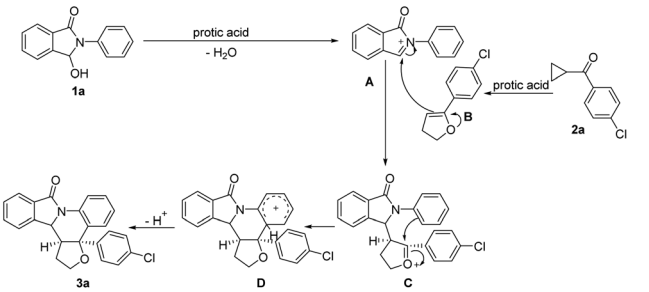


Fig. 1 Proposed reaction mechanism.

(cyclopropyl)methanone **2c** with 3-hydroxy-2-mesitylisoindolin-1-one **1b** provided a non-cyclized product **5** in 49% yield. It means that hydrogen at the *ortho*-position of Ar^2 is necessary for the [4 + 2]-cycloaddition process.

On the basis of the above control experiment results, a reasonable mechanism of reaction was proposed (Fig. 1). Initially, the removal of the hydroxyl group at the 3-hydroxy-2-phenylisoindolin-1-one **1a** generates 4π diene **A** with the use of TfOH. Subsequently, the *N*-acyliminium cation **A** was attacked by nucleophile 5-phenyl-2,3-dihydrofuran **B**,[13] which produced from **2a** *via* the ring-opening/intramolecular cross-cycloaddition process, leading to coupling intermediate **C**, followed by an intramolecular annulation to give intermediate **D**. Finally, the deprotonation of intermediate **D** affords the final product pentacyclic isoindolin-1-one **3a**. The [4 + 2] cycloaddition with *N*-acyliminium cation **A** should preferentially occur on the top face of 5-phenyl-2,3-dihydrofuran **B**, because the other face of **B** might be shielded by the phenyl group, which leads to the formation of (3a*S*,13b*R*,13c*S*)-**3a** as the major diastereoisomer.

In summary, a cascade reaction of 3-hydroxy-2-phenylisoindolin-1-one and cyclopropyl ketone has been developed *via* a TfOH mediated ring-opening/intramolecular cross-cycloaddition/[4 + 2]-cycloaddition process. The developed methodology provides straightforward access to pentacyclic isoindolin-1-one derivatives under simple reaction conditions. Further studies to explore the possibility for the synthesis of various complicated isoindolinones are currently underway in our laboratory.

Experimental section

General information

All reactions were carried out under an air atmosphere. Various reagents were purchased from Aldrich, Acros or Alfa. Flash column chromatography was performed using silica gel (200–300 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–300 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were recorded in $CDCl_3$ on Bruker NMR-400 (400 MHz) and NMR-500 (500 MHz) spectrometers with TMS as an internal reference. HRMS were recorded on an Agilent 6540

Q-TOF mass spectrometer (ESI). MS were recorded on an Agilent 7890A/5975C mass spectrometer (EI). Melting points were determined on a SGW X-4B melting point apparatus.

Procedure for the synthesis of compound 3-hydroxy-2-arylisoindol-1-ones 1 [14]

All reactants **1** except **1h** are known compounds. In a sealed tube, to a solution of phthalic anhydride (10 mmol) in DCM (20 mL), aniline was added (12 mmol). The reaction mixture was stirred for 1 h at room temperature, then acetic anhydride and sodium acetate were added, and the resulting mixture was stirred at 90 °C for 3 h to afford the corresponding *N*-aryl-1*H*-pyrrole-2,5-diones in 72–89% yields. Finally, to a solution of *N*-aryl-1*H*-pyrrole-2,5-diones (0.803 g, 3.6 mmol) in THF (36 mL) in an ice bath at 0–5 °C, $NaBH_4$ (0.137 g, 3.6 mmol) was added in portions over 10 min. Then, methanol (4 mL, 10 times) was added dropwise and the remaining $NaBH_4$ was quenched with 0.5 M HCl solution until pH 4. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate, washed with water (three times) and dried over anhydrous Na_2SO_4. The organic layer was evaporated under vacuum to dryness, affording the pure product **1** in 68–79% yield.

Procedure for the synthesis of compound cyclopropyl ketones 2 [15]

All reactants **2** are known compounds. To a mixture of arylboronic acid (0.435 g, 3.6 mmol), cyclopropanecarbonitrile (0.201 g, 3.0 mmol), $Pd(OAc)_2$ (0.027 g, 0.12 mmol), 2,2′-bypyridyl (0.018 g, 0.16 mmol), triflic acid (2.4 mL) and H_2O (0.8 mL) were added. The obtained mixture was stirred for 6 h at 60 °C. Then the reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with ether. The combined ether solution was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using petroleum ether/acetate to obtain cyclopropyl ketones **2** in 81–94% yield.

General procedure for the preparation of compound 3

A solution of 3-hydroxy-2-phenylisoindolin-1-one **1** (0.3 mmol), cyclopropyl ketone **2** (0.45 mmol), and TfOH (3.5 equiv.) in 1,2-dichloroethane (DCE) (2 mL) was stirred at 110 °C for 30 min. After the completion of the reaction (observed on TLC), the solvent was evaporated under reduced pressure to obtain the crude mixture. The residues were purified by silica-gel column chromatography (ethyl acetate/petroleum ether = 1/4–1/2) to afford the pure product **3**. The obtained product was analyzed by ^1H NMR, ^{13}C NMR and HRMS.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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References

1 (*a*) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; (*b*) D. J. Mack and J. T. Njardarson, *ACS Catal.*, 2013, **3**, 272; (*c*) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504; (*d*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; (*e*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*f*) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404; (*g*) S. J. Gharpure and L. N. Nanda, *Tetrahedron Lett.*, 2017, **58**, 711; (*h*) E. Richmond, J. Yi, V. D. Vuković, F. Sajadi, C. N. Rowley and J. Moran, *Chem. Sci.*, 2018, **9**, 6411.

2 (*a*) E. Wenkert, *Acc. Chem. Res.*, 1980, **13**, 27; (*b*) H.-U. Reissig, *Top. Curr. Chem.*, 1988, **144**, 73; (*c*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (*d*) D. Agrawal and V. K. Yadav, *Chem. Commun.*, 2008, 6471; (*e*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; (*f*) J. Sabbatani and N. Maulide, *Angew. Chem., Int. Ed.*, 2016, **55**, 6780; (*g*) H. Xu, J.-L. Hu, L. Wang, S. Liao and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 8006; (*h*) Q.-Q. Cheng, Y. Qian, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2015, **17**, 3568; (*i*) D. D. Borisov, R. A. Novikov and Y. V. Tomilov, *Angew. Chem., Int. Ed.*, 2016, **55**, 12233; (*j*) L. K. B. Garve, M. Petzold, P. G. Jones and D. B. Werz, *Org. Lett.*, 2016, **18**, 564.

3 (*a*) A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 3122; (*b*) S. J. Gharpure, M. K. Shukla and U. Vijayasree, *Org. Lett.*, 2009, **11**, 5466; (*c*) A. Karadeolian and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2010, **49**, 1133; (*d*) F. De Simone, J. Gertsch and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 5767; (*e*) F. Nanteuil and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 12075; (*f*) S. Roy and O. Reiser, *Angew. Chem., Int. Ed.*, 2012, **51**, 4722; (*g*) F. Benfatti, F. de Nanteuil and J. Waser, *Org. Lett.*, 2012, **14**, 386.

4 (*a*) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804; (*b*) J. Zhang, S. Xing, J. Ren, S. Jiang and Z. Wang, *Org. Lett.*, 2015, **17**, 218; (*c*) Y. Bai, W. Tao, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 4112; (*d*) T. F. Schneider, J. Kaschel, S. I. Awan, B. Dittrich and D. B. Werz, *Chem. – Eur. J.*, 2010, **16**, 11276.

5 P. A. Wender, T. M. Pedersen and M. J. C. Scanio, *J. Am. Chem. Soc.*, 2002, **124**, 15154.

6 (*a*) Y.-H. Lim, K. F. McGee Jr. and S. M. Sieburth, *J. Org. Chem.*, 2002, **67**, 6535; (*b*) M. Shi, Y.-H. Yang and B. Xu, *Tetrahedron*, 2005, **61**, 1893.

7 (*a*) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1999, **38**, 3186;

(*b*) F. Bertozzi, M. Gustafsson and R. Olsson, *Org. Lett.*, 2002, **4**, 3147; (*c*) F. Bertozzi, M. Gustafsson and R. Olsson, *Org. Lett.*, 2002, **4**, 4333; (*d*) M. Lautens and W. Han, *J. Am. Chem. Soc.*, 2002, **124**, 6312.

8 V. K. Yadav and R. Balamurugan, *Org. Lett.*, 2003, **5**, 4281.

9 J. Li, S. Bai, Y. Li, Z. Wang, X. Huo and L. Liu, *J. Org. Chem.*, 2018, **83**, 8780.

10 (*a*) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, 1989, p. 819; (*b*) E. C. Lawson, D. K. Luci, S. Ghosh, W. A. Kinney, C. H. Reynolds, J. Qi, C. E. Smith, Y. Wang, L. K. Minor, B. J. Haertlein, T. J. Parry, B. P. Damiano and B. E. Maryanoff, *J. Med. Chem.*, 2009, **52**, 7432; (*c*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902.

11 (*a*) A. V. Stepakov, A. G. Larina, V. M. Boitsov, V. V. Gurzhiy, A. P. Molchanov and R. R. Kostikov, *Tetrahedron Lett.*, 2014, **55**, 2022; (*b*) A. G. Larina, V. E. Nosova, A. S. Filatov, A. P. Molchanov, G. L. Starova, A. A. Zolotarev, V. M. Boitsov and A. V. Stepakov, *Tetrahedron*, 2016, **72**, 5064; (*c*) A. G. Larina, A. S. Filatov, V. V. Suslonov, A. P. Molchanov and A. V. Stepakov, *Tetrahedron*, 2017, **73**, 3949.

12 (*a*) E. Wenkert, M. E. Alonso, B. L. Buckwalter and K. J. Chou, *J. Am. Chem. Soc.*, 1977, **99**, 4778; (*b*) B. Hofmann and H.-U. Reissig, *Synlett*, 1993, 27.

13 (*a*) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431; (*b*) J. Royer, M. Bonin and L. Micouin, *Chem. Rev.*, 2004, **104**, 2311; (*c*) W. Zhang, A. Zheng, Z. Liu, L. Yang and Z. Liu, *Tetrahedron Lett.*, 2005, **46**, 5691.

14 (*a*) Z. Al-Jaroudi, P. P. Mohapatra and A. Jha, *Tetrahedron Lett.*, 2016, **57**, 772; (*b*) A. G. Larina, A. S. Filatov, V. V. Suslonov, A. P. Molchanov and A. V. Stepakov, *Tetrahedron*, 2017, **33**, 3949; (*c*) A. Jóźwiak and M. Ciechańska, *J. Heterocycl. Chem.*, 2014, **51**, 357.

15 (*a*) Y. Sun, X. Huang, X. Li, F. Luo, L. Zhang, M. Chen, S. Zheng and B. Peng, *Adv. Synth. Catal.*, 2018, **360**, 1082; (*b*) E. Benoit, J. Dansereau and A. Gagnon, *Synlett*, 2017, **28**, 2833; (*c*) J. Li, J. Chen, W. Jiao, G. Wang, Y. Li, X. Cheng and G. Li, *J. Org. Chem.*, 2016, **81**, 9992; (*d*) R. C. Krauss, R. M. Strom, C. L. Scortichini, W. J. Kruper, R. A. Wolf, W. W. Wu, A. A. Carr, D. A. Hay, D. E. Rudisill and G. Panzone, *U.S*, US6242606B120010605, 2001.

