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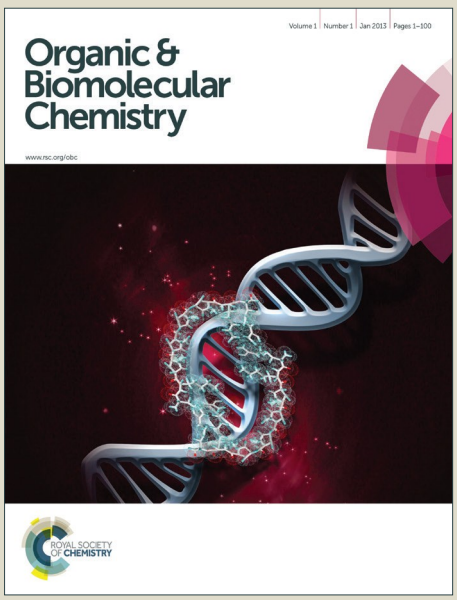

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ARTICLE

Radical-mediated divergent cyclization of benzamides toward perfluorinated or cyanated Isoquinolinediones†

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A simple and efficient copper-controlled divergent cyclization of benzamides leading to perfluorinated or cyanated isoquinolinediones was developed. In the presence of AIBN, methacryloyl benzamides with perfluoroalkyl iodides underwent cascade radical addition/cyclization to give perfluoroinated isoquinolinediones as the major product under metal-free conditions, whereas the use of CuI (10 mol %) was able to redirect the cyclization to yield isoquinolinediones bearing an α-cyano quaternary carbon center. The cyclization features controllable divergent synthesis and broad substrates scope as well as highly practical reaction conditions, thereby making such strategy as a highly attractive means to fluorinated or cyanated isoquinolinediones.

Introduction

Isoquinoline-1,3(2*H*,4*H*)-diones are prevalent structural units presented in naturally occurring products and pharmaceuticals with important biological functionality.[1] In Figure 1, several representative bioactive isoquinolinedione derivatives are shown, which exhibit various bioactivities such as antiviral agent targeting HIV-I enzyme,[1a,b] 5-HT_3 receptor antagonist[1c] and TrkA/p75NTR inhibitor.[1d] Thus, elegant construction of the modified and functionalized isoquinolinediones are expected to serve as popularly fundamental processes in organic synthesis and pharmaceutical industry. Recently, a strategy for the

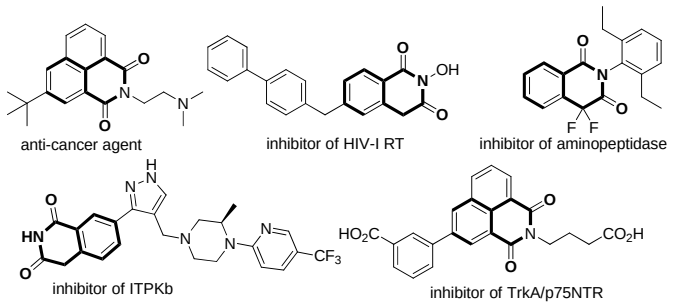
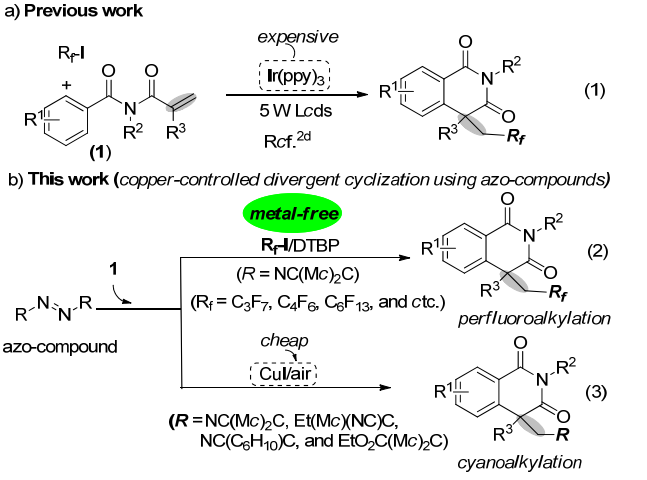


Figure 1. Selected Examples of Biologically Active Isoquinoline-1,3-dione Derivatives.

synthesis of such molecular skeleton *via* difunctionalization of alkenes involving cascade addition/cyclization has attracted great interest.[2] In this context, given that the higher solubility and lipophilicity imparted by the fluorinated groups leading to better cell membrane fusion and permeability and increased bioavailability,[3] the introduction of fluorinated substituents into isoquinolinedione skeleton by such strategy has also attracted increasing attention.[3a-d] For example, using commercially available and much less expensive perfluoroalkyl iodides as the R_f source,[4,5] our group recently developed a rapid and efficient approach to perfluorinated isoquinolinedione *via* visible-light photoredox catalysis under mild conditions (Scheme 1, eq 1).[2d] Although it represents an elegant and rare example toward perfluorinated isoquinolinedione, the expensive iridium-based photocatalyst6 was, nevertheless, required for good reaction efficiency, thereby limiting its application in practical organic synthesis to some extent. Therefore, developing more practically interesting and green chemistry approaches (e.g. under metal-free conditions) for such purpose is arguably of high interest by



Scheme 1. Perfluoroalkylation or cyanoalkylation of benzamides toward isoquinolinediones

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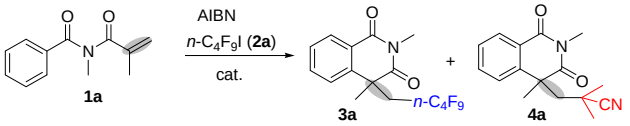
synthetic chemists. On the other hand, cyano-containing molecules exhibit important functions in synthetically or medicinally important intermediates. Undoubtedly, exploration of these strategies to construct the cyano-containing isoquinolinedione scaffold through low cost and high efficient process will be highly valuable, thereby fitting in with the demand of many promising synthetic or pharmaceutical applications. As a continuation of our ongoing project on the synthesis of functionalized isoquinolinediones,[2d,2e] we herein want to demonstrate a simple and efficient divergent cyclization of benzamides toward perfluorinated and cyanated isoquinolinediones (Scheme 1). In the divergent cascades, with AIBN (azodiisobutyronitrile) severing as the initiator of perfluorinated radical,[7,8] methacryloyl benzamides along with perfluoroalkyl iodides as the starting materials, which underwent perfluorinating cyclization to give the fluoroinated isoquinolinediones as the major product under metal-free conditions (eq 2). In contrast, when a catalytic amount of CuI (10 mol %) was used, the cyanating cyclization of benzamides with AIBN and analogues occurred with the removal of perfluoroalkyl iodides, thereby leading to various isoquinolinediones bearing an α-functionalized quaternary carbon center in high efficiency (eq 3).

Results and discussion

We began the reaction exploration by optimizing the cascade cyclization of *N*-methyl-*N*-methacryloyl benzamide[1a] with *n*-C_4F_9I (Table 1). At the outset, a combination of AIBN/DTBP described in our former work[9a] was firstly investigated, and the reaction, nevertheless, resulted in the perfluorinated isoquinolinedione **3a** in only 16% yield, accompanying a small amount of cyanated by-product **4a** possibly resulting from the cascade addition/cyclization of benzamide **1a** with AIBN (entry 1).[9,10] The replacement of DTBP with other similar oxidants such as TBPB and TBHP did not allow a further increase in **3a** yield (entries 2 and 3). To further improve the **3a** yield, several metal salts were next used in the reactions (entries 4-6). However, they did not lead to **3a** in higher yield, whereas the by-product **4a** appeared to form more efficiently in the presence of the copper catalysts (entries 4 and 5). Considering that a base could facilitate the removal of the aryl hydrogen in the catalytic cycle,[3d] several bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 was next investigated (entries 7-9). As expected, K_3PO_4 sharply improve the yield of **3a** to 71%, and the formation of the cyanated by-product **4a** was also suppressed efficiently with the removal of copper catalyst (entry 7). Notably, reducing the amount of initiator AIBN could exactly suppress the cyclization resulting in the by-product **4a**, but the yield of desired product **3a** decreased simultaneously (entry 10). In the control experiment, the cyclization reactions were found to be completely restrained with the removal of the AIBN (entry 11). Further screening disclosed that the optimal temperature for the fluoroalkylating cyclization was 100 °C, and an elevated temperature (>120 °C) would result in some unidentified side-reactions possibly resulting from the free radicals produced by AIBN[11] or DTBP[12] decomposition (entries 12 and 13). On the other hand, although a rapid access to 7-*tert*-alkylated isoquinolinediones by using AIBN and analogues has recently disclosed in our group,[2e] the cyanated skeleton outlined as **4a** was, in our opinion, also of synthetic and medicinal importance. Therefore, we next set out to optimize the conditions for the cyclization toward cyanated isoquinolinedione **4a**. Notably, the copper catalyst was observed to be important for the formation of **4a**, as well as the use of air as the oxidant turned out to be more efficient to promote the cyclization than DTBP (entries 14-16). In addition, a slightly decreased temperature (90 °C) was, compared with above perfluoroalkylating cyclization, more beneficial for the cyanating cyclization. Further screening disclosed that the solvent had important impact on the cyclization, and DMF proved to be best choice solvent/ media and could efficiently suppress the formation of another by-product 7-*tert*-alkylated isoquinolinedione (entries 17-19).[2e]

Table 1 Optimization of reaction conditions[a]



entry	initiator	oxidant	solvent	base	yield **3a** (%)[b]	yield **4a** (%)[b]
1	AIBN	DTBP	DMF	—	16	9
2	AIBN	TBPB	DMF	—	13	7
3	AIBN	TBHP	DMF	—	9	trace
4	CuI/AIBN	DTBP	DMF	—	14	21
5	CuBr/AIBN	DTBP	DMF	—	12	19
6	$FeBr_2$/AIBN	DTBP	DMF	—	11	7
7	***AIBN***	***DTBP***	**DMF**	***K_3PO_4***	***65***	***12***
8	AIBN	DTBP	DMF	K_2CO_3	41	9
9	AIBN	DTBP	DMF	Cs_2CO_3	22	7
10[c]	AIBN	DTBP	DMF	K_3PO_4	32	8
11	—	DTBP	DMF	K_3PO_4	trace	0
12[d]	AIBN	DTBP	DMF	K_3PO_4	18	9
13[e]	AIBN	DTBP	DMF	K_3PO_4	29	10
14[f,g]	CuI/AIBN	O_2	DMF	K_3PO_4	0	61
15[f,g]	***CuI/AIBN***	***air***	***DMF***	***K_3PO_4***	***0***	***67***
16[f,g]	AIBN	*air*	DMF	K_3PO_4	0	14
17[f,g]	CuI/AIBN	air	dioxane	K_3PO_4	0	17
18[f,g]	CuI/AIBN	air	CH_3CN	K_3PO_4	0	29
19[f,g]	CuI/AIBN	air	DCE	K_3PO_4	0	25

[a] Reaction conditions: **1a** (0.3 mmol), *n*-C_4F_9I (2 equiv), metal (10 mol %) and/or initiator (2 equiv.), oxidant (2 equiv) or O_2/air (1 atm), and solvent (2 mL) at 100 °C for 12 h. DTBP = di-*tert*-butyl peroxide, AIBN = azodiisobutyronitrile, TBPB = *tert*-butylperoxyl benzoate, TBHP = *tert*-butyl hydrogenperoxide (70% aqueous solution). [b] Yield of the isolated product. [c] Using 1 equiv. of AIBN. [d] At 80 °C. [e] At 120 °C. [f] With the removal of *n*-C_4F_9I. [g] At 90 °C.

With the optimal conditions for the fluorinating cyclization in hand, we sequentially turned our attention to investigate the substrate scope (Scheme 2). Firstly, we embarked on investigating the compatibility of *N*-substituents of the methacryloyl benzamides in this cyclization. A series of *N*-substituents of methacryloyl benzamides such as Me, Bu and Bn were observed to be well reactive in the cyclization, but the CH_2CO_2Et, unfortunately, led to **3e** in only 29% yield (**3a-d**). Next, we set out to evaluate the substitution effect on the aromatic moiety of the methacryloyl benzamides in the

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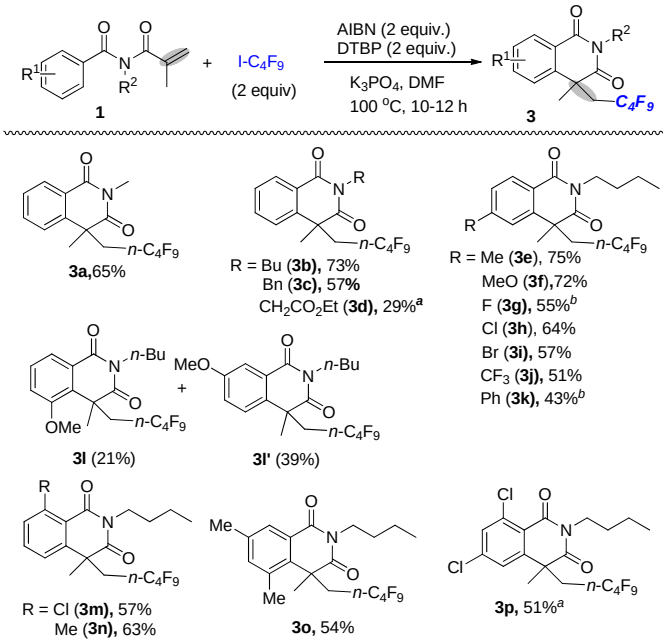
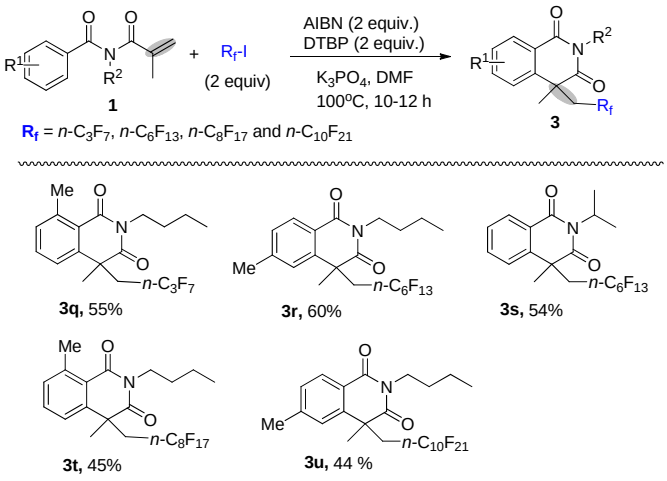
cyclization cascades. Gratefully, a wide variety of para-substituents (e.g., Me, MeO, F, Cl, CF_3 and Ph) on the aromatic ring displayed good reactivity irrespective of electronic and steric character of the substituent groups (**3e-k**). Additionally, when the *meta*-methoxyl substituted benzamide was examined under the reaction conditions, two regioselective products **3l** and **3l'** was observed to form with a moderate regioselectivity (2:1). Notably, the benzamides bearing *ortho*-substituents (e.g., Me and Cl) appeared to be less subject to steric hindrance, and be able to undergo the cyclization cascade to give the desired **3m** and **3n** efficiently. In addition, the 2,4-dichloro or 3,5-dimethyl benzamides were also viable substrates, thereafter leading to **3o** and **3p** in 54% and 51% yields respectively.



Scheme 2. Scope of methacryloyl benzamides in the reaction with *n*-C_4F_9I. Reaction conditions: **1** (0.3 mmol), *n*-C_4F_9I (2 equiv), AIBN (2 equiv), DTBP (2 equiv), K_3PO_4 (2 equiv.), and DMF (2 mL) at 100 °C for 10-12 h. [a] CH_3CN instead of DMF as the solvent. [b] With methyl group on the *N*-atom.

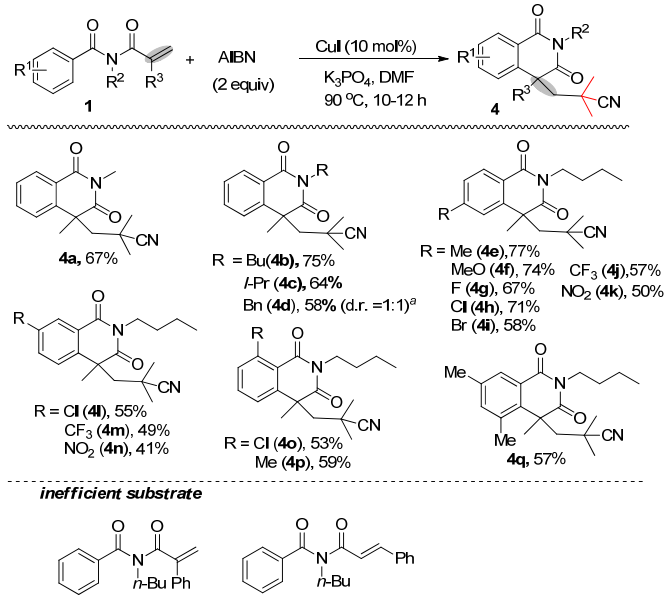
Subsequently, we also investigated the compatibility of other perfluoroalkyl iodide in the cyclization, thereby resulting in the incorporation of perfluoroalkyl moieties with various carbon-chain lengths into isoquinolinedione skeleton (Scheme 3). To our delight, a series of perfluoroalkyl iodides including C_3F_7I, $C_6F_{13}I$, $C_8F_{17}I$, and etc. were observed to be reactive with the perfluoroalkylation conditions, thereby leading to the isoquinolinediones bearing various perfluorinated moieties in moderate yields (**3q-u**). Moreover, the perfluoroalkylation reaction was expected to be employed as an efficient approach for the synthesis of lipophilic-controllable isoquinolinediones for the screening of fluoro-based bioactive compounds.

With the identification of cyanoalkylation conditions, we also investigated the substrate scope in the cyanoalkylation leading to isoquinolinediones bearing an α-cyano quaternary centre (Scheme 4). Delightedly, AIBN mediated the cyanoalkylating cyclization smoothly to afford the isoquinolinediones bearing a nitrile moiety in moderate to good yields irrespective of the electronic and steric character of the substituent groups on the benzamide scaffold (**4a-k**). Being different from above fluoroalkylating cyclization, the cyanating



Scheme 3 Scope of perfluoroalkyl iodides. Reaction conditions: **1** (0.3 mmol), R_fI (2 equiv), AIBN (2 equiv), DTBP (2 equiv), K_3PO_4 (2 equiv.), and DMF (2 mL) at 100 °C for 10-12 h.

cyclization of the *meta*- substituted benzamides mainly gave the isoquinolinediones regioselectively *via* cyclizing at the *para*-position of the substituents, albeit with slightly decreased yield (**4l-n**). In addition, the *ortho*- substituted benzamides, as well as the 3,5-dimethyl benzamide, were also viable substrates for the cyanating cyclization (**4o-q**). However, further investigations disclosed that the substituent phenyl group at both the 2 and 3-position of the acrylamide unit was inefficient for the cyclization, and failed to yield desired cyanated isoquinolinediones.



Scheme 4. Scope of substrates in cyanoalkylation. Reaction conditions: **1** (0.3 mmol), CuI (10 mol %), AIBN (2 equiv), air (1 atm), K_3PO_4 (2 equiv.), and DMF (2 mL) at 90 °C for 10-12 h. [a] Diastereomeric ratios (d.r.) was determined by ^1H NMR.

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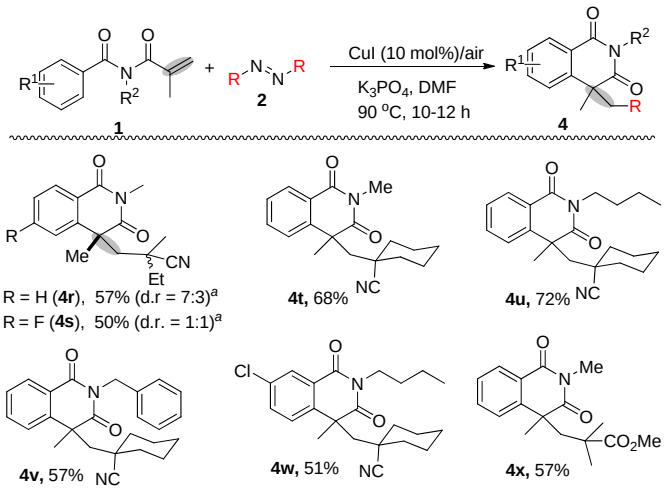
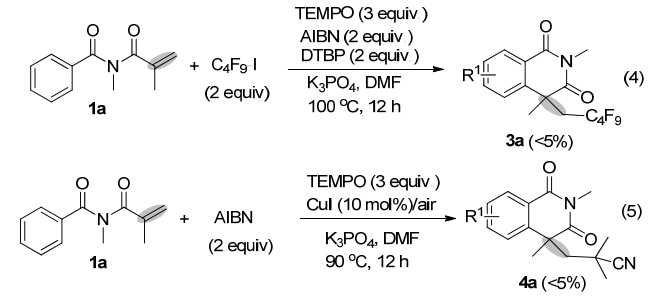
In addition, we also investigated the reactivity of other alkyl azo-compounds in the cyanoalkylating cyclization (Scheme 5). Encouragingly, several other azo-compounds containing an a-functionalized *tert*-alkyl groups such as Et(Me)(NC)C and NC(C_6H_{10})C, as well as $EtO_2C(Me)_2C$, were also observed to be well reactive under the optimal conditions, leading to various isoquinolinediones bearing bearing an α-functionalized quaternary centre in moderate to good yield (**3r-x**).



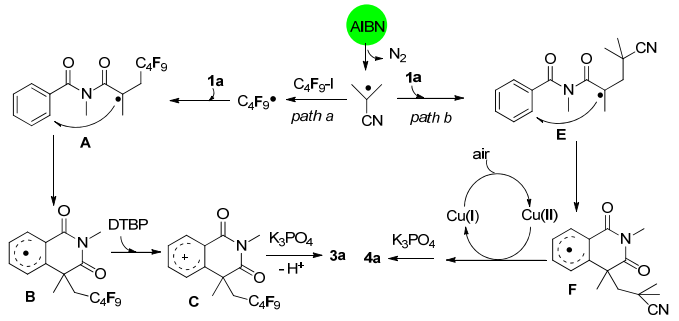
Scheme 5. Scope of alkyl azo-Compounds in the cyanoalkylation. Reaction conditions: **1** (0.3 mmol), azo-compound **2** (2 equiv), air (1 atm), CuI (10 mol %), K_3PO_4 (2 equiv.), and DMF (2 mL) at 90 °C for 10-12 h. [a] Diastereomeric ratios (d.r.) was determined by ^{1}H NMR

To further insight into the mechanism, we performed two control experiments shown as Scheme 6. First, by adding the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), the perfluoroalkylation cyclization of 1a with perfluorobutyl iodide was seriously inhibited (eq 4). Being consistent with the above event, the copper-catalyzed cyanoalkyalting cyclization of benzamide **1a** and AIBN was also suppressed completely in the presence of excess TEMPO, thus suggesting that the free radical intermediates might involve both of the present two divergent reactions (eq 5).



Scheme 6. Control experiments for the perfluoroalkylation and cyanoalkyaltion

On the basis of above experimental results, we proposed a possible working mechanism process for the divergent cascades (Scheme 7).[2,5,7-13] For the fluoroalkylating cyclization (*path a*, Scheme 7), firstly perfluorinated radical C_4F_9• is generated from C_4F_9I with the initiation of AIBN under heating conditions, and then adds onto the C=C bond of methacryloyl benzamide **1a** leading to radical intermediate **A**. Next, intramolecular cyclization of intermediate **A** occurs to form intermediate **B**, and then oxidation of the radical **B** by DTBP takes place to afford cyclohexadienyl cation **C**. Finally, the abstraction of an aromatic hydrogen of intermediate **C** by K_3PO_4 occurs to afford perfluorinated isoquinolinedione **3a**. Regarding the cyanoalkylation cyclization of methacryloyl benzamide **1a** with AIBN, a similar mechanism process involving Cu/air oxidative combination[13] is responsible for this cyclization (*path b*, Scheme 7).



Scheme 7. Proposed mechanism for the divergent perfluoroalkylation and cyanoalkyaltion

Conclusions

In summary, we have disclosed a simple and efficient copper-controlled divergent cyclization of methacryloyl benzamide leading to perfluorinated or cyanated isoquinolinediones by using AIBN and analogues for the first time. The reaction represents a rare and general example of AIBN-mediated divergent cyclization cascades of methacryloyl benzamide leading to different functionalized isoquinolinedione motifs in single step. Under transition-metal-free conditions, AIBN mainly acts as the initiator of R_f radical from R_fI to mediate the perfluorinating cyclization of benzamides, whereas the use of CuI may switch the role of AIBN from the radical initiator to a reactant leading to cyanated isoquinolinedione. Notably, the successful perfluoroalkylation reaction paves an efficient way to prepare new perfluoroalkyl-containing isoquinolinediones with different carbon-chain lengths, which may bring them versatile lipophilicity and cell permeability. The use of comparatively low cost R_fI as R_f radical sources, readily available azo-compounds as an initiator or reactant and naturally abundant air as the oxidant, broad substrate scope, as well as the copper catalysis or metal-free reaction conditions and controllable divergent synthesis, arguably make this protocol a highly attractive means to perfluorinated and cyanated isoquinoline-1,3(2*H*,4*H*)-diones.

Experimental

General. All manipulations of oxygen- and moisture-sensitive materials were conducted with a Schlenk technique under a nitrogen or argon atmosphere. Solvent were purified and dried

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in a standard manner. Flash column chromatography was performed using EM Silica gel 60 (300-400 mesh). Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. ^1H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz NMR spectrometer with trimethylsilane resonance as the internal standard. Unless otherwise noted, reagents were commercially available and were used without further purification. *N*-Alkyl-*N*-methacryloyl benzamides (**1)** were prepared according to literature procedures.[2]

General procedure for the synthesis of perfluoroalkylatedi isoquinoline-1,3(2*H*,4*H*)-diones (products 3a-u). To a mixture of methacryloyl benzamide **1a** (0.3 mmol), AIBN (0.06 mmol), DTBP (0.6 mmol), K_3PO_4 (0.6 mmol) in DMF (2.0 mL) was added perfluoroalkyl iodine (0.6 mmol) under N_2 atmosphere, and then the resulting solution was stirred at 100 ^oC for 10-12 h. Then the resulted mixture was diluted with Et_2O, and washed with water and then brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 10:1 as the eluant) on silica gel to afford the corresponding perfluorinated isoquinoline-1,3-diones **3a** as yellowish oil (89.7 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.52 – 7.43 (m, 2H), 3.51– 3.35 (m, 1H), 3.42 (s, 3H), 2.78 (ddd, J = 28.1, 15.3, 8.2 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ:174.7, 163.8, 140.6, 133.8, 129.3, 128.1, 125.7, 124.0, 120.5 – 106.1 (m), 43.3, 40.5 (t, J = 19.6 Hz), 31.9, 27.5, 23.4; HRMS m/z (ESI-TOF) calcd for $C_{16}H_{13}F_9NO_2$ $[M+H]^+$ 422.0798, found: 422.0796.

General procedure for the synthesis of cyanated isoquinoline-1,3(2*H*,4*H*)-diones (products 4a-x). To a mixture of methacryloyl benzamide **1a** (0.3 mmol), AIBN (0.06 mmol), CuI (0.003 mmol, 10 mol%), K_3PO_4 (0.6 mmol) in DMF (2.0 mL) was added perfluoroalkyl iodine (0.6 mmol), and then the resulting solution was stirred at 90 ^oC for 10-12 h under air atmosphere. Then the resulted mixture was diluted with Et_2O, and washed with water and then brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 5:1 as the eluant) on silica gel to afford the corresponding cyanated isoquinoline-1,3-diones **4a** as yellowish solid (54.2 mg, 67%). ^{1}HNMR (400 MHz, CDCl3) δ: 8.33 (dd, J = 8.2, 1.3 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.52 (t, J = 7.3 Hz, 2H), 3.42 (s, 3H), 2.77 (d, J = 14.5 Hz, 1H), 2.29 (d, J = 14.5 Hz, 1H), 1.65 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.6, 163.9, 141.0, 133.8, 129.4, 128.2, 126.6, 124.7, 123.2, 50.4, 45.9, 33.1, 30.6, 29.2, 27.7, 27.3; HRMS m/z (ESI-TOF) calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 271.1442, found: 271.1440.

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Notes and references

1 For selected examples, see: (*a*) S. K. V. Vernekar, Z. Liu, E. Nagy, L. Miller, K. A. Kirby, D. J. Wilson, J. Kankanala, S. T. Sarafianos, M. A. Parniak and Z. Wang, *J. Med. Chem*., 2015, **58**, 651; (*b*) Y.-L. Chen, J. Tang, M. J. Kesler, Y. Y. Sham, R. Vince, R. J. Geraghty and Z. Wang, *Bioorg. Med. Chem*., 2012, **20**, 467; (*c*) M. Langlois, J. L. Soulier, V. Rampillon, C. Gallais, B. Brkmont, S. Shen, D. Yang, A. Giudice and F. Sureau, *Eur. J. Med. Chem*., 1994, **29**, 925; (*d*) X. Gui, G. Gill, Z. Gan, Z. Dube and R. Vohra, Wo2009/39635 A1, 2009.

2 (*a*) W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem*., 2013, **125**, 13324; *Angew. Chem. Int. Ed*., 2013, **52**, 13086; (*b*) L. Li, M. Deng, S.-C. Zheng, Y. P. Xiong, B. Tan and X.-Y. Liu, *Org. Lett*., 2014, **16**, 504; (*c*) L. Zhang, C. Yang, Z. Xu, F. Gao and W. J. Xia, *J. Org. Chem*., 2015, **80**, 5730; (*d*) S. Tang, Y.-L. Deng, J. Li, W. Wang, G. Ding, M. Wang, Z. Xiao, Y. Wang and R. Sheng, *J. Org. Chem*., 2015, **80**, 12599; (*e*) S. Tang, Y.-L. Deng, J. Li, W. Wang, Y. Wang, Z.-Z. Li, L. Yuan, S.-L. Chen and R. -L. Sheng, *Chem. Commun*., 2016, **52**, 4470; (*f*) X.-F. Xia, S.-L. Zhu, Y. Li and H. Wang, *RSC Adv*., 2016, **6**, 51703.

3 For selected reports, see: (*a*) J. Wang, M. Sanchez-Rosello, J. Acena, C. L. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev*., 2014, **114**, 2432; (*b*) G. K. S. Prakash and S. Chacko, *Curr. Opin. Drug Discovery Dev*., 2008, **11**, 793; (*c*) O. A. Tomshenko and V. V. Grushin, *Chem. Rev*., 2011, **111**, 4475; (*d*) J. Nie, H.-C. Guo, D. Gahard and J.-A. Ma, *Chem. Rev*., 2011, **111**, 455.

4 Price from Alfa Aesar: nonafluoro-1-iodobutane, (97%, $45.7 for 25 g); nonafluorobutanesulfonyl chloride (98%, $317 for 5g), and nonafluorobutyl Togni reagent is not commercially available.

5 For selected examples of reactions of fluoroalkyl iodides, see: (*a*) P. V. Pham, D. A. Nagib and D. W. C. MacMillan, *Angew. Chem. Int. Ed*., 2011, **50**, 6119; (*b*) A. Hafner, A. Bihlmeier, M. Nieger, W. Klopper and S. Bräse, *J. Org. Chem*., 2013, **78**, 7938; (*c*) R. Zeng, C. Fu and S. Ma, *Angew. Chem. Int. Ed*., 2012, **51**, 3888; (*d*) Q. Qi, Q. Shen and L. Lu, *J. Am. Chem. Soc*., 2012, **134**, 6548; (*e*) A. T. Herrmann, L. L. Smith and A. Zakarian, *J. Am. Chem. Soc*., 2012, **134**, 6976; (*f*) T. Xu, C. W. Cheung and X. Hu, *Angew. Chem. Int. Ed*., 2014, **53**, 4910; (*g*) B. Zhang and A. Studer, *Org. Lett*., 2014, **16**, 3990; (*h*) Q. Luo, M. L. Chun, J. J. Tong, Y. Shao, W. Y. Shan, H. H. Wang, H. Zheng, J. Cheng and X. B. Wan, *J. Org. Chem*., 2016, **81**, 3103.

6 Price from Sigma-Aldrich: $Ir(ppy)_3$ (99%, $277.5 for 250 mg), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (98%, $125 for 100 mg).

7 For a review on fluorinated radicals, see: W. R. Dolbier, *Chem. Rev*., 1996, **96**, 1557.

8 (*a*) X. Fang, X. Yang, S. Mao, Y. Wang, G. Chen and F. Wu, *Tetrahedron*., 2007, **63**, 10684; (*b*) M. Napoli, C. Fraccaro, L. Conte, G. P. Cambaretto and E. Legnaro, *J. Fluorine Chem*. 1992, **57**, 219; (*c*) N. O. Brace, *J. Org. Chem*., 1663, **28**, 2093.

9 (*a*) D. Zhou, Z.-H. Li, S.-H. Li, M.-J. Fu, G.-L. Ding, Y.-C. Wang, R.-L. Sheng and S. Tang, *Eur. J. Org. Chem*., 2015, **7**, 1606; (b) S. Tang, Z.-H. Li, D. Zhou, S.-H. Li and R.-L. Sheng, *Tetrahedron Lett*., 2015, **56**, 142; (*c*) W. Wei, J. Wen, D. Yang, M. Guo, L. Tian, J. You and H. Wang, *RSC Adv*., 2014, **4**, 48535.

10 For selected reviews, see: (*a*) W. Mai, J. Wang, L. Yang, J. Yuan, P. Mao, Y. Xiao and L. Qu, *China. J. Org. Chem.*, 2014, **14**, 1958; (*b*) R. J. Song, Y. Liu, Y. X. Xie, J. H. Li and Y.-X. Xi, *Synthesis*., 2015, **47**, 1195 and references cited therein.

11 Q. Dai, T. Yu, X. Feng, H. Yang, Y. Jiang and J. Cheng, *Chem. Commun*., 2014, **50**, 12139.

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12 F.-L. Tan, R.-J. Song, M. Hu and J.-H. Li, *Org. Lett*., DOI: 10.1021/acs.orglett.6b01419.
13 For a review, see: A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem. Int. Ed*., 2011, **50**, 11062.

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