

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2019, 9, 2703

Synthesis of 4-(1*H*-isochromen-1-yl)isoquinolines through the silver-catalysed homodimerization of *ortho*-alkynylarylaldehydes and subsequent condensation of the 1,5-dicarbonyl motif with NH₃†

Minghui Guo,^a Xin Meng,^{*a} Yang Zhao,^a Yuexia Dong,^a Xuejun Sun,^a Laijin Tian^{*ab} and Ziping Cao ^{*ab}Received 9th November 2018
Accepted 7th January 2019

DOI: 10.1039/c8ra09269a

rsc.li/rsc-advances

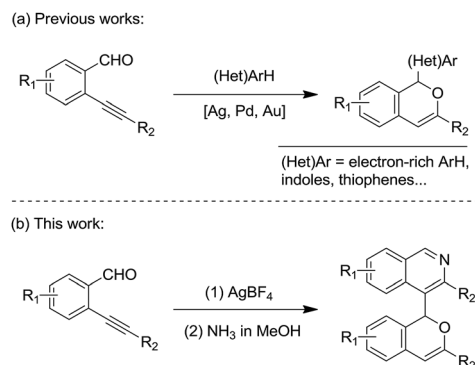
4-(1*H*-Isochromen-1-yl)isoquinoline derivatives were synthesized in high yields *via* the AgBF₄-catalyzed self-reaction of *ortho*-alkynylarylaldehydes to give isochromene intermediates, followed by the dehydration of the 1,5-dicarbonyl motif with NH₃. Compared with electron-rich aromatic substituents, this strategy can provide the desired isochromene products with an electron-deficient isoquinoline unit. The reactions feature simple experimental operations, mild reaction conditions and high product yields.

Introduction

The 1*H*-isochromene skeleton is the core structure of many biologically active molecules possessing important pharmaceutical activities, such as the those involved in the inflammatory activation of microglia,¹ antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pneumoniae*,² selective receptor antagonists of neurokinin-1 (NK1),³ and antagonists of *Mycobacterium bovis* BCG.⁴ Isoquinoline derivatives are also a class of important heterocycles having acetylcholinesterase inhibitory activities,⁵ murine tumor cell cytotoxicity,⁶ antiplasmodial activities,⁷ and so on. Thus, compounds with a combination of these two structural motifs could possess important potential bioactivity properties. Therefore, the synthesis of these kinds of product is of great significance.

Ortho-alkynylarylaldehydes are a class of important organic intermediates that can be converted into products possessing polycyclic skeletons.^{8,9} In particular, 1*H*-isochromenes can be readily constructed through metal- or non-metal-catalyzed reactions.^{10–17} Pioneering work by Yamamoto and co-workers revealed a Pd(OAc)₂-catalyzed reaction of enynals with alcohols to afford alkoxy-substituted 1*H*-isochromenes.¹⁰ⁱ From that time on, many methods were developed to access 1*H*-

isochromene derivatives starting from *ortho*-alkynylarylaldehydes, with a series of nucleophilic reagents.⁸ Recently, electron-rich (hetero)arenes, such as alkoxybenzenes and indoles, have been utilized as nucleophiles leading to the synthesis of functionalized 1*H*-isochromene compounds with high efficiency (Scheme 1(a)).¹⁷ However, electron-deficient heteroarene-substituted 1*H*-isochromenes could not be synthesized *via* direct methods due to weak nucleophilic abilities. In this context, and following our ongoing interest in the reactions of enynal substrates,^{17a,18,21a,c} we envisaged that these heteroarene-substituted 1*H*-isochromenes could be obtained *via* indirect ways involving the late-stage synthesis of the cyclic skeletons. Herein, we provide an efficient strategy to achieve the synthesis of isoquinoline-substituted 1*H*-isochromenes through a two-step route, which contains the AgBF₄-catalyzed self-reaction of *ortho*-alkynylarylaldehydes to give intermediate



Scheme 1 Access to (hetero)aromatic substituted 1*H*-isochromene derivatives.

^aSchool of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, P. R. China. E-mail: caozp_qfnu@163.com; mengxin1108@163.com; laijintian@163.com

^bShandong Key Laboratory of Life-Organic Analysis, Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, Qufu 273165, P. R. China

† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds. See DOI: 10.1039/c8ra09269a

isochromenes with a 1,5-dicarbonyl motif followed by dehydration with NH_3 to form the isoquinoline skeleton (Scheme 1(b)). It should be mentioned that the homodimerization of *ortho*-alkynylarylaldehydes was discovered by Porco Jr *et al.* in 2007, while only one example was provided for forming the isochromene efficiently.^{13c} The present study exhibited better substrate compatibility and the efficient synthesis of isoquinoline-substituted 1*H*-isochromenes. Furthermore, the reactions feature mild reaction conditions, simple operation procedures and high efficiency.

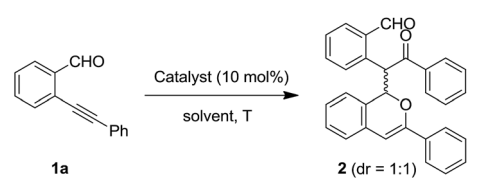
Results and discussion

We started from a dimerized product **2**, which has a 1*H*-isochromene ring and a 1,5-dicarbonyl motif. Compound **2** can be obtained in 80% yield as a mixture of two diastereoisomers (*dr* = 1/1 (ref. 19)) through the self-reaction of the *ortho*-alkynylbenzaldehyde **1a** under conditions involving the presence of silver salt (AgBF_4 ; 10 mol%) with 1,2-dichloroethane (DCE) as the solvent (Table 1, entry 1). Notably, the two isomers of **2** can be isolated carefully *via* column chromatography. In order to further improve the yield of **2**, a series of metal salts were screened (Table 1, entries 2–8). The results showed that AgBF_4 was the optimal catalyst. Other silver salts such as AgSbF_6 and

AgNO_3 couldn't afford product **2** at all, whereas the use of an AgOTf catalyst could lead to the formation of **2** in 66% yield (Table 1, entries 2–4). Copper(i) and zinc(ii) catalysts showed no catalytic reactivity under the presented conditions (Table 1, entries 5–7). Notably, $\text{Pd}(\text{OAc})_2$ could promote the formation of product **2**, albeit with a slightly lower yield (Table 1, entry 8). Subsequently, several solvents were investigated, revealing that tetrahydrofuran (THF) was suitable for the present transformation and the yield of **2** could be improved to 89% (Table 1, entries 9–12). Furthermore, the temperature effects indicated that the homodimerization product **2** could be readily obtained in 91–93% yield when the reaction was carried out at room temperature or under heating (Table 1, entries 14–16), while lowering the temperature to 0 °C led to a slightly lower yield (Table 1, entry 13). In order to consider the water effect, control experiments were carried out. The use of completely dry THF led to a low yield of **2** under an N_2 atmosphere (Table 1, entry 17). The addition of water (such as 1.0 equiv.) into dry THF did not obviously influence the reaction (Table 1, entry 18). In addition, the reaction couldn't proceed at 100 °C in the absence of AgBF_4 (Table 1, entry 19). So, the final conditions were established as those shown by entry 14 in Table 1.

To achieve the cyclization of the 1,5-dicarbonyl motif of compound **2** to an isoquinoline skeleton, different nitrogen sources and reaction conditions were investigated, and these are shown in Table 2. It could be found that the use of NH_3 solution in MeOH proved to be suitable, affording the desired product **3a** in 62% yield with the decomposed product **4** present in 20% yield (Table 2, entry 3). Other nitrogen sources such as NH_4OAc and $\text{NH}_3 \cdot \text{H}_2\text{O}$ could lead to the formation of **3a** but with more side-product **4** (Table 2, entries 1 and 2). Temperature studies showed that the cyclized product **3a** could be

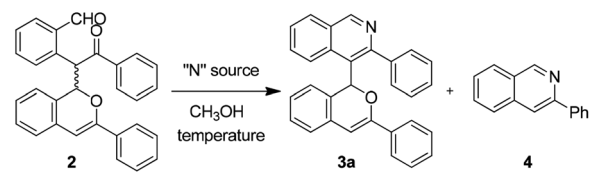
Table 1 Optimization of the conditions for the homodimerization of **1a**^a



Entry	Catalyst	Solv.	Temp. (°C)	Yield ^b (%)
1	AgBF_4	DCE	15	80
2	AgSbF_6	DCE	15	0
3	AgNO_3	DCE	15	0
4	AgOTf	DCE	15	66
5	CuI	DCE	15	0
6	ZnCl_2	DCE	15	0
7	ZnBr_2	DCE	15	0
8	$\text{Pd}(\text{OAc})_2$	DCE	15	71
9	AgBF_4	DCM	15	73
10	AgBF_4	THF	15	89
11	AgBF_4	CH_3CN	15	76
12	AgBF_4	1,4-Dioxane	15	84
13	AgBF_4	THF	0	85
14	AgBF_4	THF	25	93
15	AgBF_4	THF	45	91
16	AgBF_4	THF	60	91
17 ^c	AgBF_4	Dry THF	25	68
18 ^{c,d}	AgBF_4	Dry THF	25	92
19	—	THF	100	0

^a All reactions were carried out with **1a** (0.4 mmol) and catalyst (0.04 mmol, 0.1 equiv.) in the indicated solvent (1.6 mL) under air for about 7 and 8 hours. ^b The yield of isolated products. ^c Under an N_2 atmosphere. ^d 1 equiv. of H_2O was added.

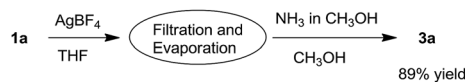
Table 2 Optimization of the conditions for the condensation of 1,5-dicarbonyl **2** with NH_3 ^a



Entry	"N" source (equiv.)	Temp. (°C)	Yield ^b (%)	
			3a	4
1	NH_4OAc (3)	50	32	73
2	$\text{NH}_3 \cdot \text{H}_2\text{O}$ (3)	50	47	50
3	NH_3 in CH_3OH (3)	50	62	20
4	NH_3 in CH_3OH (3)	40	75	14
5	NH_3 in CH_3OH (3)	25	87	7
6	NH_3 in CH_3OH (3)	0	82	7
7	NH_3 in CH_3OH (1.5)	25	93	—
8	NH_3 in CH_3OH (1.0)	25	75	8

^a All reactions were carried out with **2** (0.2 mmol) and the nitrogen source (0.2–0.6 mmol, 1.0–3.0 equiv.) in methanol (1.6 mL) at the indicated temperature for about 12 hours. ^b The yield of isolated products based on **2**.





Scheme 2 The convenient synthesis of the 4-(1*H*-isochromen-1-yl)isoquinoline **3a**.

obtained in 87% yield with a lower amount of **4** under room temperature conditions (Table 2, entry 5). In addition, lowering the loading of NH_3 solution in MeOH could also add to the yield of **3a** to 93%, with trace amounts of side-product **4** (Table 2, entry 7).

The one-pot synthesis of the isoquinoline **3a** with an isochromene unit was also subsequently examined. The AgBF_4 -catalyzed self-reaction was accomplished and the NH_3 source was then injected in a straightforward manner, affording the final product **3a** in only 31% yield. To our delight, after the filtration of the metal salt and the evaporation of solvent following the first reaction, the residue was dissolved in methanol and the NH_3 source was then added to provide the isoquinoline **3a** with higher efficiency (Scheme 2). The low yield for the direct one-pot reaction may be owing to the use of an improper solvent for the second step.

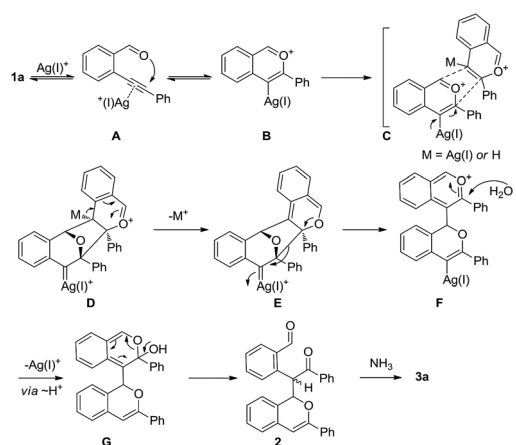
With the optimal process for the synthesis of **3a** in hand, the scope of *ortho*-alkynylarylaldehyde substrates was next investigated (Table 3). It could be found that a variety of *ortho*-alkynylbenzaldehyde derivatives could be applied to the present reaction, leading to the synthesis of the 4-(1*H*-isochromen-1-yl)isoquinolines **3a–p** in 31–91% yields. The substrates **1b–c**, having an electron-rich group at the *para*-position of the alkynylaryl part, were suitable for this transformation, giving the corresponding products **3b–c** with good efficiency. The halo-substituted (F, Cl and Br) phenylethynylbenzaldehydes **1d–f** could be also converted to the desired isoquinolines **3d–f** efficiently. The substrate **3g**, with an electron-deficient cyano group, could afford the desired isoquinoline **3g**, albeit with a low yield. The *meta*-substituted-phenylethynylbenzaldehydes **1h–j** were also good substrates, leading to the formation of the 4-(1*H*-isochromen-1-yl)isoquinolines **3h–j** in 70–86% yields. In addition, the alkynylarylaldehydes **1k–p**, having groups with different electronic natures in the arylaldehyde part, could generate efficiently the cyclized products **3k–p** under the current conditions. Alkyl-substituted-alkynylbenzaldehydes such as **1q** were also examined. However, the synthesis of the desired polycycle **3q** was not observed.

A possible mechanism for the synthesis of the isoquinoline **3a** is proposed in Scheme 3.^{13c} The coordination of the alkyne motif of **1a** to a silver(I) cation could give complex **A**, which then undergoes 6-*endo-dig* cycloisomerization to form the vinyl metal benzopyrylium **B**. The *exo*[3+2]-cycloaddition of **B** could afford the polycyclic intermediate **D** via **C**.^{20,21} The isomerization of the double bonds of **D** with the departure of Ag(I)^+ (or H^+) leads to the formation of intermediate **E**, followed by fragmentation to yield the oxonium species **F**.²² The addition of water to the oxonium **F** and its protodemetalation could form the hemiketal **G**, which could be converted to the ketoaldehyde product **2** via

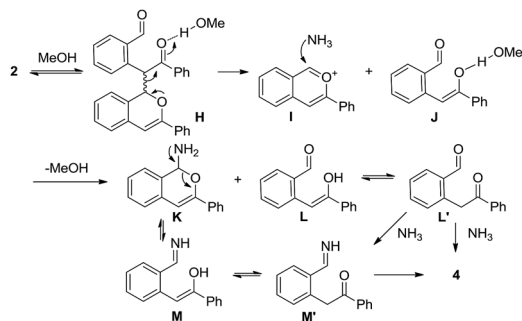
Table 3 Scope of substrates^{a,b}

1	3
3a , 89%	3b , 62%
3d , 76%	3e , 63%
3g , 31%	3h , 76%
3j , 86%	3k , 71%
3m , 71%	3n , 76%
3p , 87%	3q , mixture

^a See the Experimental section. ^b The yield of isolated products.



Scheme 3 The proposed mechanism for the formation of **3a**.



Scheme 4 The proposed mechanism for the formation of the side-product 4.

aromatization. The condensation of the 1,5-dicarbonyl motif of 2 with NH_3 could afford the final isoquinoline product 3a.

Scheme 4 outlines a proposed pathway for the formation of the isoquinoline 4. The homodimer 2 could give species H through the solvation of methanol to activate the ketocarbonyl, followed by fragmentation (retro-aldol type reaction) to yield the benzopyrylium I and species J.²³ The addition of NH_3 to I and the desolvation of J could afford the intermediates K and L, respectively. The fragmentation of the *N,O*-acetal K could give M (or the tautomer M'), leading to the formation of 4 through dehydration. Furthermore, the condensation of L (or the tautomer L') with NH_3 via the intermediate M' affords the final isoquinoline 4.

Experimental

Representative procedure for the synthesis of 4-(1*H*-isochromen-1-yl)isoquinolines

To a stirred solution of the *ortho*-alkynylbenzaldehyde 1a (82.5 mg, 0.4 mmol, 1.0 equiv.) in THF (1.6 mL), AgBF_4 (7.8 mg, 0.04 mmol, 0.1 equiv.) was added at room temperature. The reaction proceeded for about 8 hours. The mixture was filtered using a short silica gel column and volatiles were then evaporated off. The resulting crude 1,5-dicarbonyl 2 was dissolved in methanol (1.6 mL), followed by the injection of a solution of NH_3 in methanol (0.15 mL, 2.0 mol L^{-1} , 1.5 equiv.). The mixture was then stirred at room temperature for about 12 hours. After the evaporation of the solvent, the residue was then subjected to column chromatography to afford the desired isoquinoline 3a.

Conclusions

In summary, we have developed a new method to prepare 4-(1*H*-isochromen-1-yl)isoquinoline derivatives in high yields. This method contains two reactions involving the silver-catalyzed self-reaction of *ortho*-alkynylarylaldehydes and the subsequent condensation of the 1,5-dicarbonyl motif with NH_3 , without the chromatographic purification of the intermediates. Notably, this method could provide the desired isochromene products with an electron-deficient isoquinoline unit, which can't be obtained through the direct reaction of isoquinolines with *ortho*-alkynylarylaldehydes. Further work will focus on potential bioactivity studies of these heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the NSFC (21402106), the Shandong Natural Science Foundation (ZR2018JL013 and ZR2014BQ024), and the Research Start-up Foundation of Qufu Normal University (bsqd20130115).

Notes and references

- 1 A. R. Togni, V. Latina, G. Trefiletti, M. Guiso, S. Moschini and G. I. Togni, *Brain Res. Bull.*, 2013, **95**, 33.
- 2 Y. Li, S. Niu, B. Sun, S. Liu, X. Liu and Y. Che, *Org. Lett.*, 2010, **12**, 3144.
- 3 Y. Shishido, H. Wakabayashi, H. Koike, N. Ueno, S. Nukui, T. Yamagishi, Y. Murata, F. Nagane, M. Mitzutani, K. Shimada, Y. Fujiwara, A. Sakakibara, O. Suga, R. Kusano, S. Ueda, Y. Kanai, M. Tsuchiya and K. Satake, *Biomed. Chem.*, 2008, **16**, 7193.
- 4 C. W. Brown, S. Liu, J. Klucik, K. D. Berlin, P. J. Brennan, D. Kaur and D. M. Benbrook, *J. Med. Chem.*, 2004, **47**, 1008.
- 5 J. Zhang, Q.-Y. Zhang, P.-F. Tu, F.-C. Xu and H. Liang, *J. Nat. Prod.*, 2018, **81**, 364.
- 6 D. J. Milanowski, K. R. Gustafson, J. A. Kelley and J. B. McMahon, *J. Nat. Prod.*, 2004, **67**, 70.
- 7 C. W. Wright, S. J. Marshall, P. F. Russell, M. M. Anderson, D. Phillipson, G. C. Kirby, D. C. Warhurst and P. L. Schiff Jr., *J. Nat. Prod.*, 2000, **63**, 1638.
- 8 For leading reviews on the reactions of enynal substrates, see: (a) L. Chen, K. Chen and S. Zhu, *Chem*, 2018, **4**, 1208; (b) J. Ma, L. Zhang and S. Zhu, *Curr. Org. Chem.*, 2016, **20**, 102; (c) A. L. S. Kumari, A. S. Reddy and K. C. K. Swamy, *Org. Biomol. Chem.*, 2016, **14**, 6651; (d) H. Wang, Y. Kuang and J. Wu, *Asian J. Org. Chem.*, 2012, **1**, 302; (e) N. T. Patil and Y. Yamamoto, *ARKIVOC*, 2007, **5**, 6; (f) N. Asao, *Synlett*, 2006, 1645.
- 9 For recent examples, see: (a) H. Luo, R. Liang, L. Chen, H. Jiang and S. Zhu, *Org. Chem. Front.*, 2018, **5**, 1160; (b) M. Michalska, K. Grudzień, P. Małeck and K. Grela, *Org. Lett.*, 2018, **20**, 954; (c) C. R. Reddy and K. Mallesh, *Org. Lett.*, 2018, **20**, 150; (d) X. Zhang, C. Lyu, P. Li, W. Yong, J. Li and X. Zhu, *Chin. J. Org. Chem.*, 2018, **38**, 208; (e) S. Qiu, L. Chen, H. Jiang and S. Zhu, *Org. Lett.*, 2017, **19**, 4540; (f) W.-J. Hao, Y. Du, D. Wang, B. Jiang, Q. Gao, S.-J. Tu and G. Li, *Org. Lett.*, 2016, **18**, 1884; (g) T. Arto, P. Fernández, F. J. Fañanás and F. Rodríguez, *Chem. Commun.*, 2016, **52**, 13405.
- 10 For examples with oxygen nucleophiles: (a) S. Handa and L. M. Slaughter, *Angew. Chem., Int. Ed.*, 2012, **51**, 2912; (b) L.-P. Liu and G. B. Hammond, *Org. Lett.*, 2010, **12**, 4640; (c) A. Kotera, J. I. Uenishi and M. Uemura, *Tetrahedron Lett.*, 2010, **51**, 1166; (d) T. Godet, C. Vaxelaire, C. Michel, A. Milet and P. Belmont, *Chem.-Eur. J.*, 2007, **13**, 5632; (e) N. T. Patil and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 5139;



- (f) D. Yue, N. D. Cá and R. C. Larock, *Org. Lett.*, 2004, **6**, 1581; (g) S. Mondal, T. Nogami, N. Asao and Y. Yamamoto, *J. Org. Chem.*, 2003, **68**, 9496; (h) J. Barluenga, H. V. Villa, A. Ballesteros and J. M. González, *J. Am. Chem. Soc.*, 2003, **125**, 9028; (i) N. Asao, T. Nogami, K. Takahashi and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 764.
- 11 For examples with nitrogen nucleophiles: (a) A. K. Verma, D. Choudhary, R. K. Saunthwal, V. Rustagi, M. Patel and R. K. Tiwari, *J. Org. Chem.*, 2013, **78**, 6657; (b) G. Dyker, D. Hildebrandt, J. Liu and K. Merz, *Angew. Chem., Int. Ed.*, 2003, **42**, 4399.
- 12 For examples with phosphite nucleophiles: X. Yu, Q. Ding, W. Wang and J. Wu, *Tetrahedron Lett.*, 2008, **49**, 4390.
- 13 For examples with activated methylene nucleophiles: (a) D. Malhotra, L.-P. Liu, M. S. Mashuta and G. B. Hammond, *Chem.-Eur. J.*, 2013, **19**, 4043; (b) S. Obika, H. Kono, Y. Yasui, R. Yanada and Y. Takemoto, *J. Org. Chem.*, 2007, **72**, 4462; (c) A. B. Beeler, S. Su, C. A. Singleton and J. A. Porco Jr., *J. Am. Chem. Soc.*, 2007, **129**, 1413.
- 14 For examples with terminal alkyne nucleophiles: X. Yao and C.-J. Li, *Org. Lett.*, 2006, **8**, 1953.
- 15 For examples with allylsilane nucleophiles: (a) S. Bhunia, K.-C. Wang and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5063; (b) N. Asao, C. S. Chan, K. Takahashi and Y. Yamamoto, *Tetrahedron*, 2005, **61**, 11322.
- 16 For examples with hydride nucleophiles: (a) E. Tomás-Mendivil, J. Starck, J.-C. Ortuno and V. Michelet, *Org. Lett.*, 2015, **17**, 6126; (b) M. Terada, F. Li and Y. Toda, *Angew. Chem., Int. Ed.*, 2014, **53**, 235; (c) K. Saito, Y. Kajiwarra and T. Akiyama, *Angew. Chem., Int. Ed.*, 2013, **52**, 13284.
- 17 For examples with (hetero)arene nucleophiles: (a) H. Zhu, X. Meng, Z. Cao, G. Chen, X. Sun and J. You, *Synth. Commun.*, 2017, **47**, 463; (b) G. Mariaule, G. Newsome, P. Y. Toullec, P. Belmont and V. Michelet, *Org. Lett.*, 2014, **16**, 4570; (c) H. Wang, X. Han and X. Lu, *Chin. J. Chem.*, 2011, **29**, 2611; (d) B. Ouyang, J. Yuan, Q. Yang, Q. Ding, Y. Peng and J. Wu, *Heterocycles*, 2011, **82**, 1239; (e) R.-Y. Tang and J.-H. Li, *Chem.-Eur. J.*, 2010, **16**, 4733; (f) J. Barluenga, V.-V. Henar, I. Merino, A. Ballesteros and J. M. González, *Chem.-Eur. J.*, 2006, **12**, 5790; (g) D. Yue, N. D. Cá and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 3381.
- 18 For selected examples: (a) X. Meng, H. Zhu, G. Chen, L. Tian, X. Sun, Z. Cao and J. You, *Asian J. Org. Chem.*, 2017, **6**, 921; (b) R. Zhang, H. Zhu, X. Meng, Z. Cao, G. Chen, L. Tian, X. Sun and J. You, *Eur. J. Org. Chem.*, 2017, 2615; (c) H. Zhu, Z. Cao, X. Meng, L. Tian, G. Chen, X. Sun and J. You, *Tetrahedron*, 2017, **73**, 3310; (d) Z. Cao, H. Zhu, X. Meng, J. Guan, Q. Zhang, L. Tian, X. Sun, G. Chen and J. You, *Chem.-Eur. J.*, 2016, **22**, 16979; (e) Z. Cao, R. Zhang, X. Meng, H. Li, J. Li, H. Zhu, G. Chen, X. Sun and J. You, *RSC Adv.*, 2016, **6**, 74582; (f) Z. Cao, H. Zhang, X. Zhang, L. Zhang, X. Meng, G. Chen, X.-E. Zhao, X. Sun and J. You, *RSC Adv.*, 2015, **5**, 103155.
- 19 The dr value of **2** was determined by ^1H NMR analysis of crude reaction mixtures.
- 20 The intermediate **B** could be very prone to protodemetalation, also see (a) J. T. R. Liddon, M. J. James, A. K. Clarke, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem.-Eur. J.*, 2016, **22**, 8777; (b) J. T. R. Liddon, J. A. Rossi-Ashton, A. K. Clarke, J. M. Lynam, R. J. K. Taylor and W. P. Unsworth, *Synthesis*, 2018, **50**, 4829.
- 21 For the case of carbenoid type intermediates, see ref. 13c, also, (a) Z. Cao, H. Zhu, X. Meng, L. Tian, X. Sun, G. Chen and J. You, *Chem.-Eur. J.*, 2016, **22**, 9125; (b) R. Liang, T. Ma and S. Zhu, *Org. Lett.*, 2014, **16**, 4412; (c) Z. Cao, H. Zhu, X. Meng, L. Tian, G. Chen, X. Sun and J. You, *J. Org. Chem.*, 2016, **81**, 12401.
- 22 Another possible mechanism involving the direct self-addition of intermediate **B** (or protodemetalated type) to give **F** could not be ignored.
- 23 For leading examples on acid or solvent-promoted retro-Aldol reaction, see: (a) K. L. Ivanov, I. M. Vatsouro, S. I. Bezzubov, M. Y. Melnikov and E. M. Budynina, *Org. Chem. Front.*, 2018, **5**, 1655; (b) M. Sasaki, K. Goto, K. Tajima, T. Adschiri and K. Arai, *Green Chem.*, 2002, **4**, 285.

