Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2020, **18**, 81

Synthesis of lactone-fused pyrroles by ruthenium-catalyzed 1,2-carbon migration-cycloisomerization†

Takuma Watanabe, Yuichiro Mutoh * and Shinichi Saito *

Received 1st November 2019,
Accepted 22nd November 2019

DOI: 10.1039/c9ob02363a

rsc.li/obc

A ruthenium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones *via* 1,2-carbon migration was developed. Various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones were synthesized in good to excellent yields. The reaction was applied to the formal total synthesis of marine natural products Ningalin B and Lamellarin H. The efficient synthesis of γ-butyrolactone-fused pyrrole derivatives was also achieved.

Introduction

1-Arylchromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton is found in natural products such as Ningalin B, Lamellarin H, and related compounds (Fig. 1).[1] These alkaloids are isolated from marine organisms and known to exhibit biological activities[1] such as cytotoxicity,[2] MDR reversal activity,[2] HIV-1 integrase inhibition,[3] and antitumor activity.[4] Due to their promising pharmacological potentials, these pyrrole-containing natural products have been synthesized by various strategies over the years.[1,5]

Recent examples for the synthesis of the chromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton include palladium-catalyzed cycloisomerization,[6] one-pot multistep synthesis from 4-chloro-3-nitrocoumarin,[7] the functionalization of 2,3-diarylpyrrole,[8] the cyclization of 3-nitrocoumarin and papaverine,[9] and so on. Among these synthetic methods, the palladium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones is a straightforward and powerful method (Scheme 1a).[6] The reaction proceeds *via* intramolecular nucleophilic amination of the π-activated alkyne, and 2-substituted chromeno[3,4-*b*]pyrrol-4(3*H*)-ones were isolated.

We have recently developed ruthenium-catalyzed cycloisomerization reactions that involve the vinylidene rearrangement of internal alkynes by 1,2-carbon migration and cyclization.[10–13] For example, in the presence of a cationic ruthenium catalyst, various 2-alkynylanilides were converted into the 3-substituted indoles in high yields (Scheme 1b).[11] The mode of the reaction is different from other metal-catalyzed cycloisomerization of 2-alkynylanilines, where no 1,2-carbon migration was involved, and 2-substituted indoles were isolated.[14] In that study, we reported one example that 1-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one can be synthesized by applying the reaction. Considering the importance of the chromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton in medicinal chemistry and recent active studies related to the synthesis of Ningalin and Lamellarin derivatives, the development of a new and general method for the synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives would be highly desirable. In this paper, we report a ruthenium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones that leads to various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones *via* 1,2-carbon migration (Scheme 1c). This new methodology enabled the formal total synthesis of Ningalin B and Lamellarin H. Moreover, we describe the synthesis of rare γ-lactone-fused pyrrole derivatives by a similar ruthenium-catalyzed 1,2-carbon migration/cyclization strategy.

Results and discussion

We investigated the scope and limitation of the reaction using various 3-amino-4-alkynyl-2*H*-chromen-2-one derivatives (**1**, Table 1). As previously reported, when a mixture of

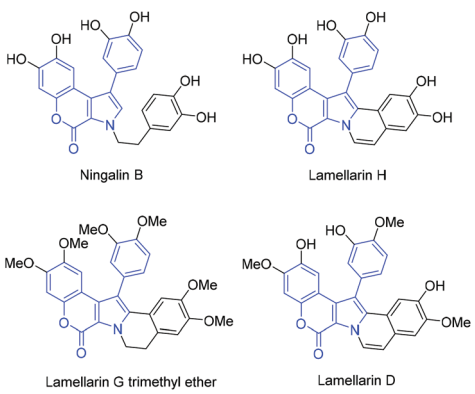
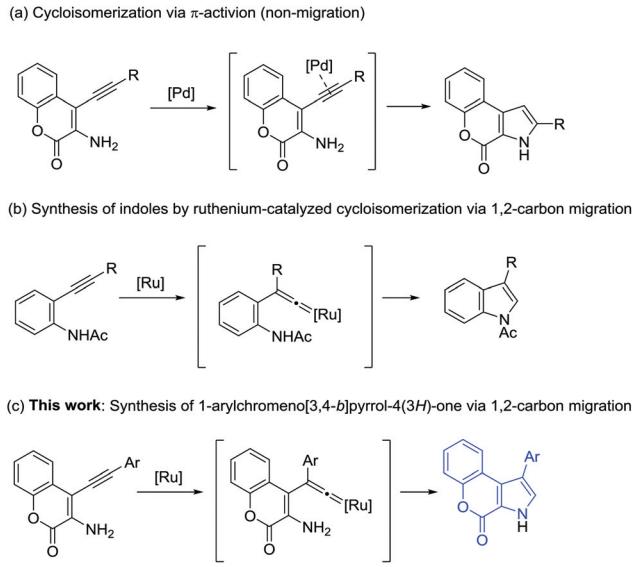


Fig. 1 Representative natural products and analogue containing 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton.

Department of Chemistry, Faculty of Science Tokyo University of Science, 1-3 Kagurazaka Shinjuku-ku, Tokyo 162-8601, Japan. E-mail: ymutoh@rs.tus.ac.jp, ssaito@rs.kagu.tus.ac.jp

†Electronic supplementary information (ESI) available: Experimental procedures and characterization data. CCDC 1961068–1961070. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob02363a

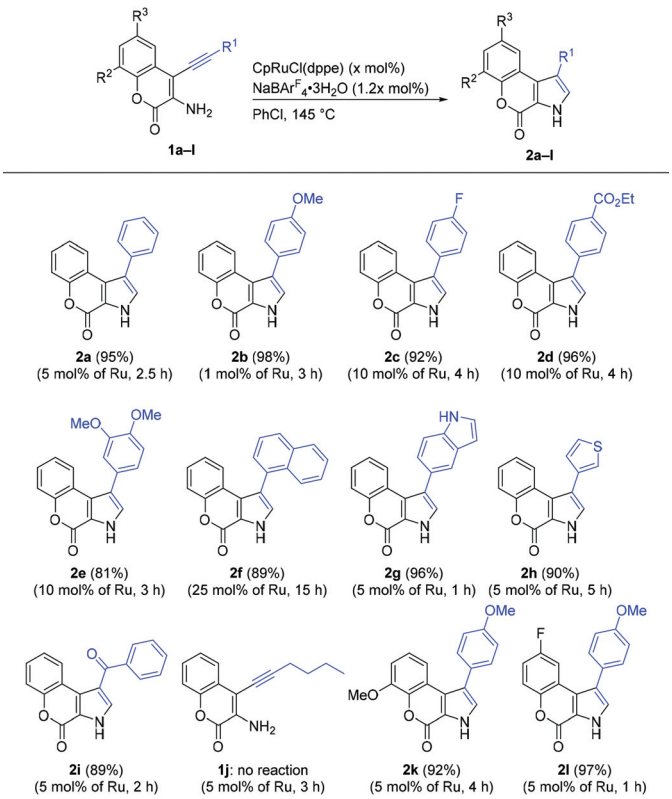


Scheme 1 Cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones.

aminocoumarin **1a**, [CpRuCl(dppe)] (Cp = η^5-$C_5H_5^-$; dppe = $Ph_2PCH_2CH_2PPh_2$) (5 mol%), and $NaBAr^F_4{\cdot}3H_2O$ (Ar^F = 3,5-$(CF_3)_2C_6H_3$) (6 mol%) was stirred at 145 °C for 2.5 h in chlorobenzene, the desired 1,2-aryl migration product 3-phenylpyrrolocoumarin (**2a**) was formed in 95% yield.[10,15] Isomeric 2-substituted pyrrole was not observed in the reaction mixture. Although the reaction of **1a** at 130 °C completed in 16 h at the same catalyst loading, the yield of **2a** was lower (82%). [IndRuCl(dppe)] (Ind = η^5-$C_9H_7^-$) and [CpFeCl(dppe)] were inactive catalysts for this reaction, and **2a** was not formed.

We studied the impact of the aryl groups bound to the ethynyl group (R^1) on the reaction. Under the similar reaction conditions described above, 4-methoxyphenyl pyrrole **2b** was obtained in 98% yield with lower catalyst loading. Electron-withdrawing groups were tolerated for this reaction, and pyrrolocoumarins **2c** (92% yield) and **2d** (96% yield) were synthesized in the presence of 10 mol% [CpRuCl(dppe)]. The low reactivity of the alkynes with electron-withdrawing groups (**1c** and **1d**) compared to the substrate with electron-donating group (**1b**) was consistent with our previous studies on the ruthenium-catalyzed cycloisomerizations *via* 1,2-carbon migration[10,11] and probably attributed to the rates of the formation of the disubstituted ruthenium vinylidene complex.[16] Pyrrolocoumarin **2e** with 3,4-dimethoxyphenyl group was also formed from **1e** in 81% yield. When the reaction of sterically congested amionocoumarin **1f** bearing 1-naphthyl group at the alkyne terminus was examined in the presence of 5 mol% of the ruthenium catalyst, the progress of the reaction was sluggish. In the presence of an increased amount (25 mol%) of [CpRuCl(dppe)], however, the corresponding product **2f** was isolated in 89% yield. The compatibility of the substrates with heteroaryl groups was also evaluated, and 5-indolyl derivative **2g** (96% yield) and thiophen-3-yl derivative **2h** (90% yield) were synthesized cleanly.

Table 1 Scope of the ruthenium-catalyzed 1,2-carbon migration/cyclization of 3-amino-4-ethynyl-2*H*-chromen-2-one derivatives (**1**)[a,b]

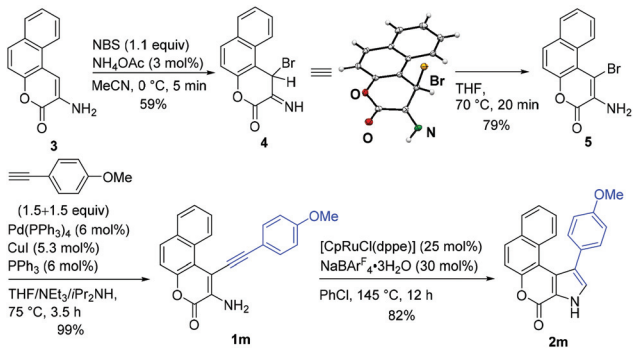


[a] Reaction conditions: **1** (0.25–0.5 mmol, $[\mathbf{1}]^0$ = 0.025–0.2 M in chlorobenzene), [CpRuCl(dppe)] (1–10 mol%), $NaBAr^F_4{\cdot}3H_2O$ (1.2–12 mol%). [b] Isolated yields are shown in parentheses except for **1j**.

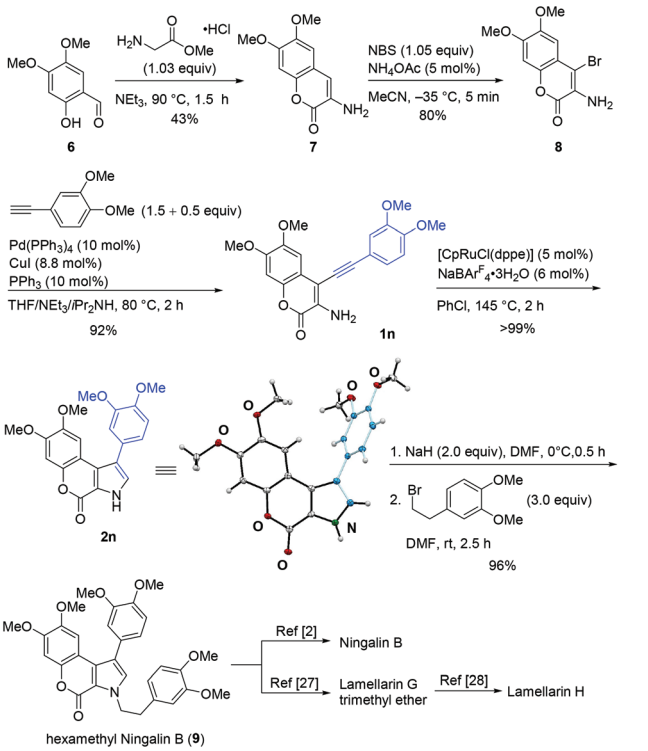
The scope of the reaction was further studied by introducing non-aromatic substituents as R^1. The reactivity of benzoyl aminocoumarin **1i** was similar to that of aryl-substituted aminocoumarins, and the corresponding pyrrole **2i** was prepared in 89% yield. The reaction of **1j** (R^1 = Bu) did not proceed, and the starting material was recovered. The low reactivity of **1j** is in contrast to our previous result: the cycloisomerization of a 2-hexynylaniline derivative generated the corresponding 3-butylindole derivative.[10] The reaction of **1j** in the presence of [CpRuCl(dppbz)] (dppbz = 1,2-bis(diphenylphosphino) benzene), which is a more effective catalyst for the synthesis of alkylated indoles,[10,17] also afforded no desired product. We assume that the decreased rate for the alkyne-to-vinylidene rearrangement of electron-deficient and alkyl-substituted acetylene[16,18] could be the reason for this unsuccessful result.

The effect of the substituents introduced to R^2 and R^3 on the coumarin moiety was explored. A methoxypyrrolcoumarin (**2k**, R^2 = OMe, R^3 = H) as well as a fluoropyrrolocoumarin (**2l**, R^2 = H, R^3 = F) were synthesized in high yields.

We further extended our study to the synthesis of a benzo-fused pyrrolocoumarin derivative.[19] The synthesis and ruthenium-catalyzed cycloisomerization of a benzochromenone derivative **1m** was summarized in Scheme 2. When we



Scheme 2 Preparation of **1m** and the synthesis of **2m**.



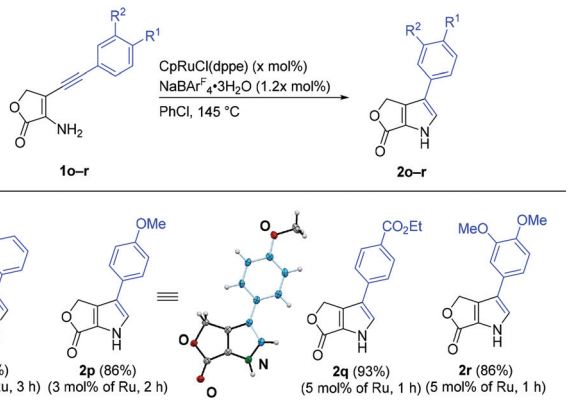
Scheme 3 Synthesis of the key intermediate **2n** for the synthesis of bioactive compounds.

tried to synthesize **5** by the bromination of **3** [20] with NBS in the presence of a catalytic amount of NH_4OAc at 0 °C,[21] an unexpected product **4** was isolated in 59% yield. Since the corresponding bromide was not isolated in the reaction of the bicyclic 3-amino-2*H*-chromen-2-one under similar reaction conditions,[21] we assume that the presence of the C–H bond in the proximity of the bromine atom inhibited the isomerization reaction of **4** at 0 °C. Due to the steric hindrance, the rate of the conversion of **4** to **5** should be lower compared to those of other aminocoumarins. The isomerization of **4** smoothly proceeded at elevated temperature (70 °C), and compound **5** was isolated in 79% yield. Subsequently, **1m** was synthesized in 99% yield by Sonogashira reaction of **5** with 4-methoxyphenylacetylene under modified Stoddart's conditions.[22] The reactivity of **1m** was similar to that of sterically congested substrate **1f**: the desired product **2m** was isolated in 82% yield when a larger amount (25 mol%) of the catalyst was employed.

Next, we applied this reaction to the formal total synthesis of Ningalin B and Lamellarin H (Scheme 3). When **6** [23,24] was treated with methyl aminoacetate hydrochloride,[25] aminocoumarin **7** was obtained in 43% yield. The bromination of **7** proceeded at −35 °C to afford **8** in 80% yield. No α-bromoimine, which was similar to **4**, was isolated. Compound **1n** was synthesized in 92% yield by Sonogashira reaction. To our delight, **2n** was obtained in quantitative yield in the presence of 5 mol% of the ruthenium catalyst. The structure of **2n** was confirmed by an X-ray diffraction analysis.[26] With the key intermediate (**2n**) in hand, hexamethyl Ningalin B (**9**) was synthesized in 96% yield by alkylation of **2n**.[7] The demethylation of **9** to Ningalin B was reported by Boger and co-workers.[2] Compound **9** is also the intermediate of Lamellarins, and the conversion of **9** into Lamellarin G trimethyl ether[27] and subsequent transformation to Lamellarin H were reported.[28] Therefore, we achieved the formal total synthesis of natural products, Ningalin B and Lamellarin H.

Furthermore, we examined the synthesis of γ-butyrolactone-fused pyrroles to exemplify the application of this reaction (Table 2). In spite of the simplicity of the structure, only a couple of γ-butyrolactone-fused pyrroles has been reported in the literature,[29,30] and a general method for the synthesis of these compounds has not been established. We successfully

Table 2 Synthesis of γ-butyrolactone-fused pyrrole derivatives[a,b]



[a] Reaction conditions: **1** (0.25–0.4 mmol, $[\mathbf{1}]^0$ = 0.1–0.2 M in chlorobenzene), [CpRuCl(dppe)] (3–5 mol%), $NaBAr^F_4{\cdot}3H_2O$ (3.6–6.0 mol%). [b] Isolated yields are shown in parentheses.

synthesized a series of γ-butyrolactone-fused pyrroles by the ruthenium-catalyzed cycloisomerization of 3-amino-4-arylethynylfuranones. Under the established reaction conditions described for the reaction of 3-amino-4-alkynyl-2*H*-chromen-2-one, the desired γ-butyrolactone-fused pyrroles **2o** and **2p** were isolated in 87% and 86% yields, respectively. The molecular structure of **2p** was confirmed by a single-crystal X-ray diffraction analysis. The reaction of aminobutenolide **1q** with an

ethoxycarbonyl group also afford the corresponding pyrrole **2q** in high yield. The reaction of **1r** with 3,4-dimethoxyphenyl group proceeded cleanly, and **2r** was obtained in 86% yield.

Conclusions

We have developed a synthetic method for various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones by ruthenium-catalyzed cycloisomerization of 3-amino-4-ethynyl-2*H*-chromen-2-ones *via* 1,2-carbon migration. The formal total synthesis of Ningalin B and Lamellarin H was achieved by employing this reaction. Moreover, a general method for the synthesis of uncommon γ-butyrolactone-fused pyrroles was established. Our studies will contribute to the development of a new method for the synthesis of heavily substituted pyrrole derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported in part by JSPS KAKENHI Grant Number JP19J14232 (T. W.), as well as Taisho Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry, Japan (Y. M.), the JGC-S Scholarship Foundation (Y. M.), and the Promotion Expenses for Mid-term Research Strategic Plan by Tokyo University of Science.

Notes and references

1 H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.
2 D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hendrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479.
3 C. P. Ridley, M. V. R. Reddy, G. Rocha, F. D. Bushman and D. J. Faulkner, *Bioorg. Med. Chem.*, 2002, **10**, 3285.
4 D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio and M. Álvarez, *J. Med. Chem.*, 2006, **49**, 3257.
5 For reviews, see: (*a*) T. Fukuda, F. Ishibashim and M. Iwao, *Heterocycles*, 2011, **83**, 491; (*b*) D. Imbri, J. Tauber and T. Opatz, *Mar. Drugs*, 2014, **12**, 6142.
6 (*a*) L. Chen and M.-H. Xu, *Adv. Synth. Catal.*, 2009, **351**, 2005; (*b*) K. C. Mujumdar, N. De and B. Roy, *Synthesis*, 2010, 4207; (*c*) Z. Wang, X. Xing, L. Xue, F. Gao and L. Fang, *Org. Biomol. Chem.*, 2013, **11**, 7334.
7 C.-K. Wu, Z. Weng and D.-Y. Yang, *Org. Lett.*, 2019, **13**, 5225.
8 R. Mei, S.-K. Zhang and L. Ackermann, *Synlett*, 2017, **28**, 1715.
9 K. B. Manjappa, J.-M. Lin and D.-Y. Yang, *J. Org. Chem.*, 2017, **82**, 7648.
10 T. Watanabe, Y. Mutoh and S. Saito, *J. Am. Chem. Soc.*, 2017, **139**, 7749.
11 T. Watanabe, H. Abe, Y. Mutoh and S. Saito, *Chem. – Eur. J.*, 2018, **24**, 11545.
12 For recent reviews on catalytic processes that involve vinylidene intermediates, see: (*a*) J. A. Varela, C. González-Rodríguez and C. Saá, *Top. Organomet. Chem.*, 2014, 237; (*b*) S. W. Roh, K. Choi and C. Lee, *Chem. Rev.*, 2019, **119**, 4293.
13 For stoichiometric internal alkyne-to-vinylidene rearrangements, see: (*a*) P. J. King, S. A. R. Knox, M. S. Legge, A. G. Orpen, J. N. Wilkinson and E. A. Hill, *J. Chem. Soc., Dalton Trans.*, 2000, 1547; (*b*) M. J. Shaw, S. W. Bryant and N. Rath, *Eur. J. Inorg. Chem.*, 2007, 3943; (*c*) Y. Ikeda, T. Yamaguchi, K. Kanao, K. Kimura, S. Kamimura, Y. Mutoh, Y. Tanabe and Y. Ishii, *J. Am. Chem. Soc.*, 2008, **130**, 16856; (*d*) Y. Mutoh, Y. Ikeda, Y. Kimura and Y. Ishii, *Chem. Lett.*, 2009, **38**, 534; (*e*) E. Bustelo, I. de los Rios, M. C. Puerta and P. Valerga, *Organometallics*, 2010, **29**, 1740; (*f*) Y. Mutoh, K. Imai, Y. Kimura, Y. Ikeda and Y. Ishii, *Organometallics*, 2011, **30**, 204; (*g*) V. K. Singh, E. Bustelo, I. de los Ríos, I. Macías-Arce, M. C. Puerta, P. Valerga, M. A. Ortuño, G. Ujaque and A. Lledós, *Organometallics*, 2011, **30**, 4014; (*h*) Y. Mutoh, Y. Kimura, Y. Ikeda, N. Tsuchida, K. Takano and Y. Ishii, *Organometallics*, 2012, **31**, 5150; (*i*) M. Otsuka, N. Tsuchida, Y. Ikeda, Y. Kimura, Y. Mutoh, Y. Ishii and K. Takano, *J. Am. Chem. Soc.*, 2012, **134**, 17746; (*j*) Y. Ikeda, Y. Mutoh, K. Imai, N. Tsuchida, K. Takano and Y. Ishii, *Organometallics*, 2013, **32**, 4353; (*k*) F. E. Fernández, M. C. Puerta and P. Valerga, *Inorg. Chem.*, 2013, **52**, 6502; (*l*) M. Otsuka, N. Tsuchida, Y. Ikeda, N. Lambert, R. Nakamura, Y. Mutoh, Y. Ishii and K. Takano, *Organometallics*, 2015, **34**, 3934; (*m*) Y. Ikeda, S. Kodama, N. Tsuchida and Y. Ishii, *Dalton Trans.*, 2015, **44**, 17448; (*n*) T. Kuwabara, S. Takamori, S. Kishi, T. Watanabe, Y. Ikeda, S. Kodama, Y. Minami, T. Hiyama and Y. Ishii, *Synlett*, 2018, **29**, 727; (*o*) T. Kuwabara, K. Sakajiri, Y. Oyama, S. Kodama and Y. Ishii, *Organometallics*, 2019, **38**, 1560.
14 For selected examples, see: (*a*) D. Pflästerer, P. Dolbundalchok, S. Rafique, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2013, **355**, 1383; (*b*) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 794; (*c*) X. Tian, L. Song, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Org. Lett.*, 2019, **21**, 4327.
15 The use of distilled chlorobenzene as the solvent is important to obtain reproducible results. We did not use silver salts in place of $NaBAr^F_4$ in this study, since silver salts were less effective in a closely related reaction which involves alkyne-to-vinylidene rearrangement. See, ref. 13*d*.
16 It has been reported that the rate of the 1,2-carbon migration decreases in the reaction of an electron-deficient aromatic alkyne or an aliphatic alkyne. See, ref. 13*d* and *f*.
17 The importance of dppbz ligand is unclear at this stage.

18 Compared to phenylacetylene, 4-alkynylchromen-2-one would be an electron-deficient alkyne.
19 The synthesis of a closely related compound was reported. See ref. 9.
20 For details, see the ESI.†
21 (*a*) S. B. Paul, K. C. Majumdar, S. Anwar and S. Choudhury, *Synlett*, 2015, **26**, 1039; (*b*) B. Das, K. Venkateswarlu, A. Majhi, V. Siddaiah and K. R. Reddy, *J. Mol. Catal. A: Chem.*, 2007, **267**, 30.
22 Y.-L. Zhao, L. Liu, W. Zhang, C.-H. Sue, Q. Li, O. Š. Miljanić, O. M. Yaghi and J. F. Stoddart, *Chem. – Eur. J.*, 2009, **15**, 13356.
23 D. H. Dethe, S. Mahapatra and S. K. Sau, *Org. Lett.*, 2018, **20**, 2766.
24 S. Blumberg and S. F. Martin, *Tetrahedron*, 2018, **74**, 4981.
25 H.-C. Song, Z.-L. Xu, Y.-W. Chen, J.-H. Yao, J. S. Bradshaw, P. B. Savage and R. M. Izatt, *J. Heterocycl. Chem.*, 2003, **40**, 475.
26 Although the synthesis of **2n** was recently reported, the spectroscopic data of **2n** synthesized by us does not match those reported previously in ref. 7.
27 M. Iwao, T. Takeuchi, N. Fujikawa, T. Fukuda and F. Ishibashi, *Tetrahedron Lett.*, 2003, **44**, 4443.
28 V. Kumar, A. Awasthi, A. Salam and T. Khan, *J. Org. Chem.*, 2019, **84**, 11596.
29 P. DeShong, D. A. Kell and D. R. Sidler, *J. Org. Chem.*, 1985, **50**, 2309.
30 D. L. Boger and M. Patel, *J. Org. Chem.*, 1988, **53**, 1405.