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

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A ruthenium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2H-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 activities¹ 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-2H-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-2H-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-2H-chromen-2-one derivatives (1, Table 1). As previously reported, when a mixture of

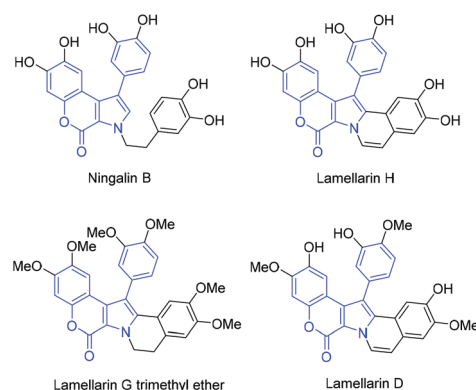
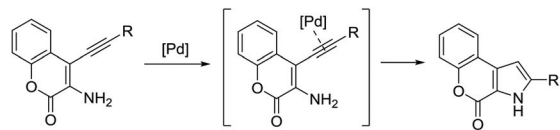


Fig. 1 Representative natural products and analogue containing 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton.

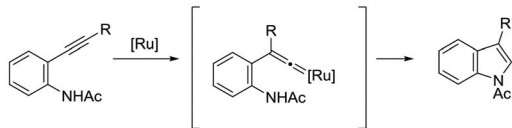
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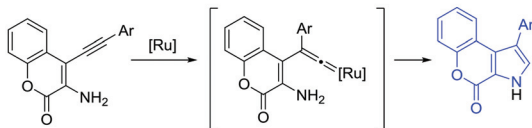


(a) Cycloisomerization via π -activation (non-migration)

(b) Synthesis of indoles by ruthenium-catalyzed cycloisomerization via 1,2-carbon migration



(c) This work: Synthesis of 1-arylchromeno[3,4-b]pyrrol-4(3H)-one via 1,2-carbon migration

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

aminocoumarin **1a**, [CpRuCl(dppe)] (Cp = η^5 -C₅H₅[−]; dppe = Ph₂PCH₂CH₂PPh₂) (5 mol%), and NaBAR^F₄·3H₂O (Ar^F = 3,5-(CF₃)₂C₆H₃) (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 -C₉H₇[−]) 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 (R¹) 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 aminocoumarin **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-2H-chromen-2-one derivatives (**1**)^{a,b}

1a-l	2a-l
2a (95%) (5 mol% of Ru, 2.5 h)	2b (98%) (1 mol% of Ru, 3 h)
2c (92%) (10 mol% of Ru, 4 h)	2d (96%) (10 mol% of Ru, 4 h)
2e (81%) (10 mol% of Ru, 3 h)	2f (89%) (25 mol% of Ru, 15 h)
2g (96%) (5 mol% of Ru, 1 h)	2h (90%) (5 mol% of Ru, 5 h)
2i (89%) (5 mol% of Ru, 2 h)	1j : no reaction (5 mol% of Ru, 3 h)
2k (92%) (5 mol% of Ru, 4 h)	2l (97%) (5 mol% of Ru, 1 h)

^a Reaction conditions: **1** (0.25–0.5 mmol), [**1**]⁰ = 0.025–0.2 M in chlorobenzene, [CpRuCl(dppe)] (1–10 mol%), NaBAR^F₄·3H₂O (1.2–12 mol%).

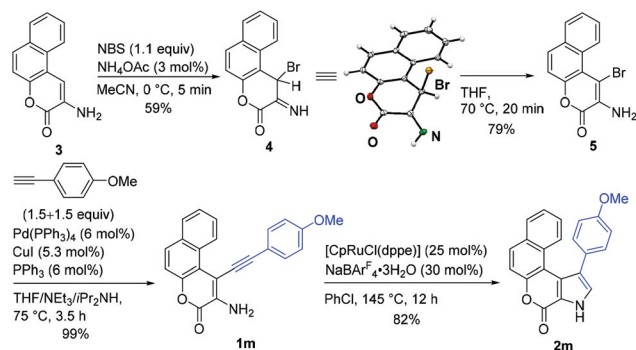
^b Isolated yields are shown in parentheses except for **1j**.

The scope of the reaction was further studied by introducing non-aromatic substituents as R¹. 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** (R¹ = 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-butyldole 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 R² and R³ on the coumarin moiety was explored. A methoxypyrrolocoumarin (**2k**, R² = OMe, R³ = H) as well as a fluoropyrrolocoumarin (**2l**, R² = H, R³ = F) were synthesized in high yields.

We further extended our study to the synthesis of a benzofused pyrrolocoumarin derivative.¹⁹ The synthesis and ruthenium-catalyzed cycloisomerization of a benzochrome-none derivative **1m** was summarized in Scheme 2. When we

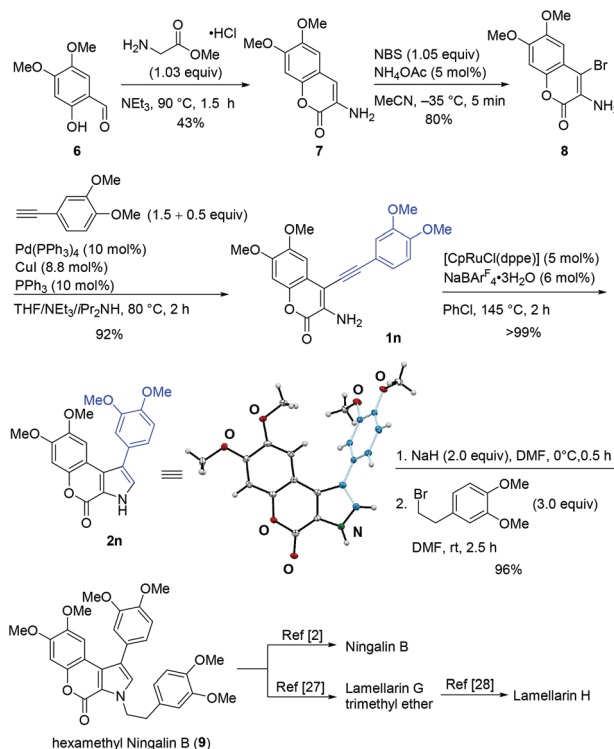
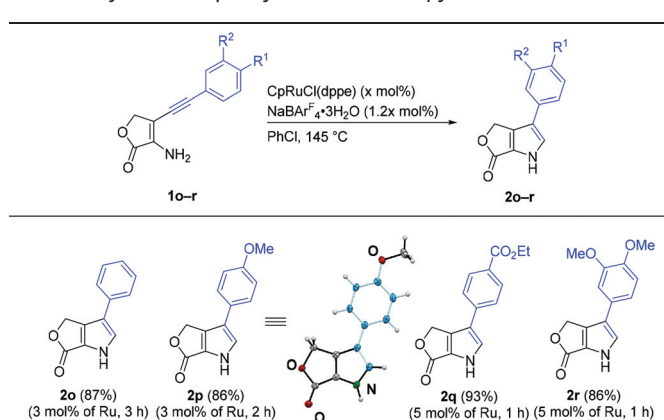


Scheme 2 Preparation of **1m** and the synthesis of **2m**.

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 ether²⁷ 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

Scheme 3 Synthesis of the key intermediate **2n** for the synthesis of bioactive compounds.Table 2 Synthesis of γ -butyrolactone-fused pyrrole derivatives^{a,b}

^a Reaction conditions: **1** (0.25–0.4 mmol), $[\mathbf{1}]^0 = 0.1\text{--}0.2\text{ M}$ in chlorobenzene, $[\text{CpRuCl}(\text{dppe})]$ (3–5 mol%), $\text{NaBARF}_4 \cdot 3\text{H}_2\text{O}$ (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.

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Notes and references

- H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.
- D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hendrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479.
- C. P. Ridley, M. V. R. Reddy, G. Rocha, F. D. Bushman and D. J. Faulkner, *Bioorg. Med. Chem.*, 2002, **10**, 3285.
- D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio and M. Álvarez, *J. Med. Chem.*, 2006, **49**, 3257.
- 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.
- (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.
- C.-K. Wu, Z. Weng and D.-Y. Yang, *Org. Lett.*, 2019, **13**, 5225.
- R. Mei, S.-K. Zhang and L. Ackermann, *Synlett*, 2017, **28**, 1715.
- K. B. Manjappa, J.-M. Lin and D.-Y. Yang, *J. Org. Chem.*, 2017, **82**, 7648.
- T. Watanabe, Y. Mutoh and S. Saito, *J. Am. Chem. Soc.*, 2017, **139**, 7749.
- T. Watanabe, H. Abe, Y. Mutoh and S. Saito, *Chem. – Eur. J.*, 2018, **24**, 11545.
- 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.
- 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.
- 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.
- The use of distilled chlorobenzene as the solvent is important to obtain reproducible results. We did not use silver salts in place of NaBar^F₄ in this study, since silver salts were less effective in a closely related reaction which involves alkyne-to-vinylidene rearrangement. See, ref. 13*d*.
- 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*.
- 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.

