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Construction of Pyrrolocoumarin Cores through Double C–H Annulation Cascade

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Abstract. The rhodium(III)-catalyzed double C–H annulation of 3-(acetylmino)coumarins with internal arylacetylenes proceeds smoothly accompanied by two C–C and two C–N bond formation to produce 8-aryl-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-ones selectively. The reaction provides a straightforward route to natural product inspired pentacyclic pyrrolocoumarin derivatives from readily available building blocks.

Keywords: Annulation; C–C coupling; C–H activation; Homogeneous catalysis; Rhodium

utilities, a variety of synthetic routes toward them have been developed. However, most of them involve complicated multi-steps for constructing the fused heterocycle cores.^[4]

Meanwhile, the transition-metal-catalyzed C–H annulation reactions of aromatic substrates possessing a heteroatom-containing directing group with internal alkynes have become recognized to be powerful tools for constructing fused heterocyclic frameworks in terms of step- and atom-economies (Scheme 1a).^[5]

Introduction

Coumarin-fused heterocycles have attracted much attention in the functional materials field for their photo- and electrochemical properties.^[1] The fused coumarin scaffolds have also been recognized as important structures in the medicinal chemistry field because of their frequent occurrence in natural and synthetic bioactive molecules. In particular, natural marine alkaloid lamellarins,^[2] containing pyrrolocoumarin cores, have been reported to exhibit various biological activities as a cytotoxin and topoisomerase I inhibitor.^[3] The structures of representative examples of pentacyclic lamellarin alkaloids are shown in Figure 1. In light of these

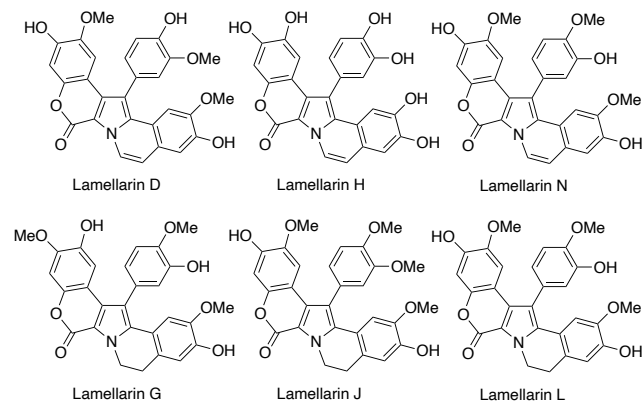
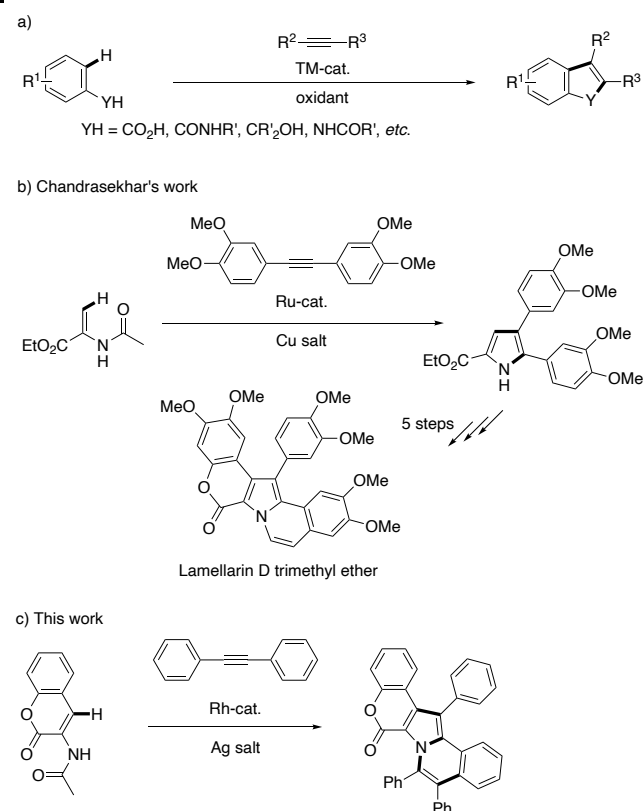


Figure 1. Representative Lamellarins.



Scheme 1. Transition-Metal-Catalyzed C–H Annulation.

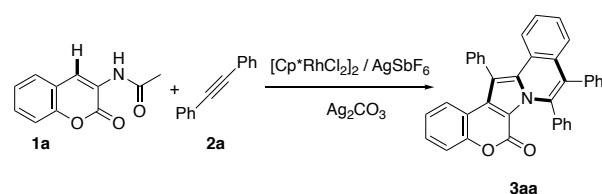
They can provide shortcuts in synthesizing complex polycyclic molecules. Chandrasekhar and co-workers utilized a ruthenium-catalyzed alkenyl C–H annulation of enamines with diarylacetylenes for constructing the pyrrole core in the total synthesis of lamellarins (Scheme 1b).^[6] In the context of our

studies on C–H annulation for constructing nitrogen-containing fused heterocycles,^[7] we succeeded in finding that treatment of 3-(acetylamino)coumarins with internal arylacetylenes under rhodium catalysis leads to double C–H annulation to form a pentacyclic pyrrolocoumarin system (Scheme 1c).^[8,9] This is one example for recently developed L-type double annulations.^[10] Note that 3-(acetylamino)coumarins can be easily prepared by the condensation of salicylaldehydes with *N*-acetyl glycine.^[11] The procedure provides a straightforward pathway to lamellarin cores from stable, readily available building blocks. These new findings are described herein.

Results and Discussion

In an initial attempt, 3-(acetylamino)coumarin (**1a**) (0.3 mmol) was treated with diphenylacetylene (**2a**) (0.3 mmol) in the presence of catalytic amounts of [Cp*RhCl₂]₂ (0.0075 mmol; 2.5 mol%) and AgSbF₆ (0.03 mmol; 10 mol%) and Ag₂CO₃ (0.6 mmol) as an oxidant in diglyme (3 mL) under Ar at 130 °C for 20 h. As a result, unexpected double C–H annulation took place accompanied by deacetylation to give 8,9,14-triphenyl-6*H*-chromeno[4',3':4,5]pyrrolo[2,1-*a*]isoquinolin-6-one (**3aa**) as a 1:2 coupling product in

Table 1. Reaction of 3-(Acetylamino)coumarin (**1a**) with Diphenylacetylene (**2a**)^a.



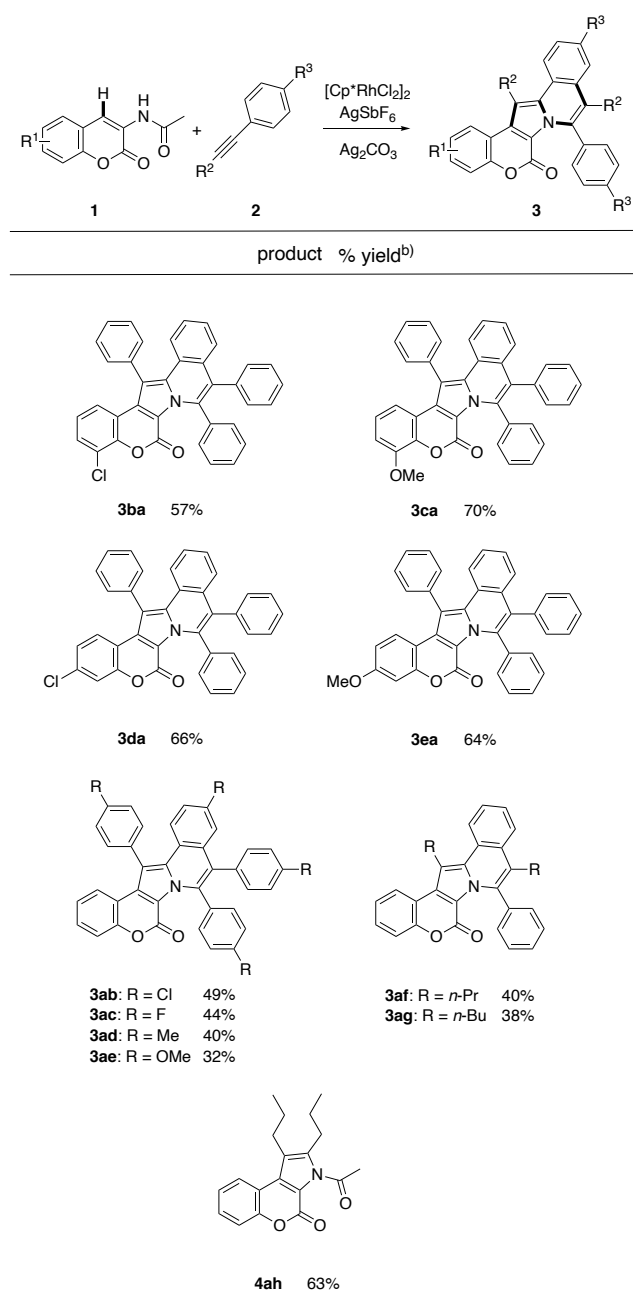
Entry	Solvent	Time [h]	Yield of 3aa [%] ^b
1 ^c	diglyme	20	19 ^d
2	diglyme	5	45
3	<i>o</i> -C ₆ H ₄ Cl ₂	5	56
4 ^e	<i>o</i> -C ₆ H ₄ Cl ₂	5	56
5	diglyme / <i>o</i> -C ₆ H ₄ Cl ₂ (1:1)	5	44
6	diglyme / <i>o</i> -C ₆ H ₄ Cl ₂ (2:1)	5	29
7 ^f	<i>o</i> -C ₆ H ₄ Cl ₂	5	66

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cp*RhCl₂]₂ (0.01 mmol), AgSbF₆ (0.04 mmol), Ag₂CO₃ (0.2 mmol) in solvent (2 mL) under Ar at 130 °C, unless otherwise noted. ^b Isolated yield based on the amount of **1a** used. ^c **1a** (0.3 mmol), **2a** (0.3 mmol), [Cp*RhCl₂]₂ (0.0075 mmol), AgSbF₆ (0.03 mmol), and Ag₂CO₃ (0.6 mmol) were employed in diglyme (3 mL). ^d Yield based on the amount of **2a** used. In this case, a minor amount (6%) of 1:1 coupling product was also formed. ^e Ag₂CO₃ (0.4 mmol) was employed. ^f At 110 °C.

19% yield (entry 1 in Table 1).^[12] In the reaction mixture, a minor amount (6%) of expected 1:1 coupling product was also detected. Using 2 equivalents of **2a** and increased amounts of [Cp*RhCl₂]₂ (10 mol%) and AgSbF₆ (40 mol%) promoted the double annulation. Thus, **3aa** was obtained in 45% yield within 5 h (entry 2). In this case, only a trace amount of 1:1 coupling product was formed. The **3aa** yield increased to 56% in *o*-dichlorobenzene (entry 3). Increasing the amount of Ag₂CO₃ did not affect the reaction efficiency (entry 4). The **3aa** yield somewhat decreased in mixed solvents diglyme / *o*-dichlorobenzene 1:1 and 2:1 (entries 5 and 6). Finally, the yield was enhanced up to 66% by decreasing the reaction temperature to 110 °C (entry 7).

Under the conditions in entry 7 of Table 1, we next examined the reactions of variously substituted 3-(acetylamino)coumarins **1** with **2a** (Table 2). 8-Chloro- (**1b**) and 8-methoxy-3-(acetylamino)coumarins (**1c**) underwent the reaction smoothly to give **3ba** and **3ca** in 57 and 70% yields, respectively. Substitution at the C7 position of 3-(acetylamino)coumarins did not affect the reaction efficiency significantly. Thus, 3-chloro- (**3da**) and 3-methoxychromenopyrroloisoquinolinones (**3ea**) were obtained in 64–66% yields in the reactions of 7-chloro- and 7-methoxy-3-(acetylamino)coumarins **1d** and **1e** with **2a**. The reactions using various alkynes **2** in place of **2a** could also be conducted under similar conditions. 4-Chloro- (**2b**), 4-fluoro- (**2c**), 4-methyl- (**2c**), and 4-methoxysubstituted diphenylacetylenes (**2d**) reacted with **1a** to produce the corresponding tetrasubstituted 8,9,14-triphenylchromenopyrroloisoquinolinones **3ab–3ae** in moderate yields. Unsymmetrical alkylphenylacetylenes such as 1-phenyl-1-pentyne (**2f**) and 1-phenyl-1-hexyne (**2g**) coupled with **1a** regioselectively to afford 9,14-dialkyl-8-phenylchromenopyrroloisoquinolinones **3af** and **3ag** in 40 and 28% yields. In both cases, no regioisomers were detected. Expectedly, dialkylacetylene, 4-octyne (**2h**), underwent the coupling with **1a** in a 1:1 manner to give 3-acetyl-1,2-dipropylchromeno[3,4-*b*]pyrrolo-4(3*H*)-one (**4ah**) in 63% yield.

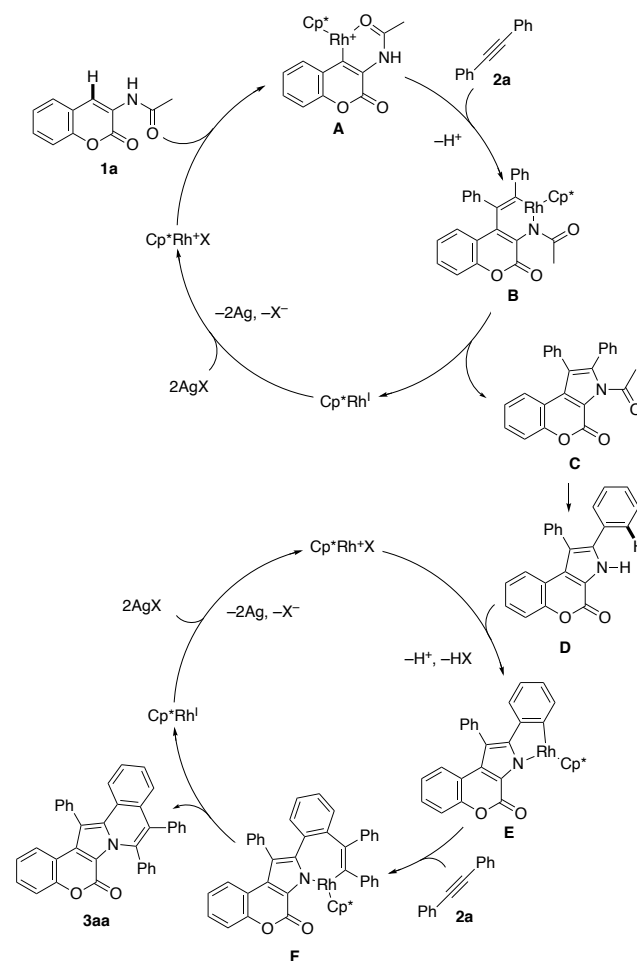
Table 2. Reaction of 3-(Acetylamino)coumarins **1** with Alkynes **2a**.



a) Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (0.01 mmol), AgSbF_6 (0.04 mmol), Ag_2CO_3 (0.2 mmol) in *o*-dichlorobenzene (2 mL) under Ar at 110 °C for 5 h. b) Isolated yield based on the amount of **1** used.

A plausible pathway for the reaction of **1a** with **2a** is illustrated in Scheme 2. The first annulation seems to proceed as previously proposed for the reaction of simple *N*-acetylanilines with alkynes,^[13] through coordination of the acetylamino directing group of **1a** to a cationic $\text{Cp}^*\text{Rh}^+\text{X}$ species, cyclorhodation at the C4-position, alkyne insertion into the formed C–Rh bond of intermediate **A** to form intermediate **B**, and C–N reductive elimination to form **C** and Cp^*Rh^1 species. The latter may be reoxidized by Ag salts to regenerate an active $\text{Cp}^*\text{Rh}^{\text{III}}$ species. Formed **C** may undergo deacetylation by a trace amount of water presenting in the present system to form **D**. The N–H of **D** may next

act as a directing group to induce the second cyclorhodation to give a five-membered rhodacycle intermediate **E**.^[7i] Then alkyne insertion to form intermediate **F** and subsequent reductive elimination may occur to afford the final product **3aa**.



Scheme 2. Plausible Mechanism for the Reaction of **1a** with **2a**.

Conclusion

We have demonstrated that 3-(acetylamino)coumarins undergo dehydrogenative coupling upon treatment with diarylacetylenes in the presence of a rhodium catalyst in a 1:2 manner to afford pentacyclic pyrrolocoumarin derivatives. The reaction with unsymmetrical alkylphenylacetylenes has also been found to occur regioselectively to give 1:2 coupling products. Work is underway for constructing other polycyclic systems.

Experimental Section

Experimental Details: To a 20 mL two-necked flask with a reflux condenser, a balloon, and a rubber septum were added 3-(acetylamino)coumarin **1** (0.1 mmol), alkyne **2** (0.2 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (0.01 mmol, 6 mg), AgSbF_6 (0.04 mmol, 14 mg), Ag_2CO_3 (0.2 mmol, 55 mg), *o*-dichlorobenzene (2 mL), and 1-methylnaphthalene (ca.

15 mg) as internal standard. The mixture was stirred under Ar (1 atm) at 110 °C (bath temperature) for 5 h. The reaction mixture was diluted by ethyl acetate (40 mL). The organic layer was washed by water (40 mL, four times) and dried over Na₂SO₄. After evaporation of the solvents under vacuum, product **3** was isolated by column chromatography on silica gel using hexane–ethyl acetate as eluent. Further purification by GPC (gel permeation chromatography) was performed, if needed.

Acknowledgements

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References

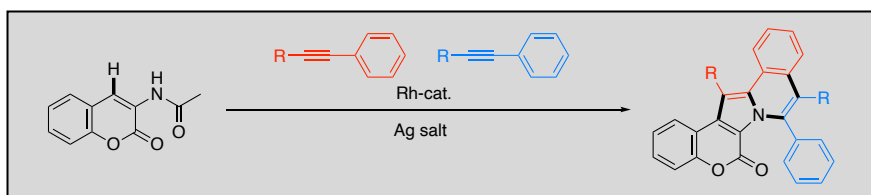
- [1] For recent examples, see: a) C.-K. Wu, Z. Weng, D.-Y. Yang, *Org. Lett.* **2019**, *21*, 5225; b) M. K. Weclawski, I. Deperasinska, M. Banasiewicz, D. C. Young, A. Leniak, D. T. Gryko, *Chem. Asian J.* **2019**, *14*, 1763; c) C.-H. Lin, D.-Y. Yang, *Org. Lett.* **2013**, *15*, 2802; d) A. Y. Bochkov, I. O. Akchurin, O. A. Dyachenko, V. F. Traven, *Chem. Commun.* **2013**, *49*, 11653.
- [2] For selected reviews, see: a) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264; b) D. Baunbæk, N. Trinkler, Y. Ferandin, O. Lozach, P. Ploypradith, S. Rucirawat, F. Ishibashi, M. Iwao, L. Meijer, *Mar. Drugs* **2008**, *6*, 514.
- [3] For representative examples, see: a) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly, F. Gago, *J. Med. Chem.* **2005**, *48*, 3796; b) F. Ishibashi, S. Tanabe, T. Oda, M. Iwao, *J. Nat. Prod.* **2002**, *65*, 500.
- [4] For example, see: a) E. A. Silyanova, A. V. Samet, L. K. Salamandra, V. N. Khrustalev, V. V. Semenov, *Eur. J. Org. Chem.* **2020**, 2093; b) H. J. Shirley, M. Koyioni, F. Muncan, T. J. Donohoe, *Chem. Sci.* **2019**, *10*, 4334; c) R. Klintworth, C. B. de Koning, T. Opatz, J. P. Michael, *J. Org. Chem.* **2019**, *84*, 11025; d) F. Ishibashi, Y. Miyazaki, M. Iwao, *Tetrahedron* **1997**, *53*, 5951.
- [5] For selected reviews for C–H functionalization, see: a) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245; b) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788; c) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192; d) C. Sambigioglio, D. David Schöbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603; e) Y. Minami, T. Hiyama, *Tetrahedron Lett.* **2018**, *59*, 781; f) M. Gulías, J. L. Mascareñas, *Angew. Chem.* **2016**, *128*, 11164; *Angew. Chem., Int. Ed.* **2016**, *55*, 11000; g) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107; h) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; i) J. Ye, M. Lautens, *Nature Chem.* **2015**, *7*, 863; j) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc.* **2014**, *87*, 751; k) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; l) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; m) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; n) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; o) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; p) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.
- [6] D. M. Lade, A. B. Pawar, P. S. Mainkar, S. Chandrasekhar, *J. Org. Chem.* **2017**, *82*, 4998; Ackermann and co-workers have also independently reported a similar ruthenium-catalyzed reaction: b) R. Mei, S.-K. Zhang, L. Ackermann, *Synlett* **2017**, *28*, 1715.
- [7] a) R. Michikita, Y. Usuki, T. Satoh, *Asian J. Org. Chem.* **2021**, *10*, 868; b) R. Yoshimoto, H. Morisaka, Y. Usuki, Y. Shibata, K. Tanaka, T. Satoh, *Chem. Lett.* **2020**, *49*, 1481; c) T. Okada, A. Sakai, T. Hinoue, T. Satoh, Y. Hayashi, S. Kawauchi, K. Chandrababunaidu, M. Miura, *J. Org. Chem.* **2018**, *83*, 5639; d) R. Morioka, K. Nobushige, T. Satoh, K. Hirano, M. Miura, *Org. Lett.* **2015**, *17*, 3130; e) C. Suzuki, K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Adv. Synth. Catal.* **2014**, *356*, 1521; f) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2011**, *40*, 600; g) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato, M. Miura, *J. Org. Chem.* **2011**, *76*, 13; h) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744; i) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068. For a review, see: T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212.
- [8] For examples of pyrrolocoumarin synthesis via C–H functionalization, see: a) X. Yang, Z. Chen, W. Zhong, *Eur. J. Org. Chem.* **2017**, 2258; b) C.-X. Gu, W.-W. Chen, B. Xu, M.-H. Xu, *Tetrahedron* **2019**, *75*, 1605; c) K. Ueda, K. Amaike, R. M. Maceiczkyk, K. Itami, *J. Am. Chem. Soc.* **2014**, *136*, 13226.
- [9] For a Rh-catalyzed double annulation for constructing simple indoloisoquinolines, see: H. Sun, C. Wang, Y.-F. Yang, P. Chen, Y.-D. Wu, X. Zhang, Y. Huang, *J. Org. Chem.* **2014**, *79*, 11863.
- [10] a) A. Saha, M. Shankar, S. Sau, A. K. Sahoo, *Chem. Commun.* **2022**, 58, 4561 and references therein. See also recent examples for double annulations: b) M. Shankar, A. Saha, S. Sau, A. Ghosh, V. Gandon, A. K. Sahoo, *Chem. Sci.* **2021**, *12*, 6393; c) M. Shankar, R. K. Rit, S. Sau, K. Mukherjee, V. Gandon, A. K. Sahoo, *Chem. Sci.* **2020**, *11*, 10770; d) J. Phukon, S. Gogoi, *Chem. Commun.* **2020**, *56*, 1133; e) J. Li, J. Liu, J. Yin, Y. Zhang, W. Han, J. Lan, D. Wu, Z. Bin, J. You, *J. Org. Chem.* **2019**, *84*, 15697; f) M. Shankar, K. Ghosh, K. Mukherjee, R. K. Rit, A. K. Sahoo, *Org. Lett.* **2016**, *18*, 6416; g) D. Ghorai, J. Choudhury, *ACS Catal.* **2015**, *5*, 2692; h) X. Tan, B. Liu, X. Li, B. Li, S. Xu, H. Song, B. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 16163; i) T. Yasukawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 12680.
- [11] A. A. Kudale, J. Kendall, C. C. Warford, N. D. Wilkins, G. J. Bodwell, *Tetrahedron Lett.* **2007**, *48*, 5077.
- [12] CCDC 2161136 contains the supplementary crystallographic data. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[13] a) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; b) D. R. Stuart, M.

Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474.

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Double C–H annulation takes place accompanied by two C–C and two C–N bond formation upon treatment of 3-(acetylamino)coumarins with internal arylacetylenes under rhodium catalysis to construct natural product inspired pentacyclic systems.