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Advanced Synthesis & Catalysis

Synthesis of Highly Substituted Benzofuran–containing Natural Products via Rh–catalyzed Carbonylative Benzannulation

Ji-tian Liu,[a, b] Christopher J. Simmons,[a, c] Haibo Xie,[a] Fan Yang,[a] Xian-liang Zhao,[a, d,*] Yu Tang,[b, e,*] and Weiping Tang[a, c,*]

[a] School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705, USA
Phone: (608) 890-1846
Fax: (608) 262-5345; e-mail: wtang@pharmacy.wisc.edu
[b] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072 P. R. China
E-mail: tangyu114@gmail.com
[c] Department of Chemistry, University of Wisconsin-Madison, Madison, WI, 53706 USA
[d] School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou, 310023, P. R. China
E-mail: xlzhao@iccas.ac.cn
[e] Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao, 266003, P. R. China.

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Abstract: We recently developed a novel Rh-catalyzed carbonylative benzannulation for the synthesis of indoles, benzofurans, and many related heterocycles. In this update, we demonstrated the utility of this method for the synthesis of several highly substituted benzofuran-containing natural products. The scope and limitation of the Rh-catalyzed carbonylative benzannulation was investigated in the context of natural product synthesis for the first time. This study also revealed the site-selectivity for Pd-catalyzed cross-coupling of substituted benzofurans. Two one-pot sequential cross-couplings were realized based on the observed site-selectivity. The strategy of preparing bicyclic heterocycles such as benzofurans by de novo synthesis of the benzene ring will find applications in many other related bioactive heterocycles.

Keywords: Carbonylation; rhodium; annulation; benzofuran; propargylic ester

Benzofuran is a common structural motif in numerous natural products, such as amurensin H (or viniferifuran) **1**,[1] gnetuhainin B **3**,[2] malibatol A **4**,[3] shoreaphenol (or hopeafuran) **5**,[4] anigopreissin A **6**,[5] and fuliginosin A **8** (Figure 1).[6] These highly substituted benzofurans and their derivatives possess broad range of pharmacological activities.[3,7] Among them, compound **1** showed anti-inflammatory effect on asthma-like reaction induced mice,[8] and the permethylated anigopreissin A (PAA) **7** showed inhibitory activity for human hepatoma cell proliferation.[9]

The benzofuran core of these natural products and their derivatives were generally constructed by annulation of the five-membered ring starting from poly-substituted benzene derivatives in previous syntheses (Scheme 1).[10] For example, natural product **1** was synthesized by Kraus using phosphazene base-mediated intramolecular condensation of 2-acylphenol ether to afford permethylated precursor **2** followed by demethylation.[11] An earlier approach to malibatol A **4** by Kraus utilized an intramolecular condensation of aryllithium with ketone to form the benzofuran moiety.[12] Kim's approach for compounds **1, 4**, and **5** employed a $Bi(OTf)_3$-catalyzed cyclodehydration of trisubstituted benzene derivatives for the formation of furan ring in benzofurans.[13] A modified version of the cyclodehydration strategy was applied to the total synthesis of diptoindonesin G.[14] This strategy was also adopted by other groups for the synthesis of benzofuran-containing natural products.[15] Chen's group prepared the benzofuran core of intermediate **2** by adopting Kraus's approach and converted it to natural products malibatol A **4** and shoreaphenol **5**.[16]

Constructing the benzene portion of benzofuran via benzannulation of furan derivatives would comprise a completely new strategy for the synthesis of benzofuran-containing natural products as shown in Scheme 1. This strategy will provide new derivatives that cannot be easily accessed using previous ap-

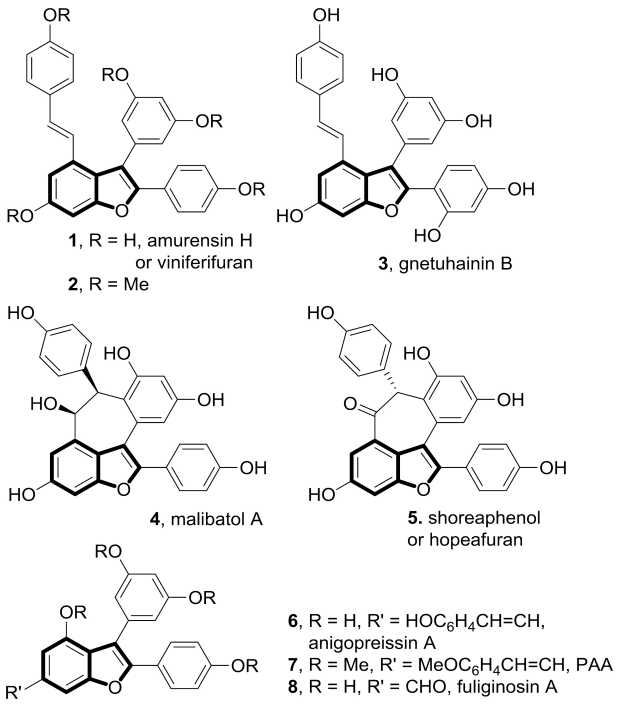
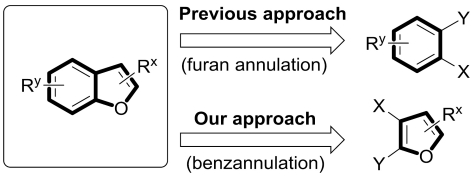


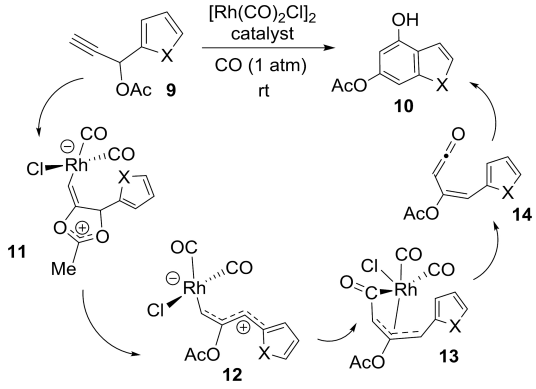
Figure 1. Representative Benzofuran-containing Natural Products.



Scheme 1. Two Distinct Approaches for Benzofuran-containing Natural Products.

proaches for structure activity relationship studies. We recently developed such a catalytic benzannulation method using propargylic ester **9** as the starting material and rhodium(I) complex as the catalyst (Scheme 2).[17] This represents a novel and unified approach for various heterocycles under very mild conditions. DFT calculations indicated that the formal [5+1] carbonylative benzannulation was initiated by a metal-mediated 1,2-migration of propargylic ester, followed by the formation of a zwitterion intermediate **12**, metallacycle **13**, and ketene intermediate **14**, and completed by a 6π-electrocyclization and aromatization to afford product **10**.

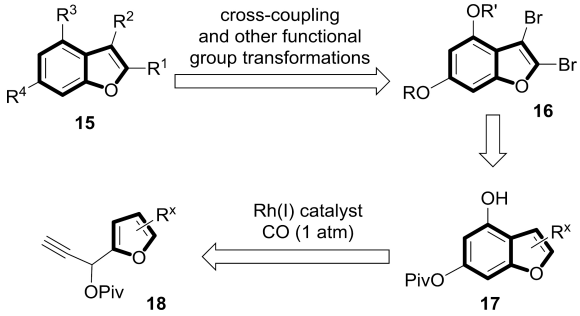
In this update, we demonstrated the utility of our newly developed Rh-catalyzed carbonylative benzannulation method to the synthesis of highly substituted benzofuran-containing natural products, including the first total synthesis of fuliginosin A **8**. We also revealed the scope and limitation of the carbonylative benzannulation method in the context of these



Scheme 2. Rh-catalyzed Carbonylative Benzannulation.

applications. In addition, our study uncovered the site-selectivity for Pd-catalyzed cross-coupling of polysubstituted benzofurans.

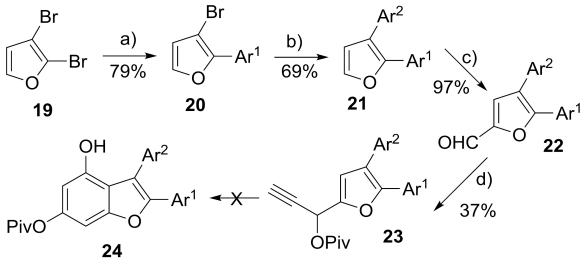
Based on the Rh-catalyzed carbonylative benzannulation method outlined in Scheme 2, we proposed that various highly substituted benzofuran-containing natural products such as those in Figure 1 could be derived from simple furyl propargylic ester **18** via intermediates **16** and **17** as shown in Scheme 3.



Scheme 3. A divergent Strategy for the Synthesis of Highly Substituted Benzofurans.

Starting from commercially available 2,3-dibromofuran **19**, we first prepared diaryl furan **21** by sequential cross-coupling reactions (Scheme 4). Formylation followed by addition of ethynyl Grignard reagent and esterification yielded substrate **23** via aldehyde **22**. Under previously established conditions, we were not able to convert this furyl propargylic ester to benzofuran **24**. We suspected that the Ar^2 substituent might prevent the cyclization event to occur in the 6π-electrocyclization step. This is still somewhat surprising to us as alkyl substituents on the same position could be tolerated during the development of the methodology.[17]

Next, we introduced only one aryl substituent to substrate **27** by starting from either dibromofuran **19** or dibromofurfural **25** (Scheme 5). We were pleased to



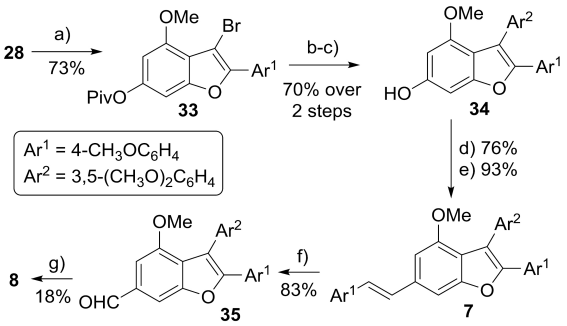
Ar^1 = 4-$CH_3OC_6H_4$; Ar^2 = 3,5-$(CH_3O)_2C_6H_4$

a) $Ar^1B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C; b) $Ar^2B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 80 °C ; c) $POCl_3$, DMF; d) ethynylmagnesium bromide, then PivCl, Et_3N, DMAP (5 mol%), CH_2Cl_2.

Scheme 4. Initial Attempt for the Synthesis of Benzofurans from 2,3-Diarylfurans via Rh-catalyzed Benzannulation.

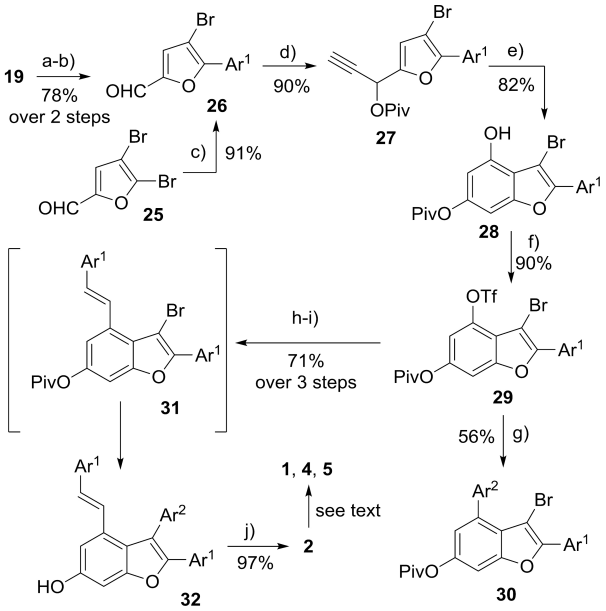
find that the key benzannulation reaction worked smoothly for substrate **27**, which bears a smaller bromine substituent. With the highly substituted benzofuran core **28** in hand, we tried to directly couple it with $Ar^2B(OH)_2$. It failed to give us any desired product. Instead of protecting the phenolic OH, we next prepared triflate **29** and explored the site-selectivity for the cross-coupling reaction. Product **30** was obtained when **29** was reacted with $Ar^2B(OH)_2$, suggesting that the C-4 triflate is more reactive. We then switched the order and coupled **29** with vinylboronic acid first to afford intermediates **31**, which was then converted to **32** after the second cross-coupling reaction. The pivalate groups was hydrolysed during this step. Methylation of **32** yielded compound **2**, which has been converted to natural products **1**, **4** and **5** in literature.[11,16] The overall yields for **2** are 35.7% or 41.6% from **19** or **25**, respectively.

Starting from intermediate **28** (Scheme 6), methylation followed by cross-coupling with $Ar^2B(OH)_2$ and removal of pivalate provided benzofuran **34**, which could be converted to anti-proliferation compound



a) MeI, K_2CO_3; b) $Ar^2B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C; c) DIBALH; d) Tf_2O; e) $Ar^1CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 75 °C; f) K_2OsO_4, $NaIO_4$; g) BBr_3

Scheme 6. Synthesis of PPA and Fuliginosin A via Rh-catalyzed Benzannulation.



Ar^1 = 4-$CH_3OC_6H_4$; Ar^2 = 3,5-$(CH_3O)_2C_6H_4$

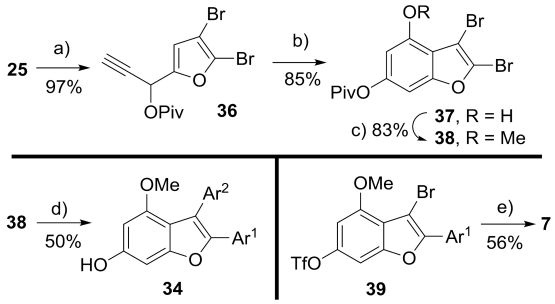
a) $Ar^1B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C; b) $POCl_3$, DMF; c) $Ar^1B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C; d) ethynylmagnesium bromide, then PivCl; e) $[Rh(CO)_2Cl]_2$ (5 mol%), CO (1 atm), rt; f) Tf_2O, 2,6-lutidine, CH_2Cl_2; g) $Ar^2B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C; h) $Ar^1CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 65 °C 9 h; then $Ar^2B(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C, 5 h; i) DIBALH, CH_2Cl_2, - 78 °C; j) MeI, K_2CO_3, acetone.

Scheme 5. Formal Synthesis of Benzofuran-containing Natural Products via Rh-catalyzed Benzannulation.

PAA **7** and natural product fuliginosin A **8** in two and four steps, respectively, through standard functional group transformations. The low yield for the removal of the methyl groups in compound **35** may be attributed to the sensitivity of **35** or **8** to strong acidic conditions. This represents the first total synthesis of natural product fuliginosin A, whose structure is now confirmed by synthesis. The overall yields for **7** and **8** are 24.3% and 3.6%, respectively, form **25**.

We also prepared dibromobenzofurans **37** and **38** by the Rh-catalyzed benzannulation of dibromofuranyl propargylic ester **36** derived from dibromofurfural **25** (Scheme 7). Diarylbenzofuran **34** could be more efficiently synthesized by an one-pot sequential coupling[18] process from **38**. PAA **7** could also be prepared by the one-pot sequential cross-coupling with **39**, which was derived from intermediate **33** by hydrolysis and formation of triflate. Our results uncovered the order of reactivity for 2-, 3-, and 6-positions of benzofurans towards Pd-catalyzed cross-coupling reactions.

In summary, we developed a divergent synthesis of several highly substituted benzofuran-containing natural products from simple furan derivatives. We demonstrated the utility of our Rh-catalyzed carbonylative benzannulation reaction in natural product synthesis



a) ethynylmagnesium bromide, then Piv_2O; b) $[Rh(CO)_2Cl]_2$ (5 mol%), CO (1 atm), rt; c) MeI, K_2CO_3, acetone; d) $Ar^1B(OH)_2$, $Pd(dba)_2$ (5 mol%), DMF, PPh_3, K_2CO_3, 70 °C, 18 h; then $Ar^2B(OH)_2$, 100 °C, 9 h. e) $Ar^1CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$ (5 mol%), DMF, K_2CO_3, 70 °C, 3h; then $Ar^2B(OH)_2$, 100 °C, 5 h.

Scheme 7. Pd-catalyzed One-pot Sequential Cross-Couplings.

for the first time and investigated the scope and limitation of this novel catalytic transformation in the context of formal synthesis of amurensin H (or viniferifuran) **1**, malibatol A **4** and shoreaphenol (or hopeafuran) **5**, and total synthesis of PPA **7** and fuliginosin A **8**. This unique approach of de novo synthesis of the benzene ring should find applications in many other highly substituted benzofurans and related heterocycles.

Experimental Section

Procedure for the preparation of phenol **28** by Rh-catalyzed carbonylative benzannulation:

To an oven-dried flask was added pivalate **27** (105 mg, 0.27 mmol), anhydrous DCM (20 mL) and $[Rh(CO)_2Cl]_2$ (5 mg, 5 mol%). The flask was degassed and attached with a CO balloon (1 atm). The reaction was stirred at room temperature and monitored by TLC. After the reaction was completed, the solvent was evaporated. The residue was purified by flash column chromatography to give phenol **28** (90 mg, 0.22 mmol, 82% yield) as light yellow solid. m.p. = 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.38 (s, 9H), 3.86 (s, 3H), 6.37 (d, J = 1.8 Hz, 1H), 6.56 (brs, 1H), 6.83 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 9.1 Hz, 2H), 7.91 (d, J = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 39.4, 55.6, 88.2, 98.2, 104.5, 114.2, 114.3, 121.9, 128.4, 149.6, 150.2, 150.3, 154.1, 160.3, 177.9; IR: ν 3382, 2970, 2360, 1738, 1265, 738 cm^{-1}. HRMS (ESI) for $C_{20}H_{19}BrNaO_5$(M + Na), 441.0308 (Calc.), found 441.0302.

Procedure for the preparation of phenol **37** by Rh-catalyzed carbonylative benzannulation:

To an oven-dried flask was added pivalate **36** (108 mg, 0.29 mmol), anhydrous DCM (20 mL) and $[Rh(CO)_2Cl]_2$ (5 mg, 5 mol%). The flask was degassed and attached with a CO balloon (1 atm). The reaction was stirred at room temperature and monitored by TLC. After the reaction was completed, the solvent was evaporated. The residue was purified by flash column chromatography to give phenol **37** (97 mg, 0.25 mmol, 85% yield) as light yellow solid. m.p. = 159-161 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.37 (s, 9H), 6.27 (d, J = 1.8 Hz, 1H), 6.55 (brs, 1H), 6.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 39.5, 96.4, 98.2, 105.1, 113.8, 127.6, 149.4, 149.5, 155.8, 178.5; IR: ν 3380, 2958, 2360, 1738, 1127, 739 cm^{-1}. HRMS (ESI) for $C_{13}H_{12}Br_2NaO_4$(M + Na), (Calc.) 414.8975, found 414.8969.

Acknowledgements

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UPDATES

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