Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c05113 • Publication Date (Web): 25 Jun 2020

Optically Active Flavaglines-Inspired Molecules by a Palladium-Catalyzed Decarboxylative Dearomative Asymmetric Allylic Alkylation

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KEYWORDS: Palladium-Catalyzed AAA, Enantioselective Synthesis, Flavaglines, Diversity-Oriented Synthesis (DOS)

ABSTRACT: With the aid of a class of newly discovered Trost-type bisphosphine ligands bearing a chiral cycloalkane framework, the Pd-catalyzed decarboxylative dearomative asymmetric allylic alkylation (AAA) of benzofurans was achieved with high efficiency [0.2-1.0 mol% $Pd_2(dba)_3$/**L**], good generality and high enantioselectivity (> 30 examples, 82-99% yield and 90-96% ee). Moreover, a diversity-oriented synthesis (DOS) of previously unreachable flavaglines is disclosed. It features a reliable and scalable sequence of the freshly developed Tsuji-Trost-Stoltz AAA, a Wacker-Grubbs-Stoltz oxidation, an *intra*-benzoin condensation and a conjugate addition, which allows the efficient construction of the challenging and compact cyclopenta[*b*]benzofuran scaffold with contiguous stereocenters. This strategy offers a new avenue for developing flavagline-based drugs.

The palladium-catalyzed asymmetric allylic alkylation (AAA) has become one of the most powerful bond-forming reactions for accessing biologically relevant molecules in the realm of enantioselective catalysis.[1] Due to its wide applicability, the mechanism has been thoroughly explored by preeminent researchers such as Trost, Stoltz, Lloyd-Jones, etc., through experimental and/or computational methods.[2] We are now cognizant of the fact that the reaction pathway could vary greatly depending on various parameters, while chiral ligand plays a vital role in ensuring a highly enantiomeric transformation. In this context, PHOX ligands developed independently by Helmchen, Pfaltz and Williams,[3] as well as Trost's DPPBA-based ligands were soon revealed as the privileged candidates for AAA.[4] Despite the notable advancement, ligand design for surmounting highly challenging while practical enantioselective transformations continues to be a popular research area. Recently, by incorporating a chiral cyclohexane scaffold into the PHOX framework, we developed a new class of CyPHOX ligands,[5] which exhibited much better performance in Lam's nickel-catalyzed desymmetrizing arylative cyclization than the common PHOX ligands.[6] With our continuing interest in ligand design and asymmetric synthesis, we herein report the discovery of a new class of Trost-type bisphosphine ligands bearing chiral cycloalkane scaffolds, which exhibited excellent performance in the Pd-catalyzed decarboxylative dearomative AAA of benzofurans,[7,8] Furthermore, the success of this AAA

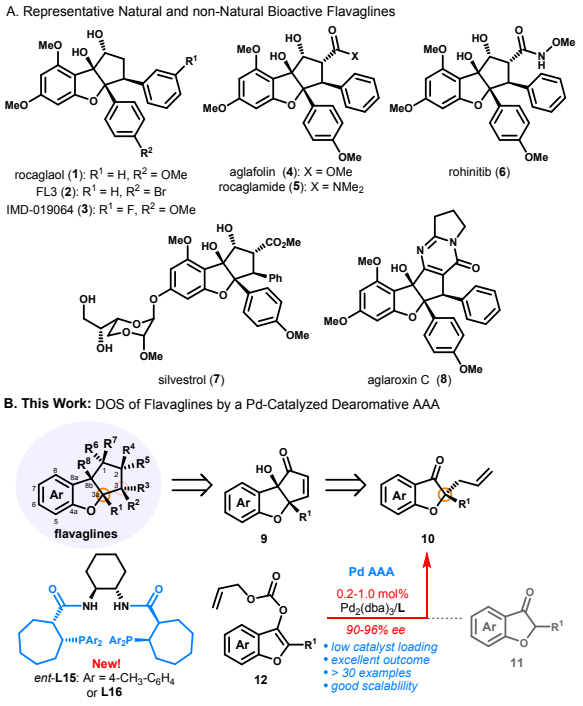


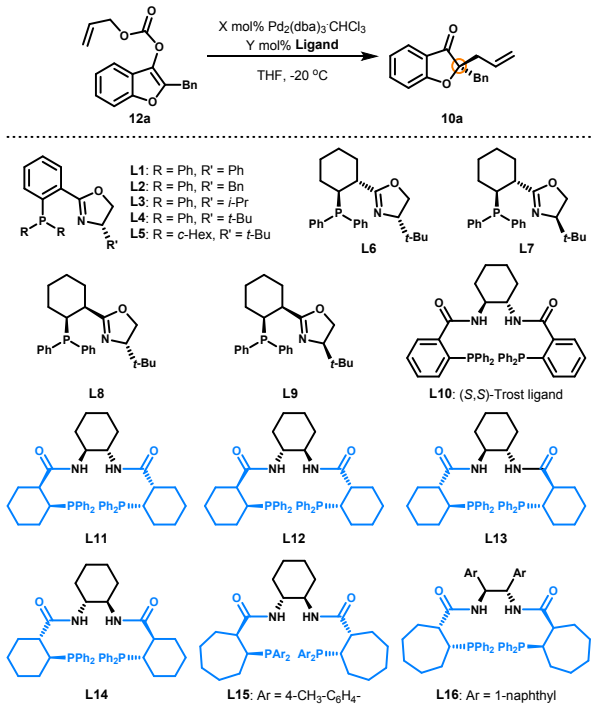
Figure 1. A Diversity-Oriented Synthesis (DOS) Approach to Flavaglines by A Palladium-Catalyzed AAA.

enabled a diversity-oriented synthesis (DOS) of unprecedented flavaglines (Figure 1).[9]

Flavaglines (rocaglates), characterized by a densely functionalized cyclopenta[*b*]benzofuran scaffold with contiguous stereocenters (*including two vicinal tetrasubstituted carbons*, Figure 1A),[10] were found to exhibit a notably wide array of biological properties, and of particular interest is their selective cytotoxicity towards a broad spectrum of cancer cell lines over normal cell lines. This activity is now believed to be due to their ability to target prohibitins (PHBs) 1 and 2 as well as translation initiation factor eIF4A.[11,12] For these reasons, flavaglines have long been the focus of numerous synthetic studies,[13] and drug development.[14] However, to the best of our knowledge, a general strategy, suitable for manipulation at C_{3a} and C_3 beyond dominant aryl groups (Figure 1B), and to overcome the critical issues such as substrate dependence, reliability and optical outcome associated with existing synthetic methods, remains a significant challenge. By close analysis of flavaglines (Figure 1B), we envisioned that an asymmetric diversity-oriented synthesis (DOS) synthesis should be viable through a two-stage diversification design: 1) the palladium-catalyzed AAA of benzofuran-3(2*H*)-ones **11** or its benzofuran derivatives **12**; and 2) classic conjugate additions or other alkene functionalizations of the tricyclic intermediates **9** derived from AAA products **10**, although establishing all the required stereocenters on such a highly compact and strained scaffold will be a formidable task.

With these considerations in mind, we started to investigate the Pd-catalyzed AAA. Initially, the direct AAA of **11** was tested, but it proved unsuccessful.[15] To our delight, the mild and neutral Tsuji-Trost-Stoltz AAA of **12a** cleanly delivered the desired allylation product **10a** by using PHOX and CyPHOX ligands (Table 1, entries 1-9), and best results were obtained with *tert*-Butyl PHOX **L5** (entry 4, 62% ee).[16] To our disappointment, our CyPHOX ligands showed poor performance in this AAA (entries 6-9). Considering completely different transition states involved in the palladium-catalyzed AAA with PHOX ligands[2h] and Trost's bisphosphine ligands,[2a-g] we thus prepared Trost-type ligands **L11**-**L14** incorporating our chiral cyclohexane scaffold (see SI for synthesis), and evaluated their performance in this AAA. To our delight, among these four new ligands, the best chirality matched one **L12** offered a significant improvement with an ee of 65% compared with the original Trost ligand **L1** (20% ee). Based upon previous pioneering mechanistic investigations,[2a-g] we reckoned that, in addition to the traditional Wall-Flap effect, the chiral cycloalkane scaffold of **L12** might play a role of further enhancing selectivity through its interaction with the nucleophile during the bond-forming step, as the π-allyl moiety involved is deeply embraced in the chiral pocket.[17] As one more tunable element introduced into the Trost Modular Ligand (TML) series, chances of success are supposed to increase. Thus, a series of this new class of ligands were prepared and evaluated in this AAA. **L15** was soon found to give best results for benzofuran **12a** (entry 15, 79% ee).[18] More intriguingly, decreasing the loading of the catalyst from 2.5 mol% to 0.2 mol% has a negligible influence on the enantiomeric outcome of this AAA (entry 19, 80% ee). Furthermore, the reaction proceeded with very good efficiency even at -20 °C with 0.2 mol% $Pd_2(dba)_3$/**L15**, and best results were thus obtained (entry 20, 89% yield and 92% ee).

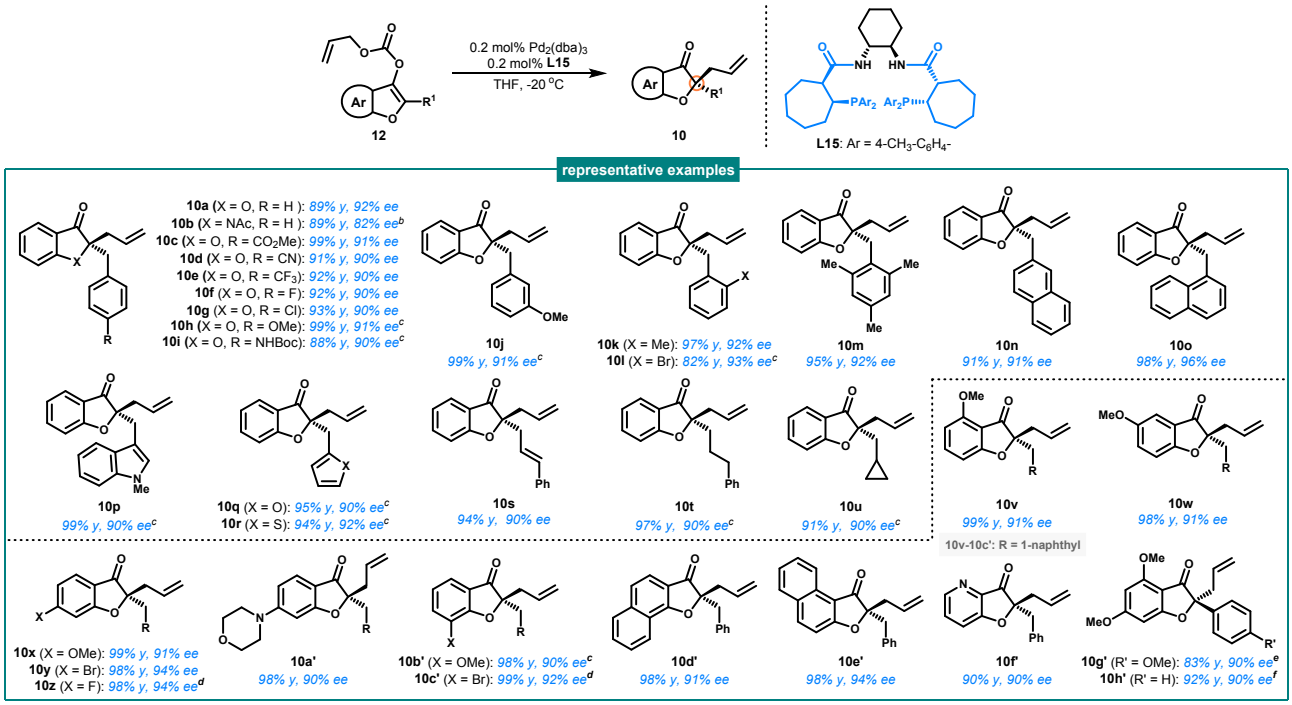
Table 1. Ligand Development and Optimization for the Palladium-Catalyzed AAA.[a]



entry	Ligand	X	Y	yield (%)[b]	ee (%)[c]
1	**L1**	5	10	61	2
2	**L2**	5	10	80	13
3	**L3**	5	10	84	46
4	**L4**	5	10	95	62
5	**L5**	5	10	78	4
6	**L6**	5	10	88	8
7	**L7**	5	10	81	3
8	**L8**	5	10	86	4
9	**L9**	5	10	83	7
10	**L10**	2.5	2.5	89	-20[d]
11	**L11**	2.5	2.5	90	40
12	**L12**	2.5	2.5	87	65
13	**L13**	2.5	2.5	87	-60[d,e]
14	**L14**	2.5	2.5	85	11[e]
15	**L15**	2.5	2.5	89	79[e]
16	**L16**	2.5	2.5	88	72[e]
19	**L15**	0.2	0.2	91	80[e]
20	**L15**	0.2	0.2	89	92

[a]Unless otherwise noted, the reactions were carried out with **12** (0.5 mmol), X mol% $Pd_2(dba)_3$·$CHCl_3$ and Y mol% ligand (**L**) in THF at -20 °C. [b]Isolated Yield. [c]Determined by Chiral HPLC. [d]Reverse sequence of peaks by HPLC. [e]Run at RT.

Table 2. Scope of the Palladium-Catalyzed Decarboxylative Dearomative AAA.[a]

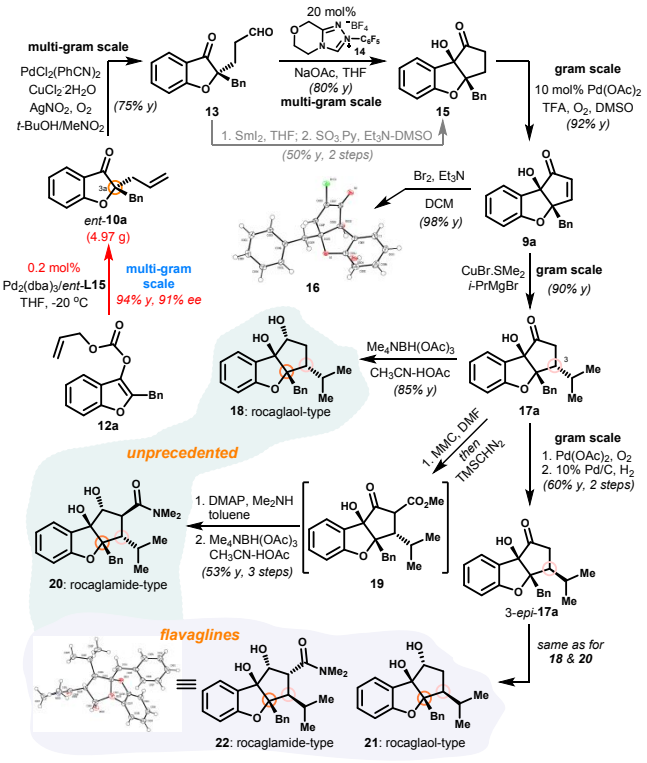


[a]Unless otherwise noted, the reactions were carried out with **12** (0.5 mmol) and 0.2 mol% $Pd_2(dba)_3$/**L15** in THF at -20 °C. [b]With 1.0 mol% $Pd_2(dba)_3$/**L16** and 4 Å MS in THF at -20 °C. [c]With 0.4 mol% $Pd_2(dba)_3$/**15** in THF at -40 °C. [d]With 0.4 mol% $Pd_2(dba)_3$/**L15** in THF at -5 °C. [e]With 1.0 mol% $Pd_2(dba)_3$/**L16** and 4 Å MS in THF at -50 °C. [f]With 1.0 mol% $Pd_2(dba)_3$/**L16** and 4 Å MS in THF at -45 °C.

With best conditions in hand, we then evaluated the scope of this Pd-catalyzed AAA (Table 2). A series of benzofurans (**12a**, **12c-u**) with various different alkyl substituent at C_{3a} position were first evaluated under the established optimal conditions. In the presence of 0.2 or 0.4 mol % of $Pd_2(dba)_3$/**L15**, all reactions proceeded smoothly to provide the desired products in excellent yields (82-99%) with excellent enantioselectivities (90-96% ee), regardless of their steric or electronic properties. More importantly, variations of the benzofuran core (**10v**-**10h'**), notably even with a heterocyclic ring pyridine, had no obvious influence on the reaction efficiency, and excellent results were preserved with low catalyst loading as well (90-99% yields, 90-94% ee). It is worth to note that **L16** evolved to be the best option for benzofurans containing aryl substituents at C_{3a} position (**10g'** and **10h'**), and additive 4Å molecular sieves are found essential for obtaining high enantioselectivities.[19] Furthermore, indole **12b** could also be applied in this AAA to produce the desired allylation product **10b** with good results (89% yield, 81% ee).[20]

This AAA is quite practical, as *ent*-**10a** could be obtained on a multigram scale without a decrease in efficiency by means of *ent*-**L15** (94% yield, 91% ee).[21] This allowed us to evaluate our DOS design for flavagline synthesis (Scheme 1). The Wacker-oxidation of *ent*-**10a** by the Grubbs-Stoltz protocol provided aldehyde **13** on a multigram scale,[22] and the subsequent cyclization was achieved either by a literature-based two-step operation (50%, 2 steps),[12] or in one step by *N*-heterocyclic carbene (NHC) catalysis (80%) affording **15** bearing the cyclopenta[*b*]benzofuran core in

Scheme 1. Diversity-Oriented Synthesis of Flavaglines.[a]

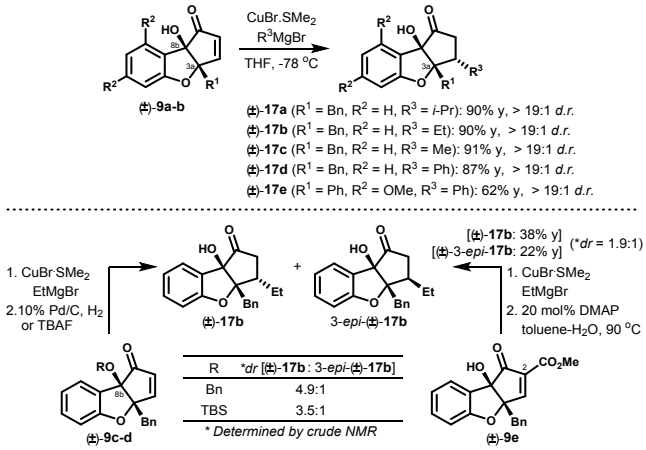


[a]See the Supporting Information for detailed procedures and characterization data. Key for the X-ray of structure of **16** and **22**: C, gray; H, white; N, blue; O, red; Br, green.

gram quantities. It is interesting to note, this *intra*-benzoin cyclization proved nontrivial, and only NHC catalyst **14** was ultimately found to be optimal for **13** to provide the desired intramolecular selectivity over the intermolecular benzoin condensation.[23,24] Next, a direct oxidative dehydrogenation by Stahl's protocol gave enone **9a**.[25] At this stage, the absolute configuration was unambiguously determined by X-ray crystallographic analysis of the mono-brominated enone product **16** derived from **9a**. For the second phase of diversification, we used readily available Grignard reagents as nucleophiles for conjugate addition with **9a** and expected that the nucleophilic addition from the convex face would provide the stereochemistry at C_3, matching that of natural products. To our surprise, only product **17a** from addition to the concave face was obtained with isopropyl cuprate.[26] From **17a**, rocaglaol-type and rocaglamide-type flavaglines (**18** and **20**, respectively) were prepared in one or three simple operations (reduction or Stiles carboxylation/transamination/reduction), respectively. Meanwhile, 3-*epi*-**17b** could be accessed in good isolated yield from a two-step oxidation-reduction process (60%, 2 steps) though the diastereoselectivity was moderate (2:1 dr). This result highlights the difficulties associated with this highly compact and strained scaffold, and two more flavaglines (**21** and **22**) were secured proving our DOS design of flavaglines efficacious.[27]

To shed some light on the concave selectivity and the hydrogenation result, we then further conducted some experimental studies with a series of (±)-**9** (Scheme 2).

Scheme 2.



Firstly, regardless of alkyl or aryl cuprates, only concave addition products were obtained with (±)-**9a** or (±)-**9b**. Secondly, diastereoselectivities were observed when the tertiary alcohol at C_{8b} was protected, with the more steric TBS giving a best 3.5:1 dr, although concave products predominated regardless of chelating and non-chelating groups. Moreover, an introduction of ester group at C_2 further increased the diastereoselectivity [concerning (±)-3-*epi*-**17b**]. These results suggest that the steric bias between the concave and convex faces is subtle in this case.[28] This also explains why the hydrogenation afforded a moderate diastereoselectivity, as hydrogen is much smaller than the cuprates.

In summary, a new blueprint for flavagline-based drug development was established by DOS design. This strategy features two diversification stages that allows access to flavaglines that are unreachable by previous synthetic methods. The first stage highlights the significance of the palladium-catalyzed asymmetric allylic alkylation (AAA). With the newly discovered class of Trost-type bisphosphine ligands incorporating a chiral cycloalkane framework, the Pd-catalyzed decarboxylative dearomative AAA of benzofurans was achieved with high efficiency [0.2-1.0 mol% $Pd_2(dba)_3$/**L**], good generality and high enantioselectivity. Studies to understand the exact effect of the chiral cycloalkane scaffold in this new class of Trost-type ligands as well as in our previous CyPHOX ligands are necessary and underway.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, and characterization data for all the products. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to the National Natural Science Foundation of China (NNSFC, 21772090) and the 1000 Youth Talents Program of China for support of this research. We thank Prof. Tian Qin at UT Southwestern for their helpful discussions, and the Instrumentation and Service Center for Physical Sciences at Westlake University for help with measurement and data interpretation.

ABBREVIATIONS

AAA = asymmetric allylic alkylation; NHC = N-heterocyclic carbene; RT = room temperature; dba = dibenzylideneacetone; Bn = benzyl; y = yield; ee = enantiomeric excess. MMC (Stiles reagent) = methoxymagnesium methyl carbonate.

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(17) A plausible reaction transition state (TS) was proposed in SI to explain the enantioface selection. Detailed mechanistic studies are underway.

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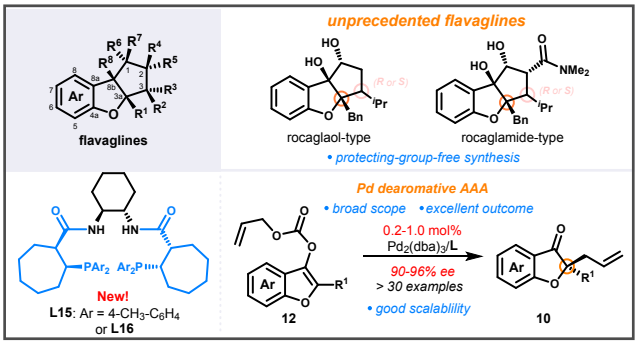
(28) The insightful idea of using chelating and non-chelating groups on the tertiary alcohol was recommended by one of the referees. In this case, the R group might point to the concave face, due to its steric interaction with Bn at C_{3a}, thus decrease the steric bias between the two faces. That is why we then introduced an etser group at C_2. Further studies are underway.


unprecedented flavaglines
flavaglines
rocaglaol-type
rocaglamide-type
• protecting-group-free synthesis
Pd dearomative AAA
• broad scope • excellent outcome
0.2-1.0 mol%
Pd2(dba)3/L
90-96% ee
> 30 examples
• good scalablility
New!
L15: Ar = 4-CH3-C6H4
or L16
12
10