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Authors: Feipeng Liu, Zhe Dong, Jianchun Wang, and Guangbin Dong

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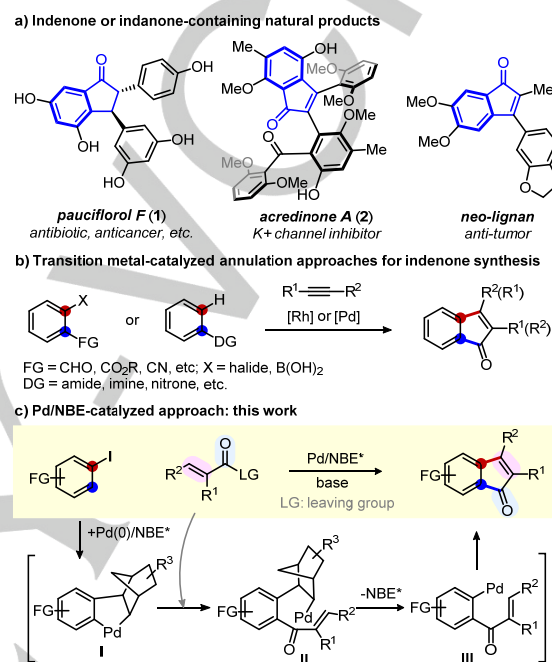
Palladium/Norbornene-Catalyzed Indenone Synthesis from Simple Aryl Iodides: Concise Syntheses of Pauciflorol F and Acredinone A

Feipeng Liu, Zhe Dong, Jianchun Wang* and Guangbin Dong*

Abstract: To show the synthetic utility of palladium/norbornene (Pd/NBE) cooperative catalysis, here we report concise syntheses of indenone-based natural products, pauciflorol F and acredione A, which are enabled by direct annulation between aryl iodides and unsaturated carboxylic acid anhydrides. Compared to the previous indenone-preparation approaches, this method allows simple aryl iodides to be used as substrates with complete control of the regioselectivity. The total synthesis of acredione A features two different Pd/NBE-catalyzed *ortho* acylation reactions for constructing penta-substituted arene cores, including the development of a new *ortho* acylation/*ipso* borylation.

Indenones are commonly found in pharmaceuticals and bioactive natural products (Scheme 1a),^[1] and often serve as versatile intermediates to access polysubstituted indanones.^[2] While a number of methods have been developed for preparing indenones, conventional approaches usually take multiple steps and/or have limited scopes.^[3] Recently, the transition metal-catalyzed cyclization with alkynes as coupling partners offers a broad and useful strategy to form various indenones (Scheme 1b).^[4,5] However, it is not trivial to control regioselectivity when unsymmetrical alkynes are used.^[2] In addition, vicinal difunctionalized aryl substrates^[4] or those containing a directing group (DG)^[5] are needed. Thus, it remains attractive to realize a general and regioselective indenone synthesis from simple readily available starting materials.

On the other hand, palladium/norbornene (Pd/NBE) cooperative catalysis,^[6] originally discovered by Catellani,^[7] has become an increasingly useful approach for preparing polysubstituted arenes via simultaneous functionalization of both *ortho* and *ipso* positions of aryl halides.^[8] Notably, Lautens has pioneered in developing bifunctional reagents, which enabled forming various condensed rings via *ipso*-annulation reactions.^[8a,9] While numerous Pd/NBE catalysis methods have been developed, only a few have been successfully applied to the total synthesis of natural products.^[8p,10] Herein, we describe concise syntheses of pauciflorol F(1) and acredione A (2), enabled by the development of a straightforward method to construct indenones from simple aryl iodides and unsaturated carboxylic anhydrides via Pd/NBE catalysis (Scheme 1c).



Scheme 1. Indenone/indanone containing natural products and indenone synthesis

In 2015, we reported an initial study on the *ortho* acylation/*ipso* hydrogenation using a mixed anhydride.^[8] Concurrently, the Liang^[8k] and Gu^[8j] groups independently developed the *ortho* acylation/*ipso* Heck reaction. Interestingly, when anhydrides derived from α,β -unsaturated carboxylic acids were employed, indenone products could be obtained (Scheme 1c). The reaction was likely initiated by oxidative addition of Pd(0) into the Ar–X bond, subsequent NBE migratory insertion and C–H metalation to generate an aryl-NBE-palladacycle (ANP) I,^[11] which would then react with the anhydride to afford intermediate II. After NBE extrusion, the resulting intermediate III could further undergo intramolecular cyclization to give the indenone product (*vide infra*, Scheme 3).

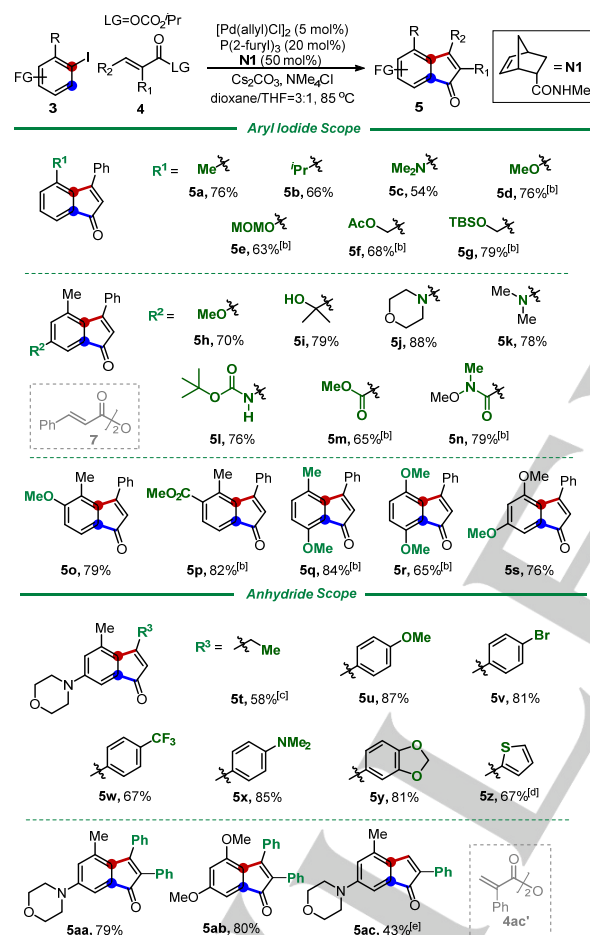
The reaction was further optimized using 2-iodotoluene (3a) as the substrate (see Supporting Information, Table S1). [Pd(allyl)Cl]₂ and tri(2-furyl)phosphine still proved to be the best metal/ligand combination, and the amide-substituted NBE (N1) was also found more efficient than simple NBE. Under the optimal conditions, the scope of the reaction was examined (Table 1). Aryl iodides contain both electron-rich and deficient substituents were suitable substrates, and different substitution patterns on arenes were tolerated. Note that sterically hindered aryl iodides, such as 2,5-disubstituted ones (5q and 5r), were

[*] F. Liu, Z. Dong, J. Wang, Prof. Dr. G. Dong
Department of Chemistry, University of Chicago
Chicago, IL, 60637 (USA)
E-mail: jcwang1992@uchicago.edu (J.W.) gbdong@uchicago.edu (G.D.)
F. Liu
Department of Applied Chemistry, China Agricultural University
Beijing 100193, China

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also competent substrates, which was the key requirement for the synthesis of acridinone **A**. Other unsaturated anhydrides were explored next as coupling partners. Anhydrides derived from alkyl (**5t**) and aryl-substituted acrylic acids (**5u-5ac**) could be successfully employed.^[12] In particular, when α - or α,β -disubstituted acrylic anhydrides were used, 2-substituted and 2,3-disubstituted indenones (**5aa-5ac**) were still afforded in good yields. Finally, a number of functional groups were found compatible, such as tertiary amine (**5c**, **5j** and **5k**), silyl ether (**5g**), tertiary alcohol (**5i**), MOM-protected alcohol (**5e**), Weinreb amide (**5n**), ester (**5f**, **5m** and **5p**), Boc-protected amine (**5l**), trifluoromethyl (**5w**), aryl bromide (**5v**) and thiophene (**5z**), making this method attractive for complex molecule synthesis.

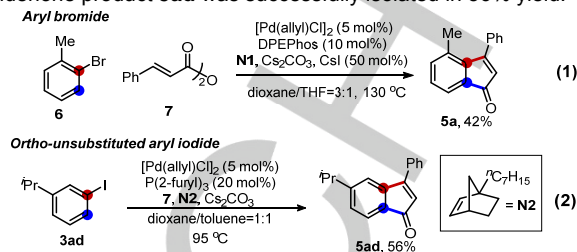
Table 1. Substrate scope of Pd/NBE-catalyzed indenone synthesis.^[a]



[a] Unless otherwise noted, the reaction was run with **3** (0.3 mmol), **4** (0.6 mmol), [Pd(allyl)Cl]₂ (0.015 mmol), P(2-furyl)₃ (0.06 mmol), **N1** (0.15 mmol), Cs₂CO₃ (1.2 mmol) and NMe₂Cl (1.2 mmol) in dioxane (2.25 mL) and THF (0.75 mL) at 85 °C for 14 h. [b] **7** (0.6 mmol) was used instead of **4** and the reaction was run at 95 °C without NMe₂Cl and THF. [c] run for 3 h. [d] run for 4 h. [e] **4ac'** (0.6 mmol) was used instead of **4** and the reaction was run for 2 h.

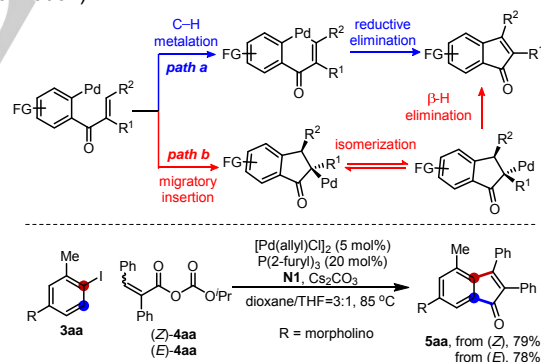
Preliminary study showed that aryl bromides^[13] could also be used as the substrate (eq. 1, Scheme 2) albeit in a lower efficiency; the use of large bite-angle (DPEPhos) ligand^[13a] and additional CsI was important. Not surprisingly, *ortho*-unsubstituted aryl iodide **3ad** was not a suitable substrate using

N1 or simple NBE under the standard conditions due to the “*ortho* constraint”.^[14] However, with the recently developed bridgehead-substituted norbornene (**N2**),^[14b] the desired indenone product **5ad** was successfully isolated in 56% yield.



Scheme 2. Further reaction exploration

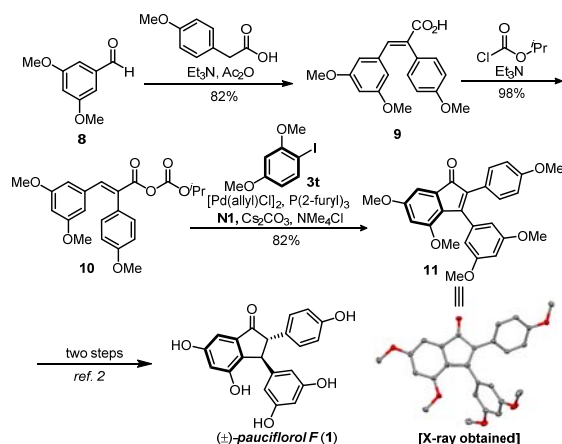
The mechanism regarding the conversion of intermediate **III** into indenone product was explored (Scheme 3). Two pathways are possible: **path a** involves activation of the vinyl β -C(sp²)-H bond of the enone intermediate followed by reductive elimination, while **path b** is through a Heck-like sequence: aryl migratory insertion into the olefin followed by β -H elimination. To differentiate these two pathways, both (*Z*) and (*E*)-anhydrides (**4aa**) were allowed to react with **3aa** in parallel under the standard conditions. Interestingly, they gave almost identical yields of **5aa** with a similar kinetic profile (see Supporting Information). Additionally, *Z/E* isomerization of the olefin moiety in **4aa** was not observed during the reaction. Taken together, the observations are consistent with the Heck-like pathway (**path b**), though other pathways including a Nazarov-type cyclization cannot be excluded at the current stage (see Supporting Information).



Scheme 3. Mechanistic exploration

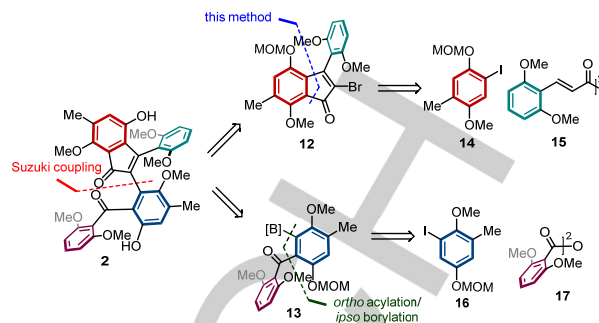
The utility of the method was first demonstrated in the formal synthesis of pauciflorol **F** (**1**) (Scheme 4). As a polyphenolic natural product derived from resveratrol, pauciflorol **F** has been an attractive synthetic target since its discovery in 2004.^[15] Several elegant routes have been developed to date.^[2,16] Our approach started with a two-step preparation of mixed anhydride **10** from commercially available aldehyde **8**.^[17] As expected, the subsequent Pd/**N1**-catalyzed annulation between anhydride **10** and aryl iodide **3t** provided indenone **11** in 82% yield, whose

structure was confirmed by X-ray crystallography.^[18] Note that the prior synthesis of indenone **11** via an alkyne insertion strategy generated a 1:1 mixture of regioisomers.^[2] Demonstrated by Jeffery and Sarpong, indenone **11** can be converted to **1** in two steps;^[2] thus, the synthesis of pauciflorol F can now be accomplished in 5 total steps and a high overall yield (~50%).



Scheme 4. Formal synthesis of pauciflorol F.

We then focused on the total synthesis of acredione A (**2**). Acridone A was recently isolated in <5 mg (with $[\alpha]_D^{25}$: 0 in CHCl_3) from a marine-sponge-associated *acremonium* sp. Fungus, which represents the first nonpeptidic natural product that can inhibit the voltage-gated potassium channel.^[19] Such an activity holds potential for developing inhibitors for treating type-II diabetes.^[20] In addition, total synthesis of acredione A has not been reported to date, and the structure-activity relationship (SAR) remains unknown. Given the pseudo-symmetry in **2**, it might be possible to establish an efficient biomimetic strategy. However, to enable rapid access to structurally diversified analogues for future SAR studies, it could be more valuable to develop a modular and convergent approach. The *challenges* are how to construct the highly congested indenone core and how to prepare the two penta-substituted arenes efficiently. From a retrosynthetic viewpoint (Scheme 5), we envisioned that acredione A could be constructed via a late-stage Suzuki-Miyaura coupling of two fragments (**12** and **13**) with similar complexity. Each fragment would be synthesized via a unique Pd/NBE catalysis. Ultimately, the natural product would be assembled using four arene building blocks (**14-17**).



Scheme 5. Retrosynthetic analysis of acredione A.

In a forward manner, aryl iodides **14** and **16** were synthesized from the same commercially available 3-methyl-4-anisaldehyde **18** in 4 steps (Scheme 6). The Pd/NBE-catalyzed indenone synthesis proceeded in a good yield on gram scales despite the bulkiness of the substrates. Bromination of indenone **19** with NBS afforded fragment **12**. Meanwhile, fragment **13** was proposed to be prepared via Pd/NBE-catalyzed *ortho* acylation/*ipso* borylation, which has been an unknown transformation. Encouraged by Ritter's *ortho* amination/*ipso* borylation,^[21] the three-component coupling of aryl iodide **16**, anhydride **17** and B_2pin_2 was carefully studied (Table 2). To our delight, the desired product **13a** was obtained in 21% yield in the first attempt using $\text{Pd}(\text{OAc})_2$ as the catalyst, and the major side-reaction was the *ipso*-hydrogenation (**13a'**) (entry 1). A quick condition screening revealed that the use of $\text{Pd}(\text{dba})_2$ could suppress the formation of side-product **13a'** (entries 1-4), though the exact reason is unclear. Further tuning the solvent and reaction temperature finally afforded the desired borylation product **13a** in 67% isolation yield (entries 5-7).

Table 2. Optimization for *ortho* acylation/*ipso* borylation.^[a]

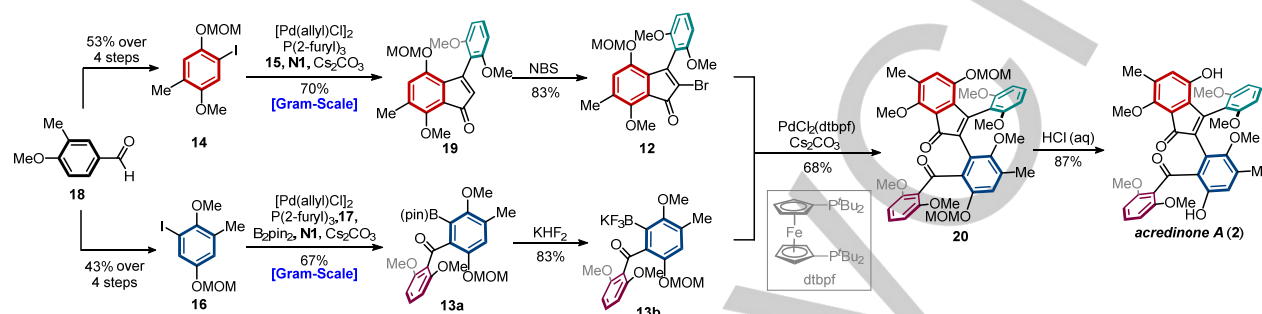
entry	[Pd]	solvent	yield of 13a	yield of 13a'
1	$\text{Pd}(\text{OAc})_2$	dioxane	21	20
2	$[\text{Pd}(\text{allyl})\text{Cl}]_2$	dioxane	54	11
3	$\text{Pd}_2(\text{dba})_3$	dioxane	38	8
4	$\text{Pd}(\text{dba})_2$	dioxane	58	5
5	$\text{Pd}(\text{dba})_2$	toluene	56	4
6	$\text{Pd}(\text{dba})_2$	dioxane:toluene (4:1)	64	6
7 ^b	$\text{Pd}(\text{dba})_2$	dioxane:toluene (4:1)	67 ^c	5

[a] Conditions: **16** (0.1 mmol), **18** (0.12 mmol), B_2pin_2 (0.105 mmol), [Pd] (0.01 mmol), $\text{P}(2\text{-furyl})_3$ (0.02 mmol), **N1** (0.05 mmol), Cs_2CO_3 (0.4 mmol), solvent (2 mL) at 100 °C for 24 h. Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] run at 120 °C. [c] isolated yield.

The Suzuki-Miyaura coupling between aryl bromide **12** and aryl boronic ester **13a** turned out to be extremely challenging due to the large steric hindrance in both coupling partners. The commonly employed monodentate or bidentate ligands, such as PPh_3 , P^tBu_3 , Buchwald's biarylphosphines, Hartwig's Q-Phos and NHC ligands, gave trace or no desired product. After extensive studies, gratifyingly, the bulky and electron-rich

bidentate dtbpf ligand afforded the desired coupling product **20** albeit in a low yield.^[22] The major side-reaction was the protonation of boronic ester **13a**, suggesting low stability of this compound under the reaction conditions. Considering that Molander salts generally exhibit enhanced stability than the corresponding boronic esters in cross couplings,^[23] the corresponding potassium aryltrifluoroborate **13b** was then

prepared. Indeed, the coupling between **12** and **13b** proceeded smoothly to afford product **20** in 68% yield, which was subsequently deprotected to give acredione A (**2**). The spectroscopic data of synthetic **2** matched those of the reported natural sample in all respects. Hence, the first total synthesis of acredione A was accomplished in eight steps in the longest linear sequence (LLS) from commercial chemicals.



Scheme 6. Total synthesis of acredione A.

In summary, a Pd/NBE-catalyzed annulation between aryl iodides and unsaturated carboxylic acid anhydrides has been developed, which provides a simple and straightforward approach for preparing indenones in a regio- and chemoselective manner. Using this method, concise syntheses of pauciflorol F and acredione A have been achieved. The utility of Pd/NBE catalysis for streamlined synthesis of tetra- and penta-substituted arenes could have broad implications beyond this work. Efforts on preparing analogues of acredione A for future SAR studies are ongoing.

Acknowledgements

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Keywords: acredione A • pauciflorol F • indenone • norbornene • palladium

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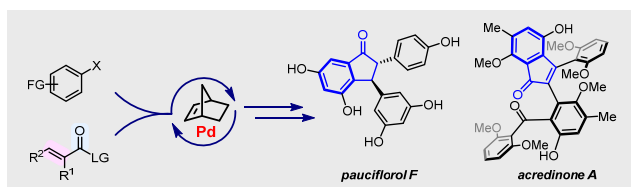
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Layout 2:

COMMUNICATION



A straightforward method for indenone synthesis was achieved via Pd/NBE-catalyzed annulation between simple aryl iodides and unsaturated carboxylic acid anhydrides. This method enabled streamlined syntheses of pauciflorol F and acredione A.

Feipeng Liu, Zhe Dong, Jianchun Wang*
and Guangbin Dong*

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**Palladium/Norbornene-Catalyzed
Indenone Synthesis from Simple Aryl
Iodides: Concise Syntheses of
Pauciflorol F and Acredione A**