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Direct Annulation between Aryl Iodides and Epoxides via Palladium/Norbornene Cooperative Catalysis

Renhe Li and Guangbin Dong*

Abstract: Herein we report a direct annulation between aryl iodides and epoxides via palladium/norbornene (Pd/NBE) cooperative catalysis. An iso-propyl ester-substituted NBE was found most efficient to suppress formation of multi-NBE-insertion by-products and afford the desired 2,3-dihydrobenzofuran derivatives in 44−99% yields. The reaction is scalable, and tolerates a range of functional groups. Asymmetric synthesis is realized using an enantiopure epoxide. Application of this method into a concise synthesis of insecticide fufenozide is demonstrated.

2,3-Dihydrobenzofuran (DHBF) moiety is frequently found in pharmaceuticals and agrochemicals (Fig. 1).[1] While a number of methods are available for its synthesis, only a few can directly give DHBFs from simple starting materials.[2] For example, DHBFs can be synthesized via a sequence of *ortho*-allylation of phenols and then hydroalkoxylation,[3] in which strong bases and/or acids are used (Scheme 1a). A (3+2) coupling between benzynes and epoxides appears to be a more attractive approach; however, the poor regioselectivity with unsymmetrical benzynes and the need for more reactive aryl epoxides limited its application.[4] Hence, a general approach that can synthesize DHBFs directly from readily available feedstock chemicals remained to be realized. In this communication, we describe the development of a simple and direct DHBF synthesis method through annulation between aryl iodides and terminal epoxides via palladium/norbornene (NBE) cooperative catalysis (Scheme 1b).

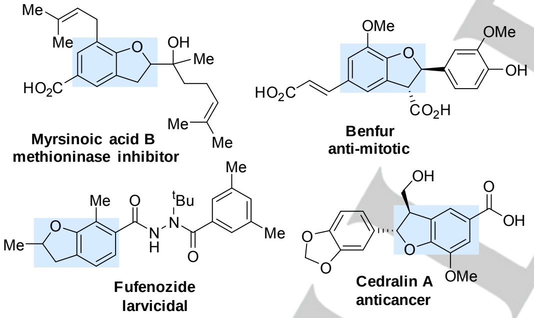
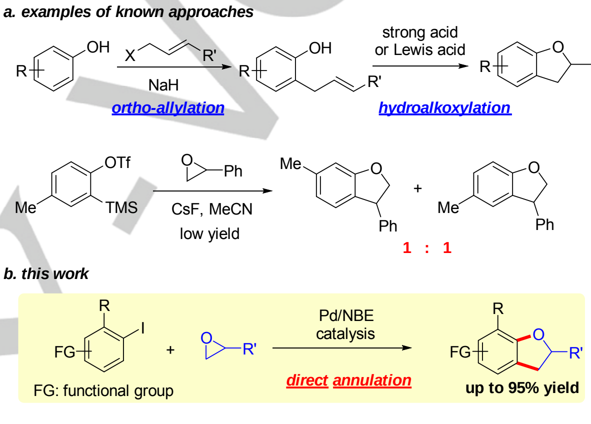


Figure 1. Bioactive compounds containing DHBFs.

Pd/NBE catalysis, namely Catellani reaction, has recently emerged as a powerful approach for vicinal bis-functionalization of arenes.[5] Using simple aryl iodides as substrates, a number of nucleophiles and electrophiles have been coupled at the *ipso* and *ortho* positions respectively through selective reactions with the aryl-NBE-palladacycle (ANP) intermediate (Fig. 2).[6-10] In particular, Lautens and coworkers have developed a suite of elegant annulation methods through tethering an electrophile with a nucleophile for synthesis of various benzo-fused rings.[11]



Scheme 1. DHBF Synthesis.

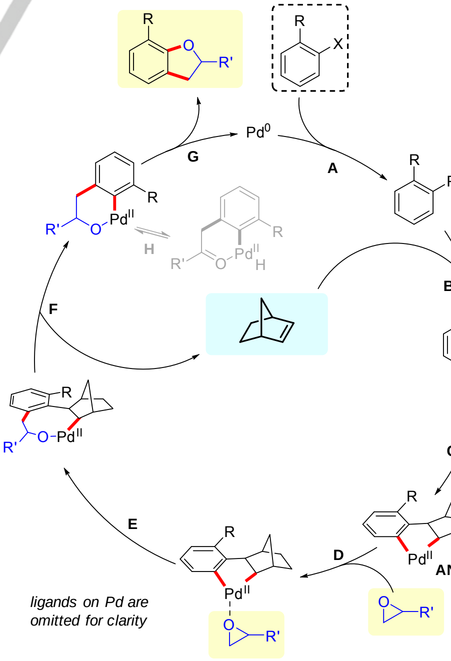


Figure 2. Proposed catalytic circle.

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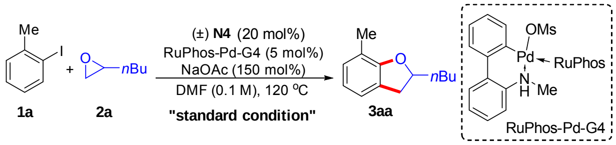
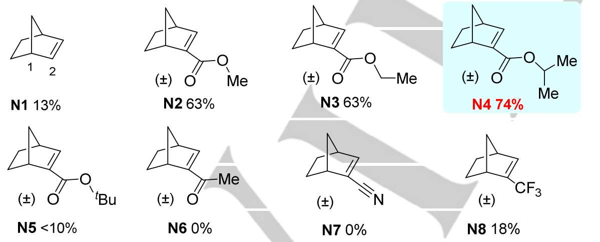
Despite the successful cyclization with highly strained *2H*-azirines (44-48 kcal/mol),[11g] the use of simple epoxides as the coupling partner in Pd/NBE catalysis has not been reported. The challenge is three-fold. First, activation of epoxides typically requires acids or Lewis acids,[12] while the Pd/NBE catalysis operates under slightly basic conditions. Second, the alkoxide generated from epoxide ring opening (step E, Fig. 2) is an excellent hydride donor and can lead to *ipso* reduction via β-hydrogen elimination.[7f,8a,9b] Third, coupling with oxygen nucleophiles with β-hydrogen has not been reported previously for Pd/NBE catalysis, likely due to the difficulty of the C−O bond reductive elimination versus β-hydrogen elimination (steps G and H, Fig. 2).

Table 1. Control experiments for annulation with epoxides.



Entry	Change from the standard condition	Yield [%][a]
1	none	74
2	toluene instead of DMF	0
3	dioxane instead of DMF	0
4	no RuPhos-Pd-G4	0
5	$Pd(OAc)_2$ + RuPhos	41
6	$Pd(OAc)_2$ + PPh_3	0
7	$Pd(OAc)_2$ + $P(2\text{-furyl})_3$	0
8	no **N4**	0
9	other NBEs	see below
10	no NaOAc	0
11	KOAc instead of NaOAc	trace
12	2.0 equiv of **2a**	57



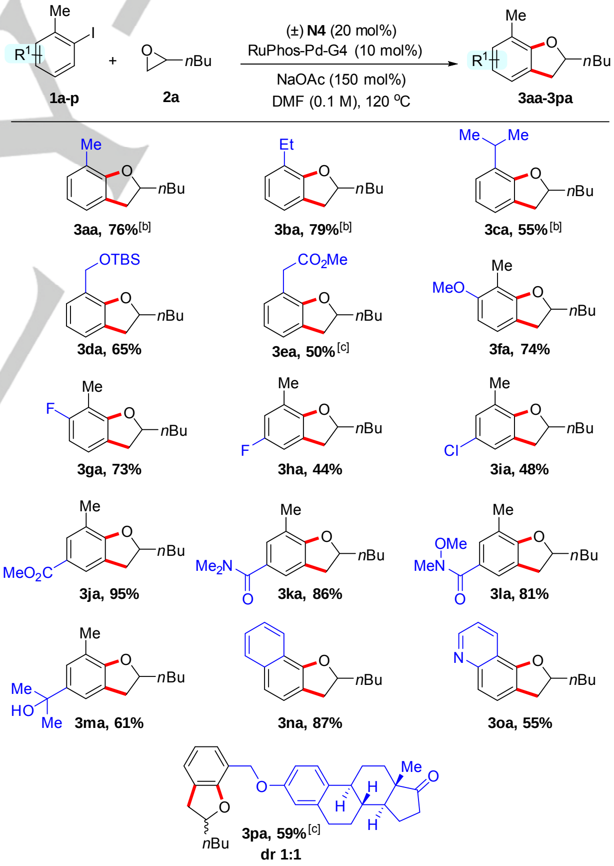
N1 13% **N2** 63% **N3** 63% **N4 74%**

N5 <10% **N6** 0% **N7** 0% **N8** 18%

[a] The reaction was run with 0.1 mmol **1a** and 0.4 mmol **2a** in 1 mL DMF for 24h. [b] Yields are determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.

To address the aforementioned challenges, we propose that 1) use of polar aprotic solvents would promote S_N2-type ring opening of epoxides; and 2) use of a sterically hindered phosphine ligand, such as Buchwald's ligands, would inhibit β-hydrogen elimination and promote the C−O reductive elimination.[13] Indeed, after a careful survey of the reaction parameters, the desired DHBF product **3aa** was observed with RuPhos/DMF as the ligand/solvent combination (Table 1). Use of less polar solvents (entries 2 and 3) or other mono-dentate phosphines (entries 6 and 7) gave no annulation product. An improved yield (74%) was obtained using 5 mol% Buchwald's Ruphos-Pd-G4 precatalyst.[14] While regular NBE (**N1**) provided the desired annulation product (entry 9), multi-NBE insertion became the major side reaction, as the **ANP** intermediate is known to react further with additional NBE when the electrophile is not reactive enough.[15] Thus, we hypothesized that use of a *less reactive NBE*, such as those with a substitution at the C2 position, would hinder the multi-NBE insertion pathway. To our delight, the isopropyl ester-derived NBE (**N4**) was found to be most efficient for this transformation.[16] NBEs with less sterically hindered ester groups (**N2** and **N3**) gave lower yields, while bulky *t*-butyl-ester substituted one (**N5**) significantly diminished the reactivity. Interestingly, the CF_3-substiutted NBE (**N8**) still afforded the desired product albeit in a lower yield. It is noteworthy that, while most prior Pd/NBE catalyzed reactions require a high loading or excess NBE, only 20 mol% **N4** was found sufficient in this reaction. NaOAc proved to be an optimal base (entries 10 and 11). While 4 equiv of epoxide **2a** was used due to its volatility, reducing the loading to 2 equiv still provided DHBF **3aa** in 57% yield (entry 12).

Table 2. Substrates scope with aryl iodides.[a]

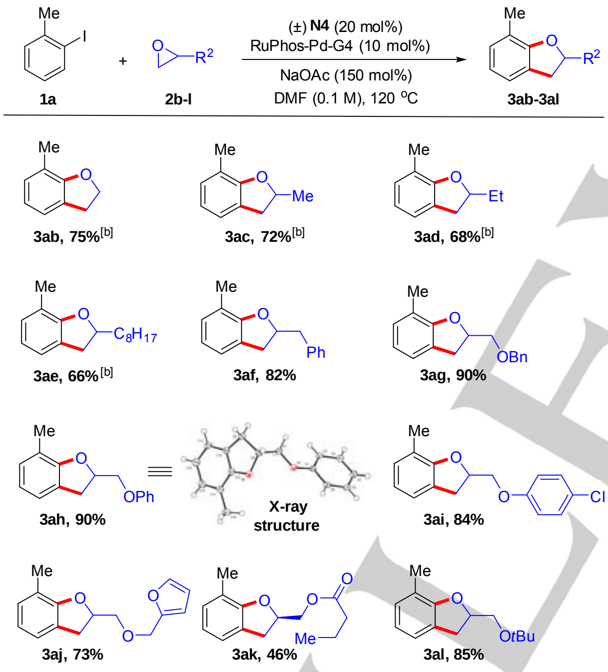


[a] All reactions were run with 0.3 mmol **1a-p** and 1.2 mmol **2a** in 3mL DMF for 24h. Isolated yields are reported. [b] 5.0 mol% of RuPhos-Pd-G4 was used. [c] 20 mol% of RuPhos-Pd-G4 was used.

With the optimal reaction conditions in hand, the scope of the aryl iodides was examined first (Table 2). To our delight, substrates with electron-donating and -withdrawing groups all worked well giving the direct annulation products in moderate to excellent yields. One important feature of this transformation is that a variety of functional groups, including alkyl, TBS-silyl protected benzyl alcohol, methyl ester, methoxy, fluoride, chloride, amide, Weinreb amide and free tertiary alcohol, were all tolerated (**3ba**-**3ma**). It is worthy to mention that aryl chloride (**3ia**), which is reactive under the Pd/RuPhos conditions, survived in this reaction.[14] Notably, polyaryl iodide **(3na)** and heteroaryl iodide **(3oa)** were also suitable substrates. Furthermore, more complex estrone-derived substrate (**3pa**) is competent in this transformation, giving the desired DHBF in 59% yield. Altogether, this method exhibits excellent chemoselectivity.

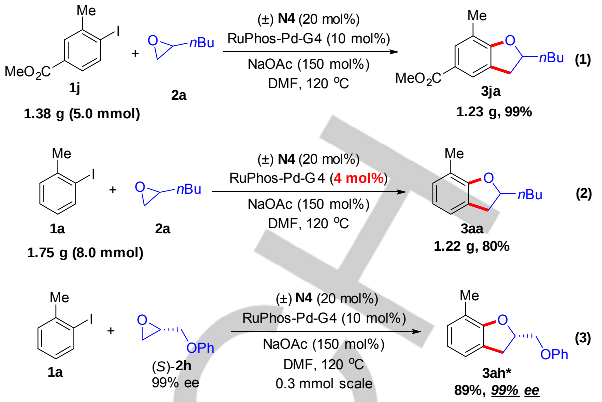
Next, the scope of epoxides was explored (Table 3).[17] Direct annulation with simple ethylene oxide, propyl oxide and other 2-alkyloxiranes occurred smoothly (**3ab**-**3ae**). Epoxides containing phenyl, ether or ester moieties all delivered the products in good to excellent yields (**3ag**-**3al**). Note that benzyl ether (**3ag**) and furan (**3aj**) are compatible under the reaction conditions.

Table 3. Substrates scope with epoxides.[a]

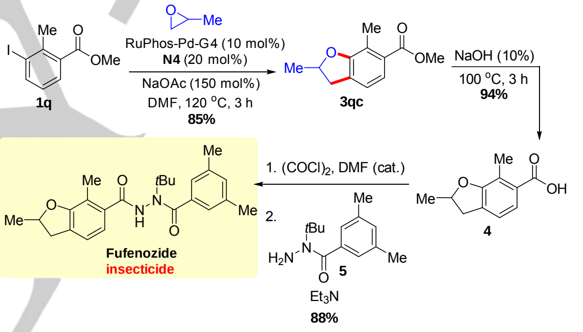


[a] All reactions were run with 0.3 mmol **1a** and 1.2 mmol epoxide in 3mL DMF for 24h. Isolated yields are reported. [b] 5.0 mol% of RuPhos-Pd-G4 was used.

The reaction is scalable. On a gram scale, DHBF **3ja** was obtained in 99% yield (Eq 1). In addition, using 1.75 g of aryl iodide **1a** (8.0 mmol), DHBF **3aa** was isolated in 80% yield with only 4.0 mol% [Pd] (Eq 2). Moreover, when an enantiopure epoxide (*S*)-**2h** was used, the annulation reaction proceeded with stereo-retention and afforded chiral DHBF **3ah*** in 99% ee with 89% yield (Eq 3). Given the wide availability of enantiopure epoxides, this transformation is anticipated to be useful for building chiral complex target molecules with DHBF moieties.



Finally, the synthetic utility of this method is demonstrated in a concise synthesis of fufenozide (Scheme 2),[18] which is an effective insect growth regulator showing high insecticidal activities towards *plutella*, *xylostella* and *mythimna*.[19] Starting from the commercially available aryl iodide **1q** and propyl oxide **2c**, their direct annulation provided the key DHBF intermediate (**3qc**) in 85% yield. Subsequent hydrolysis and peptide coupling with hydrazine **5** accomplished the synthesis of fufenozide in an excellent yield.



Scheme 2. Synthesis of insecticide fufenozide.

In summary, a direct annulation between aryl iodides and epoxides is developed via Pd/NBE cooperative catalysis. A variety of 2,3-dihydrobenzofuran derivatives have been obtained in moderate to excellent yields. The use of easily available reactants, high chemo-selectivity and scalability should make this method attractive for practical applications.

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Keywords: annulation • catalysis • epoxides • palladium • norbornene

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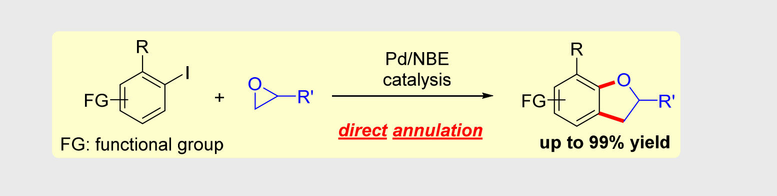
[20] CCDC 1588833 (**3ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Entry for the Table of Contents

COMMUNICATION



A simple and direct annulation between readily available aryl iodides and epoxides is enabled by palladium/norbornene (Pd/NBE) cooperative catalysis. This approach offers a practical synthesis of various 2,3-dihydrobenzofuran derivatives.

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