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Regioselective synthesis of 2,3-dihydrobenzodioxepinones from epoxides and 2-bromophenols *via* palladium-catalyzed carbonylation†

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A highly regioselective cascade synthesis of 2,3-dihydrobenzodioxepinone from 2-bromophenols and epoxides has been developed. The reactions go through nucleophilic ring-opening of epoxides and subsequent palladium-catalyzed intramolecular alkoxylcarbonylation.

Palladium-catalyzed carbonylation reactions are of broad interest in both academic research and pharmaceutical applications. Ever since the pioneering work from Heck and co-workers in 1974,[1] palladium-catalyzed carbonylations have experienced impressive progress and have already become one of the most efficient tools in modern organic synthesis.[2] The most obvious advantages of carbonylative transformation are two but not least: (1) carbon monoxide is an inexpensive and easily available C1 building block; (2) carbonyl containing molecules such as aldehydes, amides, esters, ketones, alkynones *etc.* can be obtained efficiently by varying the coupling partners, which are valuable compounds themselves and ready for further modification as well.

Epoxides are widely available compounds, generally obtained from an intramolecular S_N2 substitution reaction or epoxidation of olefins.[3] Additionally, epoxides are an important class of chemicals with broad applications in organic synthesis and advanced materials.[4] Notably, a chiral center can be easily introduced into the parent molecules by applying chiral epoxides as substrates, which are readily available by asymmetric epoxidation of the corresponding alkenes. Among all the types of reactions, the ring-opening reaction of epoxides is one of the most straightforward routes for the utilization of epoxides. In general, it undergoes the S_N1 type reaction under acidic conditions and nucleophilic attack takes place at the more substituted position, while nucleophiles attack occurs at the less hindered carbon under the S_N2 type mechanism under basic conditions.

To the best of our knowledge, no example was reported for the carbonylative cross-coupling reaction with epoxides until now.[5] Due to our continual interest in palladium-catalyzed carbonylative synthesis of heterocycles, we report herein our recent results on the synthesis of benzodioxepinones which are valuable analogues of seven-membered lactones.[6] The reaction started from commercially available 2-bromophenols and epoxides *via* the cascade ring-opening reaction and palladium-catalyzed carbonylative transformation. The desired products were produced in a highly selective manner in high yields.

The first test of the reaction was carried out with 2-bromophenol (0.5 mmol), styrene oxide (0.55 mmol), 2 mol% $Pd(OAc)_2$, 3 mol% dppf, in MeCN (2 mL) under 15 bar of CO, 7% yield of **3a** was observed at 100 °C. **3a′** which originated from the nucleophilic attack at the benzylic position, was observed as well, and the ratio between **3a** and **3a′** was 68 : 32 (Table 1, entry 1). At this point, we found carbonylation to be the rate-determining step for this reaction as 2-bromophenoxy-phenylethanol was observed as the main by-product. Then different ligands were tested to promote the carbonylation step; no desired product was formed with monodentate ligands (6 mol%) such as $BuPAd_2$ and PPh_3. To our delight, 27% yield of **3a** was observed with binap as the ligand and which was chosen for further optimizations (Table 1, entry 2). In solvent testing, moderate yields of the target molecule can be obtained in DMF or DMSO (40% and 34% respectively, with **3a** : **3a′** as 85 : 15 and 86 : 14 respectively; Table 1, entries 9 and 10). In toluene, *t*BuOH and water, low or no reactivity was observed (Table 1, entries 11–14). The pressure of CO was varied as well, but no effects were observed for this transformation (Table 1, entry 15). In the end, the yield of **3a** was successfully increased to 80% with a ratio between **3a** and **3a′** of 85 : 15 by increasing the amount of styrene oxide to 1.5 equiv. (Table 1, entry 16). Among all the tested bases, NaOAc and organic base such as Et_3N and DBU gave only trace amounts of the product; moderate yield (72%) was produced with the use of 1.1 equiv. of KOH, and the best result was obtained with K_3PO_4 as the base (90%, **3a** : **3a′** = 90 : 10; Table 1, entries 16–21). Interestingly, the selectivity was reversed by adding 30 mol% of $ZnBr_2$ as the Lewis acid

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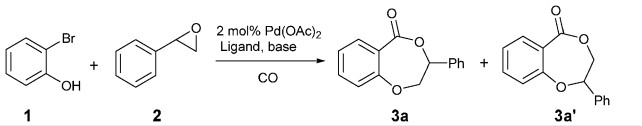
Table 1 Benzodioxepinone synthesis: optimization[a]



1 2 3a 3a'

Entry	2 : 1	Ligand	Base	Solvent	Yield[b]	3a : 3a′
1	1.1	dppf	K_2CO_3	MeCN	7	68 : 32
2	1.1	binap	K_2CO_3	MeCN	27	74 : 26
3	1.1	xantphos	K_2CO_3	MeCN	N.R	—
4	1.1	dppe	K_2CO_3	MeCN	17	76 : 24
5	1.1	dppp	K_2CO_3	MeCN	18	72 : 28
6	1.1	dppb	K_2CO_3	MeCN	24	74 : 26
7	1.1	dpppe	K_2CO_3	MeCN	N.R	—
8	1.1	DPEPhos	K_2CO_3	MeCN	13	81 : 19
9	1.1	binap	K_2CO_3	DMF	40	85 : 15
10	1.1	binap	K_2CO_3	DMSO	34	86 : 14
11	1.1	binap	K_2CO_3	Dioxane	N.R	—
12	1.1	binap	K_2CO_3	Toluene	9	40 : 60
13	1.1	binap	K_2CO_3	*t*BuOH	N.R	—
14	1.1	binap	K_2CO_3	H_2O	N.R	—
15[c]	1.1	binap	K_2CO_3	DMF	47	84 : 16
16[c]	1.5	binap	K_2CO_3	DMF	80	85 : 15
17[c]	1.5	binap	NaOAc	DMF	<5	—
18[c]	**1.5**	**binap**	**K_3PO_4**	**DMF**	**90**	**90 : 10**
19[c,d]	1.5	binap	KOH	DMF	72	91 : 9
20[c]	1.5	binap	Et_3N	DMF	<5	—
21[c]	1.5	binap	DBU	DMF	<5	—
22[c,e]	1.5	binap	K_3PO_4	H_2O	50	15 : 85

[a] $Pd(OAc)_2$ (2 mol%), ligand (3 mol%), **1** (0.5 mmol, 1 equiv.), **2** (0.75 mmol, 1.5 equiv.), base (2 equiv.) CO (15 bar), at 100 °C, 20 hours. [b] Yield was determined by GC with hexadecane as the internal standard. [c] CO (5 bar). [d] KOH (1.1 equiv.). [e] $ZnBr_2$ (30 mol%). dppf = 1,1′-bis(diphenylphosphino)-ferrocene, binap = 1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppe = ethylenebis(diphenylphosphine), dppp = 1,3-bis(diphenylphosphino)-propane, dppb = 1,4-bis(diphenylphosphino)butane, dpppe = 1,5-bis-(diphenylphosphino)pentane, DPEPhos = (oxydi-2,1-phenylene)bis-(diphenylphosphine), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

in H_2O (Table 1, entry 22). From those primary results, we found that the properties of base and solvent were the two main factors which influenced the regioselectivity between **3a** and **3a′** and the yield.

In order to confirm the molecule structure, one of the products has been analyzed using X-ray diffraction (Fig. 1). Considering the reaction pathway for this cascade reaction, the most plausible mechanism for this transformation has been given in Scheme 1. Under basic conditions, the S_N2 type nucleophilic attack at the less hindered site of the epoxide and generation of the corresponding 2-(2-bromophenoxy)ethan-1-ol was the initial step. This was followed by the oxidative

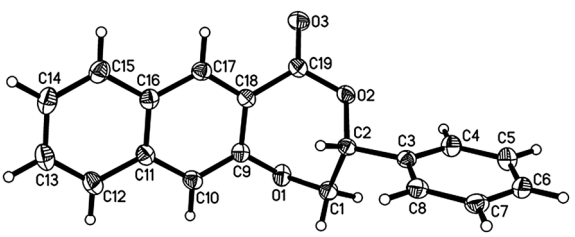
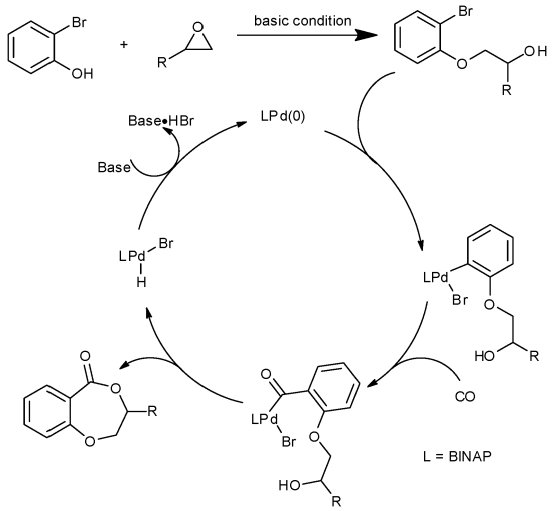


Fig. 1 Molecular structure of **3m**. Displacement ellipsoids are drawn at the 50% probability level.



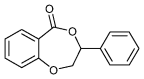
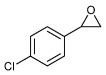
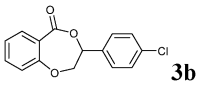
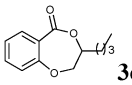
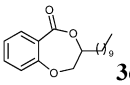
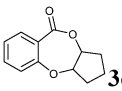
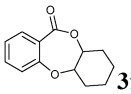
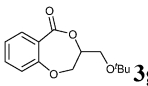
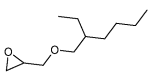
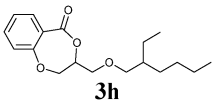
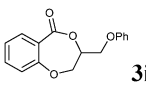
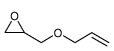
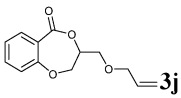
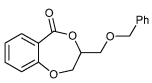
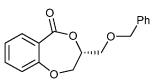
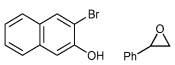
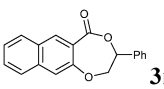
Scheme 1 Proposed reaction mechanism.

addition of the Ar–Br bond to the Pd(0) center, and the benzoyl palladium complex was produced as the key intermediate after the subsequent coordination and insertion of CO. Finally, by the intramolecular nucleophilic attack of the hydroxyl group, the seven-membered ring was eliminated as the final product and palladium(0) was regenerated under assistance of base.

With the optimized reaction conditions in hand [2 mol% $Pd(OAc)_2$, 3 mol% binap, 0.5 mmol of 2-bromophenol, 0.75 mmol of epoxide, in DMF as the solvent, with 3 equiv. of K_3PO_4 as the base, under 5 bar of CO, at 100 °C for 16 hours], we carried out the generality testing (Table 2).

Initially, different epoxides were examined with 2-bromophenol as the model substrate. Firstly, 4-chloro-styreneoxide was tested, 4,5-dihydrobenzo[*c*]oxepinone was obtained with a ratio between 3-substituted (**3c**) and 4-substitued (**3c′**) compounds of 90 : 10 and **3c** was isolated in 85% yield (Table 2, entry 2). Epoxides with aliphatic chains, 2-butyloxirane and 2-octyloxirane were subjected to the optimized conditions, moderate yields (respectively 79% and 79%) were obtained with better regioselectivity (95 : 5; Table 2, entries 3 and 4). With cyclopentene oxide as the starting substrate, the reaction also proceeded well and **3e** was isolated as a single diastereoisomer in 70% yield (Table 2, entry 5). However, when using cyclohexene oxide as the starting substrate, the product was isolated as a mixture of diastereoisomers in a diastereoisomeric ratio of 75 : 25 which might be explained by the co-existence of S_N1 and S_N2 mechanisms as the presence of palladium acetate as the Lewis acid and K_3PO_4 as base (Table 2, entry 6). With these results in hand, we then tested different glycidyl ethers under our best conditions (Table 2, entries 7–12). Notably, glycidyl ethers are another important class of epoxides and have become commercially available since the late 1940s, which are used as components of epoxy resins. Generally, different glycidyl ethers bearing aliphatic and aromatic glycidyl ethers gave moderate to good yields (66–88%). Moreover, the regioselectivity of the ring-opening reaction of glycidyl ethers are proved to be better than other aliphatic and aromatic substituted epoxides in which the selectivity is more

Table 2 Scope of the reaction under optimized conditions[a]

Entry	1	2	Product	Yield[b] (3 : 3′)[c]
1	1a		 3a	90 (90 : 10)
2	1a		 3b	85 (90 : 10)
3	1a		 3c	79 (95 : 5)
4	1a		 3d	79 (95 : 5)
5	1a		 3e	70 (dr > 99 : 1)[d]
6	1a		 3f	77 (dr: 75 : 25)[d]
7	1a		 3g	66 (>99 : 1)
8	1a		 3h	88 (>99 : 1)
9	1a		 3i	66 (98 : 2)
10	1a		 3j	79 (>99 : 1)
11	1a		 3k	85 (98 : 2)
12	1a		 3l	98% ee[e]
13			 3m	85 (90 : 10)

[a] General conditions: $Pd(OAc)_2$ (2 mol%), binap (3 mol%), **1** (0.5 mmol, 1 equiv.), **2** (0.75 mmol, 1.5 equiv.), K_3PO_4 (1.5 mmol, 3 equiv.), in DMF (2 mL), CO (5 bar), at 100 °C for 16 hours. [b] Isolated yield of **3a–m**. [c] Determined by GC. [d] Analyzed using NMR of the purified compound. [e] Analyzed using gas chromatography equipped with a chiral column of the crude product.

than 98 : 2. Remarkably, this catalytic system is proven to be tolerable towards the allyl group as 79% of **3j** was isolated by using allyl glycidyl ether as the starting material (Table 2, entry 10). In the cases of 9-oxabicyclo[6.1.0]nonane and ethyl 3-phenyloxirane-2-carboxylate, no desired products were detected.

As the achievements in asymmetric epoxidation of alkenes have been acknowledged by the Nobel Prize in 2001 and several name reactions, asymmetric epoxides are becoming readily available. It will be highly interesting if we can keep the chiral centre of the epoxide in the final products under our conditions. To our delight, when *S*-(–)-benzyl glycidyl ether was subjected to the optimized conditions, 98% of ee was obtained in the final products. Moreover, the substrate scope could also be extended to 3-bromonaphthalen-2-ol under the same conditions, which also yields the corresponding product in 85% yield (Table 2, entry 13).

In summary, a highly regioselective cascade synthesis of 2,3-dihydrobenzodioxepinone from 2-bromophenols and epoxides has been developed. Starting from commercially available substrates, moderate to good yields of versatile desired products are obtained in a regioselective manner (major product > 90%) under mild conditions.

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