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Epoxides as Dual-Functionalized Alkylating Reagents in Catellani Reactions for the Assembly of Heterocycles

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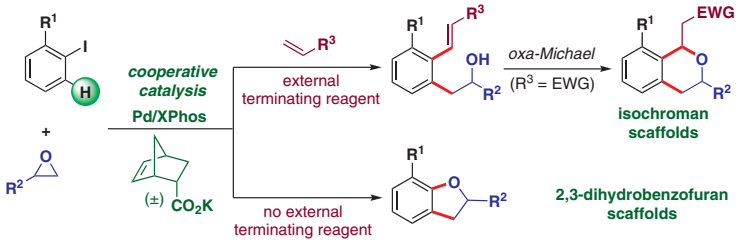

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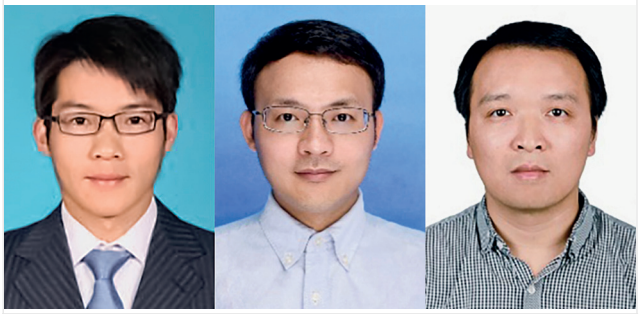
Abstract Reported is a cooperative catalytic system consisting of a complex of Pd with dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (XPhos) and the potassium salt of 5-norbornene-2-carboxylic acid that permits the use of epoxides as dual-functionalized alkylating reagents in Catellani-type reactions for the assembly of heterocycles. Salient features of this research include readily available substrates, use of the potassium salt of 5-norbornene-2-carboxylic acid as a catalytic mediator as well as a base, and excellent regioselectivity for the cleavage of epoxides. This mild, chemoselective, scalable, atom- and step-economic protocol offers a straightforward approach for the assembly of isochroman and 2,3-dihydrobenzofuran scaffolds.

Key words Catellani reaction, cooperative catalysis, epoxides, isochromans, dihydrobenzofurans

The Catellani-type reaction[1] is a powerful strategy for the synthesis of highly substituted arenes that are otherwise difficult to access through conventional transition-metal-catalyzed cross-coupling reactions.[2] It utilizes the synergistic interplay of palladium and 2-norbornene (NBE) catalysis to facilitate sequential *ortho*-C–H functionalization and *ipso*-termination of aryl halides in a single operation.[3] Since the pioneering work by the Catellani group in 1997,[1] this chemistry has attracted considerable attention from organic chemists. Dramatic progress has been made in the past two decades, especially for the development of terminating reagents.[2f,2h–i,2l] In contrast, the electrophilic reagents for *ortho* C–H functionalization are limited mainly to alkyl halides,[4] aryl halides,[5] azirines,[6a] aziridines,[6b,c] *O*-benzylhydroxy-amines,[7] and various carboxylic acid derivatives[8] (Figure 1A). Recently, the Gu and Dong groups independently reported an *ortho*-thiolation reaction based on a rational design of sulfur-containing electrophiles.[9]



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Epoxides are widely available feedstock chemicals. Recently, the groups of Kanai, Yu, and Li[10] made successful use of epoxides as alkylating reagents in directed C–H bond functionalizations, which inspired us to pursue the possibility of using epoxides as dual-functionalized alkylating reagents in Catellani reactions for the assembly of two important heterocycles: isochromans and 2,3-dihydrobenzofurans (DHBFs) (Figure 1B). We surmised that an epoxide **2** might react with the common aryl-NBE palladacycle (**ANP**; **C**) to form intermediate **D**, which would undergo β-carbon elimination to form the key intermediate **E** and regenerate the NBE mediator. **E** was expected to undergo conventional Heck termination to provide product **4**. Products of this type are an important group intermediates, permitting access valuable isochroman scaffolds through a subsequent oxa-Michael addition.[11] Alternatively, without the external terminating reagent, intermediate **E** might undergo an intramolecular etherification process[12] to afford the DHBF scaffolds **6**,[13] wherein the epoxide acts as both an alkylating and a terminating reagent (Figure 1C). Dong and co-work-

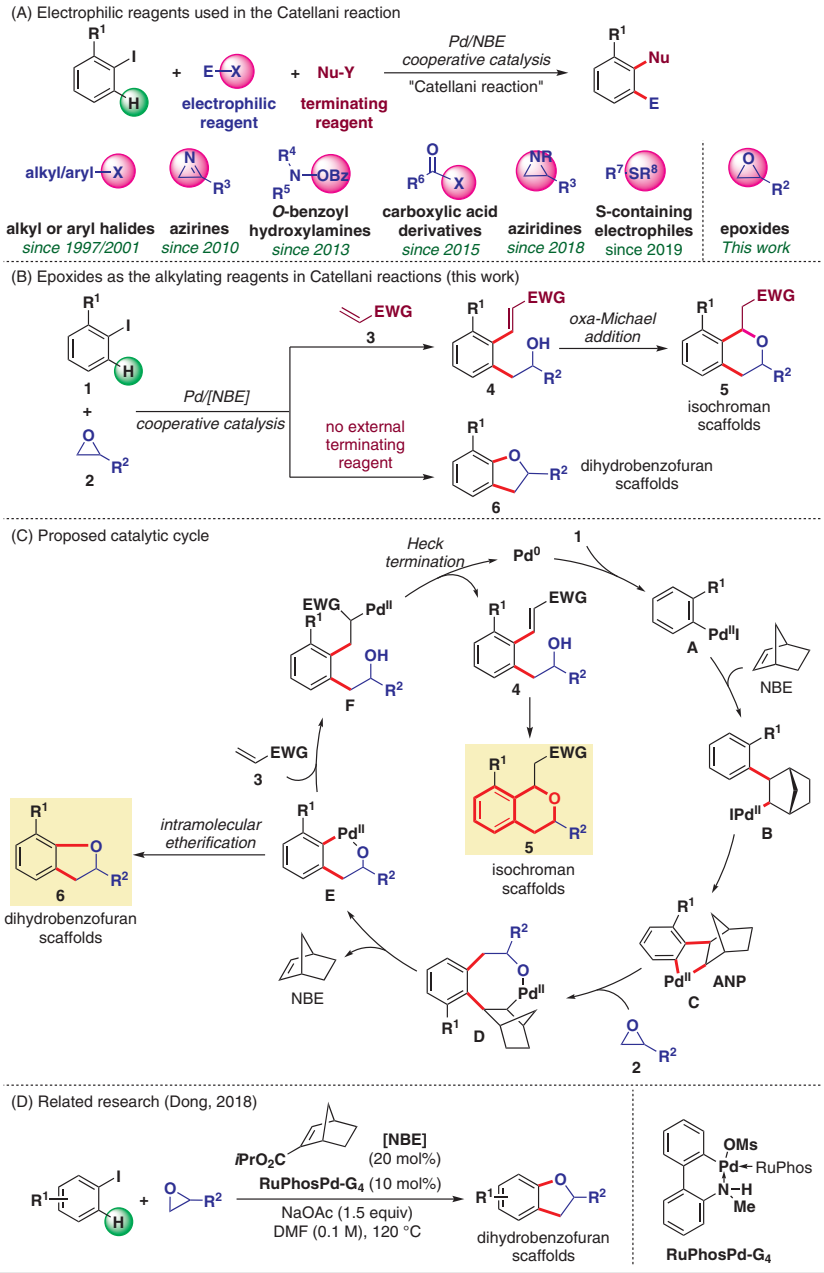
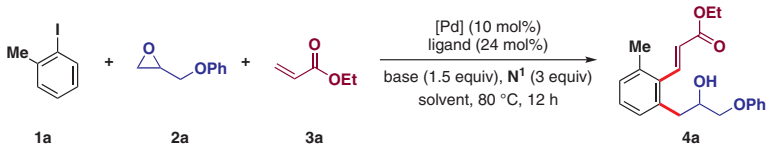


Figure 1 Epoxides in Catellani-type reactions (Reprinted from Ref. 15 with permission from Wiley–VCH)

ers recently reported an elegant related method for the assembly of DHBFs; an asymmetric version, albeit with moderate enantioselectivities, was also reported by the same group (Figure 1D).[14]

Our studies commenced with a model reaction of readily available 2-iodotoluene (**1a**, 1.5 equiv), 2-(phenoxymethyl)oxirane (**2a**, 2.0 equiv), and ethyl acrylate (**3a**, 1.0 equiv) as reactants and simple NBE (**N¹**, 3.0 equiv) as a mediator (Table 1).[15] Through extensive screening of reaction parameters (Table 1, entries 1–12), we showed that $Pd(OAc)_2$, XPhos (Figure 2),[16] CsOAc, and NMP constituted the optimal combination of reactants and reagents (Table 1, entry 1). Further optimizations showed that reducing the loading of $Pd(OAc)_2$ to 2.5 mol% and the amount of CsOAc to 0.5 equivalent, and lowering the reaction temperature to 60 °C produced no deleterious effects (Table 1, entries 13–15). Remarkably, the use of the potassium salt of inexpensive 5-norbornene-2-carboxylic acid (**N²**, 0.5 equiv) instead of **N¹** (3.0 equiv) and CsOAc (0.5 equiv) afforded a similar result (entry 16), indicating the dual roles adopted by **N²** as both a mediator and base. Interestingly, when the cesium salt of 5-norbornene-2-carboxylic acid **N³** was used instead of **N²**, the yield of **4a** fell to 78% (entry 17). Finally, the optimal conditions involved the reduction of the amount of the aryl iodide to 1.3 equivalents, which gave **4a** in 92% yield (91% isolated yield; entry 18). It is worth mentioning that the use of **N²** instead of **N¹** and CsOAc is advantageous, not only from the point of view of reaction economy, but also because it leads to greater operational simplicity of the process, as **N²** can be readily removed and recycled by simple aqueous extraction during workup.

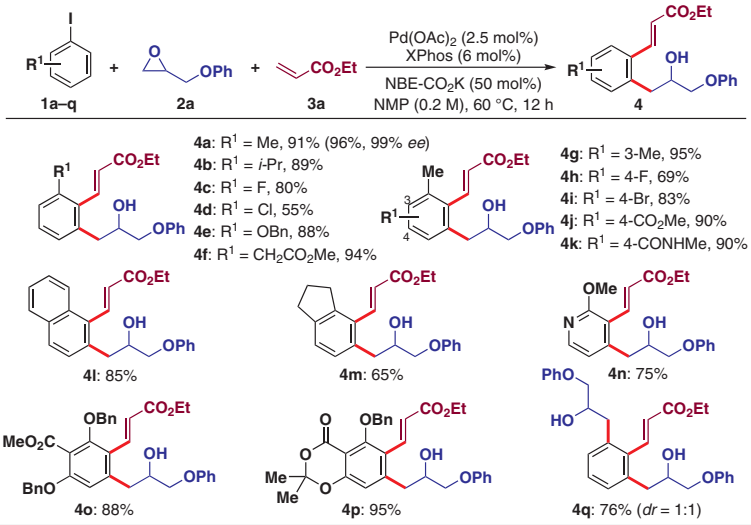
Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

Entry	Base	Solvent	[Pd]	Ligand[b]	Yield[c] (%)
1	CsOAc	NMP	$Pd(OAc)_2$	XPhos	95
2	KOAc	NMP	$Pd(OAc)_2$	XPhos	81
3	K_2CO_3	NMP	$Pd(OAc)_2$	XPhos	40
4	Cs_2CO_3	NMP	$Pd(OAc)_2$	XPhos	0
5	CsOAc	DMF	$Pd(OAc)_2$	XPhos	84
6	CsOAc	MeCN	$Pd(OAc)_2$	XPhos	44
7	CsOAc	toluene	$Pd(OAc)_2$	XPhos	0
8	CsOAc	NMP	$[Pd(C_3H_5)Cl]_2$	XPhos	90
9	CsOAc	NMP	$Pd_2(dba)_3$	XPhos	94
10	CsOAc	NMP	$Pd(OAc)_2$	SPhos	90
11	CsOAc	NMP	$Pd(OAc)_2$	TFP	90
12	CsOAc	NMP	$Pd(OAc)_2$	PPh_3	46
13[d]	CsOAc	NMP	$Pd(OAc)_2$	XPhos	94
14[e]	CsOAc	NMP	$Pd(OAc)_2$	XPhos	95
15[f]	CsOAc	NMP	$Pd(OAc)_2$	XPhos	92
16[g]	**N²**	NMP	$Pd(OAc)_2$	XPhos	94
17[h]	**N³**	NMP	$Pd(OAc)_2$	XPhos	78
18[i]	**N²**	**NMP**	**$Pd(OAc)_2$**	**XPhos**	**92 (91)[j]**

[a] Reaction conditions (unless otherwise stated): **1a** (0.3 mmol, 1.5 equiv), **2a** (0.4 mmol, 2.0 equiv), **3a** (0.2 mmol, 1.0 equiv), solvent (1 mL), 80 °C, 12 h.
[b] For structures, see Figure 2.
[c] GC yield with biphenyl as internal standard.
[d] 2.5 mol% of $Pd(OAc)_2$ and 6 mol% of XPhos were used.
[e] The reaction was conducted at 60 °C.
[f] 0.5 equiv of CsOAc was used.
[g] 0.5 equiv of **N²** was used instead of 0.5 equiv of CsOAc and 3.0 equiv of **N¹**.
[h] 0.5 equiv of **N³** was used instead of 0.5 equiv of CsOAc and 3.0 equiv of **N¹**.
[i] 0.5 equiv of **N²** and 1.3 equiv of **1a** were used.
[j] Isolated yield.



Scheme 1 The scope of the aryl iodides (Reprinted from Ref. 15 with permission from Wiley–VCH)

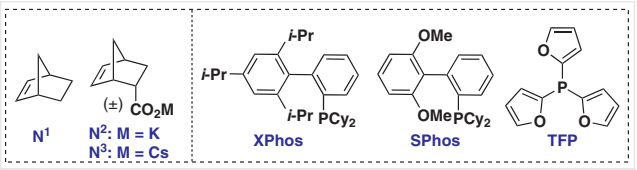
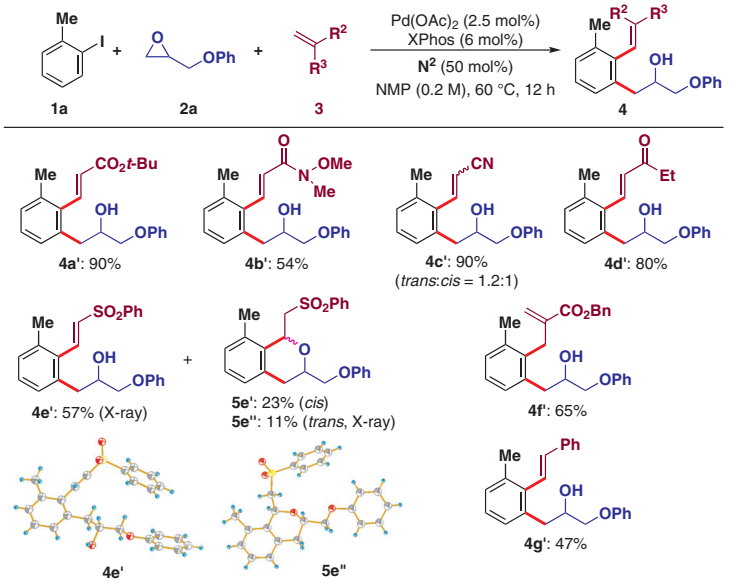


Figure 2

With the optimal reaction conditions in hand, we first examined the scope of the aryl iodide (Scheme 1). Gratifyingly, a wide range of aryl iodides bearing electron-donating or electron-withdrawing groups were competent substrates, providing the corresponding products in yields of 55–95%. Various functional groups were well tolerated, including benzyloxy, methoxy, fluoro, chloro, bromo, methyl ester, and amide, thereby providing handles for further product diversification. Notably, bicyclic aryl iodides (products **4l** and **4m**), hetaryl iodide (product **4n**), and densely functionalized aryl iodides (products **4o** and **4p**) were successfully used and gave good yields of the corresponding products (65–95%). Furthermore, even simple phenyl iodide reacted to afford the dialkylated product **4q** as a 1:1 mixture of diastereomers in 76% yield.

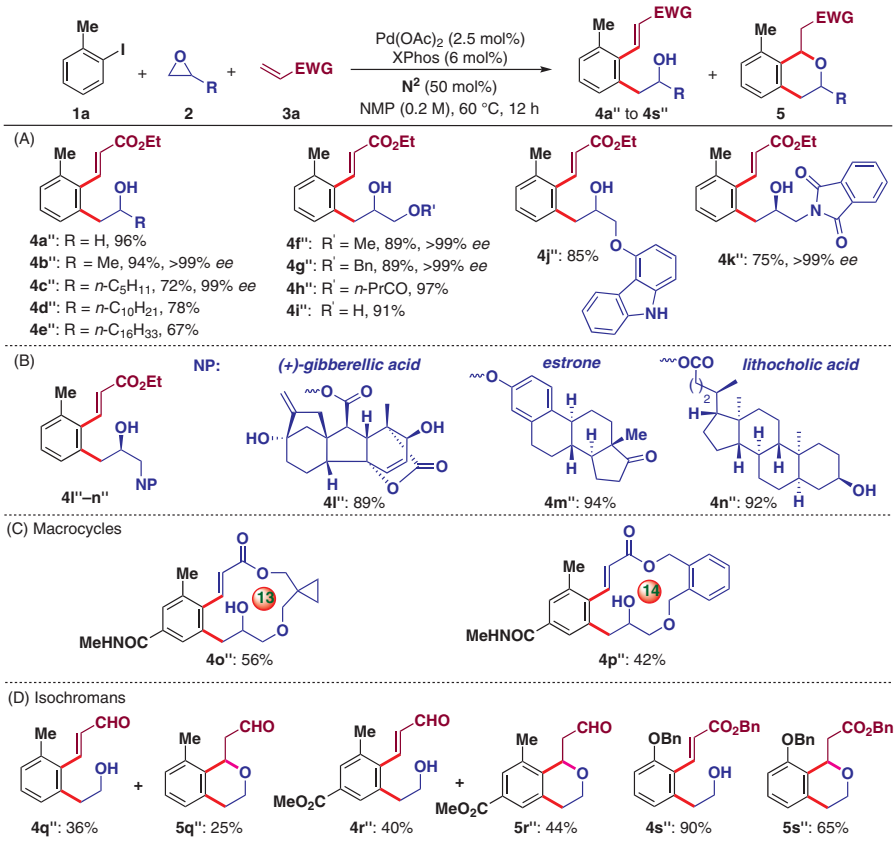
Next, the reaction scope of the olefin **3** was investigated. As can be seen from Scheme 2, a series of monosubstituted olefins with an electron-withdrawing group efficiently par-



Scheme 2 The scope of olefins (Reprinted from Ref. 15 with permission from Wiley–VCH)

ticipated in this reaction to produce the desired products **4a′–e′** in moderate to high yields. Notably, acrylonitrile afforded product **4c′** as a 1.2:1 mixture of the *trans*- and *cis*-geometric isomers in 90% yield. When phenyl vinyl sulfone was used, a consecutive intramolecular oxa-Michael addition took place partially, with poor diastereoselectivity, and the cyclized isochroman products **5e′** (*cis*) and **5e″** (*trans*) were obtained in yields of 23 and 11%, respectively, together with the major uncyclized product **4e′**. The structures of **4e′** and **5e″** were unambiguously confirmed by X-ray crystallographic analysis.[17] In addition, the 1,1-disubstituted electron-deficient olefin benzyl methacrylate afforded product **4f′**, bearing a terminal olefin, as a result of a final β-H elimination at the methyl group instead of at the benzylic position. Remarkably, simple styrene was also a suitable terminating reagent, delivering the desired product **4g′** in 47% yield.

Next, we probed the reaction scope of the epoxide. As shown in Scheme 3A, simple ethylene oxide and various 2-alkyloxiranes were found to be suitable substrates, providing the desired products **4a″–e″** in good to excellent yields (67–96%). Epoxides containing a protected 3-hydroxy or 3-amino group led to the desired products **4f″–h″** and **4j″–k″**, respectively, in excellent yields. Importantly, a free hydroxy group was compatible with this protocol, affording the versatile synthon **4i″** in 91% yield. It is noteworthy that excellent regioselectivities were observed, with the cleavage of the epoxide taking place at the less-hindered site. When enantiopure epoxides were used, the reaction proceeded with complete stereoretention, affording the corresponding chiral products **4b″**, **4c″**, **4f″**, **4g″** and **4k″** with ≥99% *ee*. Moreover, the chiral epoxides derived from several complex bioactive complex natural products were also suitable substrates, giving the corresponding products **4l″–n″** in yields of 89–94%, along with complete chemoselectivity over free hydroxy, ketone, lactone, and ester functional groups (Scheme 3B). More importantly, the use of multifunctional epoxides incorporating a terminating olefin moiety led to the formation of the corresponding 13- and 14-membered macrocyclic lactones **4o″** and **4p″** in yields of 56 and 42%, respectively, thereby offering a unique strategy for accessing macrocycles (Scheme 3C). Further exploration revealed that ethylene oxide and acrolein reacted successfully, providing the noncyclic products **4q″** and **4r″**, respectively, in moderate yields, together with considerable amounts of the corresponding oxa-Michael adducts **5q″** and **5r″**. In contrast, on switching the terminating reagent to benzyl acrylate, noncyclic **4s″** was obtained exclusively in 90% yield; this could be fully converted into isochroman **5s″** by treatment with Cs_2CO_3 in heated acetonitrile.[15] Based on these



Scheme 3 The scope of epoxides (Reprinted from Ref. 15 with permission from Wiley–VCH)

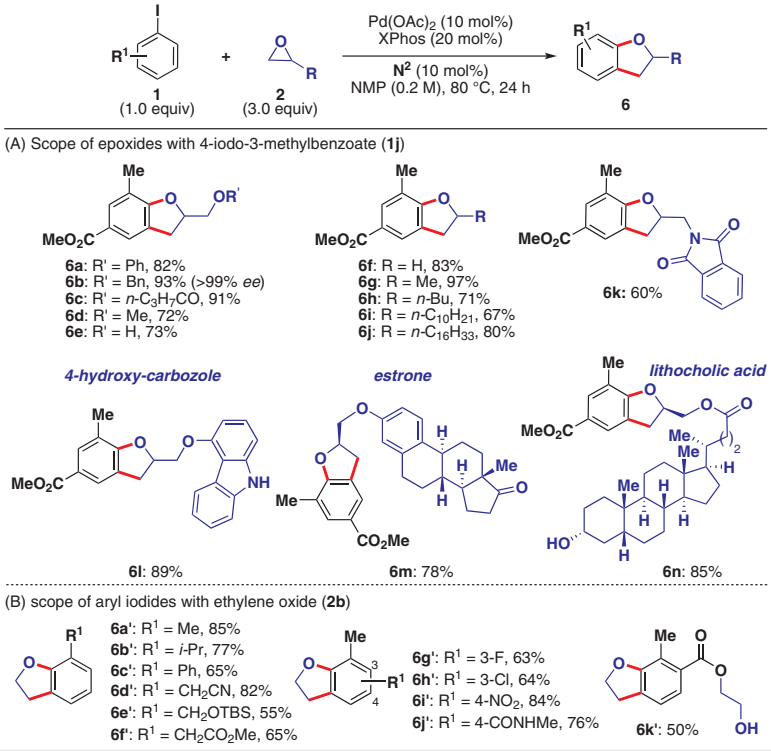
observations, we developed a one-pot procedure in which, following the completion of the Catellani reaction, Cs_2CO_3 was added directly to the reaction mixture to promote a subsequent oxa-Michael addition reaction, giving **5s″** exclusively in 65% yield (Scheme 3D).

Encouraged by the success of the three-component Catellani reaction involving epoxides, we continued to investigate the direct annulation of aryl iodides with epoxides.[14] To our delight, under slightly modified reaction conditions (mainly involving an increase in the reaction temperature to 80 °C), the expected DHBF product **6a** was obtained in 82% yield (Scheme 4).[18] Notably, only 10 mol% of the mediator **N²** was needed to promote this transformation.

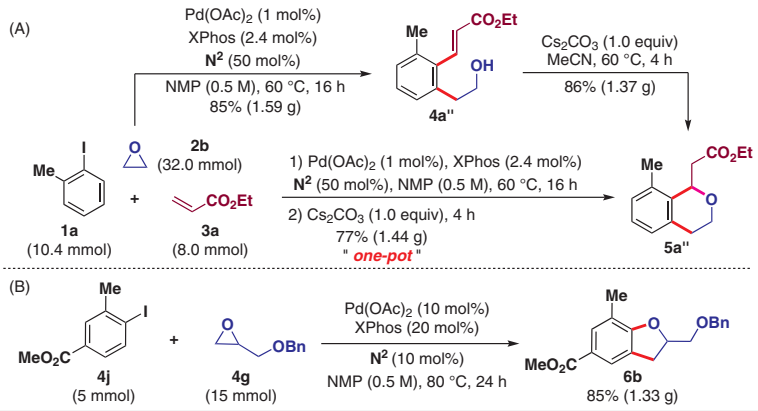
Subsequently, we examined the substrate scope of this annulation reaction. As shown in Scheme 4A, with 4-iodo-3-methylbenzoate (**1j**) as the reaction partner, a wide range of epoxides were well tolerated to furnish the corresponding products in good to excellent yields (67–97%). The length of the aliphatic chain of the epoxide had little effect on the outcome of the reaction (**6f**–**j**). Further exploration showed that a protected β-amino group in epoxide **2** was also compatible with this protocol (**6k**). Moreover, when epoxides derived from several bioactive natural products (4-hydroxycarbazole, estrone, or lithocholic acid) were examined in this transformation, the desired products **6l**–**n** were obtained in yields of 78–89%. As in the previous three-component process, excellent regioselectivities were observed for the cleavage of the epoxides. When enantiopure epoxide **2g** was used, the corresponding chiral DHBF product **6b** was obtained with complete stereoretention (>99% ee).

Next, we probed the scope of the aryl iodide component of this protocol, with simple ethylene oxide (**2b**) as the reaction partner (Scheme 4B). Aryl iodides with either electron-donating or electron-withdrawing substituents all participated smoothly in the reaction, providing the desired aryl-substituted 2,3-dihydrobenzofuran products **6a′**–**j′** in yields of 55–85%. Interestingly, an aryl iodide containing a free carboxylic group also reacted to afford the esterified product **6k′** in 50% yield; in this reaction ethylene oxide (**2b**) served as both an annulation and an esterification reagent.

To demonstrate the practicality of these two protocols, we performed some scaled-up experiments. For the three-component transformation, we found that, with only 1.0 mol% $Pd(OAc)_2$ and 2.4 mol% XPhos, the noncyclic product **4a″** was obtained in 85% yield (1.59 g) from an 8.0 mmol-scale experiment; this product was readily converted into isochroman **5a″** in 86% yield (1.37 g) upon treatment with Cs_2CO_3. To our delight, a one-pot operation on the same scale also proceeded well to provide **5a″** directly in 77% yield (1.44 g) (Scheme 5A). In addition, a gram-scale preparation of the DHBF product **6b** also proceeded successfully, giving an 85% yield (1.33 g) (Scheme 5B). It is noteworthy



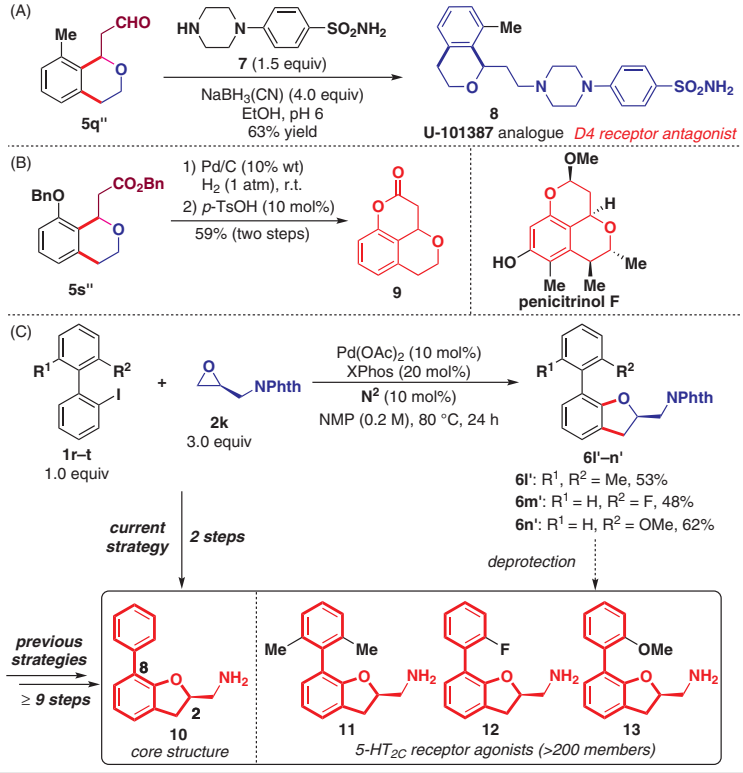
Scheme 4 Substrate scope of the direct annulation between the aryl iodides and epoxides (Reproduced from Ref. 18 with permission from the Royal Society of Chemistry)



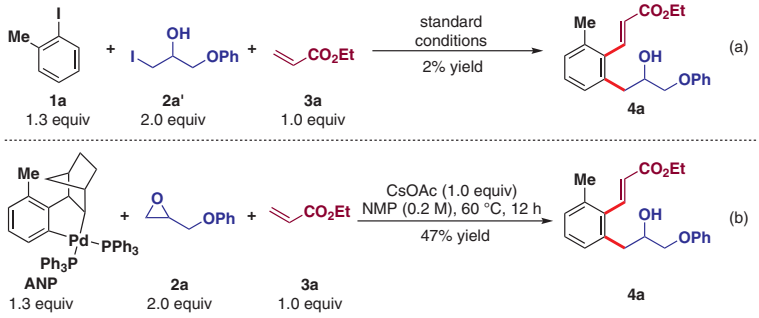
Scheme 5 Scale-up experiments (Reprinted from Refs. 15 and 18 with permission from Wiley–VCH and the Royal Society of Chemistry, respectively)

that the concentrations of the above gram-scale experiments were as high as 0.5 M; compatibility with high concentrations is another attractive feature of these methods.

To further highlight the potential utilities of these methods, several synthetic applications were examined. For example, the reaction of isochroman **5q''** with commercially available amine **7** under reductive amination conditions[19] directly gave **8**, a methylated analogue of the D4 agonist U-101387[20] (Scheme 6A). Debenzylation of **5s''** by using Pd/C under H_2 at 1 atm, followed by an acid-promoted lactonization[21] afforded the polycyclic intermediate **9** in 59% yield (two steps); this product contained the core structure of penicitrinol F[22] (Scheme 6B). This latter direct annulation method could be applied in the preparation of the key intermediates for the syntheses of 5-HT_{2C} receptor agonists.[23] As shown in Scheme 6C, biaryl iodides **1r–t** reacted well with optically pure epoxide **2k** under the standard reaction conditions to give the desired chiral DHBF products **6l′–n′** in yields of 48–62%. A subsequent deprotection of the amino group led directly to the 5-HT_{2C} receptor agonists **11**–



Scheme 6 Synthetic applications (Reprinted from Refs. 15 and 18 with permission from Wiley–VCH and the Royal Society of Chemistry, respectively)



Scheme 7 Control experiments

13.[23] Because the common 8-aryl-substituted DHBF core structure **10** is present in all (>200) members of the 5-HT_{2C} receptor agonist family, these could, in theory, be assembled in just two steps from two types of readily available starting materials, which constitutes a big breakthrough over the state-of-the-art methods (which involve nine or more steps).[23c,24] We recently extended this research to the assembly of benzo-fused dioxabicycle scaffolds.[25] More efforts are underway to utilize these methods as key steps in total syntheses of complex natural products.

Lastly, to gain some mechanistic insights into these reactions, we carried out several control experiments (Scheme 7). When β-iodohydrin **2a′** was used instead of epoxide **2a** in the model reaction under the standard reaction conditions, only a trace amount of the desired product was obtained, thereby excluding **2a′** as a possible alkylating reagent (Scheme 7A). In addition, the stoichiometric reaction of the aryl-NBE palladacycle intermediate **ANP**[26] with **2a** and **3a** in the presence of CsOAc in NMP at 60 °C provided **4a** in 47% yield, indicating that the epoxide is one of the actual alkylating reagents (Scheme 7B). These preliminary results ruled out a possible cascade pathway involving initial regioselective opening of epoxide by the iodide anion formed in situ, and a subsequent conventional Catellani-type process. Detailed mechanistic studies to gain a better understanding of these reactions are underway.

In conclusion, a cooperative catalytic system consisting of a Pd/XPhos complex and the potassium salt of 5-norbornene-2-carboxylic acid (NBE-CO_2K) was developed to permit the use of epoxides as dual-functionalized alkylating reagents in Catellani-type reactions for the assembly of heterocycles. Salient features of this method include readily available substrates, the use of NBE-CO_2K as both a catalytic mediator and a base, and excellent regioselectivity for the cleavage of the epoxide. This mild, chemoselective, scalable, atom- and step-economic protocol offers a straightforward approach for the assembly of isochroman and 2,3-dihydrobenzofuran scaffolds. Efforts towards detailed mechanistic studies to gain a full understanding of the role of the unique mediator NBE-CO_2K and to achieve total syntheses of complex natural products, as well as drug molecules, by applying these methods as key steps are currently ongoing in our laboratory.

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