EPOXIDES AS DUAL-FUNCTIONALIZED ALKYLATING REAGENTS FOR THE ASSEMBLY OF OXYGEN-CONTAINING HETEROCYCLES

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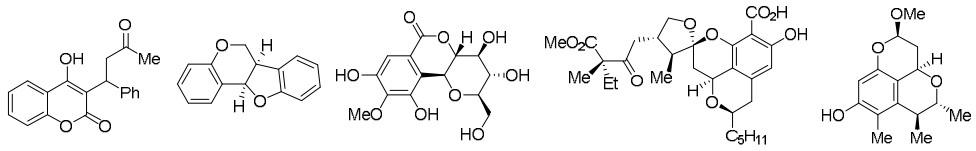
Abstract. *Epoxides, the smallest three-membered saturated O-heterocycles easily prepared in racemic or enantioenriched form, are highly useful building blocks for the synthesis of complex organic molecules. Owing to their inherent high ring-strain, epoxides are facile to undergo ring-opening reactions. A tandem process involving the opening of an epoxide ring and a following cyclization provides a convenient approach to access diverse types of oxygen-containing heterocycles with good step-economy. This chapter aims to summarize the syntheses of oxygen-containing heterocycles by using epoxides as dual-functionalized alkylation reagents.*

Contents

1. Introduction

As is widely known, heterocycles are privileged skeletons that are ubiquitous in bioactive natural products, pharmaceuticals, agrochemicals and functional materials.[1-7] Among the diversified heterocyclic compounds developed, the oxygen-containing heterocycles are the second most common ones in drugs approved by U. S. Food and Drug Administration (FDA)[4] (Scheme 1). As such, the development of practical and efficient methods for the assembly of oxygen-containing heterocycles is of significant importance in organic synthesis and medicinal chemistry.



Scheme 1. Representative examples of oxygen-containing heterocycles in pharmaceuticals and bioactive natural products.

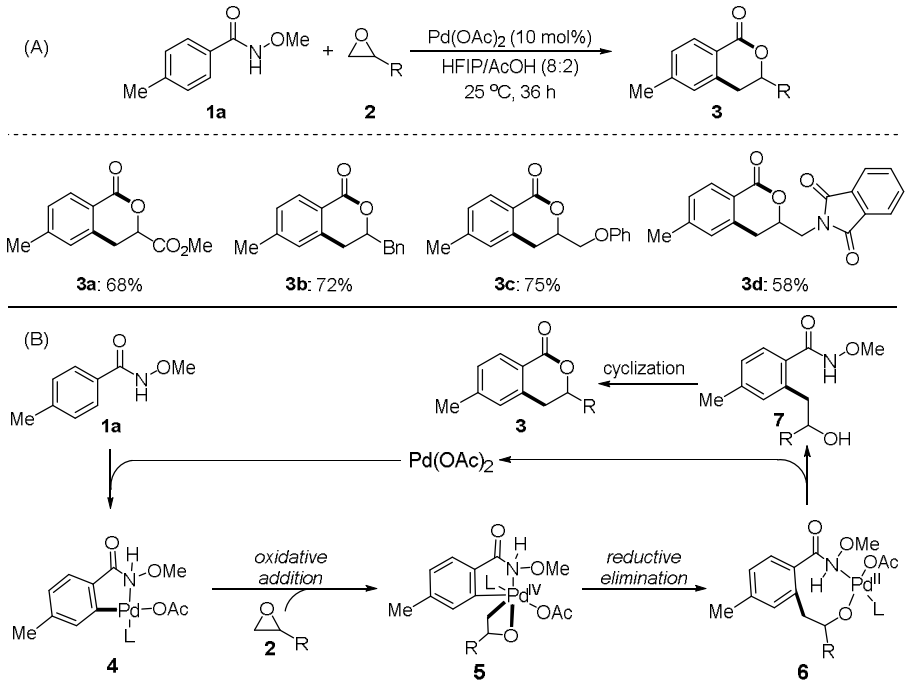
Epoxides are highly useful building blocks and have been extensively used in organic synthesis.[8-13] Due to their inherent high ring-strain, epoxides are facile to undergo ring-opening reactions which can couple with other cyclization reactions to construct many valuable oxygen-containing functionalized molecules. In this context, several advantages can be envisioned. First, epoxides are readily available

compounds and most of them are commercially available in both racemic and chiral forms. Second, the transformations triggered by epoxides ring-opening reactions are very diversified which can lead to various oxygen-containing heterocycles. Third, epoxides can be entirely incorporated into the products, indicating good atom economy. Furthermore, if optically pure epoxides are used as the reagents, the corresponding enantioenriched oxygen-containing heterocycles could be obtained conveniently. Recently, good progress has been made in the utilization of epoxides as the dual-functionalized alkylating reagents for the assembly of oxygen-containing heterocycles. In this chapter, we provide a concise overview of this research field. This chapter is catalogued according to the ring size of the obtained oxygen-containing products, with the assembly of six- and five-membered *O*-heterocycles as the major contents.

2. Assembly of six-membered oxygen-containing heterocycles

2.1. Synthesis of 3,4-dihydroisocoumarins

In 2015, the Kanai group[14] reported the first example of Pd(II)-catalyzed intermolecular direct coupling reaction between epoxides **2** and arenes with a directing group *via* C−H bond activation. A variety of directing groups such as pyridyl, aminoquinolinyl, imino or amide were all well tolerated in this reaction, providing the desired C−H alkylation products in good yields.[15] When *N*-methoxybenzamides **1a** were used as substrates, 3,4-dihydroisocoumarins **3**[16-18] were obtained in one-pot reaction (Scheme 2A).

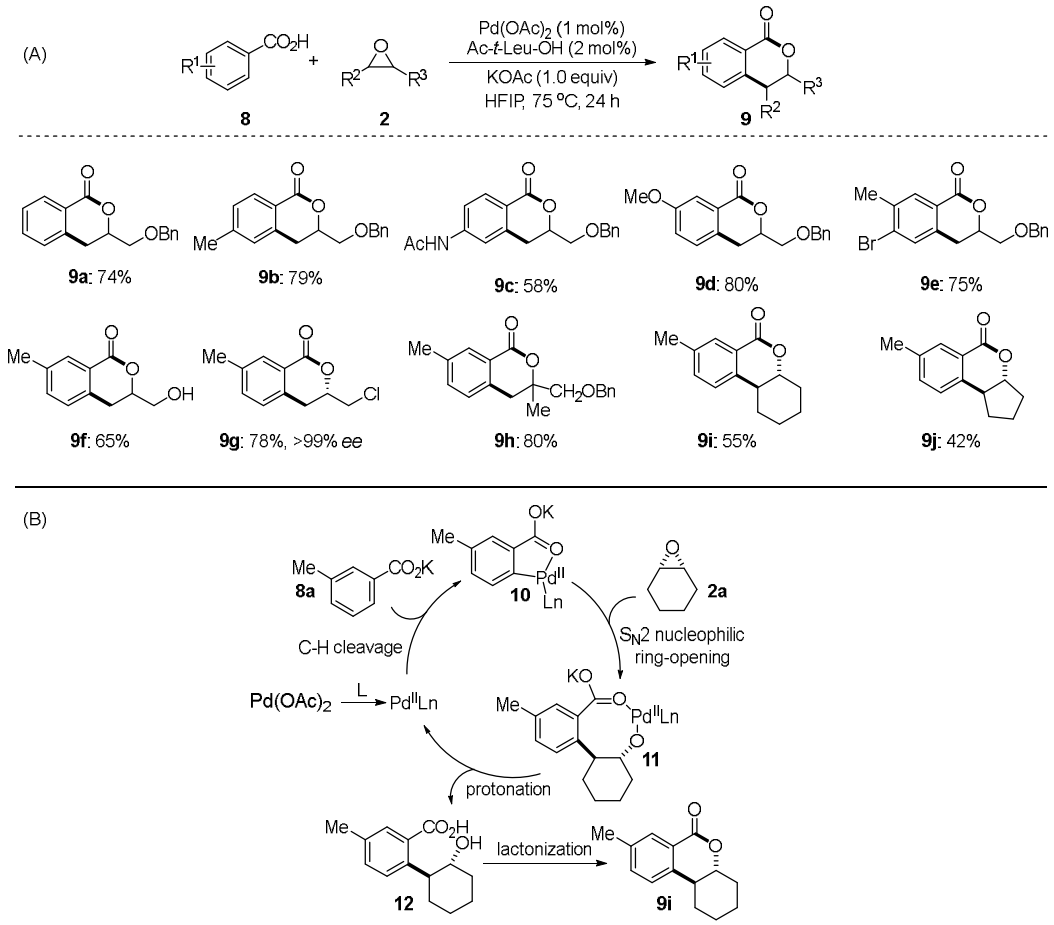


Scheme 2. (A) Synthesis of 3,4-dihydroisocoumarins through amide-directed C−H alkylation and cyclization. (B) Proposed mechanism.

Notably, the reaction proceeded under very mild conditions and could be carried out even at room temperature. A series of terminal epoxides were compatible with this protocol. However, one limitation of this reaction was that an adjacent coordinating group in the epoxides was required. For example, 2-hexyloxirane failed to afford the corresponding product at all. While 2-benzyloxirane provided the desired product **3b** in 72% yield, probably due to the coordination of π-electrons of the phenyl group of the oxirane and the palladium catalyst. Kinetic isotope effect (KIE) experiments suggested that C−H bond activation is the rate-determining step of the coupling reaction. The mechanism of this reaction was further investigated

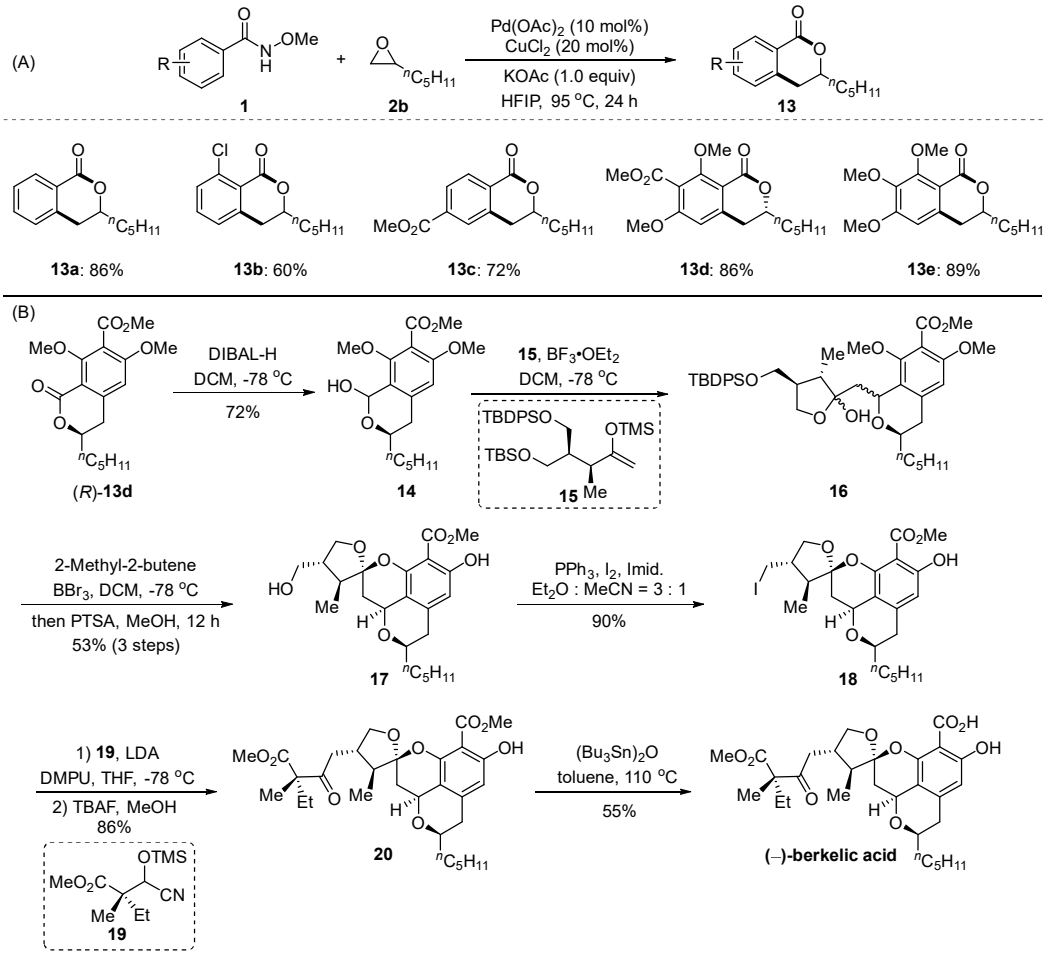
by Fang and co-workers[19] using DFT calculations. A Pd(II)/Pd(IV)/Pd(II) catalytic cycle was identified as the most favourable pathway (Scheme 2B). Initially, coordination of the directing group with Pd(II) catalyst followed by *ortho* C−H activation generates the five-membered palladacyclic intermediate **4**. Then, oxidative addition of epoxide **2** with intermediate **4** forms Pd(IV) complex **5**. Subsequently, reductive elimination delivers the Pd(II) intermediate **6**, which undergoes protonation to give coupling product **7** and regenerate Pd(II) catalyst. Finally, **7** undergoes successive cyclization to provide the desired 3,4-dihydroisocoumarins **3**.

Shortly after Kanai's work, the Yu group[20] reported a similar Pd(II)-catalyzed *ortho*-C−H alkylation of benzoic acids **8** with epoxides **2** to afford 3,4-dihydroisocoumarins **9** in one step through carboxyl-directed C−H activation (Scheme 3A). A wide range of terminal and internal epoxides were suitable for this transformation to give the products **9a-j** in good to excellent yields. Importantly, an adjacent coordinating group of epoxides was not necessary for this transformation. They found that monoprotected amino acid ligands as well as potassium cation played significant role in promoting the reaction, and the catalyst loading could be reduced to 0.5 mol%. When *cis*-1,2-disubstituted epoxides were used as the coupling partner, the *trans* products **9i-j** were obtained exclusively. A series of control experiments suggest that the reaction proceeds through a redox-neutral S_N2-type nucleophilic ring-opening pathway (Scheme 3B).



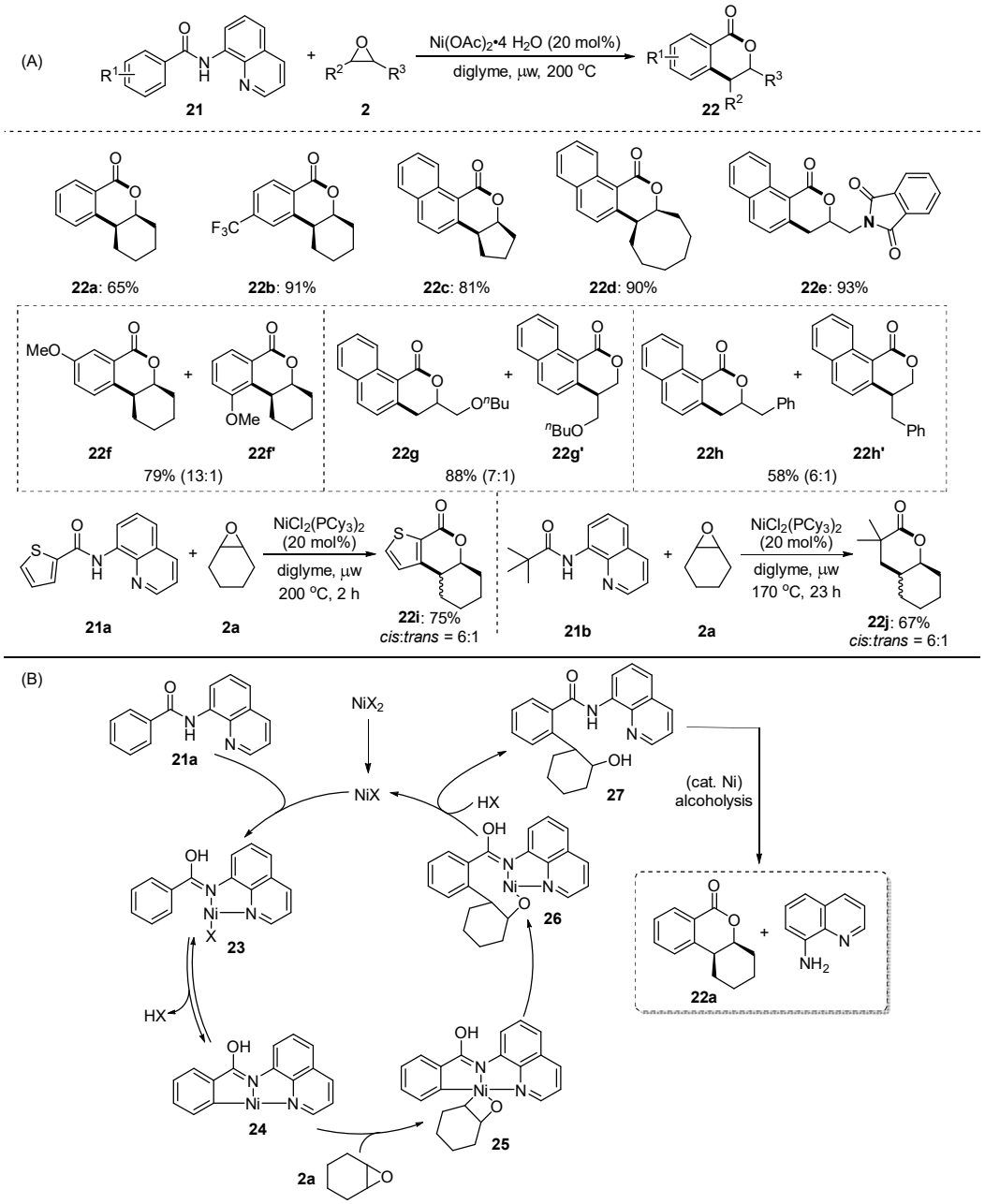
Scheme 3. (A) Synthesis of 3,4-dihydroisocoumarins through carboxyl-directed C−H alkylation and cyclization. (B) Proposed mechanism.

In 2021, Wang and co-workers[21] applied the Pd(II)-catalyzed *ortho*-alkylation of *N*-methoxybenzamide **1**[14] with epoxides **2b** as the key reaction for the total synthesis of complex natural product (–)-berkelic acid[22] (Scheme 4). The structure of (–)-berkelic acid features a unique tetracyclic isochroman spiroketal structure, a pentasubstituted phenyl ring with a free hydroxy group and six stereogenic centers, including one quaternary carbon center. After a series of reaction conditions optimization, they found higher temperature and the addition of $CuCl_2$ could greatly improve the yield. Under the optimal reaction conditions, a wide range of substituted *N*-methoxybenzamides bearing electron-withdrawing, -donating, and -neutral substituents all proved to be competent substrates of this reaction (Scheme 4A). With key dihydroisochroman (*R*)-**13d** in hand, the authors then achieved the total synthesis of (–)-berkelic acid. As illustrated in Scheme 4B, first, (*R*)-**13d** was reduced to lactol **14**, which then reacted with silyl enol ether **15** in the presence of $BF_3{\cdot}OEt_2$ to form a diastereomeric mixture of lactol **16**. Removal of the methyl protecting groups with BBr_3 at low temperature followed by spiroketalization in acidic conditions delivered spiroketal **17** as a single diastereoisomer. Subsequently, iodination and installation of the lateral chain gave the (–)-berkelic acid methyl ester **20**. Finally, selective hydrolysis of the methyl benzoate with $(Bu_3Sn)_2O$ completed the asymmetric total synthesis of (–)-berkelic acid.



Scheme 4. (A) Synthesis of 3,4-dihydroisocoumarins. (B) Total synthesis of (–)-berkelic acid.

In 2018, Hirano, Miura and co-workers[23] developed a nickel-catalyzed stereospecific C−H coupling of 8-aminoquinoline-derived benzamides **21** with epoxides **2** (Scheme 5A).



Scheme 5. (A) Synthesis of 3,4-dihydroisocoumarins through nickel-catalyzed C−H alkylation and cyclization. (B) Proposed mechanism.

The reaction proceeded with concomitant removal of 8-aminoquinoline bidentate directing group to form the 3,4-dihydroisocoumarins **22** directly. If *meta*-methyl or -methoxy substituted benzamide was applied, the corresponding products were obtained as mixtures of different regioselectivities, with the cleavage of epoxides at the less hindered site as the major pathway **22f**. In addition to the six-membered cyclohexene oxide, epoxides containing smaller or larger ring systems were also suitable substrates, and the corresponding *cis*-dihydroisocoumarins were obtained in high yields **22c-d**. The terminal epoxides were also well compatible, although most of them gave a regiomixture **22g-h**.

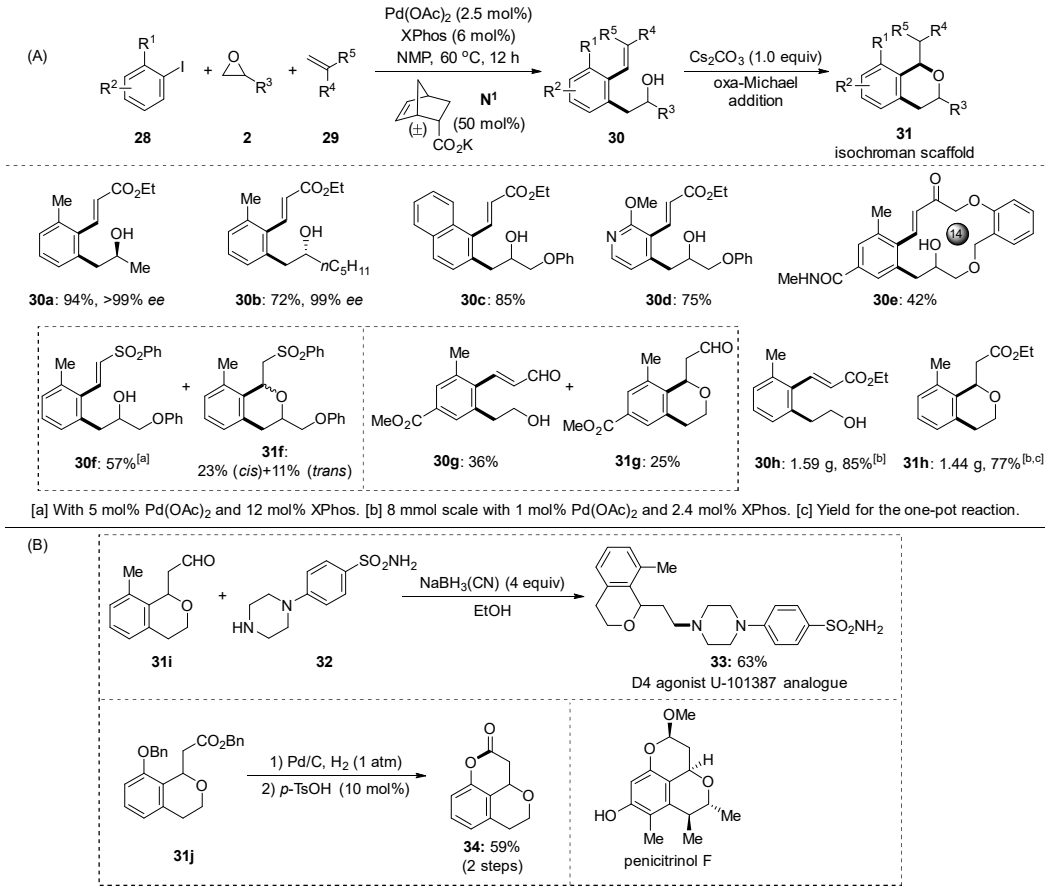
It is worth mentioning that this Ni-catalyzed C−H alkylation shows excellent stereospecificity. The *cis*- and *trans*-epoxides are converted into the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of stereoconfiguration, which is in sharp contrast to the previous results reported by the Yu group.[20] Furthermore, the more challenging heteroaromatic C(sp^2)−H **22i** and C(sp^3)−H functionalizations **22j** were also realized under the modified reaction conditions.

A possible mechanism of this reaction was proposed in Scheme 5B. First, the nickel(II) precatalyst is reduced to nickel(I), which is the active nickel catalyst. Then, intermediate **23** is formed through *N*,*N*-bidentate coordination of **21a** with nickel(I). The reversible C−H cleavage generates metallacycle **24** with the liberation of HX. Oxidative addition of **24** with **2a** gives nickel(III) complex **25**, which subsequently undergoes reductive elimination to deliver intermediate **26**. Final protonolysis with HX led to the formation of intermediate **27** and regeneration of the nickel(I) to start a new catalytic cycle. **27** undergoes an intramolecular alcoholysis to deliver the observed dihydroisocoumarin **22a** and 8-aminoquinoline.

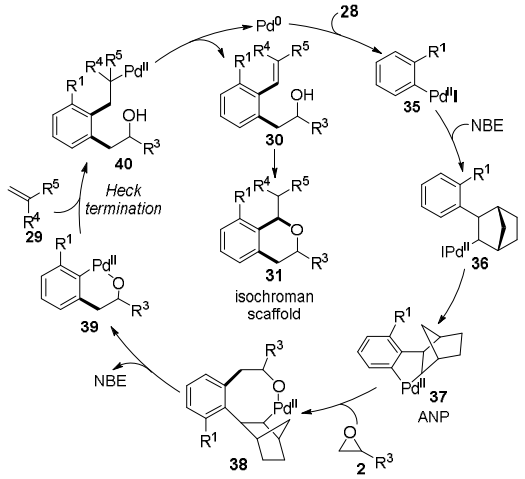
2.2. Synthesis of isochromans

The palladium/norbornene (Pd/NBE) cooperative catalysis, namely the Catellani reaction,[24] is a powerful strategy for the synthesis of polysubstituted arenes.[25-30] Compared to the conventional arene functionalization methods, this approach enables simultaneous functionalization of both *ortho* and *ipso* positions of aryl halides in a single operation. In 2018, Zhou and co-workers[31,32] reported the *ortho* alkylation/*ipso* Heck coupling by using epoxides **2** as the alkylating reagents through Pd/NBE cooperative catalysis (Scheme 6A). Notably, the potassium salt of inexpensive 5-norbornene-2-carboxylic acid **N[1]** acts as both the cocatalyst and base in the process, which could be readily removed by an aqueous extraction after the reaction. The reaction proceeded under very mild reaction conditions. A wide range of readily available functionalized aryl iodides **28**, epoxides **2**, as well as terminating olefins **29** were all compatible with this protocol. It was worth mentioning that the use of bifunctional epoxides tethering an olefin moiety led to the formation of macrolactones **30e** through sequential alkylation and intramolecular Heck termination. When phenyl vinyl sulfone or acrolein were used, in situ intramolecular *oxa*-Michael additions were observed, giving products **30f-g** in moderate yields together with cyclized isochroman products **31f-g** in 34% and 25% yield, respectively. Other resulting products could also be facile transformed into valuable isochroman scaffolds through subsequent *oxa*-Michael addition reaction in the presence of a base. This reaction can be performed on a gram scale in the presence of only 1.0 mol% $Pd(OAc)_2$ (**30h**, 1.59 g, 85%). More importantly, the isochroman product could also be obtained through a one-pot fashion on gram-scale (**31h**, 1.44 g, 77%), which demonstrates the practicality of this protocol. Furthermore, the obtained useful isochroman scaffolds could be further transformed into other valuable products (Scheme 6B). For example, compound **31i** reacted with amine **32** under reductive amination conditions to afford a methylated analogue of D4 agonist U-101387 in good yield. Debenzylation of **31j** followed by lactonization afforded the polycyclic compound **34**, which possesses the core structure of penicitrinol F.

The possible catalytic cycle is shown in Scheme 7. The reaction is initiated by oxidative addition of iodide **28** to Pd(0) catalyst, which leads to the generation of Pd(II) complex **35**. Then, the migratory insertion of norbornene generates complex **36**, which undergoes *ortho*-C–H bond activation in the presence of a base to afford the key aryl-NBE palladacycle (ANP) species **37**. Subsequently, the epoxide reacts with ANP **37** to form complex **38**, which forms complex **39** upon β-carbon elimination and regenerates NBE. In the presence of an external terminating reagent, such as an olefin, complex **39** undergoes a conventional Heck coupling to afford product **30**, which is further transformed into valuable isochroman scaffold **31** through an intramolecular *oxa*-Michael addition.

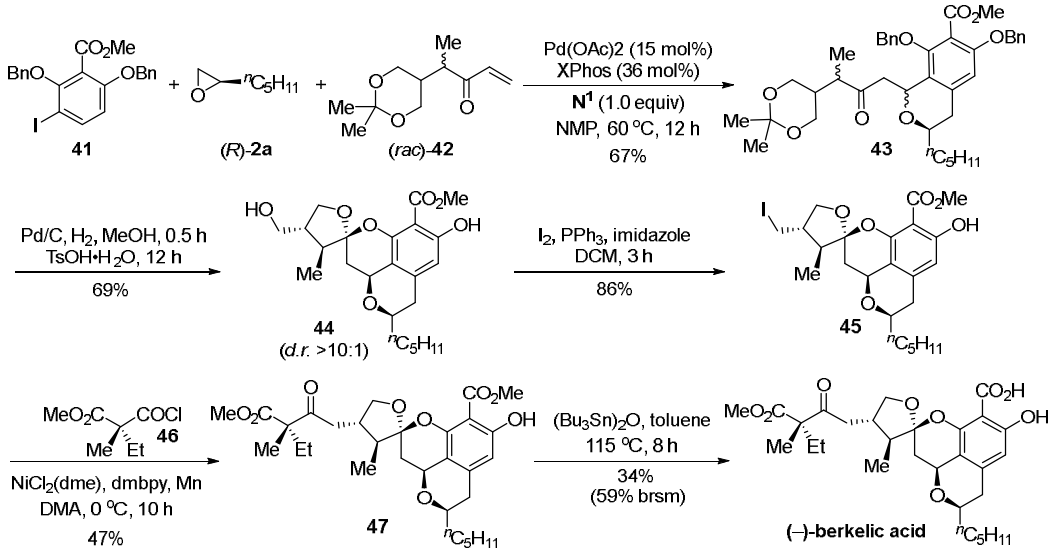


Scheme 6. (A) Assembly of isochromans through Pd/NBE cooperative catalysis. (B) Synthetic applications.



Scheme 7. Proposed mechanism.

Based on this efficient and practical synthetic method, Zhou and co-workers[33] recently realized a concise total synthesis of (–)-berkelic acid (Scheme 8). Initially, the known aryl iodide **41**, (*R*)-2-pentyl epoxide **2a** and racemic enone **42** were used as the reactants to investigate the three-component Catellani/*oxa*-Michael cascade process. Under slightly modified previous reaction conditions,[31] the key isochroman intermediate **43** was obtained as a 1.2:1 diastereomeric mixture in 67% combined yield. Then, **43** was subjected to sequential deprotection/spiroacetalization in one-pot to provide the tetracyclic intermediate **44** in good yield and excellent diastereoselectivity (69%, d.r.>10:1). Alkyl iodide **45** was formed subsequently through Appel reaction.[34] Ni-catalyzed reductive coupling of iodide **45** with chiral acyl chloride **46** afforded (–)-berkelic acid methyl ester **47** in moderate yield. Finally, (–)-berkelic acid was accessed through the reported selective saponification of the methyl benzoate in the presence of $(Bu_3Sn)_2O$.

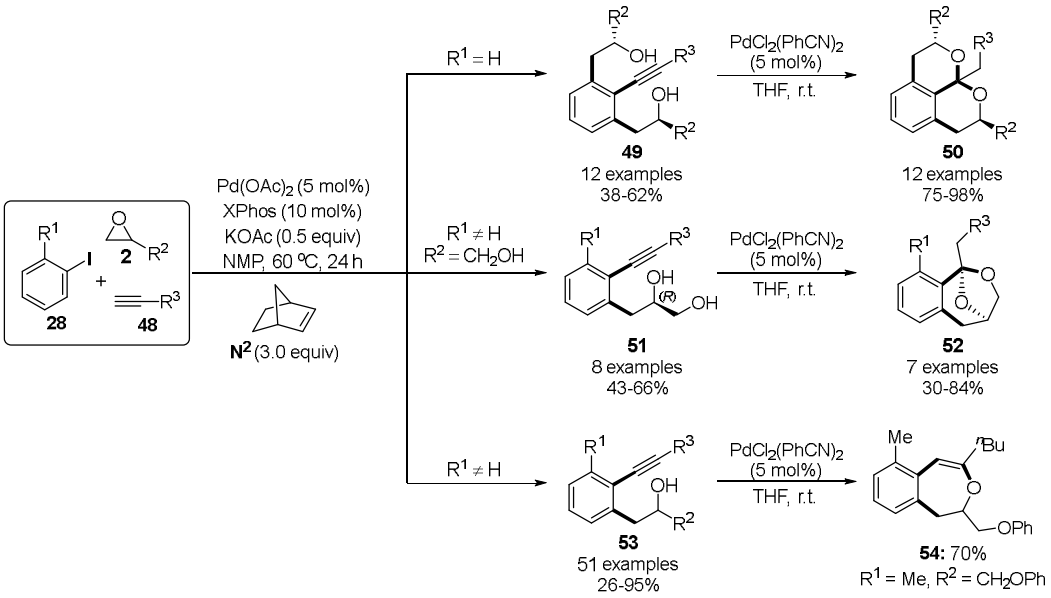


Scheme 8. Synthesis of isochroman and its application in total synthesis of (–)-berkelic acid.

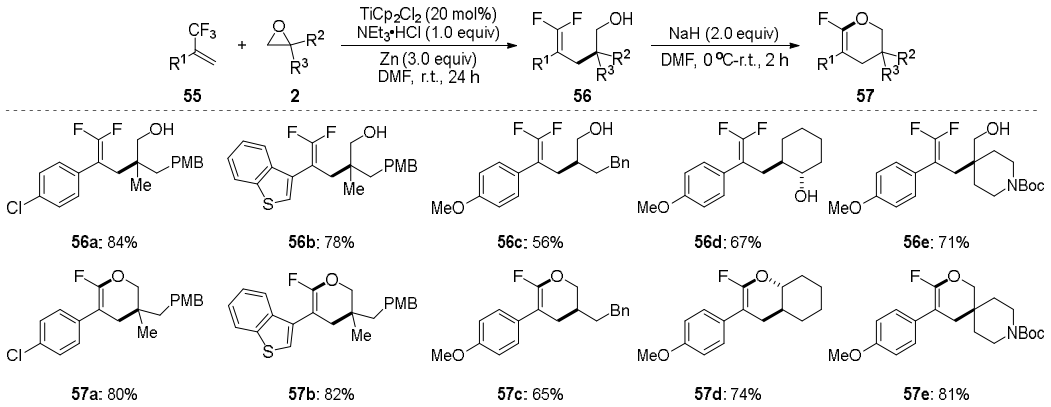
Benzofused dioxabicyclic scaffolds are prevalent in complex bioactive natural products.[35-37] It is highly desirable to developed efficient and general approaches to access these scaffolds from readily available starting materials. In 2019, Zhou and co-workers[38] developed a Pd/NBE catalyzed three-component reaction of aryl iodides **28**, epoxides **2**, and terminal alkynes **48** to provide the diversified phenylacetylenes with an *ortho*-2′-hydroxyalkyl substitution, which subsequently underwent palladium-catalyzed *oxa*-cyclization to afford the ubiquitous benzofused dioxabicycle scaffolds 2*H*-pyrano[4,3,2-*ij*]isochromenes **50** and 1,4-epoxybenzo[*c*]oxepines **52**. Moreover, with $PdCl_2(PhCN)_2$ as the catalyst, an intramolecular 7-endo-dig *oxa*-cyclization of the Catellani product **53** took place to deliver the bicyclic product **54** in 70% yield (Scheme 9).

2.3. Synthesis of dihydropyran derivatives

In 2020, the group of Wang[39] successfully applied epoxides **2** as the electrophilic coupling partner in the reductive allylic defluorinative coupling reaction with trifluoromethyl alkenes **55** under the catalysis of titanocene (Scheme 10). The reaction proceeded through a Ti(III)-mediated radical-type ring opening of epoxides **2** and the following allylic defluorinative cross-coupling reactions *via* sequential radical addition and *β*-F elimination. Remarkably, the ring opening reaction occurs exclusively at the more substituted site. Furthermore, the obtained *gem*-difluorobishomoallylic alcohols **56** could be readily transformed into a series of 6-fluoro-3,4-dihydro-2*H*-pyrans **57** through a simple base-mediated nucleophilic substitution reaction.



Scheme 9. Synthesis of benzofused oxygen-containing heterocycles *via* a Catellani reaction and an *oxa*-cyclization.

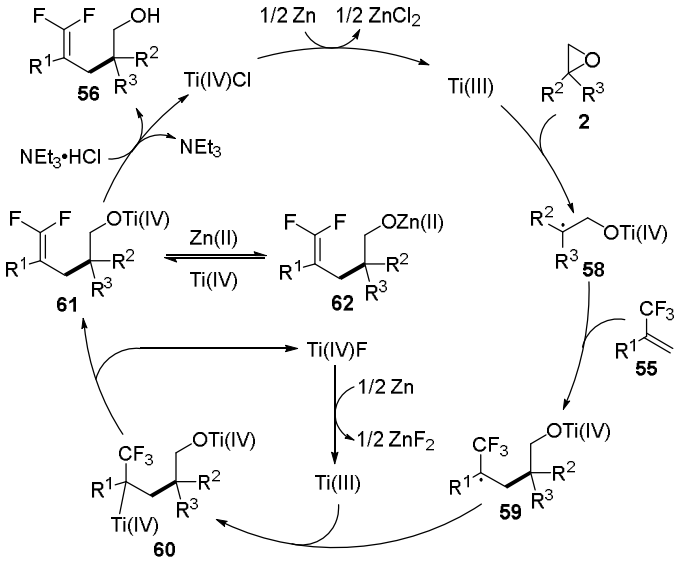


Scheme 10. Synthesis of 6-fluoro-3,4-dihydro-2*H*-pyrans.

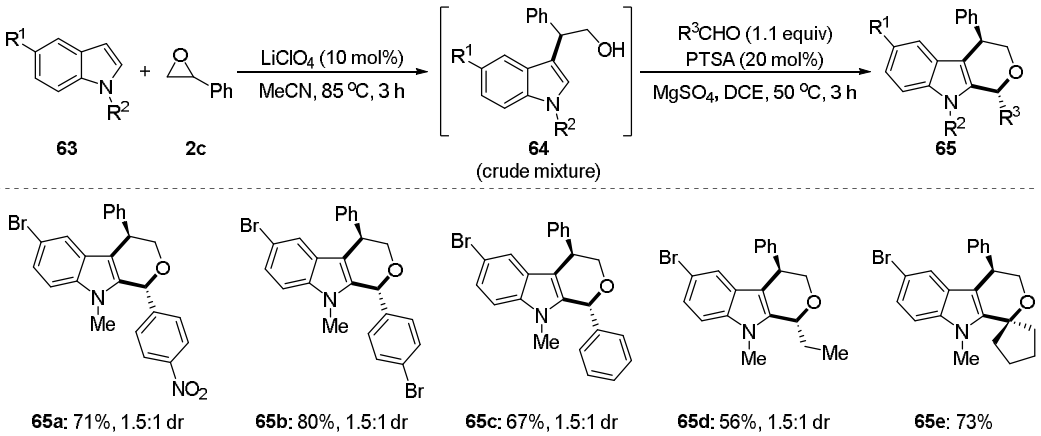
A proposed reaction mechanism was depicted in Scheme 11. Initially, Ti(III) was generated under reductive conditions and subsequently reacted with epoxides **2** involving the reductive ring opening at the more substituted site. The resulting carbon radical **58** underwent radical addition to the trifluoromethyl alkenes **55** to afford a CF_3-substituted carbon radical **59**. The following Ti(IV)-mediated *β*-F elimination from the generated complex **60** provides the complex **61**, which could stay in equilibrium with the zinc alkoxide **62** through ion exchange between Zn(II) and Ti(IV). The protonation of either the complex **61** or **62** by NEt_3·HCl leads to the formation of product **56**. The reduction of Ti(IV) by Zn regenerates Ti(III) for the next catalytic cycle.

In 2020, Ghorai and co-workers[40] developed an efficient method for the synthesis of tetrahydropyrano[3,4-*b*]indole derivatives **65** *via* a three-component reaction of epoxides **2c** with indoles **63** and carbonyl compounds (Scheme 12). This protocol involves $LiClO_4$-catalyzed S_N2-type ring opening of

epoxides **2c** with indoles **63** followed by *p*-toluenesulfonic acid (PTSA) catalyzed Pictet-Spengler reaction. The final tricyclic products **65** were obtained in high yields and moderate stereoselectivity.



Scheme 11. Proposed mechanism.

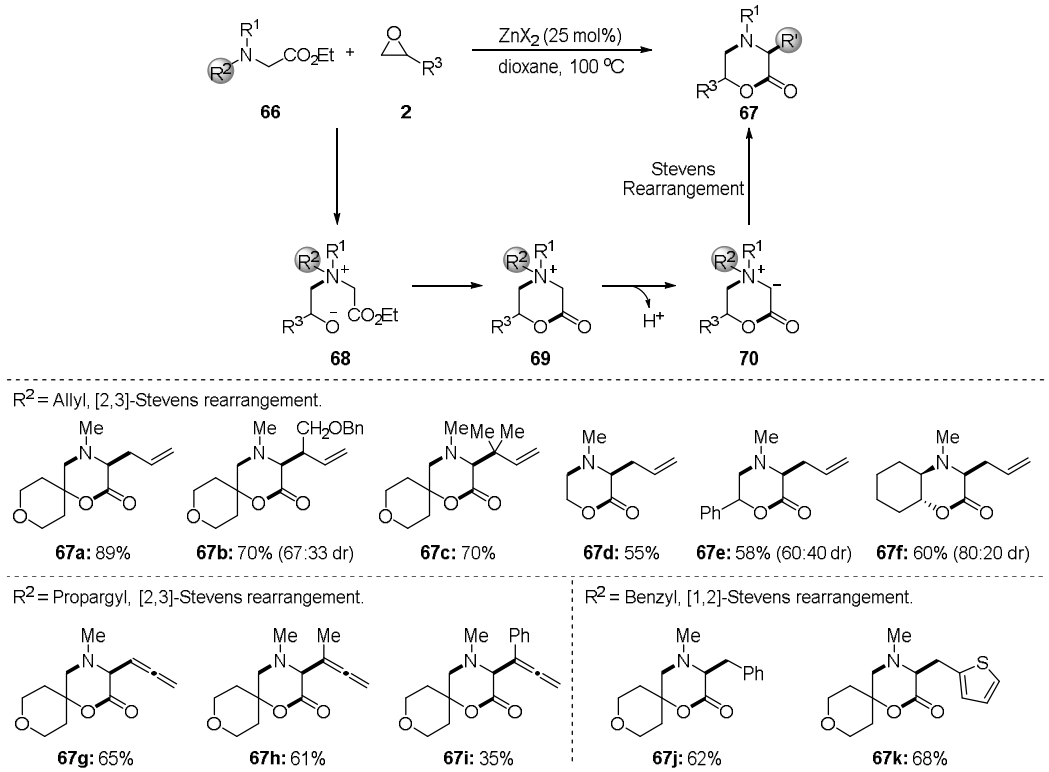


Scheme 12. Synthesis of tetrahydropyrano[3,4-*b*]indoles.

2.4. Synthesis of morpholine derivatives

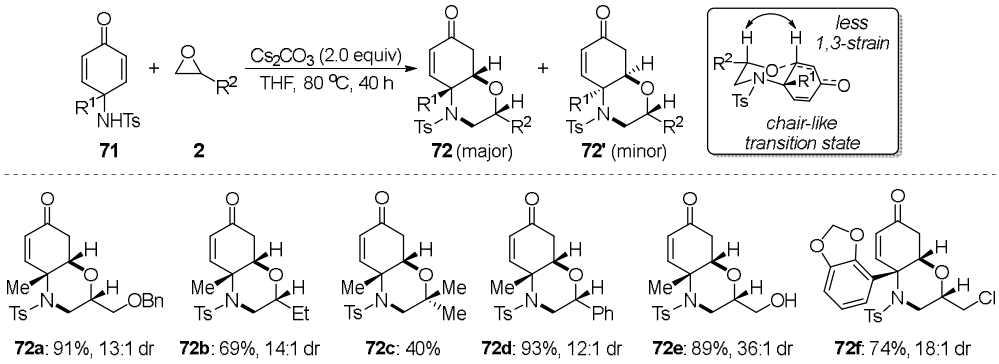
In 2019, Tian and co-workers[41] developed an efficient method for the synthesis of polysubstituted morpholin-2-ones **67** through Stevens rearrangements of α-amino-acid derived tertiary amines **66** *via* in situ activation with epoxides **2** (Scheme 13). In the presence of zinc halides, ring-opening of epoxide **2** with tertiary amine **66** affords zwitterion **68**, which was lactonized readily to form cyclic ammonium salt **69**. Then zwitterion **70** was generated and followed by a [2,3]- or a [1,2]-Stevens rearrangement to afford the desired morpholin-2-one **67**. This was a very efficient process, involving the formation of one C–N, one C–O, and one C–C bond simultaneously in a single operation. A wide range of *α*-amino acid-derived tertiary allylic, propargylic, and benzylic amines reacted with terminal and internal epoxides to afford structurally diverse

allyl- **67a-f**, allenyl- **67g-i**, and benzyl-substituted **67j-k** morpholin-2-ones in good yields and high regioselectivities.



Scheme 13. Synthesis of polysubstituted morpholin-2-ones.

In 2019, the Chegondi group[42] reported a highly diastereoselective desymmetrization of *p*-quinamines **71** with epoxides **2** for the synthesis of fused bicyclic morpholines **72** (Scheme 14).



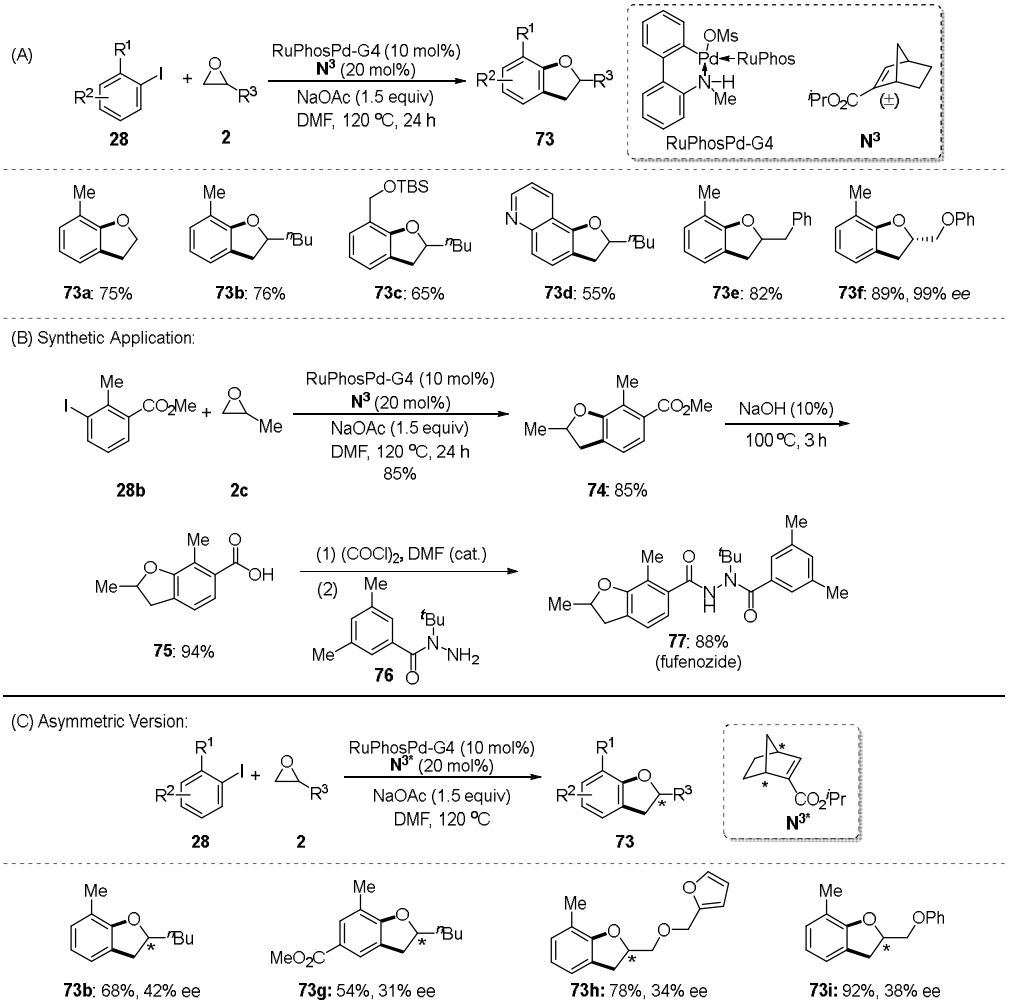
Scheme 14. Synthesis of fused bicyclic morpholines.

This transition-metal free [3+3] annulation proceeded *via* regioselective S_N2-type ring opening of epoxides **2** with prochiral *p*-quinamines **71** followed by an intramolecular *oxa*-Michael addition. When optically pure epoxides were used as the reagents, the corresponding enantioenriched morpholines were obtained conveniently in high yields. The high stereoselectivity of this annulation reaction is attribute to the chair-like six-membered transition state with minimized 1,3-diaxial interactions.

3. Assembly of five-membered oxygen-heterocycles

3.1. Synthesis of 2,3-dihydrobenzofuran

In 2018, the Dong group[43] developed a direct annulation between aryl iodides **28** and epoxides **2** to afford the valuable 2,3-dihydrobenzofurans **73** in moderate to excellent yields through Pd/NBE cooperative catalysis (Scheme 15A).

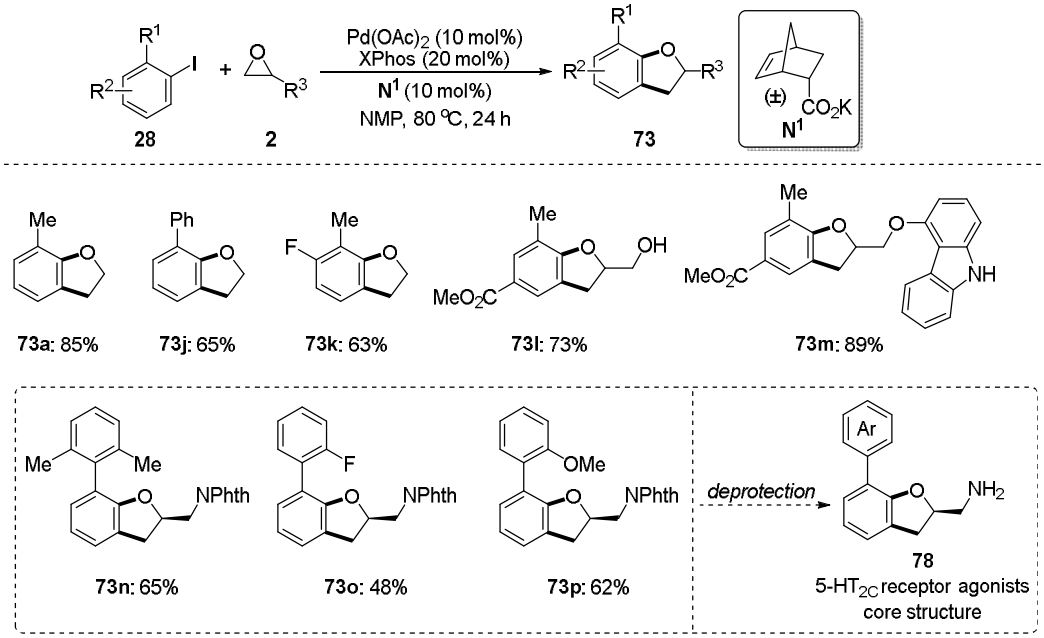


Scheme 15. (A) Synthesis of 2,3-dihydrobenzofurans. (B) Synthetic application. (C) Asymmetric version.

The epoxides served as both alkylating and terminating reagents in this Catellani-type reaction. Sterically hindered Buchwald ligand RuPhos was used to inhibit undesired *β*-hydrogen elimination and

facilitate the C−O bond formation. The novel isopropyl ester substituted NBE derivative **N**^{3} was identified as the most efficient catalytic mediator (20 mol%) to prevent the formation of multiple NBE insertion byproducts. When an enantiopure epoxide was applied, the enantiopure product **73f** was obtained with excellent stereoretention. Remarkably, the synthetic utility of this method is demonstrated in a concise synthesis of the insecticide fufenozide **77** (Scheme 15B). Under the standard reaction conditions, the key 2,3-dihydrobenzofuran intermediate **74** was obtained in 85% yield from the commercially available aryl iodide **28b** and propyl oxide **2c**. Subsequent hydrolysis and amide condensation provided fufenozide **77** efficiently. Later on, an asymmetric version[44] of this reaction involving kinetic resolution of the racemic epoxides **2** *via* palladium/chiral norbornene (optical pure **N**^{3}) cooperative catalysis was reported by the same group (Scheme 15C). Although only moderate enantioselectivity was achieved, it represents one of the early examples of Pd/chiral NBE cooperative catalysis.

Later on, the Zhou group[32,45] independently reported a convergent synthesis of 2,3-dihydrobenzofurans **73** through Pd/NBE cooperative catalysis (Scheme 16). In this transformation, $Pd(OAc)_2$ and sterically hindered XPhos were used as the best catalyst and ligand combination. Remarkably, the unique potassium salt of 5-norbornene-2-carboxylic acid **N**^{1} was found to be a highly efficient catalytic mediator and only 10 mol% was needed, which represents the lowest loading of mediators applied in Catellani-type reactions. Furthermore, the reaction proceeded under mild conditions (80 °C), and no extra base was required. The potential synthetic utility of this method was highlighted by two-step synthesis of three 5-HT_{2C} receptor agonists **78**.[46] Subjecting 2-aryl-substituted phenyliodides and enantiomerically pure epoxide to the standard reaction conditions, the desired chiral 2,3-dihydrobenzofuran products **73n-p** were obtained in moderate to high yields. A subsequent facile deprotection of the amino group would lead to the 5-HT_{2C} receptor agonists **78**.



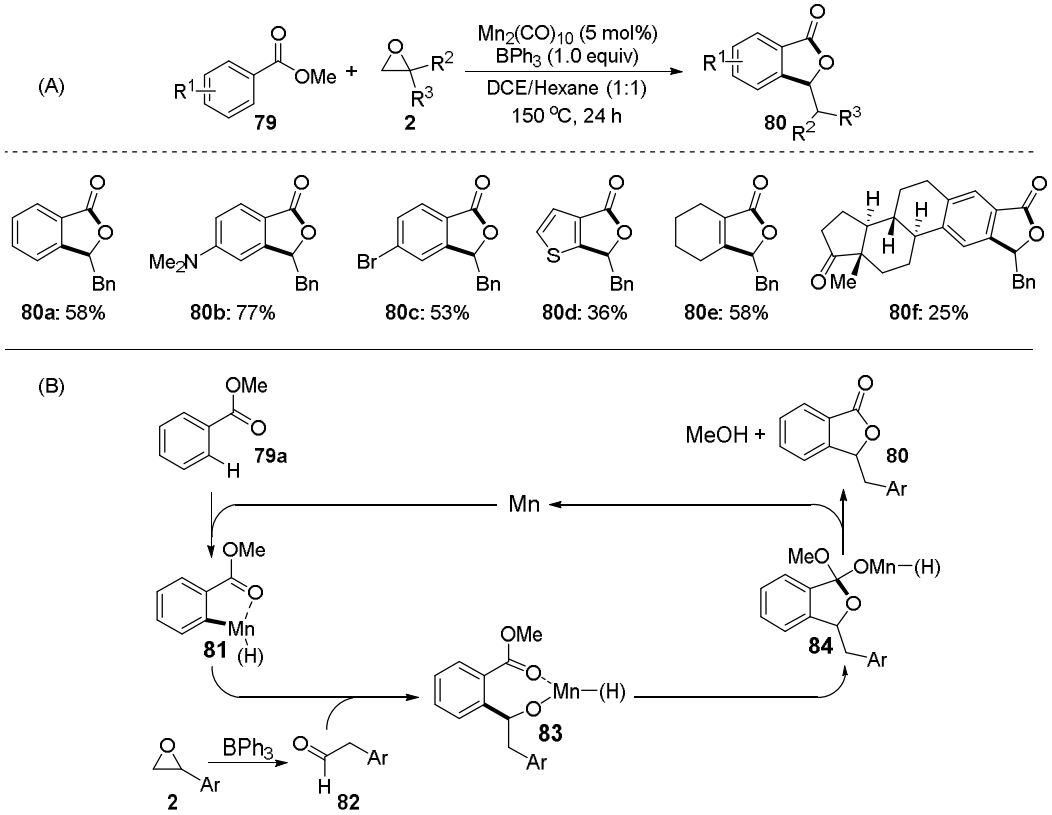
Scheme 16. Synthesis of 2,3-dihydrobenzofurans.

3.2. Synthesis of isobenzofuranone

In the aforementioned reactions, epoxides **2** are all involved in the cyclizations as two-carbon synthons. In 2016, Kuninobu and co-workers[47] found that epoxides **2** could also serve as one-carbon synthon

in manganese-catalyzed C−H alkylation and subsequent cyclization (Scheme 17A). This is the first example of manganese-catalyzed C−H transformations using an oxygen-directing group. The desired five-membered ring product isobenzofuranones **80** were obtained in moderate to good yields, which was complementary to the previous methods for the assembly of 3,4-dihydroisocoumarins. Triphenylborane played a significant role in this reaction by cooperating with the manganese catalyst to promote the reaction.

In the absence of triphenylborane, no desired product was formed at all. The scope of epoxides was mainly restricted to aryl substituted terminal epoxides. Notably, besides aromatic **80a-c** and **80f**, heteroaromatic **80d** and olefinic **80e** C−H bonds were all compatible in this transformation. The possible reaction mechanism was proposed in Scheme 17B. Oxidative addition of methyl benzoate **79a** to a manganese catalyst occurs under the promotion of triphenylborane. At the same time, the epoxide **2** isomerizes to an aldehyde **82** in situ in the presence of triphenylborane. Then insertion of the formed aldehyde **82** into Mn−C bond leads to complex **83**. Subsequently, intramolecular nucleophilic cyclization affords 5-membered intermediate **84**, which undergoes reductive elimination and removal of methanol to give the desired isobenzofuranone **80** and regenerate the manganese catalyst for the next catalytic cycle.



Scheme 17. (A) Synthesis of isobenzofuranones. (B) Plausible reaction mechanism.

4. Conclusions

In this chapter, we summarized recent advances in the assembly of oxygen-containing heterocycles using epoxides as the dual-functionalized alkylating reagents. As described above, a series of oxygen-containing heterocycle compounds, such as 3,4-dihydroisocoumarin, isochroman, dihydropyran, morpholine, 2,3-dihydrobenzofuran and isobenzofuranone derivatives were successfully synthesized with

high efficiency. Furthermore, applications of these methods in total synthesis of complex natural products and drugs underline their synthetic utility.

Despite these advances, some limitations and challenges still exist in this area. For example, the preparation of more diversified oxygen-containing heterocycles through this strategy need to be developed. Additionally, the development of catalytic asymmetric variants to access chiral oxygen-containing heterocycles will be a very significant yet challenging task. More efforts should be devoted in these directions.

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