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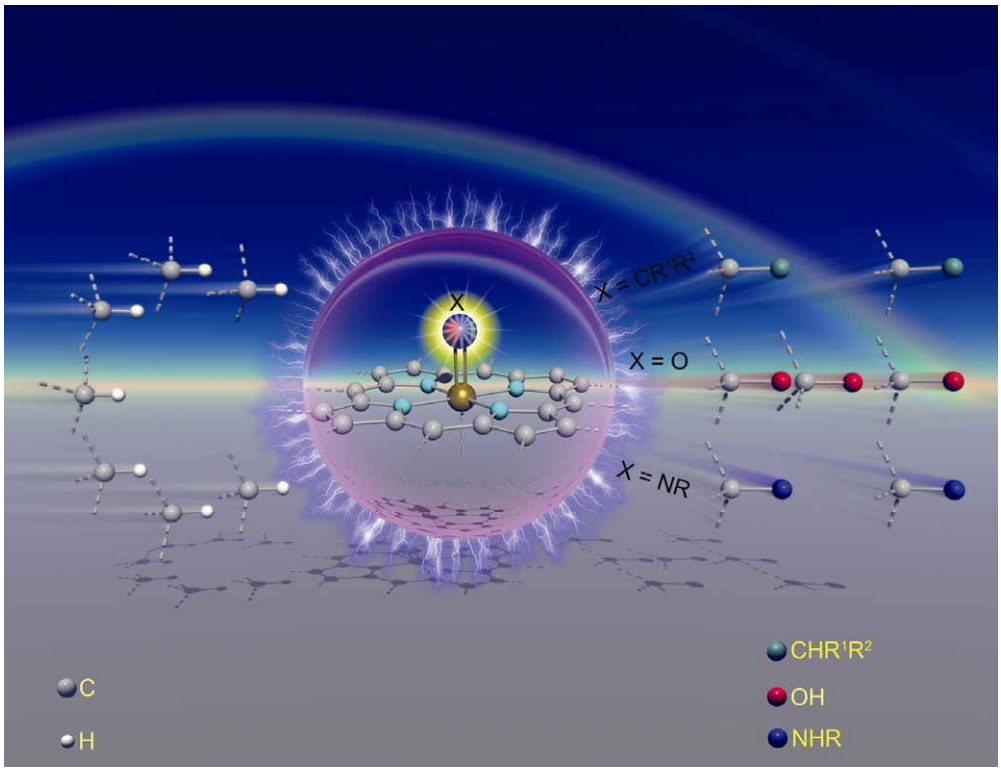

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TUTORIAL REVIEW

Direct Sp^3 α-C–H activation and functionalization of alcohol and ether†

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Seven kinds of sp^3 α-C–H activation/C–C formation reactions of alcohols and ethers have been reviewed in this *tutorial review*, from the viewpoint of both methodology and synthetic application, towards the efficiency, chemo-, regio- and stereoselectivity, catalytic system, substrate scope and mechanistic study. Section 2 describes radical-mediated α-C–H activation and addition/elimination of ethers with unsaturated (C=C and C≡C) species. Sections 3–8 discuss the α-C–H activation and additions of alcohols and/or ethers with unsaturated (C=C, C≡C, C=O and C=N) compounds, which involve the key processes of radical mediation, carbenoid insertion, *1,5*-H-migration, oxidative dehydrogenation coupling, transfer hydrogenative coupling, and metal-mediated C=C insertion into the C–H bond.

1. Introduction

The direct C–H bond activation and functionalization has been one of the most active research fields in organic chemistry not only due to the significance in basic studies of inert C–H bond chemistry but also the step economy feature in potential synthetic application. Thus research on this subject has been attracting increasing interest amongst organic chemists, and various high efficiency and versatile protocols have been explored.[1] Reactions reported could be classified mainly to: (1) the sp^2 C–H activation/functionalization reactions of arene, alkene, aldehyde, and imine and their derivatives; (2) the sp^3 α-C–H reactions of allyl, benzyl, propargyl and carbonyl compounds; (3) the sp^3 α-C–H reactions of heteroatomic (oxygen, nitrogen and sulfur) compounds; and (4) importantly but rarely the sp^3 C–H reactions of alkane wherein a directing group is generally required. Among the third type of reactions, the sp^3 α-C–H activation/C–C formation reaction of alcohol, ether and amine is of particular synthetic value because of not only the short formation of a new C–C bond but the direct introduction of active groups (hydroxyl and amino). In contrast to sp^3 α-C–H activation/functionalizations of amine which have been under prolonged investigation for several decades and summarized in several reviews,[2–6] it was not until the 1990s that the corresponding reactions of alcohols and ethers had received significant attention, and up to the present day no special review has emerged to discuss and summarize systematically these reactions. Herein, we present a review to discuss the sp^3 C–H activation/C–C bond formation of alcohols and ethers.

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† Part of a themed issue on C–H functionalisation in organic synthesis dedicated in memory of Keith Fagnou.

2. Radical-mediated addition and elimination of ether with alkene and alkyne

This section focuses on discussing the radical-mediated addition/elimination reaction *via* sp^3 α-C–H activation of

Shu-Yu Zhang

Shu-Yu Zhang (1980) studied chemistry at Lanzhou University where he received his BS in 2002. He joined the research group of Prof. Yong-Qiang Tu, and completed his PhD at Lanzhou University in 2010. His research mainly focused on transition metal catalyzed C–H activation or C–H functionalization of alcohols to form the new C–C bond.

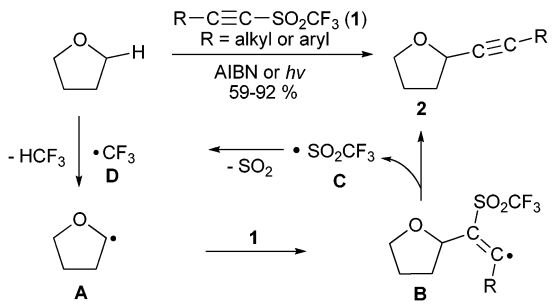
Fu-Min Zhang

Fu-Min Zhang (1970) received his PhD degree from Lanzhou University in 2006 working under the supervision of Prof. Yong-Qiang Tu. Subsequently he worked as a postdoctoral fellow in the CAMDL of the Mayo Clinic with Prof. Y. P. Pang (2007–08). He returned to the Lanzhou University as a lecturer and was then appointed as associate professor in 2009. Currently he is interested in the total synthesis of natural products.

ether with unsaturated (C=C and C≡C) compounds forming the ethylenyl and acetyl ether derivatives, respectively.

In the 1990s, Fuchs and coworkers[7–9] reported the earlier radical addition/elimination reaction of ethers with alkenyl and alkynyl triflones, which resulted in the alkenylation and alkynylation of ethers, respectively. Initially, various cyclic and acyclic aliphatic ethers were subjected to alkynlation with phenyl or n-octyl acetylenyl triflones **1** under the induction of peroxide or AIBN or uv-irradiation in DCE or neat substrate, and the corresponding α-acetylenic ethers **2** were readily generated in medium to excellent yields. Presence of BHT or dinitrobenzene would inhibit this reaction. A model radical chain-based reaction mechanism was proposed, see Scheme 1,[8] which involved the initial formation of radical **A** and then addition to acetylenic triflone **1** to produce the vinyl radical **B**, followed by release of the radical **C** to furnish the product **2**. Further fragmentation of **C** generated radical **D** as well as releasing SO_2 and thus propagated the reaction chain.

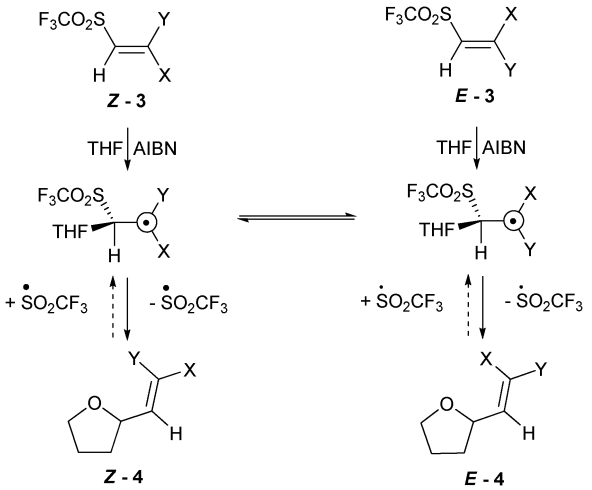
Successively, the alkenylation of ethers was investigated with aryl or alkyl substituted vinyl triflones under induction of AIBN at THF reflux temperature.[9] Due to the rotation of the single bond of the radical intermediate, however, both ***E***- and ***Z***-forms of products were possibly formed as shown in Scheme 2. Generally, if 1,2-disubstituted vinyl triflone **3** (X = H) was used, reactions with both ***E***- and ***Z*-3** afforded only the sterically preferred ***E***-α-vinyl THF products **4** and no ***Z*-4** isomer was obtained.



Scheme 1 Mechanism of radical addition/elimination of THF with acetylene derivatives.

Yong-Qiang Tu

Yong-Qiang Tu (1958) received his BS (1982), MS (1985) and PhD (1989) in organic chemistry from Lanzhou University. He worked as a postdoctoral fellow (1993–95) at Queensland University, Australia, working with W. Kitching. Then he worked as visiting professor at Bielefeld University, Germany. He obtained a professor position at Lanzhou University in 1995, and then the Director of State Key Lab. Appl. Org. Chem. (2001–2010). In 2009, he won the honor of the Academician of Chinese Academy of Sciences.



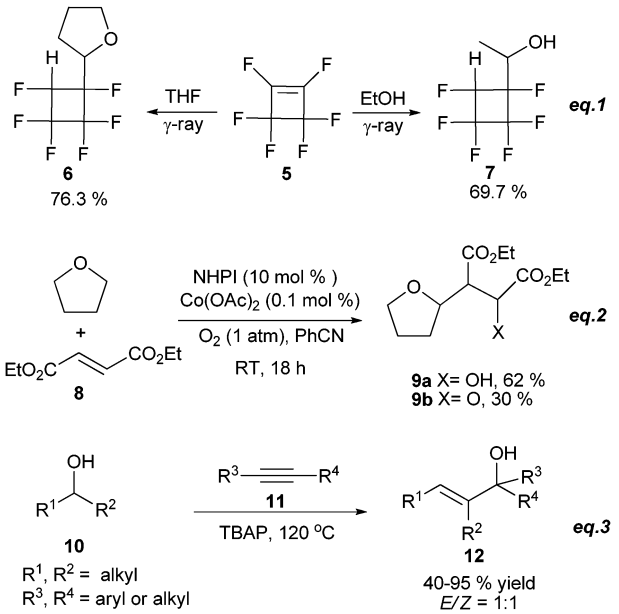
Scheme 2 Radical-mediated addition/elimination of THF with ethylene derivatives.

However, if trisubstituted ***E***- or ***Z***-vinyl triflone **3** (X ≠ H) was used, a mixture of ***Z***- and ***E***-isomers **4** would be produced and their ratios were highly dependent upon the properties of X and Y. It was important to notice that the ***Z*-3** reacted generally to yield the abundant ***Z*-4**, and so did the ***E*-3**. Further investigation results for the stereospecificity with three kinds of Y-substitutions (where X was phenyl or n-octyl) could be concluded: (1) if Y was 2-furyl, styryl or phenyl, ***Z*-3** generated 1.3–7 : 1 mixture of ***Z*/*E*-4**, and ***E*-3** generated 2.2-19 : 1 mixture of ***E*/*Z*-4**; (2) if Y was F, Br or I, ***Z*-3** generated 67–177 : 1 mixture of ***Z*/*E*-4**, and ***E*-3** generated 3–100 : 1 mixture of ***E*/*Z*-4**; and (3) if Y was carbonate or benzoate, ***Z*-3** generated 16-35 : 1 mixture of ***Z*/*E*-4**, and ***E*-3** generated 3-22 : 1 mixture of ***E*/*Z*-4**. Therefore, reaction with halogen-substituted substrates (Y = F, Br or I) afforded the highest stereoselective vinyl halides in most cases, which was of synthetic importance for stereoselectively preparing the complex vinyl derivatives through the metalation of the vinyl halides such as **4**.

3. Radical-mediated addition of alcohol and ether with alkene, alkyne, aldehyde and imine

As early as the 1950s, Lazerte and Koshar,[10] and later others[11–14] investigated the free radical-mediated addition reactions of alcohols and ethers with alkenes *via* α-C–H activation/cleavage. Their initial research focused on the coupling with polyfluoro-alkenes such as **5** under the promotion of *t*-BuO_2Bz or by means of γ-ray irradiation or electrochemical promotion for preparing α-polyfluoroalkyl alcohols or ethers. Some relationships between the reaction conversion and substrate ratio, reaction time and temperature were also discussed.[10] Two representative coupling examples using THF and EtOH with perfluorinated cyclobutene **5** forming **6** and **7**, respectively, were outlined in Scheme 3 (eqn (1)).

In 2002, Ishii and coworkers[15] explored the addition protocol of ethers with electrophilic alkenes **8** under the catalysis of NHPI (*N*-hydroxyphthalimide)/$Co(OAc)_2$ in the presence of O_2, wherein oxygen was incorporated in the



Scheme 3 Coupling of alcohol and THF with alkene and alkyne.

adducts as 2′-hydroxyl (major **9a**) and 2′-carbonyl (minor **9b**) functionals. Various cyclic ethers such as THF proved to be effective and give the good yields of products (Scheme 3, eqn (2)). While the acyclic dibutyl ether was used, the reaction with fumarate yielded the dominated 2′-hydroxy product at 54%. Of synthetic importance was the preparation of widely used butanedioic acid derivatives.

In 2009, Liu and coworkers[16] first succeeded in the radical-mediated addition of alcohols **10** to the alkynes **11** under promotion of 2 equiv. TBHP at 120 °C, which afforded the allylic alcohol **12** in medium to high yields (Scheme 3, eqn (3)). A wide range of substrates including aliphatic alcohols, cyclic ethers and the EDG bearing-alkynes were demonstrated to be effective to this reaction.

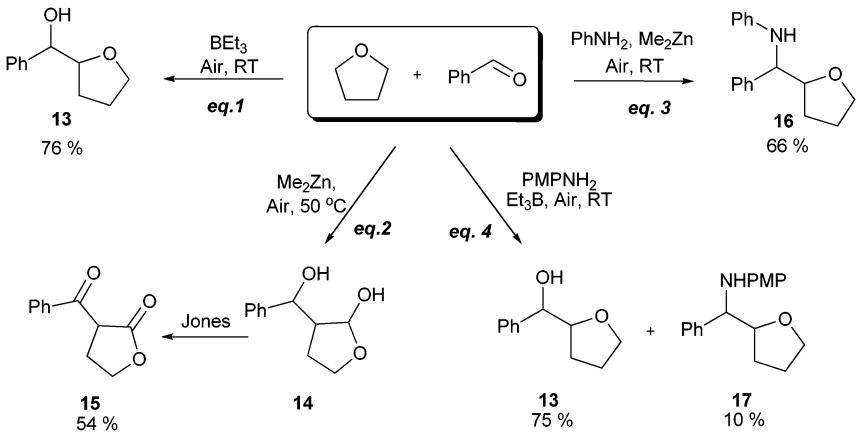
In this century, investigation of the free radical mediated addition of alcohols and ethers with the carbonyl compounds (aldehydes and aldimines) for the preparation of α-hydroxylalkyl and α-aminoalkyl alcohols and ethers has received much attention and progress. In 2003, Yoshimitsu and coworkers[17–20] developed the BEt_3/air or *t*-BuO_2H-mediated addition of ethers with aldehydes and the α-hydroxylalkyl ethers **13** could be prepared in good yield for two diastereoisomers (Scheme 4, eqn (1)). The cyclic ethers and aromatic aldehydes were demonstrated to be more effective to this procedure than other substrate combinations. By use of this methodology, Yoshimitsu and coworkers[17] have carried out the asymmetric synthesis of (−)-muricatacin from THF through the chiral induction with (+)-menthol.

At the same time, however, Tomioka and coworkers[21,22] found that the chemoselectivity of this addition was initiator dependent and employment of the Me_2Zn/air system to replace the BEt_3/air led to the formation of β-hydroxyalkyl-α-hydroxyl ether **14** rather than the α-hydroxyalkyl ether **13**. The former could be further oxidized to α-acyl lactones **15** by Jones' oxidation (Scheme 4, eqn (2)). Based on that information, an interesting mechanism involving the formation of α- and then β-radical intermediates of ether was proposed.

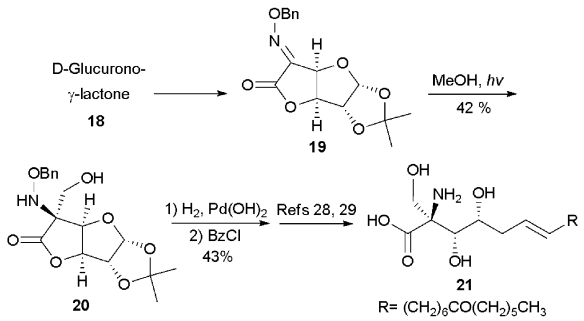
In addition, by use of Me_2Zn/air, Tomioka and coworkers[22–24] carried out the radical-mediated addition of ether with aldimine, which afforded the α-aminoalkyl ethers **16** generally in good to high yields (Scheme 4, eqn (3)). One important feature of this procedure was that the addition to the C=N bond could take place chemoselectively in advance of the C=O bond. A wide range of ethers including formic acetals, and aldimines generated from aryl aldehydes and aryl or toluenesulfinyl amines were demonstrated to be effective, and either the reformed aldimine or three components (ether, aldehyde and amine) could be directly used for running this reaction. In the latter case, however, if BEt_3 rather than Me_2Zn was employed, a competing addition forming the major α-hydroxyalkyl ether **13** would occur before the completed formation of aldimine. In this case, the α-aminoalkyl ethers **17** was formed as a minor product (Scheme 4, eqn (4)).[22]

In addition, Porta and coworkers[25] developed another Ti(III)/TBHP system to promote directly and efficiently the coupling of three components (ether, aldehyde and amine) in the aqueous and acidic medium. By employment of this procedure, the α,α′-di (aminoalkyl)-substituted ether derivatives could be prepared.

It was important for asymmetric synthesis that, by use of the chiral C=N bond donors, this addition allowed the formation of chiral amino alcohols or ethers, which established an



Scheme 4 Free radical-mediated addition of ethers to aldehydes and imines.



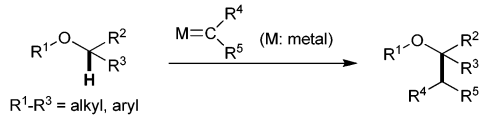
Scheme 5 Synthesis of (+)-myriocin **21** *via* photoinduced addition of MeOH to ketoxime **19**.

alternative important approach to chiral α-amino acids. For example, Alonso and coworkers[26,27] have carried out the asymmetric syntheses of amino alcohol and acid derivatives through the addition of MeOH and formic acetal to chiral ketoximes and aldohydrazones, respectively, under the photochemical induction. It was particularly worth mentioning that Alonso and coworkers[26] starting from D-glucurono-γ-lactone **18** have fulfilled a short synthesis of (+)-myriocin **21** employing the key photoinduced addition of MeOH to a chiral ketoxime ether **19** constructing the chiral azo-quaternary center of **20** (Scheme 5).[28,29] Similarly, Tomioka and coworkers[30] have also developed an approach for preparing the enantiomerically enriched sulfonamide through addition of formic acetal to the chiral *N*-toluenesulfinyl aldimine under promotion of Me_2Zn/BEt_3/air.

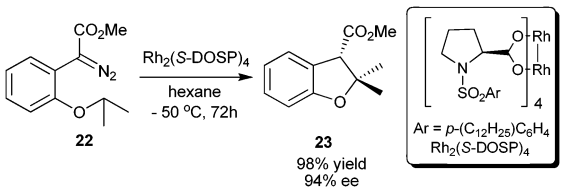
4. Metal mediated carbenoid insertion to α-C–H of ether

Metal carbenoid insertion into C–H bond could be viewed as a striking alternative approach to the metal-mediated C–H activation/functionalization. Importantly, recent research in this area has been instrumental in addressing fundamental issues of stereochemistry in C–H bond functionalization. Although several review articles have already emerged to summarize various carbenoid insertion reactions,[31,32] this review discussed specifically and comprehensively the new progress about that carbenoid insertion to the C–H bond adjacent to oxygen atom (Scheme 6).

Early in the 1990s,[33] the carbenoid insertion into the C–H bond adjacent to the oxygen atom was developed as an effective methodology. Over the past ten years, several groups have developed a series of new catalysts and established asymmetric synthetic protocols of the oxygen heterocycle. Davies and coworkers[34] have developed the Rh_2(*S*-DOSP)$_4$ catalyst to promote the intramolecular insertion of carbenoid derived from aryl diazoacetates **22** to the methine C–H bond



Scheme 6 A general form of metal carbenoid insertion into the C–H bond adjacent to the oxygen atom of ether.



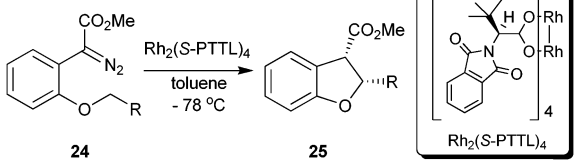
Scheme 7 Rh_2(*S*-DOSP)$_4$-catalyzed carbenoid insertion to methine α-C–H of phenyl methinyl ether.

adjacent to phenylether oxygen, and the substituted dihydrobenzofuran **23** was obtained in 94% enantioselectivity (Scheme 7).

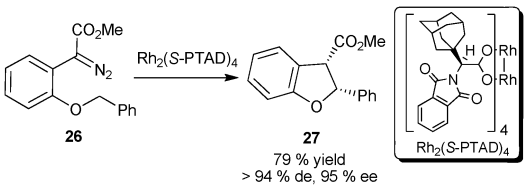
In 2002, Hashimoto and coworkers[35] reported a highly efficient methylene C–H insertion method for the diastereo and enantioselective synthesis of substituted dihydrobenzofurans **25** from **24** *via* the catalysis of Rh_2(*S*-PTTL)$_4$ in toluene. As a result, the virtually exclusive *cis* selectivities (up to >99 : 1) and good enantioselectivities were obtained (Table 1). These results suggested that the presence of both a phenyl ring and an oxygen atom adjacent to the target C–H bond was responsible for the high enantioselectivity.

In 2006, Davies and coworkers[36] developed the effective chiral catalyst Rh_2(*S*-PTAD)$_4$ derived from adamantylglycine, and realized the intramolecular carbenoid insertion to α-C–H bond of benzylic ether **26** forming **27** with high asymmetric induction (up to 94% de and 95% ee, Scheme 8). In addition, they developed an immobilization strategy for the catalytic synthesis of substituted dihydrobenzofurans,[37] wherein the immobilized chiral Rh(II) catalysts could be efficiently recycled with limited loss of stereoselectivity after three cycles.

Table 1 Rh_2(*S*-PTTL)$_4$-catalyzed intramolecular carbenoid insertion to α-C–H of phenyl ether



Entry	*R*	*Cis* : *trans*	Yield (%)	Ee (%)
1	Ph	>99 : 1	86	94
2	Me	14 : 86	91	78 : 97
3	Vinyl	77 : 23	62	86 : 92
4	*p*-ClC_6H_4	>99 : 1	79	94
5	*p*-MeC_6H_4	>99 : 1	84	91
6	*p*-$OMeC_6H_4$	>99 : 1	89	94
7	3,4-$(OTBS)_2C_6H_3$	99 : 1	85	91



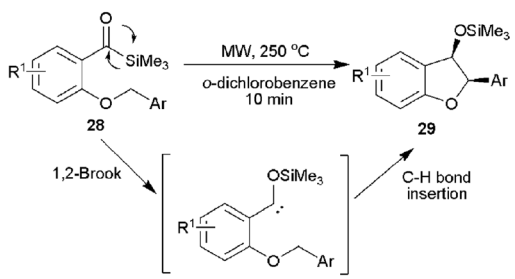
Scheme 8 Rh_2(*S*-PTAD)$_4$-catalyzed intramolecular carbenoid insertion into α-C–H of benzyl phenyl ether.

Most recently, Dong and coworkers[38] reported a novel and operationally simple strategy for functionalizing benzylic sp^3 C–H using the siloxycarbenes generated directly from acylsilane **28** under the microwave irradiation without metal catalyst. The authors envisioned that a thermally induced Brook rearrangement would generate a siloxycarbene that further undergo rapid insertion to a neighboring C–H bond (Table 2). Notably, this Brook rearrangement/insertion cascade allowed rapid access to important oxygen heterocyclic dihydrobenzofurans **29**. After a variety of high-boiling solvents were examined, *o*-dichlorobenzene proved to be the best for this irradiation reaction at 250 °C for 5–10 min, which formed the expected 2-aryl-3-silyloxy-2,3-dihydrobenzofuran **29** in excellent yield and with good stereoselectivity.

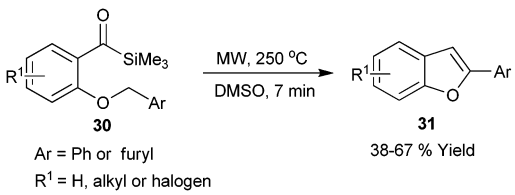
Remarkably, by simply replacing the *o*-dichlorobenzene with DMSO, a domino strategy was developed to access the benzofuran derivative **31** efficiently using **30** *via* the distinct Brook rearrangement, C–H bond insertion and the elimination of silanol. Different substituents on the aromatic ring were tolerated and the corresponding benzofurans **31** were prepared with up to 67% yield (Scheme 9).

Although the intermolecular carbenoid insertion was explored earlier, its asymmetric version was much later. Recently, the catalysts Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTTL)$_4$ were successfully explored to effect the asymmetric intermolecular α-C–H carbenoid insertion of **32** and **34** to various ethers, such as cyclic ether (THF) and benzylic ether **35** forming **33** and **36**, respectively (Scheme 10).[39] In addition, the allyl acetates/ethers, tetralkoxy silanes, and silyl ethers were all efficient carbenoid acceptors. Davies and coworkers[31,39] have already reviewed this chemistry in detail with particular emphasis on the chemo- and stereoselectivity (Scheme 10).

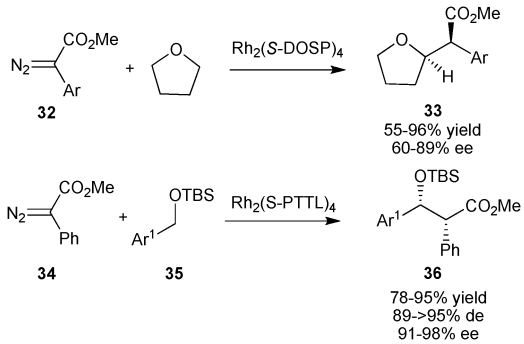
Table 2 MW-assisted Brook rearrangement/carbenoid insertion to α-C–H of phenyl ether



Entry	R^1, Ar	*Cis* : *trans*	Yield (%)
1	R^1 = H, Ar = Ph	72 : 28	87
2	R^1 = *p*-Me, Ar = Ph	70 : 30	89
3	R^1 = *p*-Cl, Ar = Ph	74 : 26	91
4	R^1 = H, Ar = furyl	76 : 24	31



Scheme 9 Intramolecular carbenoid insertion *via* domino Brook rearrangement and elimination to benzofurans

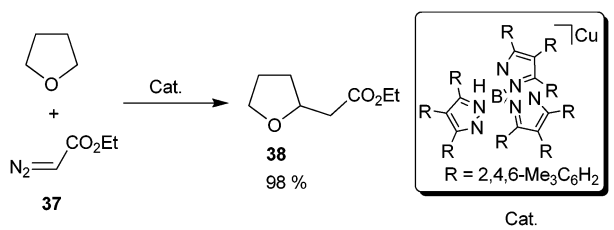


Scheme 10 Rh-catalyzed asymmetric intermolecular carbenoid insertion into α-C–H of aliphatic and benzylic ethers.

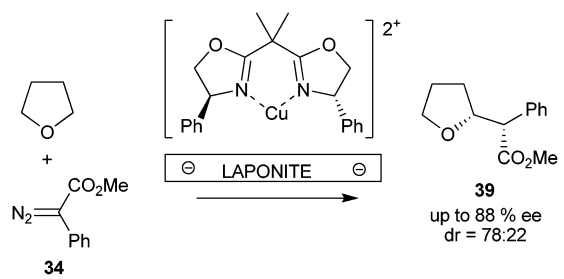
In addition, the species of Cu, Fe, *etc.* also have been developed as the catalysis for the α-C–H activation/carbenoid insertion of ether. In 2002, Pérez and coworkers[40] developed the bulky copper catalyst to effect an intermolecular α-C–H insertion carbenoid of ethyl diazoacetate **37** to ether. Thus, as an example, the α-THF-substituted product **38** was afforded in 98% yield (Scheme 11).

Later in 2007, Fraile and coworkers[41] reported a simple and efficient heterogeneous copper catalysis for the insertion of a carbene, from methyl phenyldiazoacetate **34**, into α-position of THF with high enantioselectivity. The best result gave up to 88% ee and a 78 : 22 diastereomeric ratio of **39** with the catalyst being recycled for 2–3 times (Scheme 12), thus demonstrating the stability of the Cu catalyst.

Woo and coworkers,[42] and Lovely and coworkers[43] reported the Fe(TPP)Cl and HB[3,4-$(CF_3)_2$Pz]$_3$Ag(THF) catalysis, respectively. These catalysts effectively catalyzed the carbene insertion reactions to α-C–H of ethers in good yields as well as chemoselectivities.



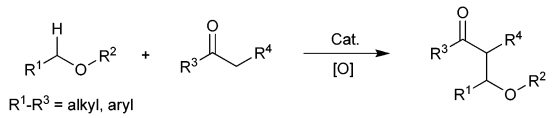
Scheme 11 Cu-catalyzed intermolecular carbenoid insertion into α-C–H of aliphatic ether.



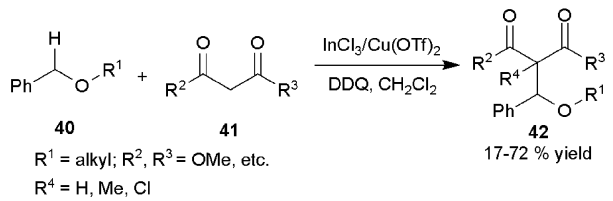
Scheme 12 Heterogeneous asymmetric Cu-catalyzed intermolecular carbenoid insertion into the α-C–H of THF.

5. Oxidative CDC reaction of ether with carbonyl compounds

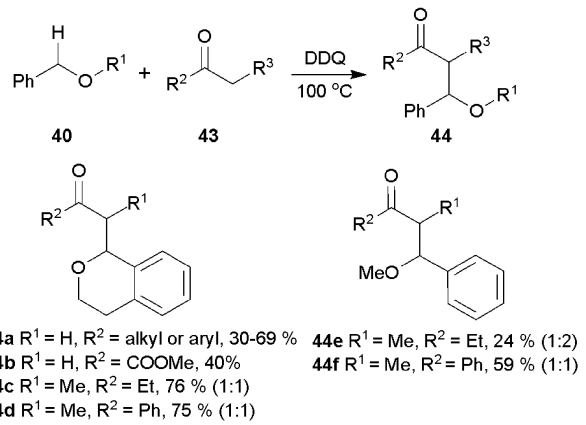
The cross-dehydrogenative coupling (CDC) reaction has provided an alternative approach to activate less reactive C–H bonds to react with nucleophilic species. In this review, the CDC reaction was generally defined as the C–C bond coupling between the α-C–H bonds of ether and carbonyl compounds *via* oxidative dehydrogenation (Scheme 13). In the past several years, Li and other groups[4,44] have developed a series of CDC reactions to effect α-C–H functionalization of amines, and allylic and benzylic compounds.



Scheme 13 The general CDC reaction of α-C–H of ether and carbonyl compounds.



Scheme 14 The CDC reaction of benzyl ethers with malonate derivatives.



Scheme 15 The CDC reaction of benzyl ethers with ketones without metal-catalyst.

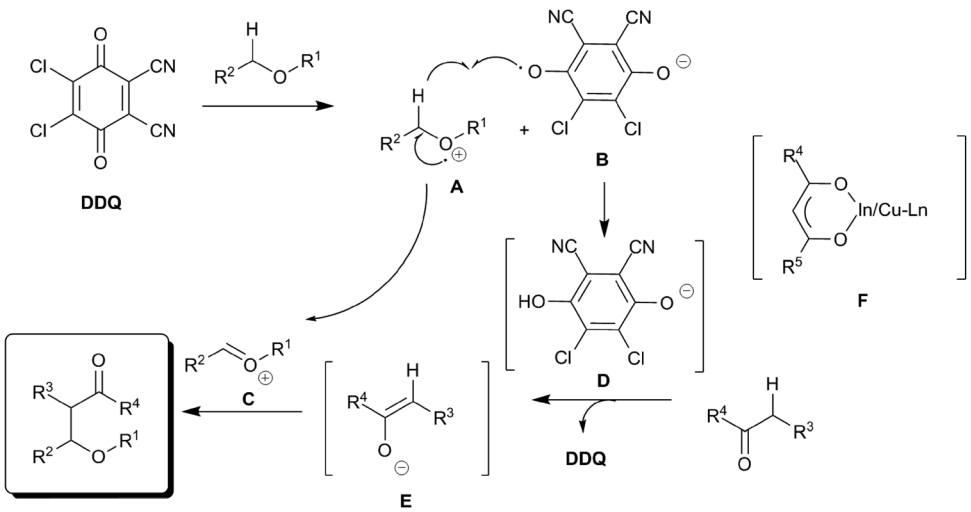
Despite activation/functionalization of the α-C–H of the oxygen atom was more difficult than that of the nitrogen atom, Li and co-workers[45] still successfully accomplished the C–C bond coupling between ether and carbonyl *via* oxidative dehydrogenation. Various combinations of In and Cu catalysts were examined for effecting the CDC reaction of isochroman and malonate derivatives, among which the combined $InCl_3/Cu(OTf)_2$ in 5 : 5 (mol%) with 1.2 equiv. DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in CH_2Cl_2 was optimized as the general catalysis system. Thus, treatment of a series of benzyl ether **40** and malonate derivatives **41** under this general condition furnished the expected β,β-dicarbonyl ethers **42** in good yields (Scheme 14).

However, the above In/Cu/DDQ-promoted CDC reaction was restricted to benzyl ethers and malonate derivatives. Soon, Li and co-workers extended the substrate to simple ketones **43** and succeeded in the CDC reaction under a simplified condition using DDQ at 100 °C without metal catalyst.[46a] A series of expected coupling products **44** were obtained in moderate yields in most cases (Scheme 15).

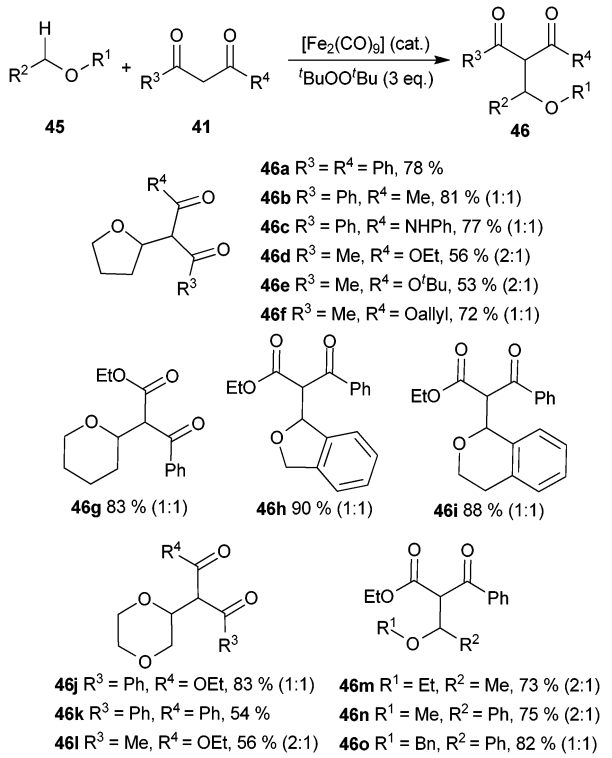
Then, the authors proposed a tentative single-electron transfer mechanism of this CDC as illustrated in Scheme 16.

At first, a single-electron transfer from the benzyl ether to DDQ generated a radical cation **A** and a DDQ radical anion **B**. The latter trapped a hydrogen from **A** and generated a benzoyl cation **C** and a DDQ radical anion **D**. The latter abstracted a hydrogen from the ketone to give an enolate **E**, which successively attacked the benzoyl cation **C** to give the final product with the DDQ was released. For the former work (Scheme 14),[45] the role of $InCl_3/Cu(OTf)_2$ was probably to promote the enolization of malonates as shown in **F**.

In addition, an In/Cu/NHPI/O_2 promoted CDC reaction between cyclic benzyl ethers with malonates was reported recently.[47]



Scheme 16 Single-electron transfer mechanism for oxidative CDC reaction of ether with ketone.

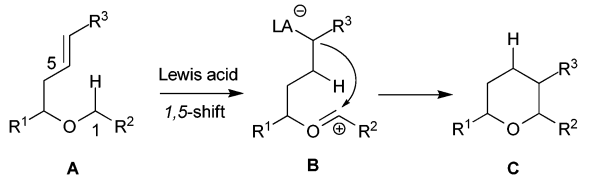


Scheme 17 Fe(II)-catalyzed CDC reaction of ethers with 1,3-dicarbonyl compounds.

In 2008, Li Zhiping and coworkers[48] further developed a new Fe(II)-catalyzed system to promote the CDC reaction of even the relatively unreactive aliphatic ether **45** (*e.g.* THF with malonates). Research results disclosed that the ferrous iron species ($FeCl_2$, $FeBr_2$, and $Fe(OAc)_2$) in combination with 2–3 equivalents of peroxides ($(t\text{-BuO})_2$, $t\text{-BuO}_2H$) could effect this reaction, but using ferric iron species ($FeCl_3$ and $Fe(acac)_3$) could not. Finally, the authors selected the best catalytic system $[Fe_2(CO)_9]$ (10 mol%) with 3 equiv. $(t\text{-BuO})_2$ to accomplish this reaction, and the corresponding products **46** were obtained in good yields (Scheme 17).

6. Intramolecular annulation of ether *via* *1,5*-hydride migration

Sames and coworkers have made a particularly important contribution to this area.[49] Initially in 2005,[50] they reported a new α-C–H *1,5*-hydride migration/annulation of ether bearing unsaturated (C=C, C=O and C≡C) moieties under the promotion of Lewis acid. The general mechanism was described in Scheme 18, wherein the Lewis acids initially activated the unsaturated moiety (C=C) and the α-C–H cleavage of ether triggered a *1,5*-hydride migration to form the zwitterionic pair **B**, followed by intramolecular ion pair coupling to form product **C**.

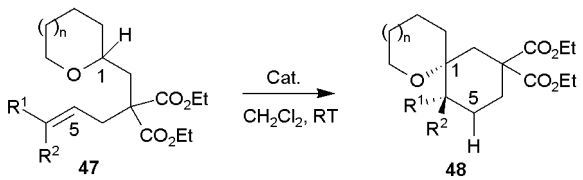


Scheme 18 Intramolecular annulation process of ether with C=C moiety *via* *1,5*-H migration.

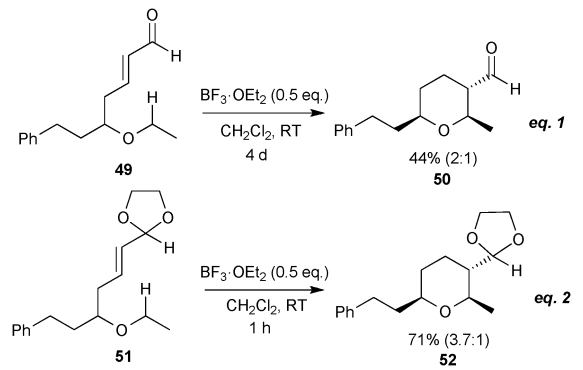
Therefore, when the well-designed substrate **47** bearing various unsaturated moieties were treated with 30 mol% $BF_3{\cdot}OEt_2$, a series of expected polysubstituted spiroether **48** (with an oxo-quaternary center) were received, whereby a sterically hindered tertiary C–H bond was directly hydroalkylated in an intramolecular version. Remarkably the spiroether products **48** were the versatile structural motifs found in a variety of biologically significant natural products and pharmaceuticals.[51] Further inspection of Table 3 revealed that the α,β-unsaturated aldehydes and ketones were effective to $BF_3{\cdot}OEt_2$-promoted reaction (entries 1–4), while the α,β-unsaturated esters was not (entry 5). Fortunately, the authors later demonstrated the $Sc(OTf)_3$ was an efficient catalyst for the reaction of α,β-unsaturated esters, and the [5,5]- and [5,6]-spiroethers could be received nearly quantitatively with 5 mol% catalyst (entries 6 and 7).

A limitation of this reaction above was that only the aliphatic cyclic ethers **47** (THP and THF) were effective. The acyclic ether usually reacted very slowly under the preferred conditions ($BF_3{\cdot}OEt_2$ at RT). This limitation has been solved recently by the transformation of the α,β-unsaturated aldehydes to corresponding acetals.[52]

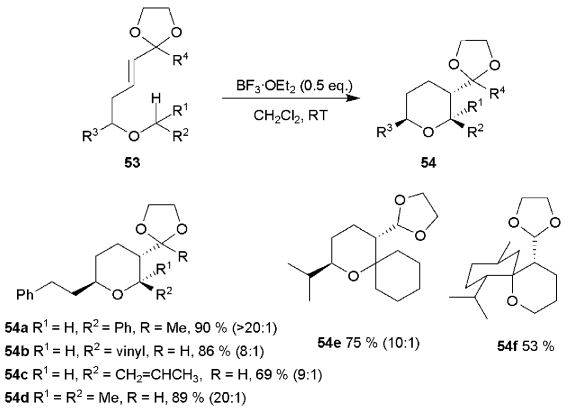
Table 3 Intramolecular annulation of ether with α,β-unsaturated carbonyl moieties to spiroether



Entry	*n*	Cat.	R^1	R^2	Dr	Yield (%)
1	1	$BF_3{\cdot}OEt_2$	CHO	H	3.7 : 1	91
2	1	$BF_3{\cdot}OEt_2$	COMe	H	2 : 1	94
3	1	$BF_3{\cdot}OEt_2$	COPh	H	3 : 1	98
4	0	$BF_3{\cdot}OEt_2$	CHO	H	1.5 : 1	99
5	1	$BF_3{\cdot}OEt_2$	CO_2Me	H		—
6	0	$Sc(OTf)_3$	CO_2Me	CO_2Me		96
7	1	$Sc(OTf)_3$	CO_2Me	CO_2Me		94



Scheme 19 Comparison of aldehyde with acetal toward the intramolecular annulations *via* 1,5-hydride migration.



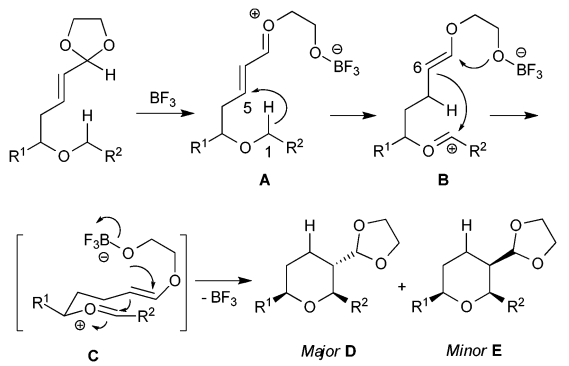
Scheme 20 More examples of intramolecular annulation of ethers with unsaturated acetals and ketals.

As indicated in Scheme 19, comparison of the reaction of aldehyde **49** (eqn (1)) with that of the corresponding acetal **51** (eqn (2)) under the standard conditions revealed a dramatic increase of reactivity and chemical yield, and to some degree the diastereoselectivity. Some more experimental examples using the acetals and ketals were indicated in Scheme 20.

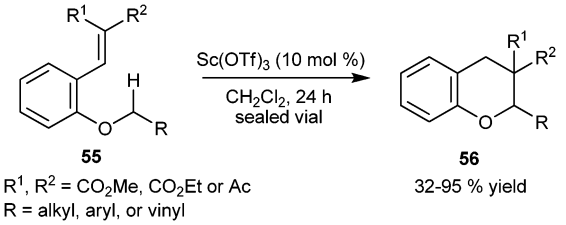
Sames and coworkers[52] also proposed the reaction mechanism for the acetal and ketal, which was depicted in Scheme 21. Initially the cyclic acetal was opened under the action of $BF_3{\cdot}OEt_2$ to generate the oxocarbenium intermediate **A**, which activated the conjugated double bond for abstracting the hydride. Subsequently the hydride transfer step resulted in oxocarbenium-enolether intermediate **B**, followed by rapid C–C coupling in **B** to produce the product **D** by releasing the Lewis acid catalyst. The observed stereoselectivity could be explained by the favorable transition state **C**, where all substituents were in equatorial positions of a chair-like conformation.

In addition, the dihydrobenzopyrans **56** were also prepared through *1,5*-hydride transfer from aryl alkyl ethers **55**.[53] As depicted in Scheme 22, a series of polysubstituted dihydrobenzopyrans **56** could be obtained. This established a concise synthetic approach to the polysubstituted dihydrobenzopyrans, an important synthon and key structural element in many biologically active natural products.

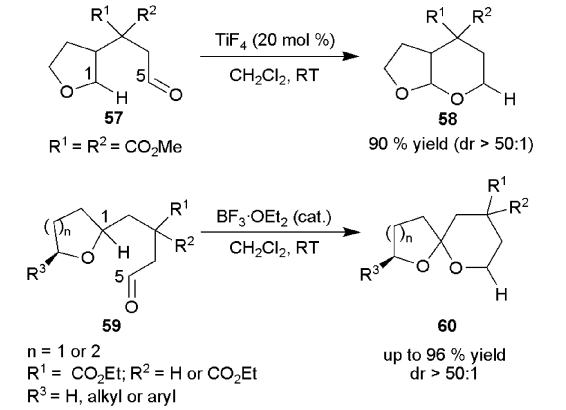
Further investigation focused on the intramolecular annulation of ether with aldehyde carbonyl (C=O) *via 1,5*-hydride migration. As indicated in Scheme 23,[54] the *1,5*-hydride



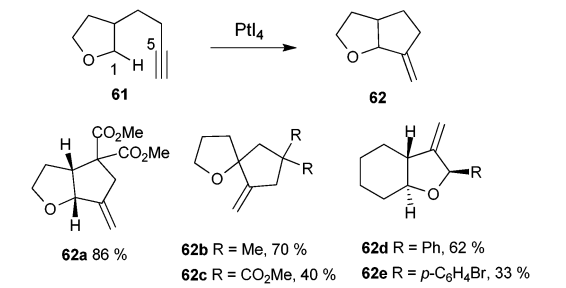
Scheme 21 Intramolecular annulation mechanism of ether with unsaturated acetal.



Scheme 22 Annulation of phenylether with α,β-unsaturated carbonyl derivative moieties to dihydrobenzopyrans.



Scheme 23 Annulation of etheryl aldehyde forming bicyclic acetals and spiroketals.



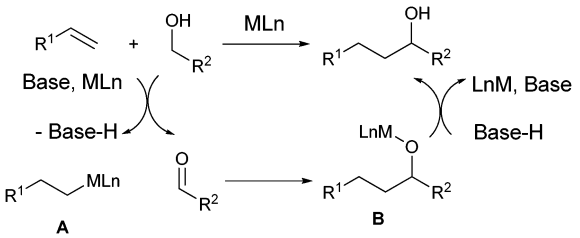
Scheme 24 Intramolecular annulation of ether bearing terminal C≡C moiety.

migration/annulation reaction of **57** and **59** also proceeded smoothly, and the bicyclic acetal **58** and [5,6]/[6,6]-spiroketals **60** could be obtained, respectively, in good to excellent yields. Remarkably, this annulation reaction has provided alternatively a powerful approach to the important naturally occurring spiroacetals.[55]

Most recently, Sames and coworkers reported a new annulation protocol of ether **61** with terminal triple bond (C≡C) *via 1,5*-hydride migration (Scheme 24).[56] Their research showed that PtI_4 could catalyze the activation of terminal alkynes for hydride attack. Although the mechanisms still could not distinguish between the *1,5*- or *1,6*-hydride transfer, this method enabled one-step preparation of complex heterocyclic compounds from readily available cyclic ethers.

7. Transfer hydrogenative coupling of alcohols with alkene and alkyne

The transfer hydrogenative coupling (THC) discussed in this section was referred to that transformation involving a



Scheme 25 General process of THC reactions of alcohol with unsaturated species.

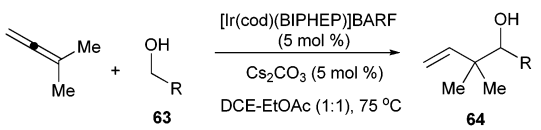
hydrogen-transfer oxidation of alcohol forming aldehyde, followed by metal-H addition to unsaturated bond (C=C) to form R-Metal **A**, and then an addition of **A** to aldehyde to give the alcohol **B** with oxygen occupied by metal, which abstracted a proton from Base-H to generate the secondary alcohol product with the metal catalyst released. This general mechanism can be illustrated in Scheme 25, but in this section the unsaturated C=C species also could be the C≡C and C=C=C substrates, and alcohols could be both aromatic and aliphatic ones.

Since 2007, Krische and coworkers[57–67] have explored a series of transition metal-catalyzed-THC protocols, including those of alcohol, aldehyde and imine with alkene, alkyne and allene, and three reviews have emerged to describe these reactions.[57–59] Herein, however, we just selectively and comprehensively discussed that THC reaction of alcohol with the C=C, C=C=C and C≡C species.

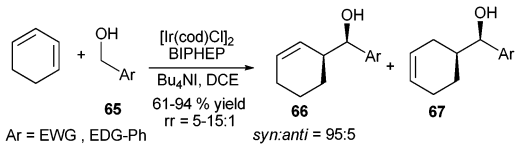
Initially, Krische and coworkers reported that dimethylallene and the primary alcohols **63** could undergo a THC under the catalysis of [Ir(cod)(BIPHEP)]BARF/ Cs_2CO_3 in the presence of DCE-EtOAc at 75 °C to give rise to the secondary homoallyl alcohol products **64**.[60] This discovery explored a new and interesting coupling reaction type and led to the establishment of synthetically significant approach to the secondary homoallyl and allyl alcohols (see below). Both EWG- and EDG-substituted alcohols **63** proved to be effective to this coupling and gave good to high yields of **64** (Table 4).

Employing the 1,3-cyclohexadiene (CHD) to replace the allene derivative above, Krische and coworkers have developed another Iridium-catalyzed THC reaction of benzylic alcohol derivatives **65**.[61] As indicated in Scheme 26, competing reactions would lead to the formation of complex regio- and diastereoisomers in this case. Therefore, improvement of the reaction specificity was performed and Bu_4NI was demonstrated to

Table 4 Ir-catalyzed THC of alcohols with 1,1-dimethylallene



Entry	*R*	Yield (%)
1	Ph	90
2	*p*-$NO_2C_6H_4$	92
3	*m*-$OMeC_6H_4$	76
4	2-Thienyl	68
5	CH_2NPhth	84



Scheme 26 Ir-catalyzed THC of alcohols with 1,3-cyclohexadiene (CHD).

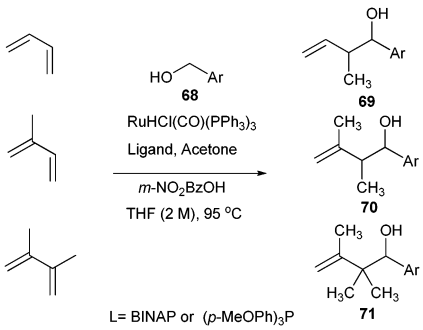
enable the 5-15 : 1 regioselection of **66** : **67** and a single *syn* **66** could be collected (*syn*/*anti*: 95/5). Various benzylic alcohols proved to be effective to this methodology in medium to high yields.

Similarly by use of the $RuHCl(CO)(PPh_3)_3$ catalyst, Krische and coworkers have carried out the THC of benzylic alcohols **68** with acyclic 1,3-butadiene derivatives.[62] Presence of *m*-NO_2BzOH and acetone, and in some cases the ligands (*p*-MeOPh)$_3$P or *rac*-BINAP were critical to gain the good results as shown in Table 5.

In contrast to the regioselectivity for forming **70** (Table 5), most recently a novel selective addition at the more sterically hindered C-2 rather than C-3 of the 1,3-butadiene derivatives **72** has been realized by Krische and coworkers by employment of the $RuH_2(CO)(PPh_3)$/DPPB/$C_7F_{15}CO_2H$ system.[63] This procedure was of synthetic significance due to the direct construction of *anti*-configured neopentyl homoallylic alcohols **73** containing the all-carbon quaternary stereocenter. Various 1,3-butadiene derivatives **72** were demonstrated to be effective with excellent diastereoselectivity and good regioselectivity (Table 6).

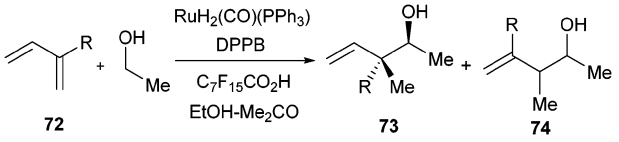
In 2008, Krische and coworkers further extended the scope of substrate to 1,3-enynes **75** and demonstrated that both [Ir(COD)Cl]$_2$/biphep] (diphep = diphenylphosphine) and $RuHCl(CO)(PPh_3)_2$/dppf (dppf = 1,1′-bis(diphenylphophino) ferrocene) could catalyze the THC reactions with primary alcohols **76**.[64] As showed in Scheme 27, under the promotion of $RuHCl(CO)(PPh_3)_2$/dppf, the benzylic, allylic and some other aliphatic alcohols **76** could couple with various 1,3-enynes **75** to the methyl homopropargyl alcohols **77** in

Table 5 Ru-catalyzed THC of benzylic alcohols with acyclic 1,3-butadiene derivatives

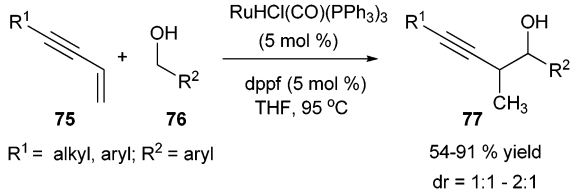


Entry	Aryl	**69** (*dr*)	**70** (*dr*)	**71**
1	*p*-$NO_2C_6H_4$	84% (1.5 : 1)	84% (2 : 1)	89%
2	Ph	61% (2 : 1)	93% (1 : 1)	91%
3	*p*-$MeOC_6H_4$	76% (2 : 1)	84% (1.5 : 1)	67%
4	2-Thienyl	87% (1.5 : 1)	82% (1 : 1)	63%
5	*p*-BrC_6H_4	90% (2 : 1)	75% (1 : 1)	61%

Table 6 Ru-catalyzed THC reaction of EtOH to 2-substituted 1,3-dienes



Entry	*R*	Yield (%)	*Anti*/*Syn* of **73**	Ratio (**73**/**74**)
1	Ph	61	17 : 1	6 : 1
2	*o*-$OMeC_6H_4$	58	18 : 1	4 : 1
3	*p*-$OMeC_6H_4$	78	> 20 : 1	6 : 1
4	Cyclohexyl	69	> 20 : 1	2 : 1
5	$Me_2CCHCH_2CH_2$	73	> 20 : 1	1 : 1
6	$TIPSOCH_2$	70	5 : 1	4 : 1
7	$BnN(Ts)CH_2$	63	> 20 : 1	7 : 1



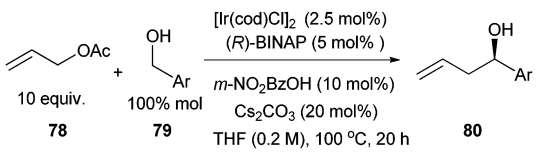
Scheme 27 Ru-catalyzed THC of alcohols with 1,3-enynes derivatives.

medium to high yields. It was remarkable that no adduct (the 1,3-butadienyl alcohol) formed from the addition to C≡C was collected, indicating the high regioselectivity of this approach.

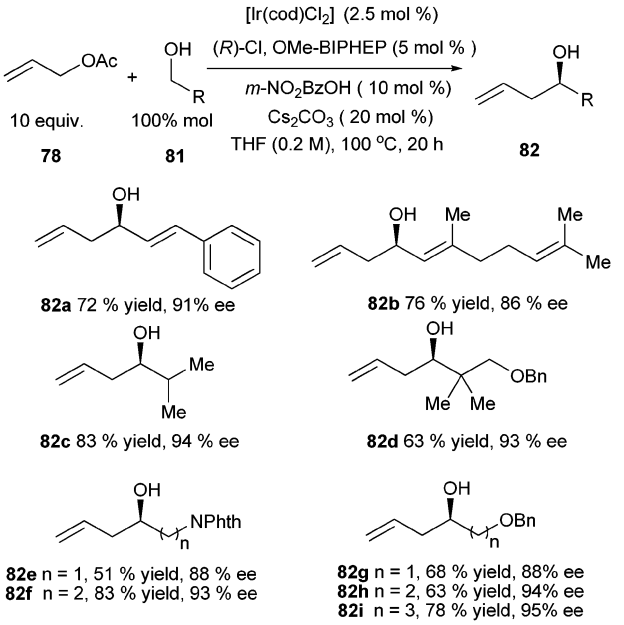
It was particularly important for asymmetric synthesis that, Krische and coworkers' further investigation resulted in the enantioselective THC of alcohols with allyl acetates by developing the chiral iridium catalysts, which established an alternative efficient approach to chiral homoallyl alcohols.[65,66] As indicated in Table 7, upon exposure to the chiral iridium catalyst derived from $[Ir(COD)Cl]_2$ and (*R*)-BINAP, couplings of benzylic alcohols **79** with allyl acetate **78** proceeded well in the presence of *m*-NO_2BzOH and Cs_2CO_3 in THF at 100 °C to give the expected products **80** in good to high enantioselectivities.

While the chiral (*R*)-Cl,MeO-BIPHEP modified-Ir catalyst was employed, asymmetric couplings of even allylic and

Table 7 Enantioselective THC of benzylic alcohols with allyl acetate

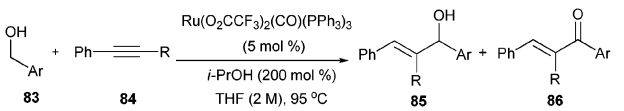


Entry	Aryl	Yield (%)	Ee (%)
1	*p*-$NO_2C_6H_4$	72	91
2	*p*-$(CO_2Me)C_6H_4$	77	93
3	Piperonyl	76	91
4	Ph	62	93
5	*p*-BrC_6H_4	74	93
6	*o*-$MeOC_6H_4$	80	92
7	*p*-$MeOC_6H_4$	73	93
8	3,5-$Cl_2C_6H_3$	61	92
9	2-(*N*-Me-indolyl)	55	90



Scheme 28 Enantioselective THC of allyl and alkyl alcohols with allyl acetate.

Table 8 Ru-catalyzed THC of benzylic alcohol with alkynes



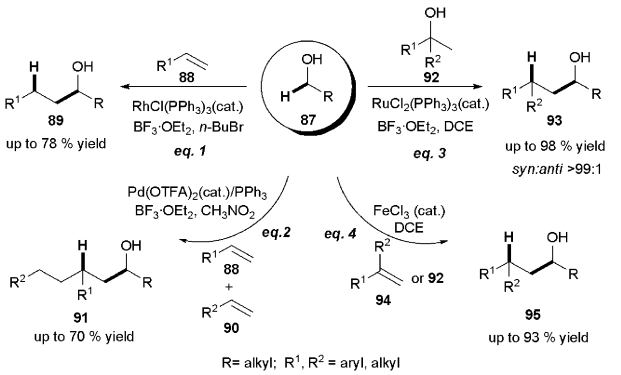
Entry	*R*	Time (h)	Yield **85** (**86**)
1	Ph	37	62% (12%)
2	$(CH_2)_2OBn$	13	58% (>1%)
3	CH_2NHBoc	13	15% (>1%)

aliphatic alcohols **81** with allyl acetate **78** could be effective to deliver good to excellent enantioselectivities of **82** (Scheme 28).[66] Further labeling and competing experimentals suggested a more detailed mechanism, which involved interestingly a catalytically active cyclometalated complex characterized by X-ray diffraction and accounted for the observed sense of absolute stereoinduction.

In 2009, Krische and coworkers[67] employed the catalyst $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ to replace the $RuHCl(CO)(PPh_3)_2$/dppf to conduct the THC to 1,3-enyne species and obtained about 11% regioselective adduct formed from C≡C addition. This observation led to the development of the novel THC reaction of alcohols **83** with alkynes **84** to allylic alcohols **85** under the condition employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ in the presence of *i*-PrOH (200%)/THF at 95 °C. The results were indicated in Table 8, wherein the role of *i*-PrOH was to minimize the formation of the corresponding α,β-unsaturated ketone **86**.

8. Transition metal-catalyzed coupling of alcohols with alkenes *via* C–H insertion

In this part, couplings discussed generally involved the metal species-mediated sp^3 α-C–H activation of alcohol, followed by



Scheme 29 Representative transition metal-catalyzed couplings of alcohols with alkenes.

insertion of the C=C bond to form the secondary alcohol products. The C=C donors also could be the corresponding alcohol precursors in some cases. Our group has developed several protocols for this reaction type.[68–74]

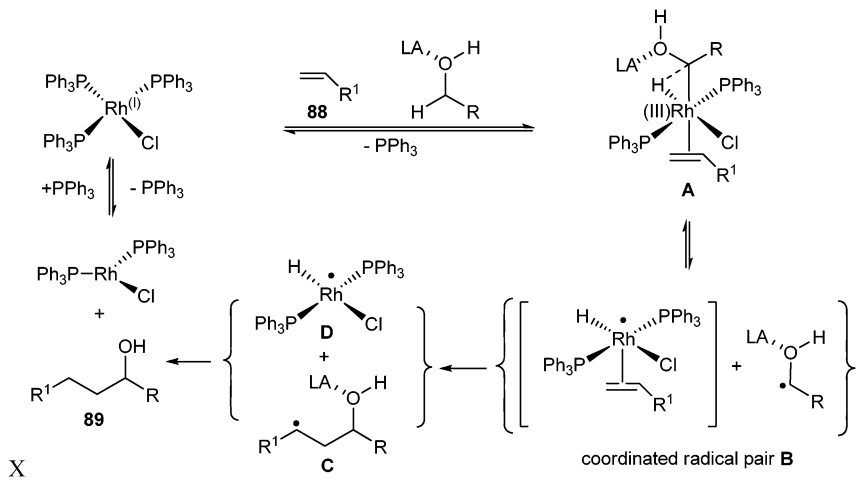
In 2005, we occasionally found in a synthetic experimental that a secondary alcohol was formed as a by-product through the direct coupling of primary alcohol at the α-position with styrene under the co-promotion of $RhCl(PPh_3)_3$ and $BF_3{\cdot}OEt_2$.[68] This observation let us establish, for the first time, the direct coupling protocol of unprotected alcohols **87** with alkenes **88** to the secondary alcohols **89** *via* C–H activation (Scheme 29, eqn (1)). Though an Ir-catalyzed coupling of ether with alkene was reported in the last century,[75] reactions with alcohol have not yet emerged up to the present. Thereafter, we explored several systems to improve and extend this kind of reaction, and four of which were summarized in Scheme 29.

Following our initial discovery above, further optimization of experimental conditions was conducted, which indicated that presence of the catalyst $RhCl(PPh_3)_3$ (2 mol%), the Lewis acid $BF_3{\cdot}OEt_2$ (2.5 equiv.) and the additive *n*-BuBr (0.5 equiv.) was required for effecting this coupling. The substrate scope expansion suggested that aryl-substituted alkenes **88** and aliphatic primary alcohols **87** were more suitable and the desired secondary alcohol products **89** could be obtained generally in medium to good yields. The mechanistic experimental suggested a possible reaction process as showed in Scheme 30, which involved the initial formation of key free radical pair **B**: the Lewis acid-occupied alcohol radical and the transition metal species coordinated alkene. Then the activated alkene combined with alcohol radical to form the product radical **C** which abstracted a proton from the transition metal species **D** to furnish the final product **89**.

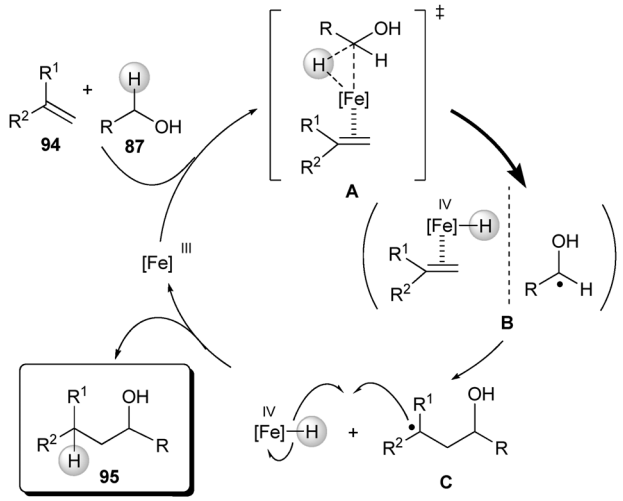
In 2008,[69] our further investigation resulted in the development of a tandem C–C bond coupling protocol of alcohol **87** with two alkene molecules **88** and **90** under co-promotion of $Pd(OAc)_2$(cat.)/$BF_3{\cdot}OEt_2$(excess) in $MeNO_2$ at 60 °C, which involves firstly a dimerization of two alkene molecules **88** and **90**, and then coupling with alcohol **87** *via* sp^3 C–H activation to give rise to the secondary alcohol **91** (Scheme 29, eqn (2)). This reaction could construct the longer carbon chain of secondary alcohol products **91** than the above reaction (Scheme 29, eqn (1)) and was still effective without any additive. But similarly, it could work better only when the aryl-substituted alkenes **88** and **90** and aliphatic primary alcohols **87** were used.

Continuing our research progress described above, we successively explored a more efficient $RuCl_2(PPh_3)_2$(cat)/$BF_3{\cdot}OEt_2$(excess) co-promoted coupling reaction of primary alcohols **87** with tertiary alcohols **92** (Scheme 29, eqn (3)), the latter being converted to 1,1-disubstituted alkene during reaction process.[70] This transformation worked quite well in DCE at 50 °C, and gave structurally more diverse secondary alcohol products **93** in good to excellent yields (two isomers). A free radical pair based-reaction mechanism similar to that in Scheme 30 was also proposed.[70]

Most recently, our continued research on this subject has resulted in an impressive exploration of an $FeCl_3$-catalyzed coupling reaction of alcohol **87** with alkene **94** (Scheme 29, eqn (4)).[71] Its synthetically important features included: high efficiency of a single, cheaper and environmentally benign catalyst $FeCl_3$ without co-promoter or additive; good tolerance of both aryl alkenes **94** and tertiary aryl alcohol precursors **92** with various substituents on aromatic rings; and simple and easy experimental handling as well as clean



Scheme 30 Mechanism of $RhCl(PPh_3)_3/BF_3{\cdot}OEt_2$-copromoted coupling of alcohol with alkene.

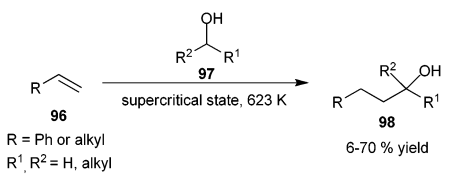


Scheme 31 Mechanism of $FeCl_3$-catalyzed coupling of alcohol with alkene.

reaction system. Based on a series of supporting experimentals, a concise reaction mechanism was proposed as showed in Scheme 31.

9. Direct α-C–H functionalization of supercritical alcohols without catalyst

In recent years, the supercritical fluids acting as reactants have been used for the organic reactions especially the C–C bond formations, and exhibited some unusual reactivities. In connection with the subject of this review, for example, Kamitanaka, Harada and coworkers[76,77] have developed the important and inspirited C–C bond forming reactions of alkenes **96** with supercritical alcohols **97** *via* α-C–H bond activation without a catalyst in spite of the low yield of the products **98** (Scheme 32). The results showed that the supercritical fluids could act not only as unique reaction media, but also as powerful reagents for organic reactions. The further development of supercritical reagents would be looking forward to receiving the practical application.



Scheme 32 Coupling of supercritical alcohols with alkenes without catalyst.

10. Conclusion

The α-C–H activation/functionalization of alcohol and ether has become a promising area, which composes the active and attracting chemistry of the inert C–H bond. The reactions discussed in this review enable the direct and efficient C–C bond construction of various oxygen-containing units in chemo-, regio- and/or stereoselective versions. We believe that these protocols will find more and more practical applications in synthetic organic chemistry, and also with more catalytic systems being explored, some new and more useful reaction types of α-C–H activation/C–C coupling reactions of alcohols and ethers will be developed in future.

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