

Fluorinated alcohols: powerful promoters for ring-opening reactions of epoxides with carbon nucleophiles

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In honor of the 70th birthday of our colleague and mentor, Professor Lanny S. Liebeskind

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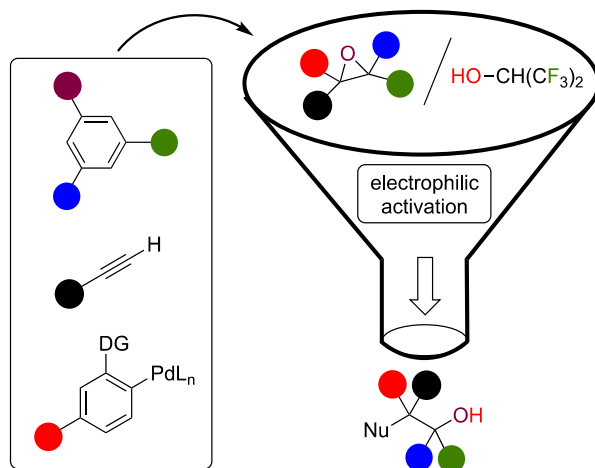
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Abstract

Ring-opening reactions of epoxides with carbon nucleophiles are valuable transformations for constructing functionalized carbon-carbon bonds. Epoxide ring-opening methods typically require Lewis acidic additives and/or strong nucleophiles to overcome the activation barrier for these reactions. Fluorinated alcohol solvents present a desirable alternative, enhancing the efficacy of these reactions with weak and neutral carbon nucleophiles by promoting electrophilic activation of the epoxide. We present here a thorough review of the literature regarding epoxide ring-opening reactions with carbon nucleophiles in fluorinated alcohol solvents, concluding with a few recent examples with aziridines.



Keywords: Carbon nucleophiles, epoxides, fluorinated alcohols, ring-opening

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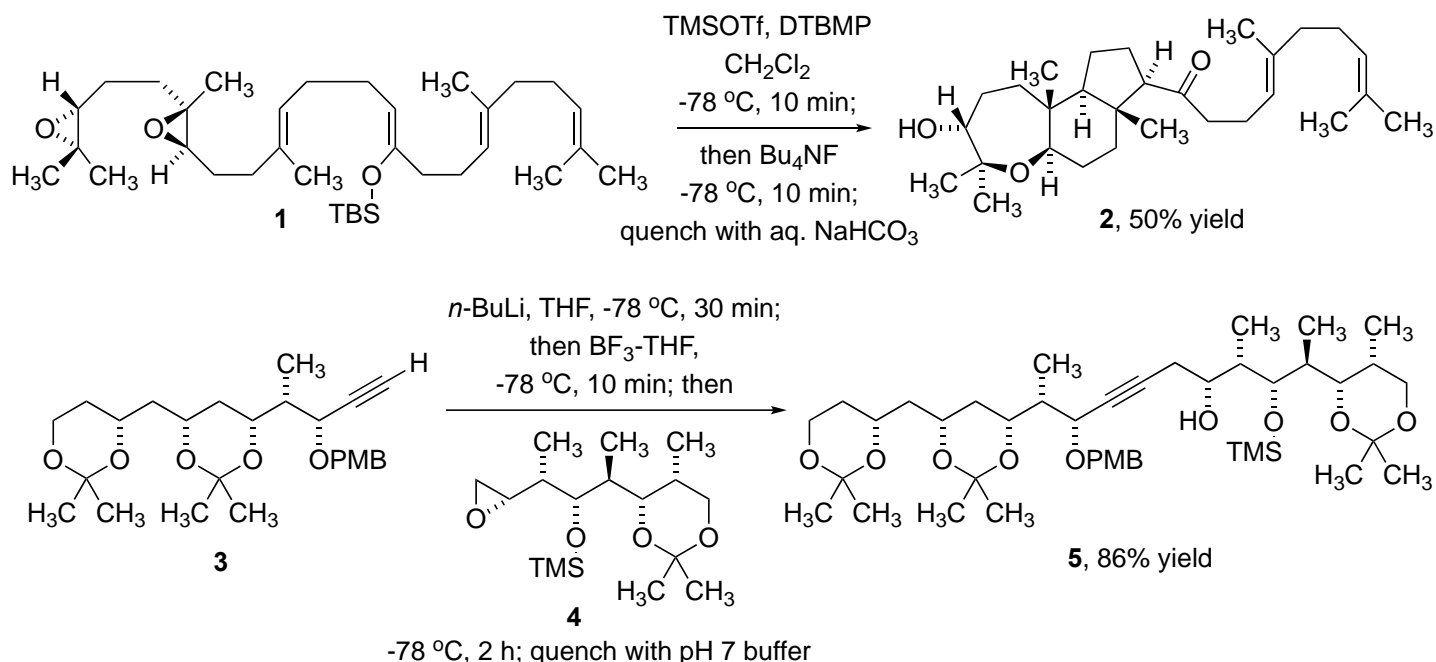
1. Introduction

1.1. General

Nucleophilic additions to epoxides are a common theme in chemical reactivity, ranging from preparations of poly(ethylene glycol) from ethylene oxide,¹ to DNA alkylations of carcinogenic epoxide metabolites of polycyclic aromatic hydrocarbons.² Despite the ring strain of the three-membered ring, epoxides are generally stable to long-term storage, due to the thermodynamic strength of the carbon-carbon and carbon-oxygen bonds. Therefore, many reactions of carbon nucleophiles with epoxides require either Lewis acidic reagents or catalysts to activate the latent electrophilicity of the epoxide, and/or highly nucleophilic main group organometallics, such as organolithium or organomagnesium compounds, which are also strongly basic.

Our interest in this topic arises from previous work from our laboratory involving epoxide electrophiles with carbon nucleophiles. These transformations have used strong Lewis acids, such as trimethylsilyl triflate (TMSOTf) for the intramolecular tricyclization of diepoxyenolsilane **1** to tricyclic ketone **2**,³ and boron trifluoride-tetrahydrofuran (BF₃-THF) for the intermolecular addition of alkyne **3** with epoxide **4** to produce alkynyl alcohol **5** (Scheme 1).⁴ Both examples required careful control of reaction time and temperature to attain the optimized yields.

In the past dozen years, other laboratories have reported several classes of ring-opening reactions of epoxides with carbon nucleophiles, *using fluorinated alcohol solvents* to promote these reactions under milder conditions or with greater efficiency than previously reported, including some transformations similar to those depicted in Scheme 1.



Scheme 1. Representative examples of epoxide electrophiles reacting with carbon nucleophiles, *without* fluorinated alcohol solvents. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; PMB = *para*-methoxybenzyl; TMS = trimethylsilyl

The substantive 2004 review of Bégué *et al.* described fluorinated alcohol solvents activating ring-opening reactions of epoxides with several classes of *heteroatom nucleophiles*, including amines, thiols, and carboxylic acids.⁵ Subsequent reviews have presented the broader scope and relevance of fluorinated alcohol solvents in modern synthetic applications.⁶⁻¹² This review focuses on ring-opening reactions of epoxides with *carbon nucleophiles* promoted by the fluorinated alcohol solvents 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE, Figure 1). Our review concludes with a few examples of ring-opening reactions of *aziridines* with carbon nucleophiles in fluorinated alcohol solvents.

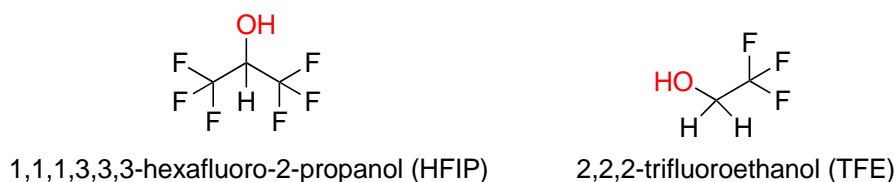


Figure 1. Structures of fluorinated alcohol solvents

To maintain focus, we have not extended this review beyond the heterocyclic *epoxide* and *aziridine* electrophiles, even though the analogous ring-opening reactions of aryl-substituted *cyclopropanes* with electron-rich aromatic nucleophiles in HFIP may be mechanistically related.¹³ Nonafluoro-*tert*-butyl alcohol (NFTB) promotes epoxide ring-opening with *oxygen nucleophiles*, including regioselective cascade cyclizations of polyepoxides terminated by alcohols,¹⁴ but we have not yet uncovered examples of NFTB with *carbon nucleophiles* adding to epoxides.

1.2. Properties of fluorinated alcohol solvents

The fluoroalkyl groups of these alcohols confer several synthetically useful benefits to these solvents. Among these are (1) increased acidity relative to their non-fluorinated analogs; (2) comparatively low boiling points; (3) strong hydrogen bond donating abilities; and (4) markedly low solvent nucleophilicities (Table 1).^{11,16-21}

Table 1. Selected properties of HFIP and TFE, compared with ethanol and water

entry	property	HFIP	TFE	CH ₃ CH ₂ OH	H ₂ O
1	pK _a (25 °C, water) ^{11,15}	9.3	12.4	15.9	14.0
2	b. p. (°C) ¹⁶⁻¹⁸	58	74.3	78.3	100
3	Hydrogen Bond Donor (α_1) ¹⁹	1.86	1.36	0.75	1.54
4	Hydrogen Bond Acceptor (β_1) ¹⁹	0.16	0.23	0.62	0.37
5	Solvent Ionizing Power (Y, 2-adamantyl tosylate) ²⁰	3.61 ^a	1.83 ^b	-1.75	n.r.
6	Solvent Ionizing Power (Y, <i>tert</i> -butyl chloride) ²⁰	2.46 ^a	1.15 ^b	-2.03	3.49
7	Nucleophilicity (N) ²¹	-5.17 ^a	-3.25 ^b	0.55	-1.47

^a For 97% (w/w) HFIP-H₂O. ^b For 97% (w/w) TFE-H₂O.

The electron-withdrawing fluoroalkyl groups are responsible for the low nucleophilicity and Brønsted acidity of fluorinated alcohol solvents. To illustrate, fluorinated alcohols exhibit enhanced acidity (pK_a, Table 1, entry 1) and strong hydrogen bond donating ability (entry 3), especially with ethereal oxygens.^{22,23} This results in an aggregation-induced decrease in the σ^*_{OH} orbital energy (Figure 2). For HFIP in the solid state, this complexation takes a helical form.²³ In addition, HFIP is a strongly ionizing solvent, and is more than five orders of magnitude less nucleophilic than ethanol (entries 5-7).^{20,21,24,25} Fluorinated alcohol solvents are more expensive than the non-fluorinated congeners. However, bulk prices are currently as low as \$100 USD per kilogram, with TFE less expensive than HFIP. The low boiling points are desirable for recovering and recycling fluorinated alcohol solvents but present an upper limit on reaction temperature under refluxing conditions.^{26,27}

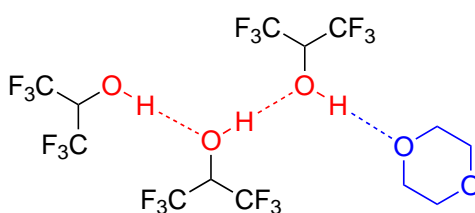


Figure 2. Aggregation of HFIP, depicting hydrogen bond donation with 1,4-dioxane

Fluorinated alcohol solvents are about one order of magnitude more toxic than ethanol or 2-propanol, with LD₅₀ values ranging from 300 - 600 mg/kg in mice (Table 2).^{28,29} The toxicity of TFE arises from metabolic oxidation pathways.³⁰ Most biological studies focus on the *in vivo* production of TFE and HFIP as metabolites from fluorinated anesthetics and other fluoroorganic drugs.³¹

Table 2. Toxicity of HFIP and TFE

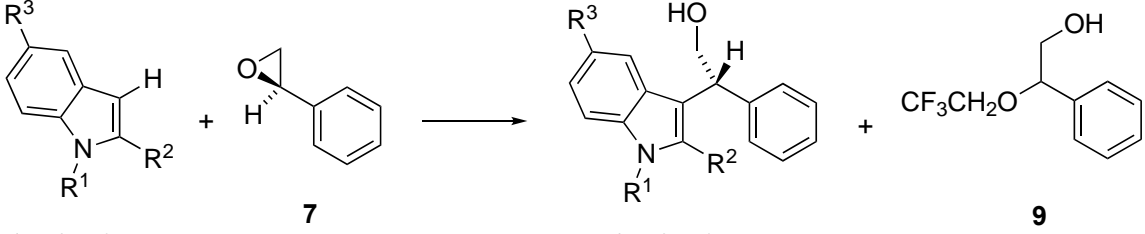
entry	route	LD ₅₀ (mouse)	
		HFIP ²⁸	TFE ²⁹
1	oral	600 mg/kg	366 ± 106 mg/kg
2	intraperitoneal	300 mg/kg	350 ± 23 mg/kg

2. Ring-opening Reactions with Neutral Carbon Nucleophiles, with Fluorinated Alcohol Solvents as Substitutes for Lewis Acid Promoters or Catalysts

2.1. Intermolecular carbon-carbon bond-forming reactions

The alkylation of indoles with epoxides has typically required Lewis acid catalysis to activate epoxide C-O bond cleavage. In 2008, Westermaier and Mayr reported that indoles **6a** - **6d** reacted with equimolar (*R*)-styrene oxide (**7**) in TFE solvent, *without additional Lewis acid*, to provide the alkylated products **8a** - **8d** (Table 3).³² The alkylations proceeded with regioselective addition at the benzylic carbon, and with complete stereospecificity, corresponding to inversion of configuration at the chiral carbon. For example, the parent indole (**6a**) reacted with styrene oxide (**7**) to give good yields of **8a** at room temperature in TFE, with only trace amounts of the trifluoroethoxy byproduct **9** (entry 1). This reaction proceeded more rapidly and cleanly at reflux (entry 2). The corresponding reaction of **6a** in aqueous acetone or aqueous ethanol solvent gave lower yield of product **8a**, and required significantly longer reaction times (entries 3, 4). Methyl-substituted indoles **6b** and **6c** also gave good yields of the corresponding alkylated products **8b** and **8c** in TFE (entries 5 - 7) vs. other solvents (entries 8, 9). However, electron-withdrawing substituents on the indole diminished nucleophilicity, so that 5-bromoindole **6d** required 72 hours for partial conversion, with the yield of **8d** diminished by the competing reaction of TFE with the epoxide (entry 10).

Table 3. TFE-promoted alkylations of indoles **6** with (*R*)-styrene oxide (**7**)

						
	6a	R ¹ , R ² , R ³ = H	8a	R ¹ , R ² , R ³ = H		
	6b	R ¹ = CH ₃ ; R ² , R ³ = H	8b	R ¹ = CH ₃ ; R ² , R ³ = H		
	6c	R ¹ , R ² = CH ₃ ; R ³ = H	8c	R ¹ , R ² = CH ₃ ; R ³ = H		
	6d	R ¹ , R ² = H; R ³ = Br	8d	R ¹ , R ² = H; R ³ = Br		
entry	indole	solvent	temperature (°C)	time (h)	yield 8 (%)	yield 9 (%)
1	6a	TFE	20	48	65	trace
2	6a	TFE	80	10	79	-
3	6a	acetone : H ₂ O (80 : 20)	60	72	9	-
4	6a	ethanol : H ₂ O (40 : 60)	80	72	45	-
5	6b	TFE	80	4	73	-
6	6c	TFE	20	24	77	-
7	6c	TFE	80	3	90	-
8	6c	acetone : H ₂ O (80 : 20)	60	14	17	-

9	6c	ethanol : H ₂ O (40 : 60)	80	12	54	
10	6d	TFE	80	72	45	19

The regioselectivity and stereospecificity outcomes were consistent with the fluorinated alcohol solvent stabilizing partial positive charge on the benzylic position in the transition state for the alkylation reaction (Figure 3).

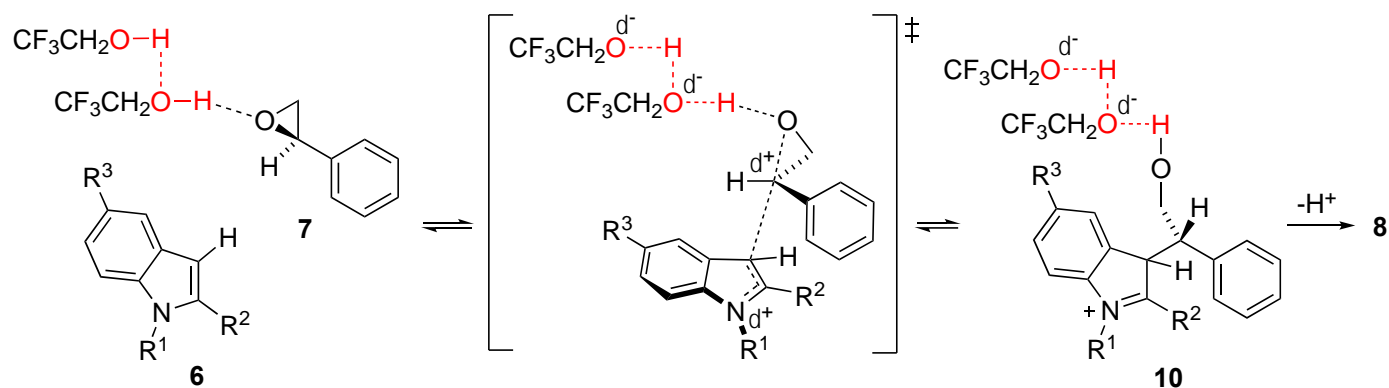
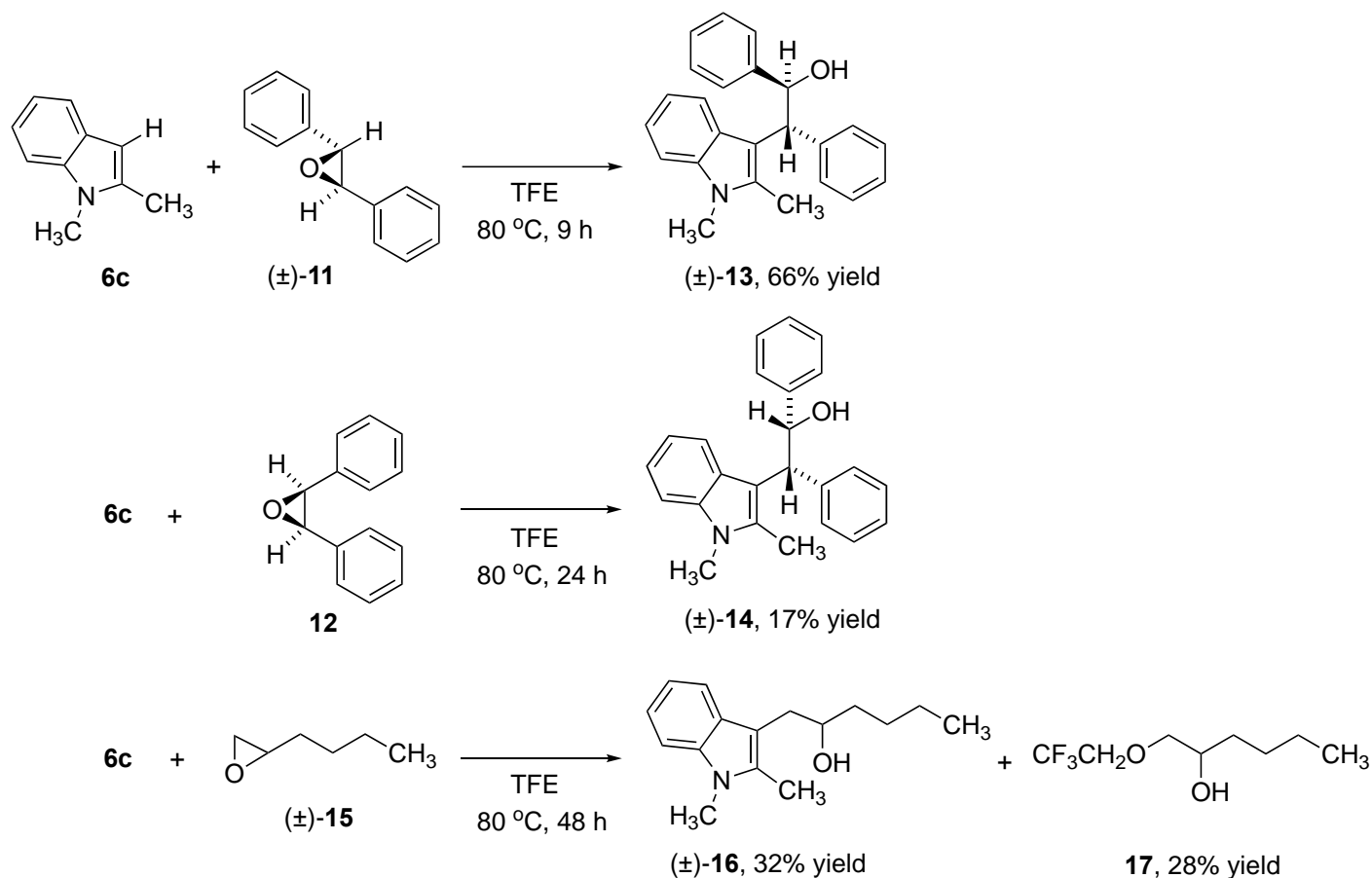


Figure 3. The electrophilic aromatic alkylation mechanism promoted by hydrogen bonding and the ionizing power of TFE

Westermaier and Mayr established that the scope of epoxide substrates with indoles was relatively limited: the reaction of **6c** with *trans*-stilbene oxide (**11**) provided **13** in good yield, but the corresponding reaction with *cis*-stilbene oxide (**12**) proceeded slowly—albeit with stereospecificity—to generate the expected diastereomer **14** (Scheme 2). The aliphatic epoxide 1,2-epoxyhexane (**15**) underwent indole alkylation only sluggishly, at the unsubstituted carbon, to produce **16**, with the competing addition of TFE giving byproduct **17**.



Scheme 2. Representative scope of epoxide substrates in TFE-promoted alkylations of indoles

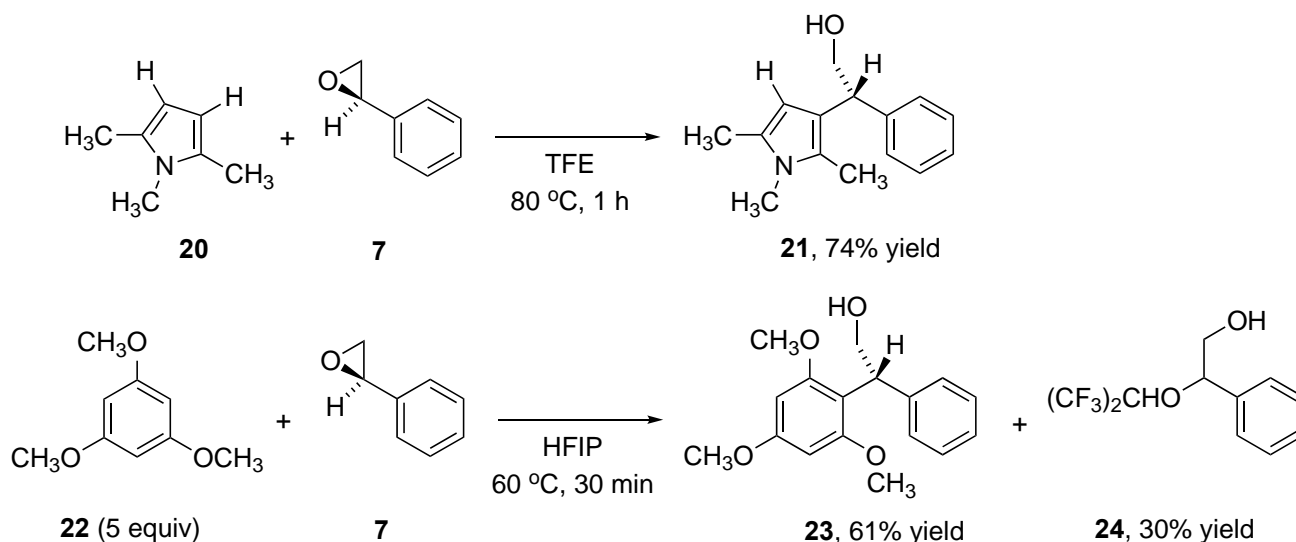
Sun, Hong, and Wang extended the alkylation of indole (**6a**) to spiroepoxyoxindole **18**, exploring several conditions with fluorinated alcohol solvents (Table 4).³³ TFE promoted the reaction even at room temperature (entry 1), with a better yield and shorter reaction time upon warming (entry 2). The more acidic and highly ionizing solvent HFIP gave a considerably faster reaction, albeit with a slight loss of regioselectivity (entry 3). However, selectivity was regained in water containing some HFIP (9 : 1 ratio) to provide **19** in excellent yield, with carbon-carbon bond-formation at the more substituted position (entry 4). Other organic solvents such as dichloromethane, dimethyl sulfoxide, methanol, tetrahydrofuran, or toluene did not give product **19**.

Table 4. Comparing the effects of TFE vs. HFIP and water on alkylation with spiroepoxyoxindole (**18**)

entry	solvent	temperature (°C)	time (h)	yield 19 (%)
1	TFE	25	80	65
2	TFE	60	32	90
3	HFIP	25	12	66 ^a
4	H ₂ O / HFIP (9 : 1)	25	32	93

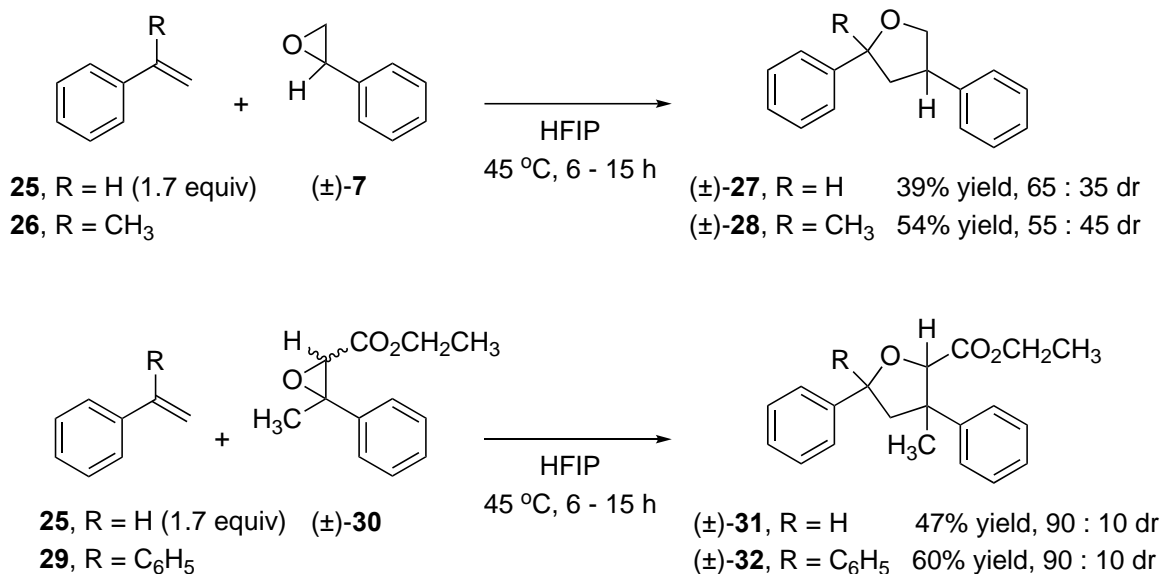
^a 15 : 1 regioisomer ratio

Westermaier and Mayr also described alkylations of pyrroles with styrene oxide (**7**) in TFE, affording regioisomer mixtures and double alkylation products with simpler pyrroles. Conversely, 1,2,5-trimethylpyrrole (**20**) selectively produced **21** as its major product (Scheme 3).³² Li and Qu subsequently reported alkylation of 1,3,5-trimethoxybenzene (**22**) in HFIP, with the electron-rich aromatic compound out-competing the HFIP solvent to favor the aromatic alkylation product **23** over the solvent addition product **24**.³⁴ Chiral non-racemic styrene oxide (*R*)-**7** stereospecifically led to both products **21** and **23**, with inversion of configuration. The yields were substantially lower with 1,4-dimethoxybenzene (35%) and with anisole (15%).



Scheme 3. Alkylations of other electron-rich aromatic compounds with (*R*)-styrene oxide (**7**)

The three-atom + two-atom annulations of epoxides with alkenes to form tetrahydrofurans have typically required transition metal catalysts, likely operating by radical or Lewis acid processes.^{35,36} However, Llopis and Baeza have reported catalyst-free conditions, simply by warming in HFIP solvent.³⁷ Although the scope is limited to aryl-substituted epoxides, the yields are modest, and the diastereoselectivity is generally low, metal-catalyzed versions of this transformation also share these limitations.^{35,36} The reactions of styrene (**25**) and *alpha*-methylstyrene (**26**) with racemic styrene oxide (**7**) in HFIP solvent exemplify these results (Scheme 4). With chiral non-racemic styrene oxide (*R*)-**7**, the reaction with styrene (**25**) gives racemic product **27**, whereas only partial racemization occurs upon forming tetrahydrofuran **28** from *alpha*-methylstyrene (**26**) (not shown). Annulations with ethyl 3-methyl-3-phenylglycidate (**30**), commercially available as a mixture of diastereomers, give higher diastereoselectivities upon reaction with styrene (**25**) and 1,1-diphenylethene (**29**). The regioselectivity is consistent with the less substituted carbon of the alkene adding to the phenyl-substituted carbon of the epoxide, with carbon-oxygen bond formation at the phenyl-substituted carbon arising from the alkene reactant. The yields of tetrahydrofuran products are diminished by competing dimerizations and trimerizations of the aryl alkene,³⁸ and solvent addition to the epoxide, forming byproducts including ether **24** (see Scheme 3 for structure).



Scheme 4. Three-atom + two-atom annulations of aryl-substituted epoxides with aryl alkenes

2.2. Intramolecular carbon-carbon bond-forming reactions

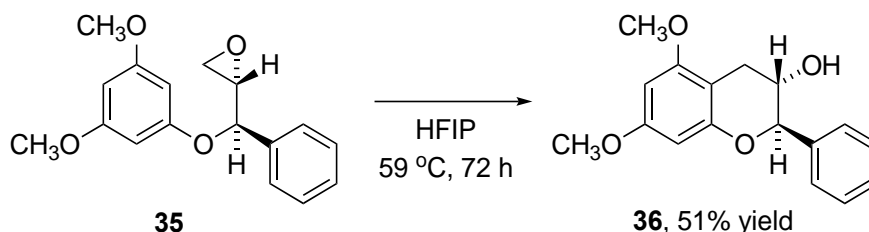
Li and Qu reported the intramolecular alkylation of epoxides tethered to electron-rich aromatic rings, using fluorinated alcohol solvents to activate the epoxide.³⁴ Although the literature includes several Lewis acid-catalyzed methods for the cycloisomerization of **33** to **34**, these workers explored the effects of highly ionizing solvents *in the absence of Lewis acids* (Table 5). In contrast to methanol or water (entries 1, 2), TFE promoted cyclization in excellent yield (entries 3, 4). HFIP was an even more effective promoter, affording the cyclized product in only five minutes at reflux (entries 5, 6). Nucleophilic addition occurred with high regioselectivity for the 6-*endo*-mode of cyclization, and with inversion of configuration at the benzylic carbon to provide the *trans*-disubstituted benzopyran **34** from the *trans*-disubstituted epoxide **33**. The significant decrease in reaction time between TFE and HFIP is consistent with the increased acidity and ionizing power of HFIP, rather than hydrogen bond donation, which diminishes at higher temperature.^{39,40}

Table 5. Solvent screening for cycloisomerization of epoxide **33**

entry	solvent	temperature (°C)	time	yield 34 (%)
1	methanol	65	26 h	18
2	water	100	10 h	55 ^a
3	TFE	20	48 h	96
4	TFE	74	4.5 h	99
5	HFIP	20	4 h	99
6	HFIP	59	5 min	99

^a remainder was diol from epoxide hydrolysis

The epoxide substrate **35** with an acid-sensitive benzylic ether, provided a valuable demonstration of the power of this HFIP-promoted transformation (Scheme 5). The previous synthesis of compound **36**, closely corresponding to the catechin natural products, required a specialized combination of Lewis acid and hydrogen bond donor catalysts (AuCl₃ / AgOTf / thiourea).⁴¹ In contrast, HFIP solvent promoted the slow but clean conversion of epoxide **35** into benzopyranol **36**, arising from 6-*endo*-mode nucleophilic addition to the unsubstituted carbon of the epoxide.³⁴



Scheme 5. HFIP-promoted cyclization of the sensitive epoxy-ether **35**

The Magauer laboratory reported the acid-catalyzed cycloisomerizations of neopentyl epoxides tethered to electron-rich aromatic rings.⁴² In the course of cyclization of substrate **37** to tetralin product **38**, a methyl group underwent 1,2-alkyl shift. Cyclizations were unsuccessful or proceeded in low yield in most solvents (Table 6, entry 1 for a representative example) but improved in fluorinated alcohol solvents, with HFIP outperforming TFE (entries 2 vs. 3). The optimized conditions used sulfuric acid in HFIP at 0 °C (entry 5). HFIP forms hydrogen bonds with the conjugate base of sulfuric acid, increasing its Brønsted acid activity.⁴³

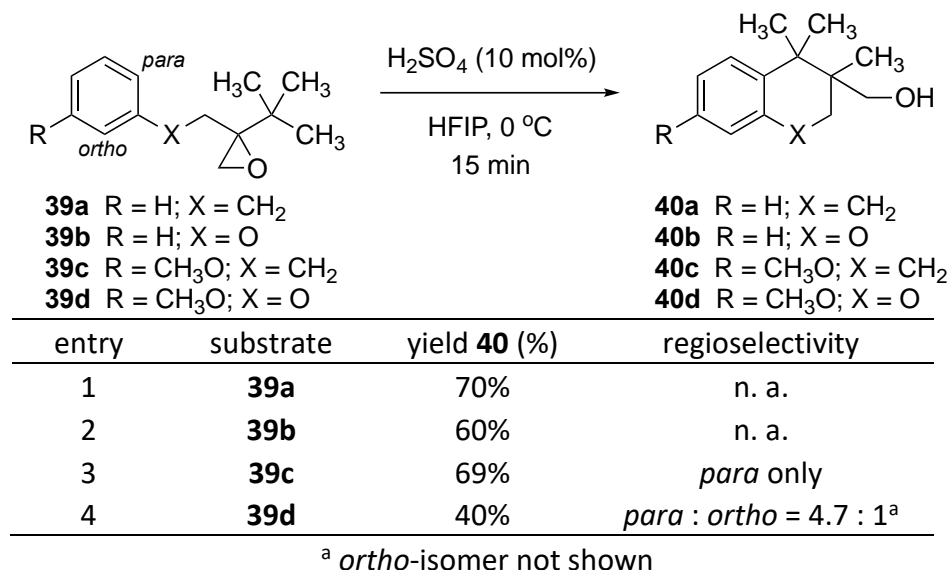
Table 6. Acid-catalyzed, HFIP-promoted cycloisomerization of neopentyl epoxide **37**

entry	Brønsted acid	solvent	temperature	yield 38 (%) ^a
1	H ₂ SO ₄	toluene	23 °C	19%
2	H ₂ SO ₄	TFE	23 °C	43%
3	H ₂ SO ₄	HFIP	23 °C	77%
4	<i>p</i> -toluenesulfonic acid	HFIP	23 °C	77%
5	H ₂ SO ₄	HFIP	0 °C	83% ^b

^a ¹H NMR yields. ^b The isolated yield of compound **38** was 80%.

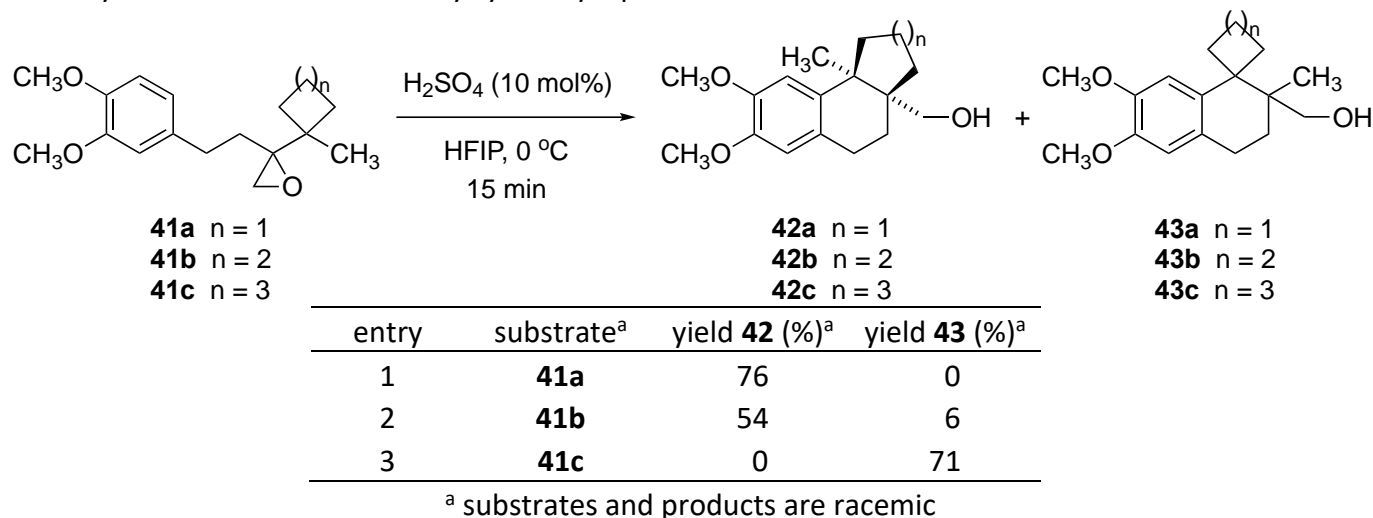
The phenyl substrate **39a** also produced the corresponding tetralin **40a** (Table 7, entry 1).⁴² The reaction conditions tolerated aryl ether tethers in **39b** to form chromane **40b** (entry 2). With electron-donating substituents, cycloisomerization favored the *para*-isomers **40c-d** with varying levels of regioselectivity (entries 3, 4). Aromatic rings with strongly electron-withdrawing substituents gave lower yields or did not cyclize.

Table 7. Alkyl vs. ether tethers, and regioselectivity of monomethoxy aromatic substrates



Neopentyl epoxide substrates containing cycloalkyl rings showed divergent behavior, depending on the degree of ring strain (Table 8).⁴² The cyclobutyl and cyclopentyl substrates **41a–41b** favored the corresponding ring-expansion fused products **42a** and **42b** (entries 1, 2), whereas the cyclohexyl substrate **41c** produced exclusively the spiro isomer **43c** arising from a 1,2-methyl shift.

Table 8. Cycloisomerizations of methylcycloalkyl epoxide substrates **41**



The partitioning of mechanistic pathways leading to products **42** and **43** is consistent with carbenium ion intermediates.⁴² As depicted in Figure 4, ring expansion exclusively occurs (path a) with strained cyclobutyl epoxide **41a** and is favored with cyclopentyl epoxide **41b**. With the unstrained cyclohexane attached to epoxide **41c**, the 1,2-methyl shift (path b) exclusively occurs. From each tertiary carbenium ion intermediate **44** and **45**, intramolecular Friedel–Crafts alkylation provides the tetralin core structures of products **42** and **43**. Figure 4 also depicts the hydrogen bonding interaction between HFIP and sulfuric acid, and HFIP stabilization of the hydrogen sulfate conjugate base,⁴³ which is also observed in other acid-catalyzed processes.^{44,45}

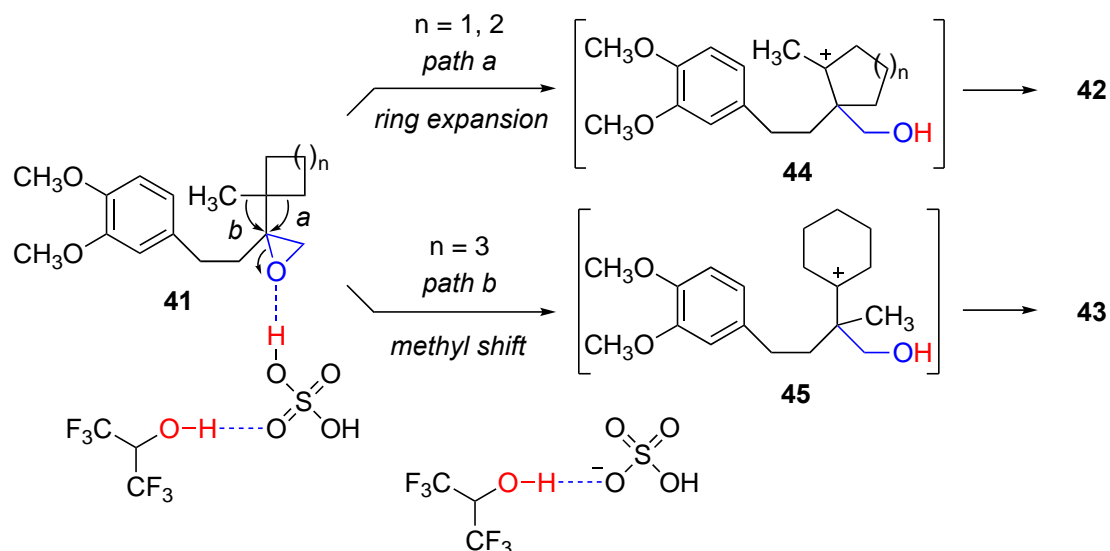
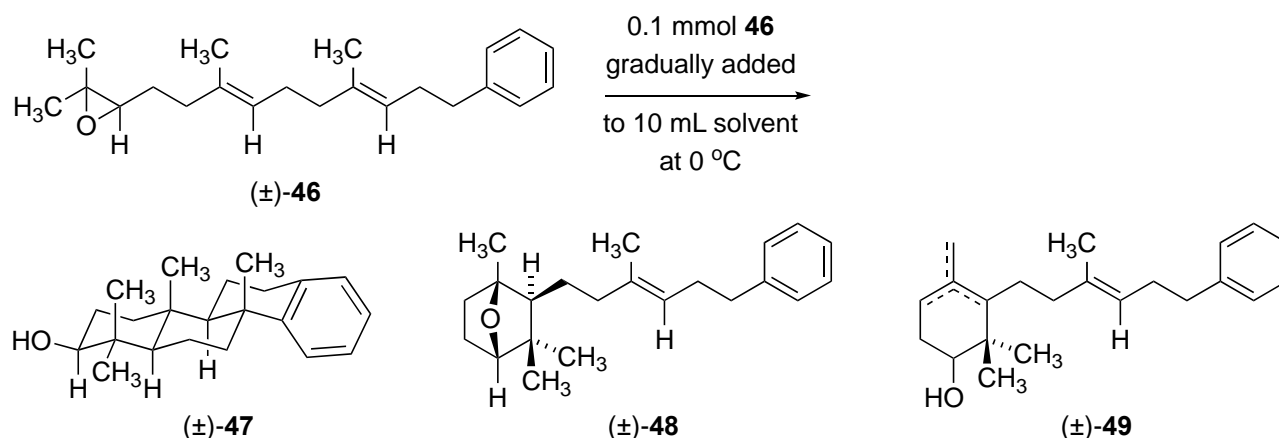


Figure 4. Possible mechanisms for cycloisomerization

Biomimetic polyene-epoxide polycyclizations have typically required Lewis acid promoters or catalysts.^{46,47} In contrast, the Qu laboratory observed slow conversion of epoxydiene **46** when dissolved in HFIP, producing a mixture of tetracyclic product **47**, the oxabicyclo[2.2.1]heptane byproduct **48**, and an inseparable mixture of partially cyclized dienes **49** (Table 9, entry 1).⁴⁸ Remarkably, epoxydiene **46** was inert in other fluorinated alcohol solvents (entries 2, 3). *p*-Toluenesulfonic acid (*p*-TSA) rapidly catalyzed the reaction of **46**, but gave a mixture favoring the partially cyclized byproducts **49** (entry 4). The reaction rate dramatically increased, with improved selectivity for tetracyclic product **47**, upon gradual addition of epoxydiene **46** to HFIP solutions of soluble organic salts with fluorine-containing non-nucleophilic anions (entries 5 - 7). Tetraphenylphosphonium tetrafluoroborate (Ph_4PBF_4) in HFIP gave the best yield of compound **47** (entry 7). Although excess water hydrolyzed the epoxide of **46** to form a diol, up to 20 equivalents of water were compatible with tricyclization (entry 8). Deliberately adding catalytic hydrogen fluoride to HFIP gave a similar enhancement in the reaction rate (entry 9), supporting a proposal that BF_4^- and PF_6^- provided trace amounts of HF. However, replacing HFIP with dichloromethane, while including Ph_4PBF_4 and HF as additives, gave no reaction (entry 10). The authors concluded that HFIP played an essential role in promoting the polycyclization, likely by stabilizing the fluoride conjugate base.

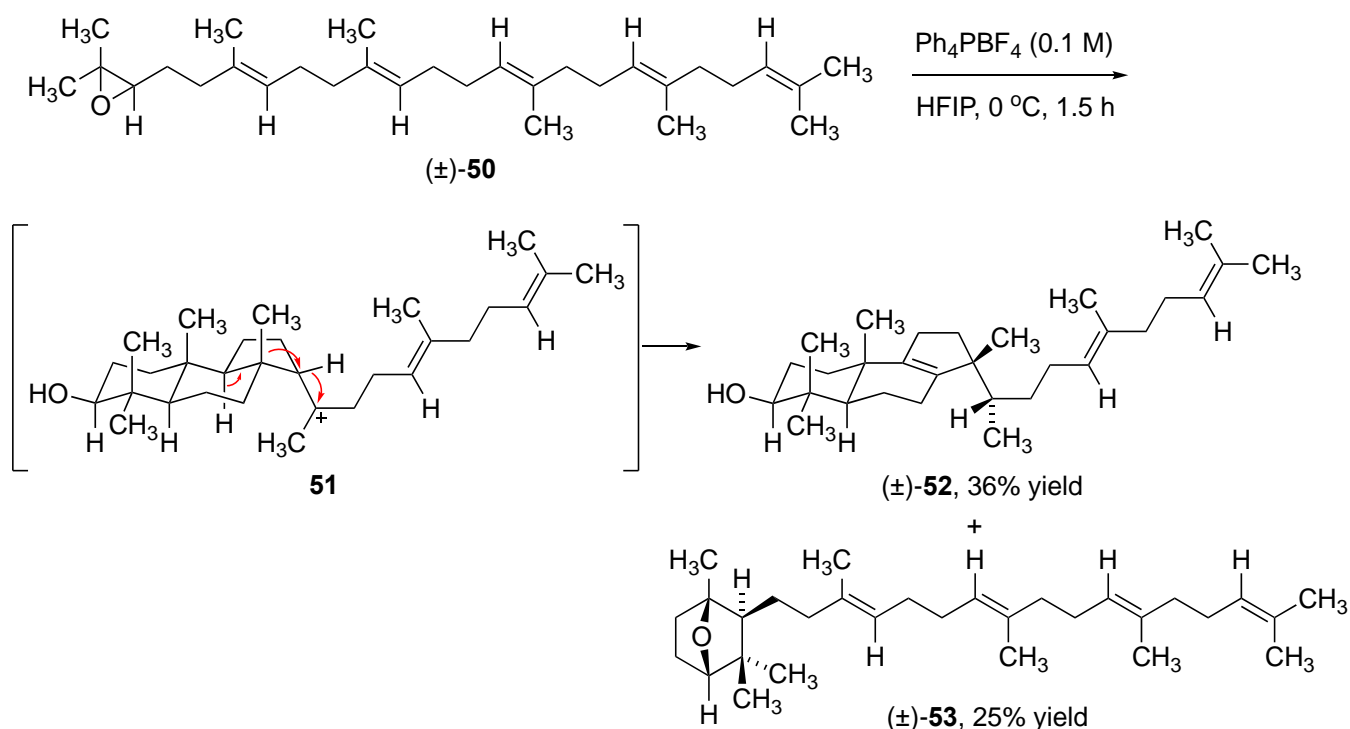
Table 9. HFIP / additive-promoted tricyclizations of epoxydiene **46**



entry	solvent	additive(s)	time	yield 47 (%)	yield 48 (%)	yield 49 (%)
1	HFIP	none	24 h	40	27	32
2	TFE	none	24 h	(no reaction)		
3	(CF ₃) ₃ COH	none	24 h	(no reaction)		
4	CH ₂ Cl ₂	<i>p</i> -TSA (0.1 equiv)	15 min	23	19	56
5	HFIP	Bu ₄ N ⁺ BF ₄ ⁻ (0.1 M)	5 min	51	n.r. ^a	n.r.
6	HFIP	Bu ₄ N ⁺ PF ₆ ⁻ (0.1 M)	5 min	51	n.r.	n.r.
7	HFIP	Ph ₄ P ⁺ BF ₄ ⁻ (0.1 M)	5 min	60	19	n.r.
8	HFIP	Ph ₄ P ⁺ BF ₄ ⁻ (0.1 M) + H ₂ O (0.2 M)	5 min	56	n.r.	n.r.
9	HFIP	HF (0.001 M)	5 min	37	n.r.	n.r.
10	CH ₂ Cl ₂	Ph ₄ P ⁺ BF ₄ ⁻ (0.1 M) + HF (0.001 M)	24 h	(no reaction)		

^a n.r. = not reported

These scientists then applied these conditions to the cyclization of squalene oxide (**50**), the biosynthetic precursor of lanosterol and other steroid natural products (Scheme 6).⁴⁸ The 36% yield of tricyclic product **52** was substantially higher than the outcomes from various Lewis acid-promoted transformations.⁴⁹⁻⁵³ The formation of compound **52** is consistent with a mechanism involving concerted cyclization of the three alkenes closest to the epoxide, thereby generating a tertiary carbenium ion **51**. The authors proposed that the cations - including protonated epoxide and the tricyclic intermediate cation **51** - were stabilized by the non-nucleophilic solvent HFIP and/or the non-nucleophilic tetrafluoroborate anions. From **51**, an intramolecular cascade of face-selective 1,2-hydride and 1,2-methyl migrations followed by deprotonation generated the principal product **52**.



Scheme 6. HFIP / Ph₄PBF₄-promoted cyclization of squalene oxide (**50**)

In summary, although most epoxide alkylations are limited to electron-rich aromatic compounds, fluorinated alcohol solvents effectively replaced the Lewis acidic reagents and catalysts customarily used for these transformations. The intramolecular alkylations of epoxides tethered to polyenes have demonstrated the powerful combination of additive Brønsted acid sources in combination with HFIP.

3. Ring-opening Reactions with Organopalladium Intermediates arising from Directed C-H Functionalization

Directed C-H functionalization of aromatic rings has traditionally required strongly basic reagents, such as *tert*-butyllithium combined with *N,N,N,N*-tetramethylethylenediamine (TMEDA). Regioselectivity *ortho*- to a Lewis basic directing group (DG) arises from coordination with the electropositive metal, bringing the electronegative alkyl ligand into proximity to the aromatic C-H bond.^{54,55} The resulting functionalized aryllithium intermediates react with many electrophiles, and the literature documents several examples with epoxides.⁵⁶ However, transition-metal catalysts offer milder conditions for directed C-H functionalization. The literature provides several examples in which HFIP has favored palladium acetate-catalyzed directed metalations of benzene rings, coupled with *in situ* alkylation of epoxides, presumably also activated by HFIP for nucleophilic addition (Figure 5).⁵⁷⁻⁶¹ A variety of Lewis basic directing groups (DG) are effective, including 2-pyridyl (**54**), and a variety of carbonyl- or carboxyl-derived compounds **55** - **59**.

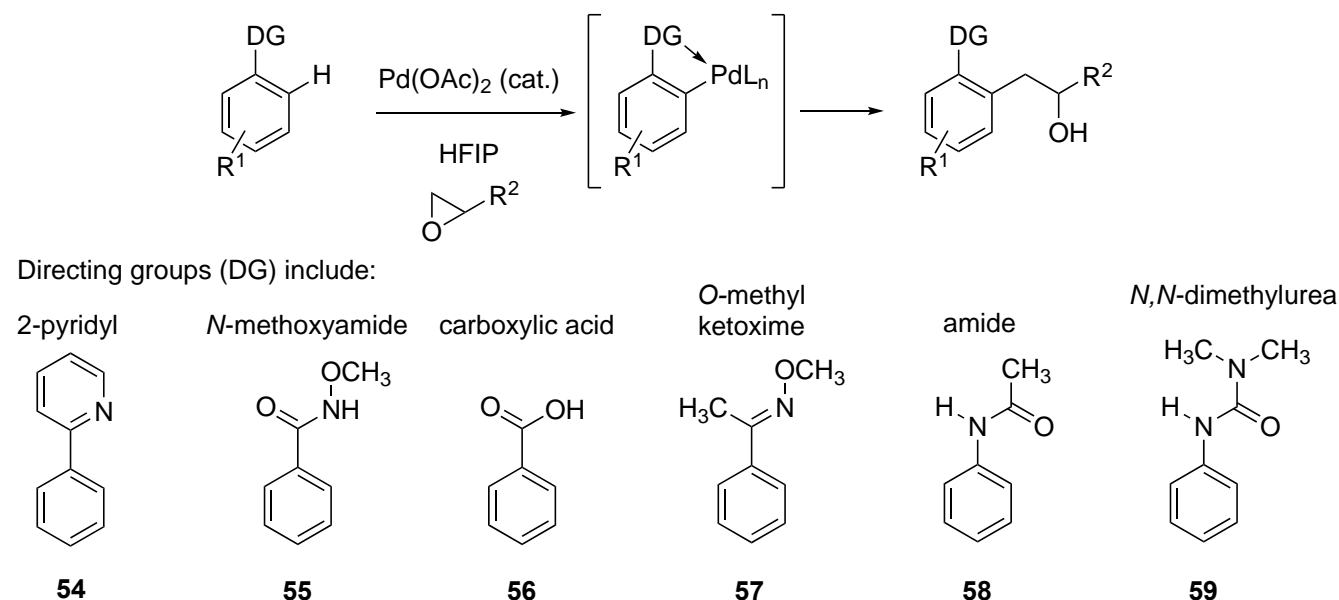


Figure 5. Directing groups for palladium acetate-catalyzed C-H functionalization / epoxide alkylation

The methods published to date have several common features:

- All use palladium acetate as the catalyst,
- The methods show broad scope with many substituents R¹ on the benzene ring, and
- A variety of monosubstituted and 1,1-disubstituted epoxides give good yields (Figure 6).

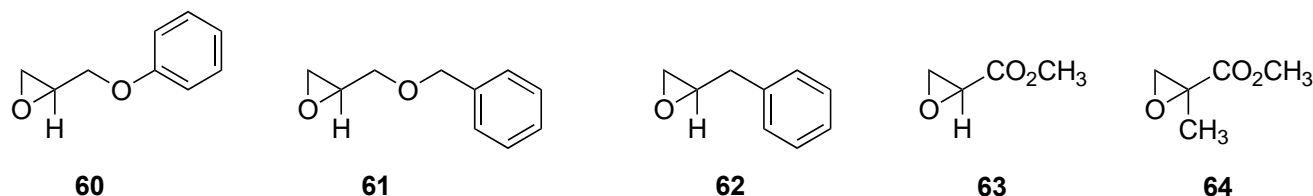


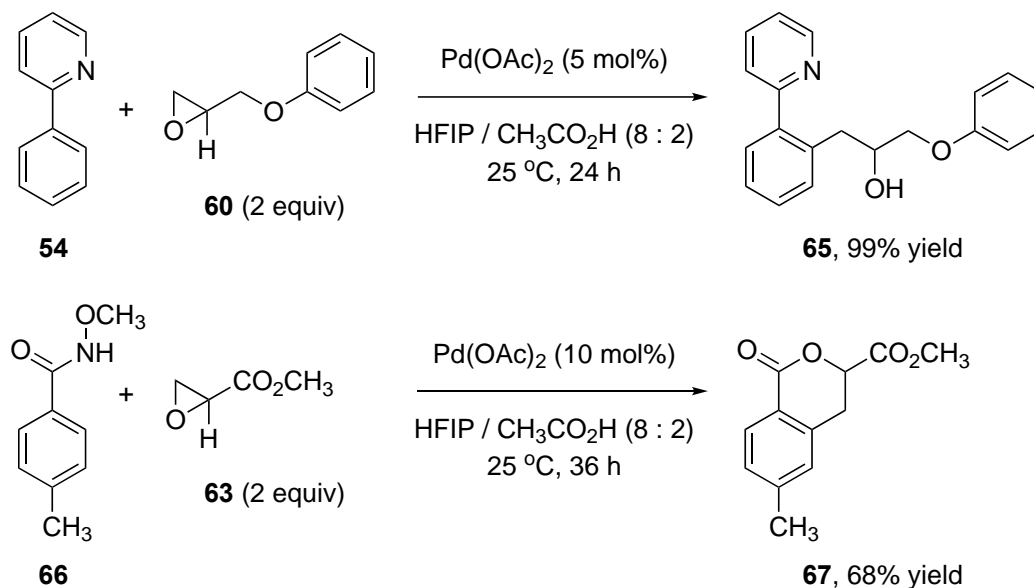
Figure 6. Representative epoxides for palladium-catalyzed C-H functionalization / epoxide alkylation

These methods also share common substrate limitations:

- To date, heterocyclic aromatic rings are not functionalized under these conditions, and
- 1,2-Disubstituted epoxides generally do not react, or give substantially lower yields.
- No examples have been reported with styrene oxide (**7**) or other aryepoxides.

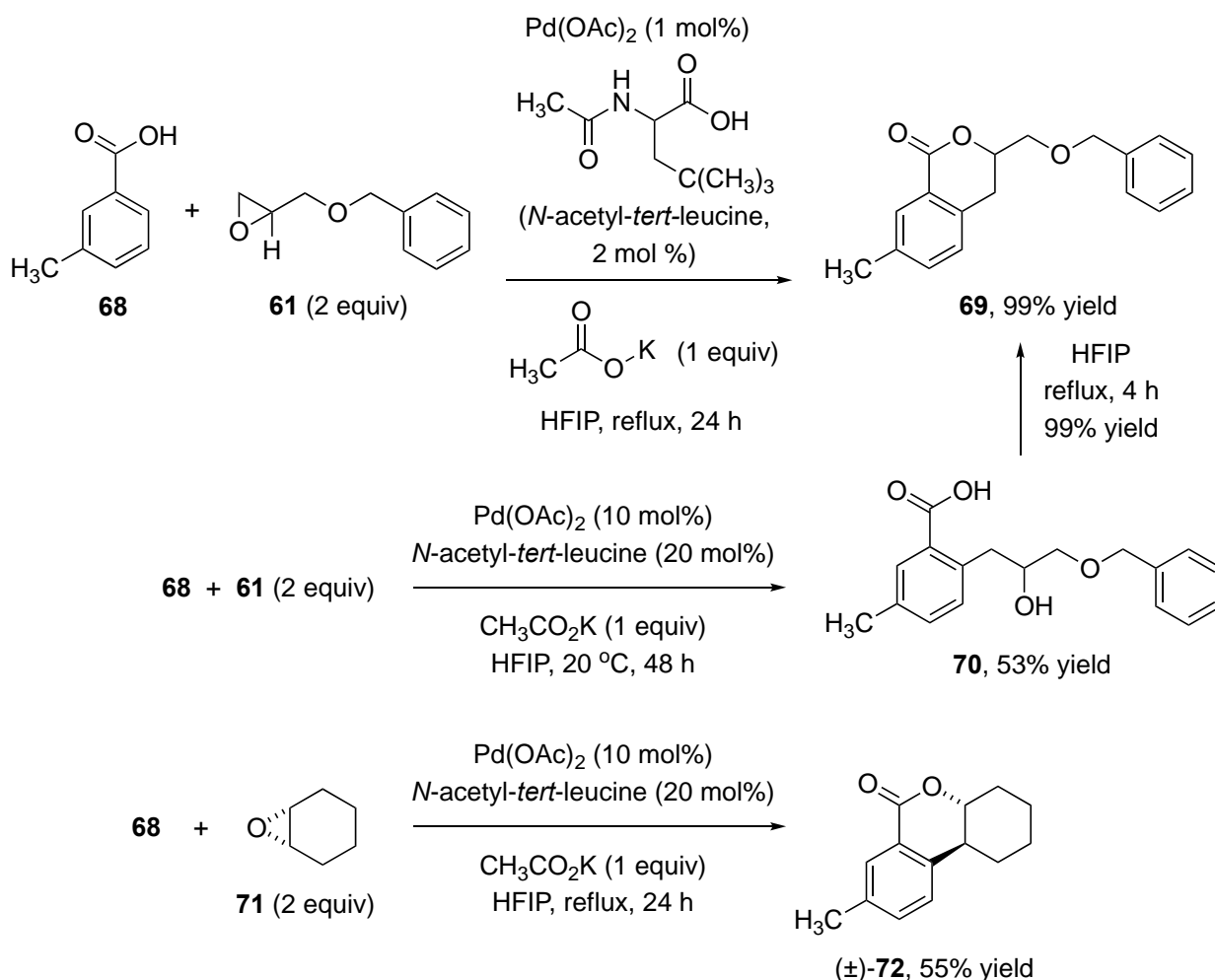
3.1. Scope of reactions and conditions

In 2015, the Kuninobu and Kanai laboratories collaboratively reported the regioselective alkylation of 2-phenylpyridine (**54**) and derivatives with epoxides including phenyl glycidyl ether (**60**), catalyzed by palladium acetate (Scheme 7).⁵⁷ The initial solvent choice, acetic acid, gave low yields due to acid-promoted decomposition of the epoxide. Diluting acetic acid with HFIP resulted in the substituted phenethyl alcohol **65** in excellent yield, provided that two equivalents of epoxide were used at room temperature, as the epoxide decomposed under these conditions at higher temperatures. These workers established that HFIP alone was not sufficient to promote this transformation. In addition to the **54** and **60** example, they also reported the analogous transformation with the *N*-methoxyamide **66** and methyl glycidate (**63**). In this example, the lactone ring of product **67** is presumably formed via acid-catalyzed intramolecular transacylation after the carbon-carbon bond-forming step.



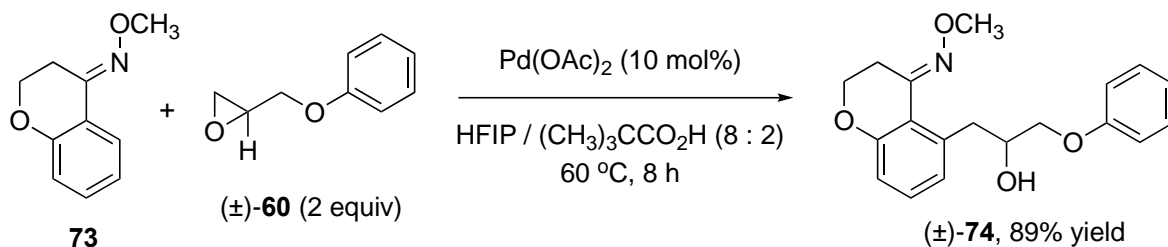
Scheme 7. Pd-catalyzed C-H functionalization with 2-pyridyl and *N*-methoxyamide directing groups, with regioselective epoxide alkylation

Later in 2015, the Yu laboratory disclosed the directed alkylation of benzoic acids, including *meta*-toluic acid (**68**), with a broad scope of epoxide substrates (Scheme 8).⁵⁸ Essential components of this reaction system included palladium acetate, potassium acetate, and HFIP solvent. Cesium acetate led to lower yields, and little or no product was formed when using sodium acetate or lithium acetate. Yields increased from 75% to 99% with the mono-*N*-protected amino acid ligand *N*-acetyl-*tert*-leucine. In a highly optimized example with benzyl glycidyl ether (**61**), product **69** was isolated in 99% yield. At room temperature, the reaction proceeded more slowly and required higher catalyst loading, but produced intermediate hydroxyacid **70**. This compound underwent HFIP-promoted lactonization at reflux to form **69**. By avoiding acetic acid as a cosolvent, a broad range of epoxide substrates were compatible with HFIP, even under reflux. This carboxyl directing group method was compatible with cyclohexene oxide (**71**), producing *trans*-fused **72** in satisfactory yield.



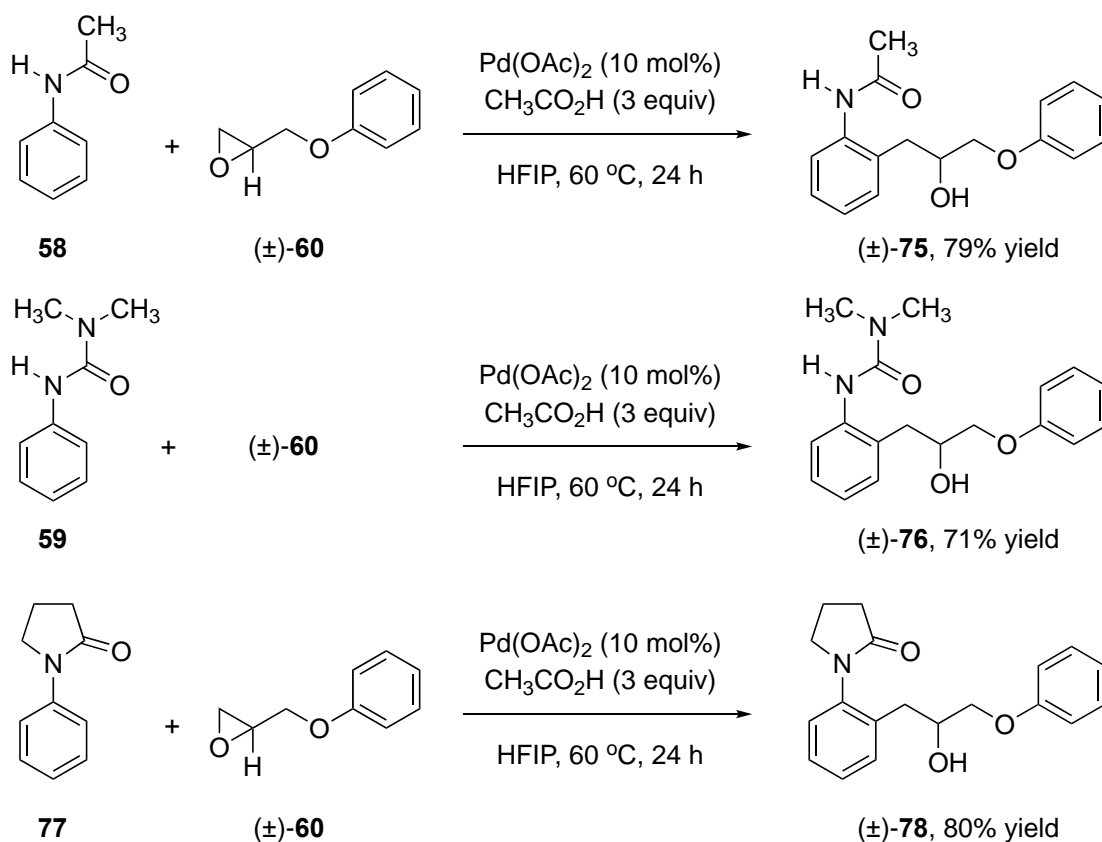
Scheme 8. Pd-catalyzed C-H functionalization using a carboxylic acid directing group, with regioselective epoxide alkylation

The Li laboratory optimized the directed alkylation of *O*-methyl ketoximes with epoxides, using HFIP and a carboxylic acid co-solvent. Pivalic acid gave much better yields than acetic acid. Neither HFIP nor pivalic acid alone were suitable solvents. The bicyclic substrate **73** with phenyl glycidyl ether (**60**, Scheme 9) afforded alcohol **74**.⁵⁹



Scheme 9. Pd-catalyzed C-H functionalization with an *O*-methyl ketoxime directing group, promoting regioselective epoxide alkylation

In 2020, the Cheong and Lee laboratories collaboratively published the corresponding directed alkylations with equimolar amounts of epoxides, using *N*-acyl aniline derivatives as the directing groups, including acetanilide (**58**), the corresponding *N,N*-dimethylurea **59**, and 1-phenylpyrrolidin-2-one (**77**) (Scheme 10).⁶⁰ Notably, the Lewis basic oxygens of the directing groups were one atom further removed from the benzene carbon undergoing C-H functionalization, yet the optimized conditions were similar to those reported for most of the other directing groups.

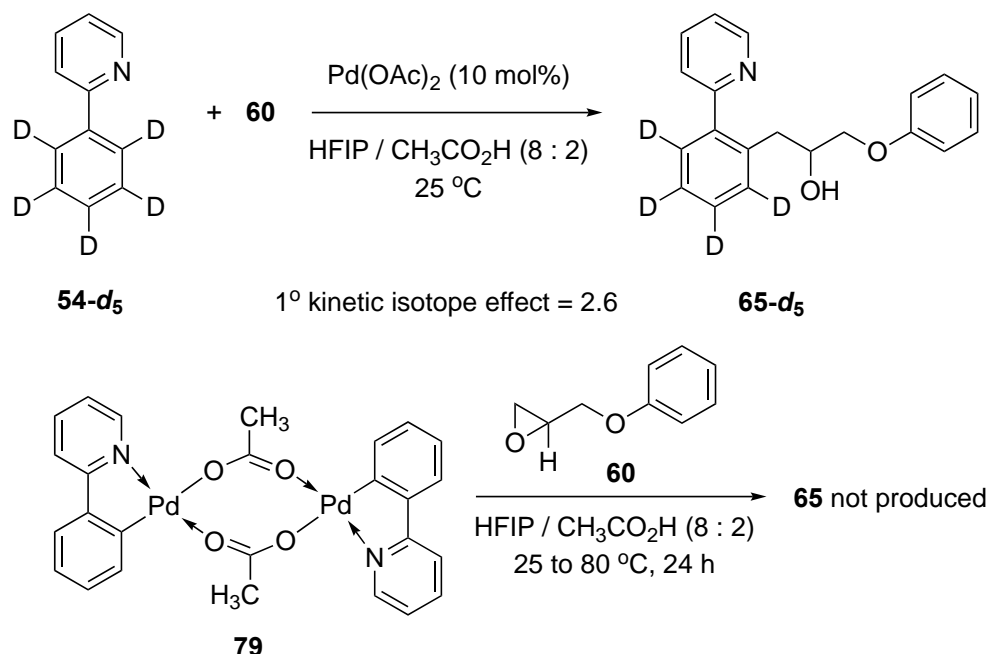


Scheme 10. Pd-catalyzed C-H functionalization with *N*-acyl directing groups, with regioselective epoxide alkylation

3.2. Mechanistic proposals

Wang, Kuninobu, and Kanai reported the relative rates of reaction of 2-phenylpyridine (**54**) vs. **54-*d*₅** with phenyl glycidyl ether (**60**), measuring a primary kinetic isotope effect $k_{\text{H}} / k_{\text{D}} = 2.6$, indicating that the rate-

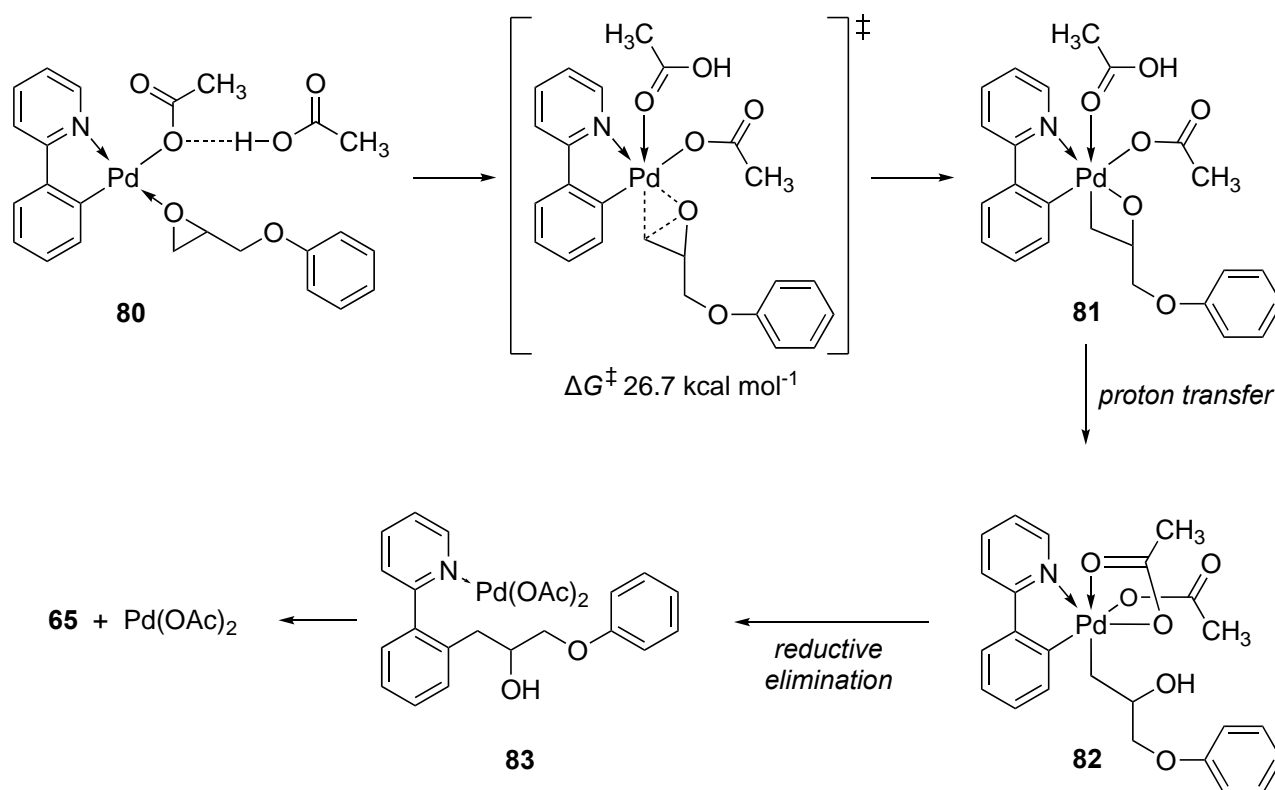
determining step was C-H bond activation (Scheme 11).⁵⁷ These scientists prepared a plausible dimeric palladacycle intermediate **79**, but this palladacycle did not promote the ring-opening reaction with epoxide **60**. They speculated that oxidation to Pd(IV) might be required for alkylation of epoxides.



Scheme 11. Kinetic isotope rate study and a stoichiometric experiment with palladacycle **79** from 2-phenylpyridine (**54**)

The Fang laboratory explored these results via density functional theory (DFT) studies.⁶¹ These scientists found that the lower energy pathway involved coordination of epoxide to a *mononuclear* palladacycle to form intermediate **80**, followed by oxidative addition of the coordinated epoxide to Pd(IV) metalloxetane **81** (Figure 7, part a). The catalytic cycle concluded with proton transfer to form intermediate **82**, followed by reductive elimination to yield the palladium complex with the directing group **83**. In contrast, mechanisms involving only Pd(II) intermediates (Figure 7, part b) required much higher energy barriers for ring-opening coupled with carbon-carbon bond-formation. The theoretical study did not consider the effects of fluorinated solvent on the C-H functionalization stage (not shown) to form intermediate **80**, or on the epoxide reaction stage.

a) via Pd(IV) intermediate **81**:



b) redox-neutral pathway via Pd(II) intermediate **80:**

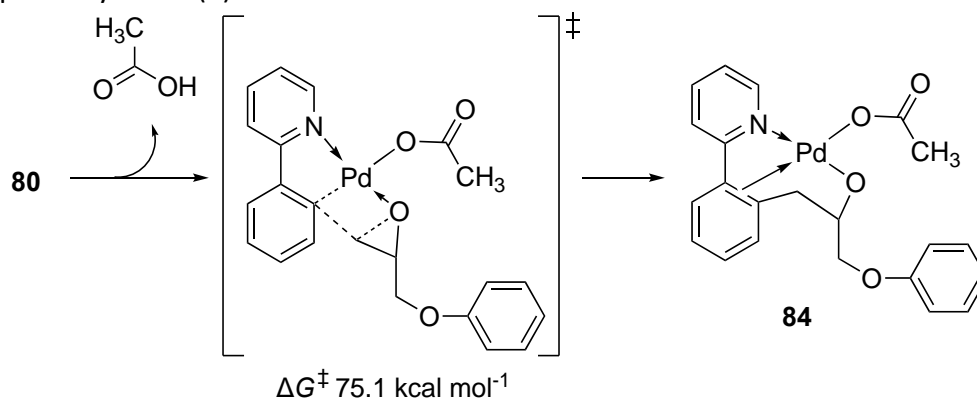
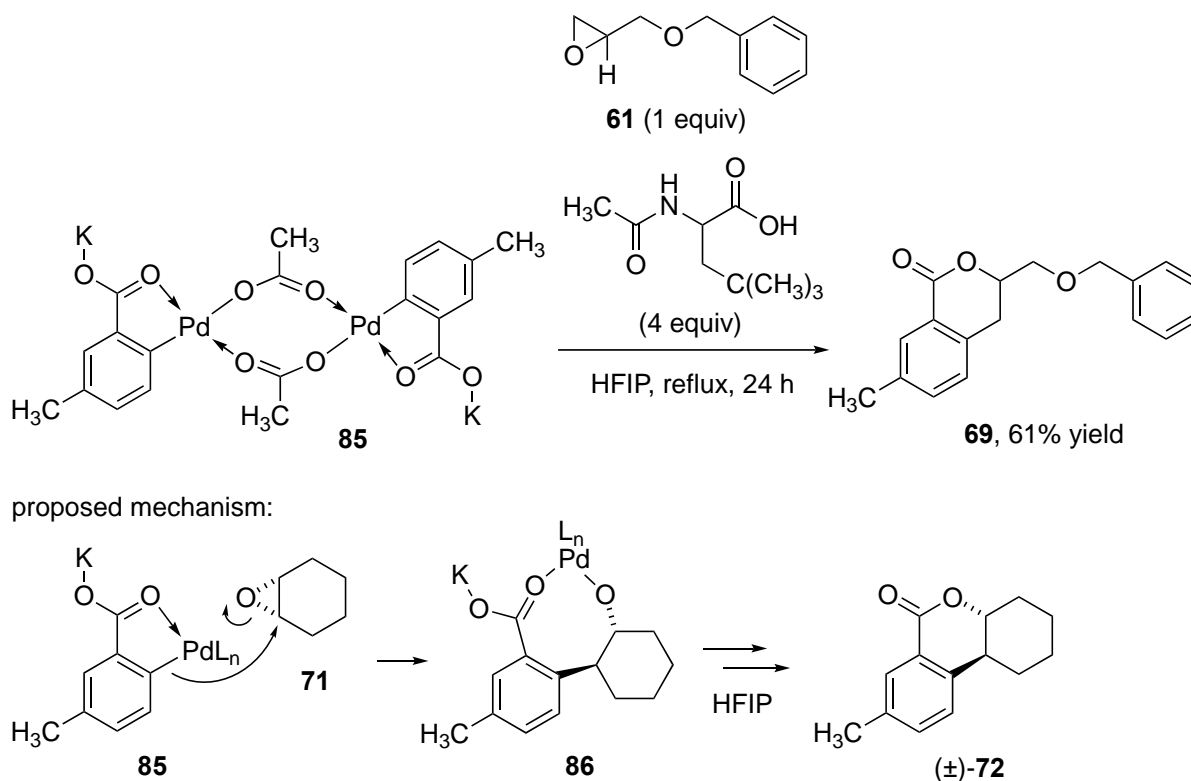


Figure 7. Partial catalytic cycles involving 2-phenylpyridine alkylation, with a Pd(IV) intermediate (path a) vs. redox-neutral pathway (path b). Determined at the B2PLYP/DGDZVP level of theory, in acetic acid ($\epsilon = 6.25$).

In contrast, the Yu laboratory conducted a stoichiometric experiment with *meta*-toluic acid-derived palladacycle **85**, which reacted with benzyl glycidyl ether (**61**) to produce the same compound **69** arising from catalytic conditions (Scheme 12). Moreover, the *trans*-stereochemistry of **72** arising from the reaction with cyclohexene oxide (**71**) suggested that the arylpalladium intermediate **85** reacted with inversion of configuration at the reactive carbon from the epoxide, without requiring a change in oxidation state from Pd(II).⁵⁸



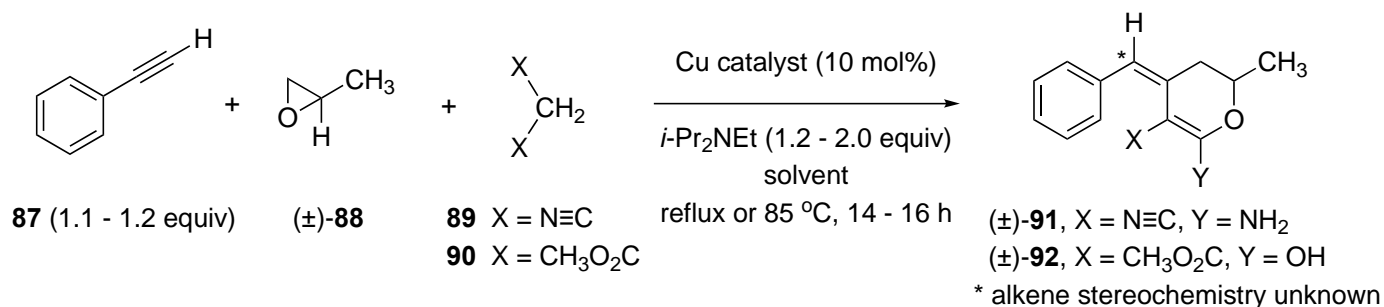
Scheme 12. A stoichiometric experiment with palladacycle **85** from *meta*-toluic acid, and a mechanistic proposal based on the stereochemistry of **72**

In summary, we note that the carboxylic acid readily forms the *anionic* carboxylate under the reaction conditions. This makes the attached aryl ligand in Pd(II) complex **85** more nucleophilic for alkylation with epoxides. *Neutral* directing groups may uniquely require a mechanism involving Pd(IV) for epoxide alkylations.

4. Ring-opening Reactions with Terminal Alkyne Nucleophiles

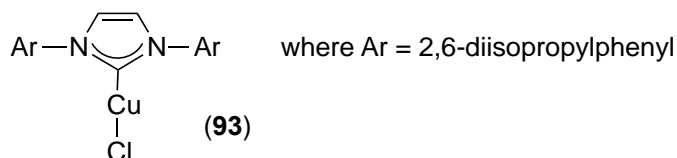
A pair of collaborative studies from the laboratories of Sedaghat and Khalaj have described three-component coupling / cyclization methods, combining terminal alkynes, epoxides, and the active methylene compounds malononitrile (**89**) or dimethyl malonate (**90**) (Table 10).^{62,63} Several Cu(I) catalysts gave good to excellent yields of highly functionalized pyrans **91** or **92**, corresponding to the active methylene reactant. In all cases, the best yields arose with HFIP as solvent, although satisfactory results were also reported with polyethylene glycol 400 (PEG 400, entries 5, 13). Both solvents can activate the electrophilic epoxide by hydrogen bonding with the epoxide oxygen, however, these workers did not propose a role for HFIP in alkyne activation. The non-nucleophilic nature of HFIP apparently prevented the competing addition of solvent to the epoxide, *even in the presence of tertiary amine*. The stereochemistry of the trisubstituted alkenes of **91** - **92** was not established in all cases, although the ¹H and ¹³C NMR data suggested that isolated products may correspond to only one alkene stereoisomer.

Table 10. Three-component reactions of phenylacetylene with propylene oxide and active methylene compounds



entry	reactant	Cu catalyst	solvent	product	yield (%)
1	89	Cu ₂ O	HFIP	91	85
2	89	Cu ₂ O	acetonitrile	91	21
3	89	Cu ₂ O	dimethylformamide	91	26
4	89	Cu ₂ O	PEG-200	91	40
5	89	Cu ₂ O	PEG-400	91	70
6	89	CuI	HFIP	91	80
7	89	CuOSO ₂ CF ₃	HFIP	91	80
8	89	(IPr)CuCl (92) ^a	HFIP	91	68
9	90	Cu ₂ O	HFIP	92	52
10	90	CuI	HFIP	92	61
11	90	CuOSO ₂ CF ₃	HFIP	92	65
12	90	(IPr)CuCl (93) ^a	HFIP	92	80
13	90	(IPr)CuCl	PEG-400	92	51

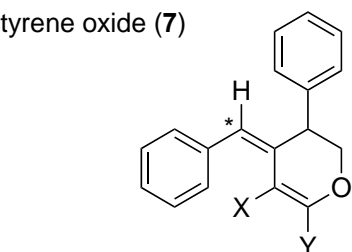
^a (IPr)CuCl is [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) chloride



This transformation shows relatively broad scope beyond phenylacetylene (**87**) and propylene oxide (**88**):

- trimethylsilylacetylene and 1-hexyne are reactive nucleophiles;
- the opposite regioselectivity is observed for styrene oxide (**7**), giving dihydropyrans **94** - **95**; and
- cyclohexene oxide (**71**) is a reactive electrophile, giving bicyclic dihydropyrans **96** - **97** (Figure 8).

a) from styrene oxide (7)

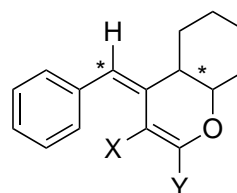


(±)-**94**, X = N≡C, Y = NH₂ (90% yield)

(±)-**95**, X = CH₃O₂C, Y = OH (81% yield)

* alkene and relative stereochemistry unknown

b) from cyclohexene oxide (71)



(±)-**96**, X = N≡C, Y = NH₂ (95% yield)

(±)-**97**, X = CH₃O₂C, Y = OH (96% yield)

Figure 8. Scope of product dihydropyrans arising from epoxide substrates **7** and **71**.

Experiments that generated the alkynyl alcohol intermediate **98**, and related experiments that converted 4-phenylbut-3-yn-1-ol (**99**) into dihydropyran **101** provide some mechanistic hints (Figure 9).⁶³

- a) The combination of phenylacetylene (**87**), propylene oxide (**88**), and dimethyl malonate (**90**) in the presence of (IPr)CuCl and refluxing HFIP, *without added base*, afforded a good yield of the alkynyl alcohol product **98**.
- This suggests that HFIP promoted the copper-promoted formation of a copper acetylide intermediate, which has added to a hydrogen bonded-complex of epoxide with HFIP, giving **98**.
- b) The combination of 4-phenylbut-3-yn-1-ol (**99**) and dimethyl malonate **90** catalyzed by (IPr)CuCl *in the absence of base* and *in the polar aprotic solvent N,N-dimethylformamide (DMF)* gave the malonate addition product **100**, albeit in modest yield. The catalytic loading of (IPr)CuCl was not specified in this experiment.
- The (IPr)CuCl catalyst may have deprotonated malonate (the imidazolium cation has pK_a 21.1)⁶⁴ and promoted regioselective malonate addition to the alkyne, giving **100**, in a step that did not require HFIP.
- c) The combination of alkynyl alcohol **99** and dimethyl malonate (**90**) catalyzed by (IPr)CuCl *in the presence of tertiary amine* and *HFIP* produced the dihydropyran **101** in good yield.
- HFIP alone may have promoted the final intramolecular transacylation and tautomerization; the role of the tertiary amine in this scenario was unclear.

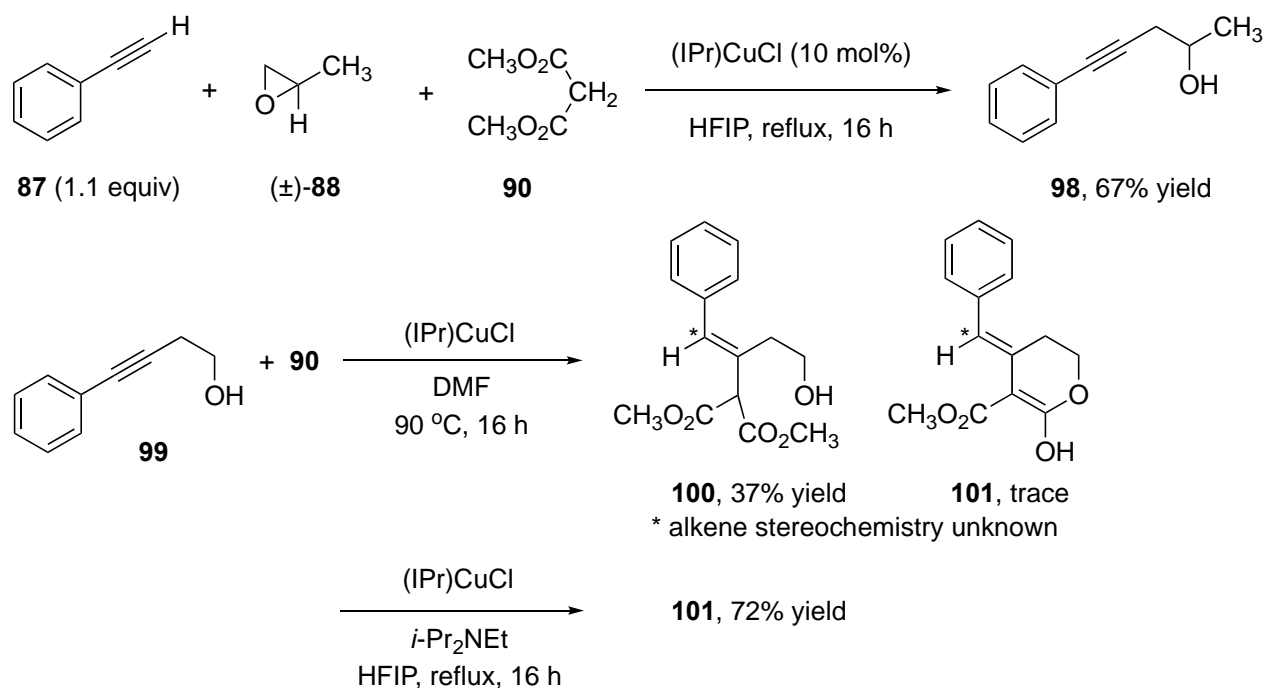
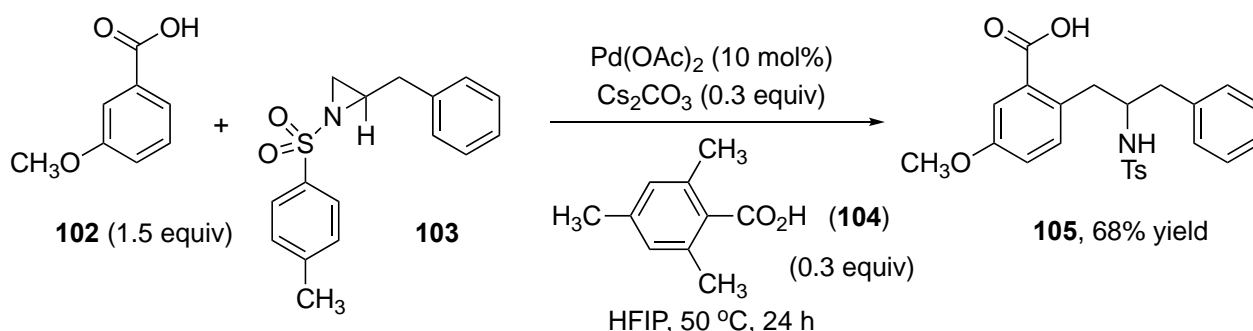


Figure 9. Individual steps via alkynyl alcohols **98** and **99**

In summary, the combination of moderately acidic HFIP solvent with basic tertiary alkylamine *without solvent addition to the epoxide* is quite interesting, as similar conditions promote hexafluoroisopropoxide nucleophilic addition to phosgene and thionyl chloride electrophiles.^{65,66} This work merits additional investigation and optimization, particularly the direct addition of alkyne to epoxide *in the absence of an active methylene compound*.

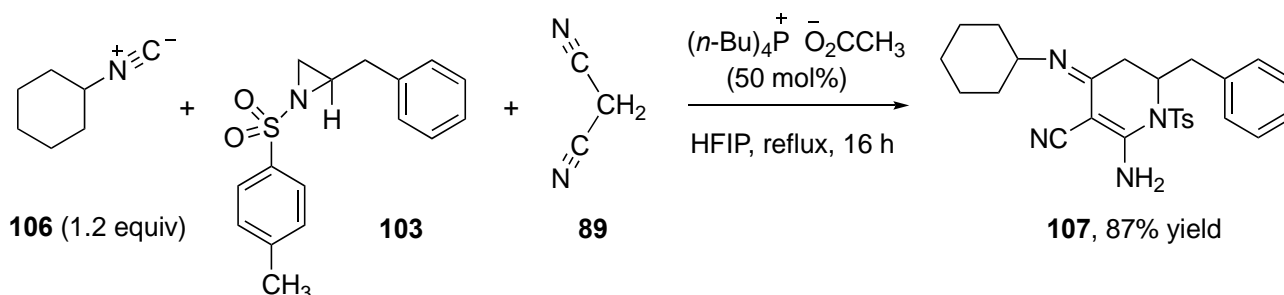
5. Ring-opening Reactions of Aziridines with Carbon Nucleophiles in Fluorinated Solvents

This review concludes with extensions of two approaches described earlier in this review, applied to aziridine electrophiles, promoted by HFIP. In 2019, the Zhao laboratory reported palladium-catalyzed C-H functionalization of 3-methoxybenzoic acid (**102**) and other arylcarboxylic acids, reacting with a relatively broad range of *N*-tosylaziridines including monosubstituted **103**, producing the protected *beta*-arylethylamine **105**, an important substructure in medicinal chemistry (Scheme 13).⁶⁷ The principal competing process was ring-opening of aziridine with the carboxylic acid, which was suppressed by diminishing the cesium carbonate loading to substoichiometric amounts. The conversion increased with 2,4,6-trimethylbenzoic acid (**104**) as a substoichiometric additive. A solvent screen revealed that a protic alcohol solvent was required, with HFIP giving the best yields.



Scheme 13. Palladium-catalyzed C-H functionalization of an arylcarboxylic acid with addition to an *N*-tosylaziridine, promoted by HFIP.

In 2019, Samzadeh-Kermani described an organocatalytic synthesis of tetrahydropyridone imines, including compound **107** (Scheme 14).⁶⁸ The carbon nucleophile was an aryl or alkyl isonitrile, with cyclohexyl isonitrile (**106**) as a representative case. Several Lewis acids gave competing isomerization of monosubstituted aziridine **103** to a *N*-tosylimine, but tetrabutylphosphonium acetate in refluxing HFIP promoted aziridine ring-opening with nucleophilic addition of the isonitrile. The base for deprotonating malononitrile (**89**) may have been the anionic *N*-tosylamide from ring opening, or the acetate counteranion. Nucleophilic addition of dinitrile-stabilized carbanion to the alkyl nitrilium cation from the initial isonitrile addition step explains the remaining carbon-carbon bond-forming step. The author proposed that the tetrabutylphosphonium cation may coordinate with one of the nitriles to promote intramolecular nucleophilic addition of the tosylamide to close the tetrahydropyridine ring.



Scheme 14. Three-component coupling of an isonitrile, an *N*-tosylaziridine, and malononitrile (**89**) to form tetrahydropyridone imines, promoted by tetrabutylphosphonium acetate in HFIP

6. Conclusions

This review describes the benefits of fluorinated alcohol solvents in promoting the ring-opening reactions of epoxides and aziridines with carbon nucleophiles. The advances presented herein fall into two categories:

- **significant electrophilic activation, due to the formation of complex structures and aggregations**, such as the formation of an activating HFIP complex with epoxides, thereby allowing reactions with weak and neutral nucleophiles; and
- **safety and environmental benefits**, especially where fluorinated alcohol solvents replace Lewis acid reagents, and even more so when the solvent is recycled.

We anticipate that other researchers will find that fluorinated alcohol solvents enable other synthetically valuable transformations that have not been previously developed. The role of these solvents in activating C-H bonds is not well-established, warranting further investigation to increase our understanding of fluorinated alcohol solvents. Additionally, there is clearly room for significant future work in aziridine ring-opening reactions in fluorinated alcohols, an area with potential for synthesizing pharmaceutical substances.

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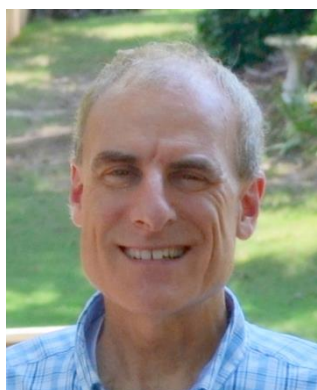
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Authors' Biographies



Taylor Dover joined the McDonald laboratory as an undergraduate researcher in January 2019, where he worked on developing strategies for the enantioselective synthesis of an important chiral precursor to a neuroprotectant therapeutic. While working remotely during the COVID-19 pandemic, Dover drafted this review to prepare for an experimental project on catalytic alkyne-epoxide couplings. Dover will receive his B.S. in Chemistry with a minor in Mathematics from Emory University in May 2021, after which he will pursue graduate study in Chemistry. Dover has accumulated several accolades at Emory, including the Barry M. Goldwater Scholarship (2020) and induction into the Phi Beta Kappa Society (2020).



Frank McDonald completed his B.S. degree at Texas A&M University and the Ph.D. degree at Stanford University with Prof. Paul Wender. After an American Cancer Society postdoctoral fellowship at Yale University with Prof. Samuel Danishefsky, he was assistant professor at Northwestern University, rising to the rank of associate professor, before moving to Emory University in 1998, where he is currently Professor of Chemistry. Awards and honors include the Alfred P. Sloan Research Fellowship (1995), the National Science Foundation CAREER Award (1995), Camille Dreyfus Teacher-Scholar Award (1997), Japan Society for the Promotion of Science Fellowship (2005), and the Emory Williams Distinguished Teaching Award (2008).

