# Epoxide Migration (Payne Rearrangement) and Related Reactions

Robert M. Hanson, St. Olaf College, Northfield, Minnesota

1. Introduction

Under a variety of basic conditions 2,3-epoxy alcohols rearrange with inversion at C-2 (Eq. 1). The reaction, originally referred to in the literature as the β-*oxanol rearrangement*, (1) is now exclusively referred to as *epoxide migration* (2) or *Payne rearrangement*. (3, 4)

(1)
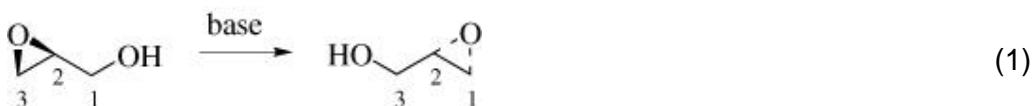
Epoxide migration is reversible, often leading to a mixture of epoxy alcohol isomers. Furthermore, in the presence of hydroxide or other nucleophiles, in situ opening of the equilibrating species may be observed (Scheme I). When such opening is desired, epoxide migration becomes a powerful method for the introduction of functionality into a substrate containing a 2,3-epoxy alcohol moiety. However, when opening is not desired, epoxide migration can become a significant problem.

Scheme I.
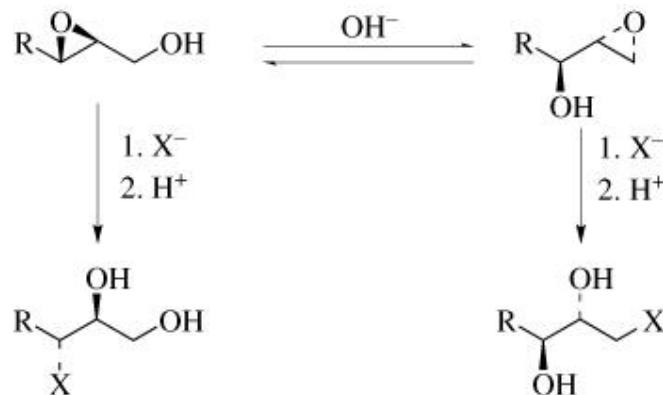
The epoxide migration process lends itself to other synthetically useful manipulations. For example, the anionic equilibrating species may also be

trapped with electrophiles such as alkyl and silyl halides, alkyl sulfonates, and epoxides (Scheme II). Electrophilic trapping may be inter- or intramolecular, and has been used as a means of delivering functionality to either C-2 or C-3 selectively.

Scheme II.
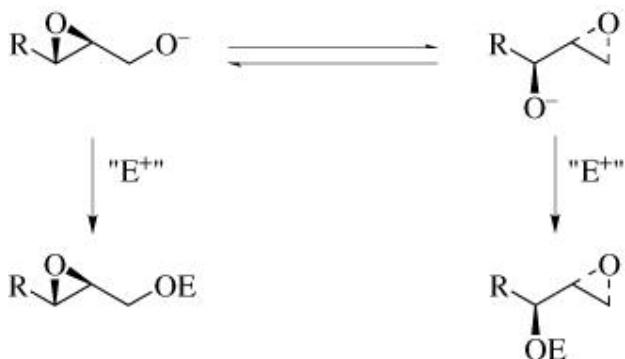
The intent of this chapter is to provide a comprehensive review of epoxide migration, including factors influencing the equilibrium position, conditions leading to in situ epoxide opening, and examples of electrophilic trapping. The reaction is discussed in relation to its utility as a synthetic method as well as its prevention as an unwanted side reaction.

Related rearrangements in which either the epoxide or hydroxy oxygen has been replaced with nitrogen or sulfur have also been studied (Eq. 2). These reactions, referred to in the literature as aza-Payne and thia-Payne rearrangements, respectively, are comprehensively included in this chapter as well. For the purposes of this discussion, the term "forward" aza-Payne rearrangement refers to the direction of reaction leading from oxirane to aziridine. Similarly, "forward" thia-Payne rearrangement refers to the direction of reaction leading from oxirane to thiirane. In the case of aza-Payne rearrangements, both forward and reverse reactions have been effected, and in this chapter the term "reverse" aza-Payne rearrangement refers to reactions leading from aziridine to oxirane.

O—X¹ $\xrightarrow{\text{"forward"}}$ $\xleftarrow{\text{"reverse"}}$ HO—X²

(2)
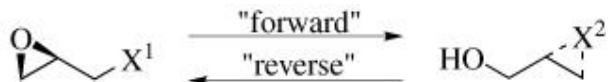
| X¹	X²	Direction
NH_2	NH	forward
NHR	NR	forward
NHBoc	NBoc	forward
NR_2	NR_2^+	both
NHMs, NHTs	NMs, NTs	both
SAc	S	forward
SR	SR^+	forward
SPh	SPh^+	forward

Epoxides have long been considered important in the chemistry of carbohydrates, and epoxide migration in the context of carbohydrate chemistry has been discussed in several reviews. [5-14] In addition, particularly since discovery of the catalytic asymmetric epoxidation of allylic alcohols [15] and the rise in importance of enantiomerically enriched acyclic epoxy alcohols, epoxide migration with in situ opening in acyclic systems has been much studied. A recent chapter of *Organic Reactions* discusses epoxide migration with in situ opening in the context of asymmetric epoxidation. [16] Two reviews of the stereoselectivity and regioselectivity observed for the opening of selected acyclic epoxy alcohols derived from asymmetric epoxidation are also available. [4, 17] Reviews relating specifically to aza-Payne rearrangements [18-20] and thia-Payne rearrangements [18, 21] have been published. However, to date there is no comprehensive review of epoxide migration, aza-Payne rearrangements, or thia-Payne rearrangements. The tabular survey summarizes the literature of epoxide migration and related reactions, including equilibration, in situ opening and trapping, aza-Payne rearrangements, and thia-Payne rearrangements, from 1931 to 1999. Reports referring to reactions involving addition at C-1 or C-3 without inversion of stereochemistry at C-2 as "Payne rearrangements" are not covered in this review. [22, 23]

2. Mechanism and Stereochemistry

2.1. Epoxide Migration
2.1.1. Proposed Mechanism
The vast majority of epoxide migrations have been carried out in the presence of strong base in protic (usually aqueous) media. The accepted mechanism of epoxide migration under these conditions, first proposed by Angyal and Gilham in 1957, (2) involves deprotonation of the epoxy alcohol to form an alkoxide followed by direct intramolecular displacement at the adjacent epoxide center. An isomeric alkoxide with inverted stereochemistry is produced (Eq. 3). Reprotonation of this alkoxide by solvent completes the reaction.

$$(3)$$
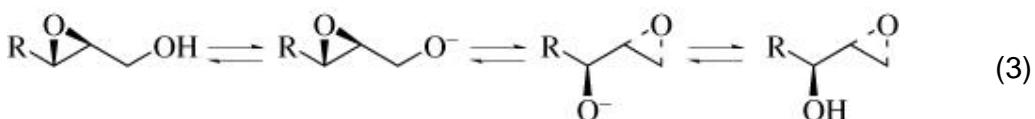
However, the mechanism of epoxide migration is almost certainly not this simple. In particular, the migration itself seems to depend strongly upon solvent, as the example in Eq. 4 indicates. In tetrahydrofuran using sodium hydride to deprotonate the alcohol, there is no evidence of reaction even after refluxing for 2 hours. In aqueous medium using sodium hydroxide as the base, the migration is complete within 1 hour at room temperature. (24) Thus, although epoxide migration requires deprotonation, deprotonation in and of itself does not necessarily lead to epoxide migration. Similarly, reaction of epoxide **1** with sodium hydride in tetrahydrofuran for 1.5 hours at 10° returned only starting material.


$$(4)$$
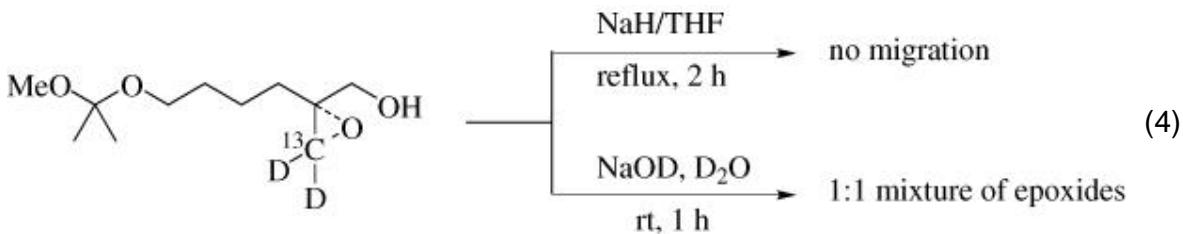
It is important to realize that equilibration under protic conditions involves the

protonated epoxy alcohols, while equilibration under aprotic conditions using an irreversible base such as sodium hydride does not. It has been suggested that under aprotic conditions, association of the metal cation with the initial alkoxide prevents further isomerization. (3) Nonetheless, numerous examples of epoxide migration under aprotic conditions do exist. (25, 26) No mechanistic or theoretical studies have addressed the issue of solvent or counterion effect in epoxide migration.

### 2.1.2. Thermodynamic vs. Kinetic Control

Theoretical calculations at the G2 level suggest that all epoxide migrations are technically the result of kinetic rather than thermodynamic control. (27, 28) Thus, as depicted in Figure I, for the anion of 2,3-epoxypropanol in the gas phase, the lowest energy isomer is not an epoxide at all. Rather, it is oxetane **2**. (28) In a mass spectrometer there is enough energy to effect an equilibration among all three of these species. (28) In solution there is far less energy available, and the oxetane isomer has never been observed in the solution-phase product mixture of epoxide migration. Thus, in solution, epoxide migration per se may be considered to be under local thermodynamic control.

Figure I.
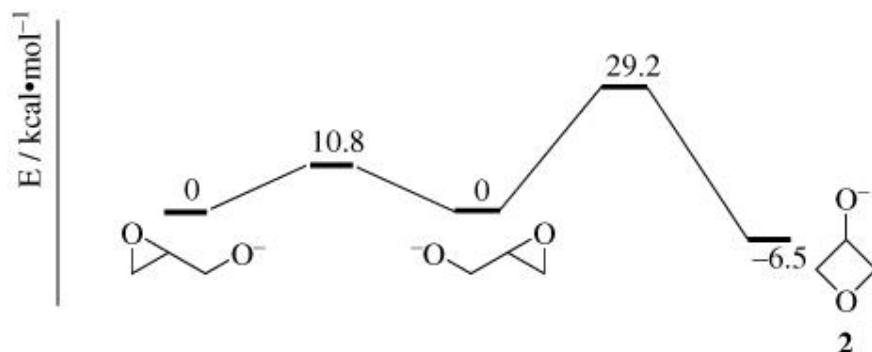
The selectivity of opening of equilibrating epoxy alcohols is governed by the Curtin-Hammett principle. (29) Thus, while two equilibrating epoxy alcohol isomers may be of similar energy, the product of epoxide migration and opening may not reflect this, because opening is generally a considerably slower process than migration (Figure II). Thus, epoxide migration *with opening* is under kinetic control, with selectivity governed by the slow opening of relatively rapidly equilibrating epoxy alcohol species.

Figure II.

reaction coordinate
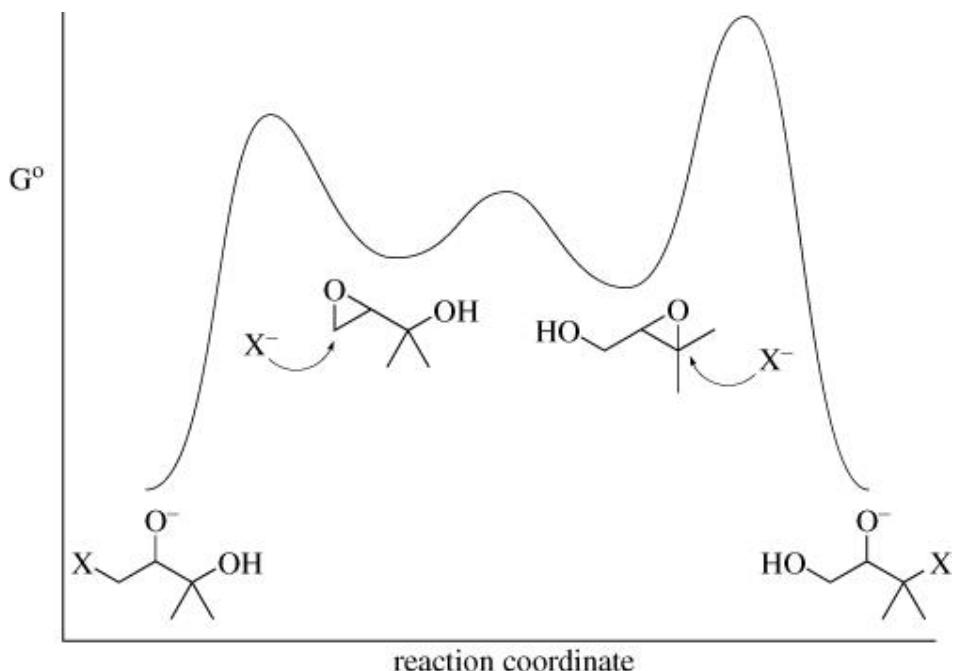
For example, consider Eqs. 5,6, and 7. Treatment of either epoxide **3** (25) or its rearranged isomer **4** (30) with aqueous base leads to a roughly 1:1 ratio of isomers. Thus, these two isomers are of approximately the same free energy. Nonetheless, treatment of epoxide **3** with base in the presence of thiophenol leads to an 81% yield of sulfide **5**, the product of epoxide migration to monosubstituted epoxide **4** followed by selective opening at the less substituted position. (31)

$$3 \xrightarrow[\text{1,4-dioxane, 65°, 3 h}]{\text{PhSH, NaOH, H}_2\text{O}} \quad \textbf{5} \quad (81\%) \qquad (7)$$
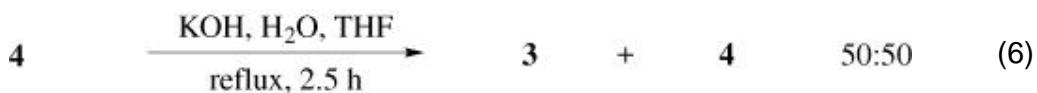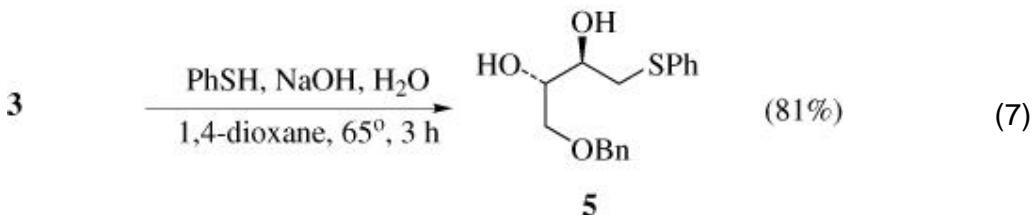
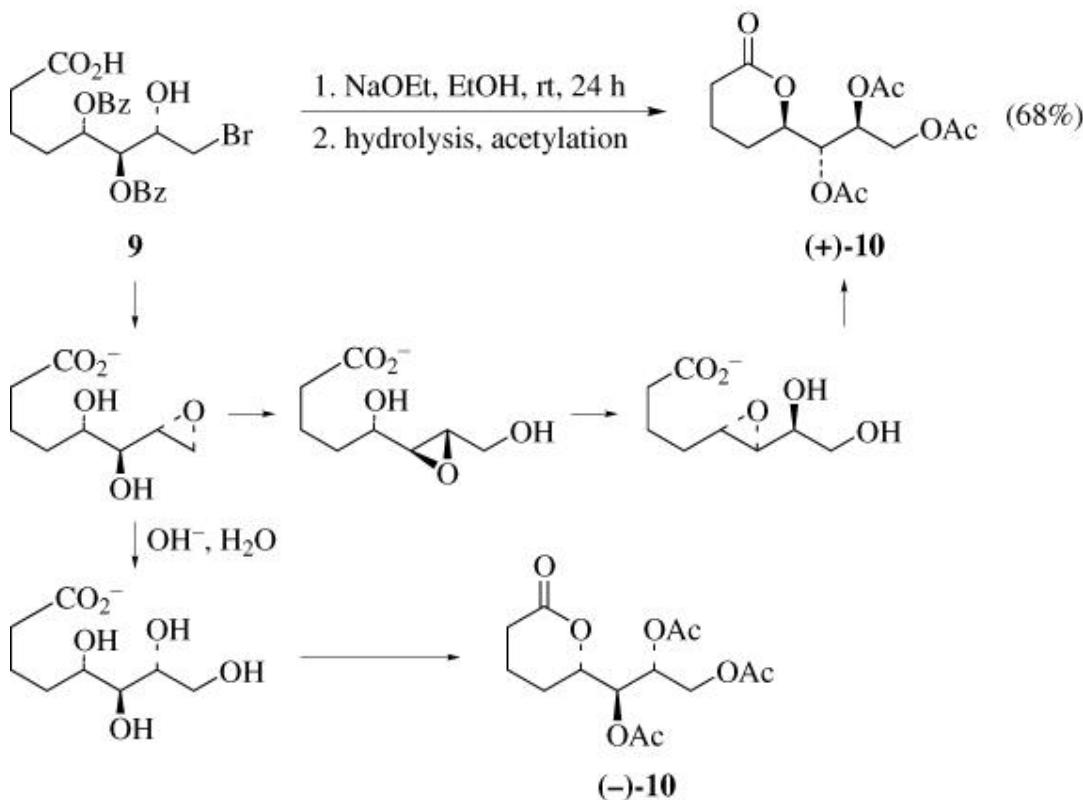### 2.1.3. Stereochemical Considerations

Epoxide migration by definition involves stereochemical inversion at C-2. Extensive work with carbohydrates has demonstrated that multiple epoxide migrations may occur for substrates with more than one hydroxy group, leading to multiple stereochemical inversions. For example, treatment of lactone **6** (Scheme III) with aqueous potassium hydroxide for 5 minutes results in the quantitative formation of epoxide **7**, the product of bromide displacement and one epoxide migration. (32) However, with prolonged exposure to hydroxide, this product is completely converted into tetraol **8**, the product of a second epoxide migration (to give a *cis*-disubstituted epoxide), intramolecular opening of the epoxide by the carboxylate to form a lactone, and hydrolysis. Note that all three stereocenters in the substrate have been inverted.

Scheme III.
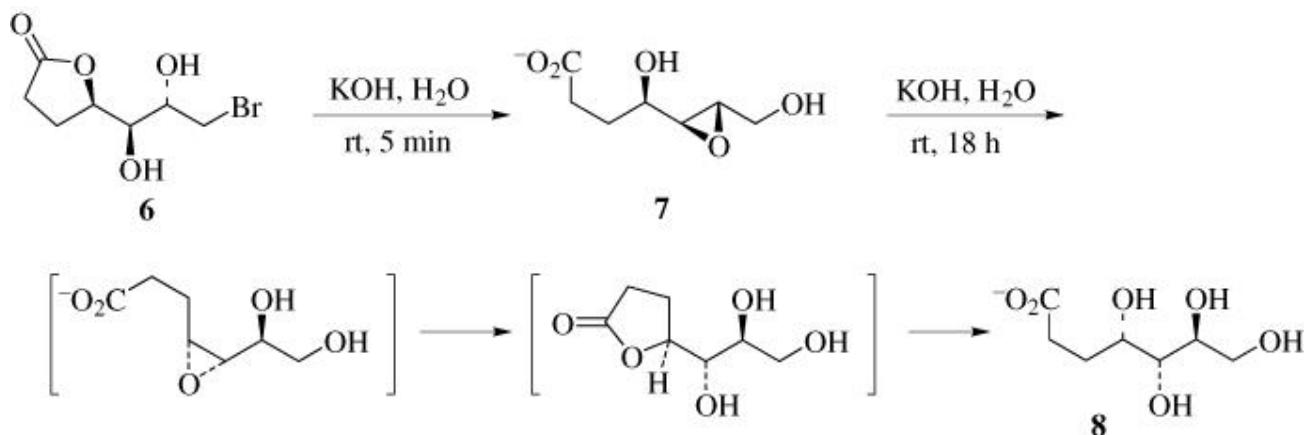
A closely related study involved the conversion of carboxylic acid **9** into lactone **10** (Scheme IV). (33) In this and related cases (34) it was found that the solvent has to be scrupulously anhydrous for effective epoxide migration. If it is not, then direct reaction of the initially formed terminal epoxide with hydroxide ion competes with epoxide migration. In that case, no stereocenters are inverted, and the competitive pathway leads to a decrease in enantiomeric excess.

Scheme IV.

9 → **(+)-10** (68%)

Reagents: 1. NaOEt, EtOH, rt, 24 h; 2. hydrolysis, acetylation

OH⁻, H₂O → **(−)-10**

In fact, whenever epoxide migrations are effected in the presence of hydroxide, an additional stereochemical concern must be addressed. Specifically, when the stereocenters in the substrate consist solely of the carbons involved in epoxide migration, then, as illustrated in Scheme V, opening with and without epoxide migration may lead to full or partial racemization. (35) (Scheme V is a generalization of the case in Scheme I when X = OH.)

Scheme V.
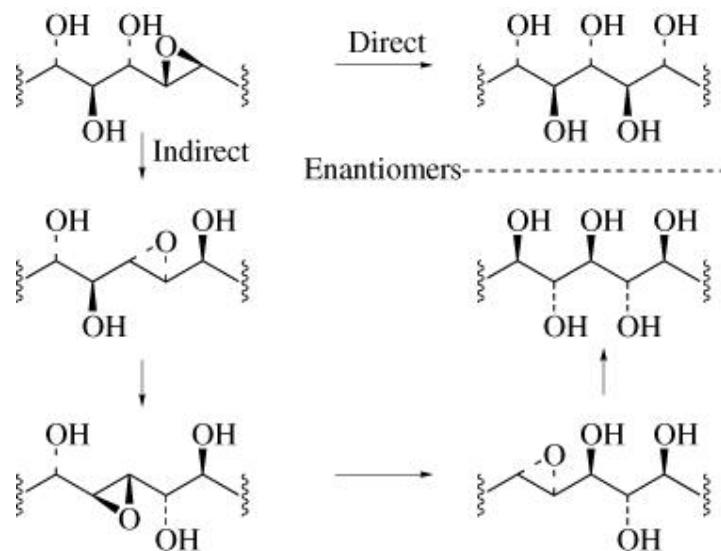
As a further example, consider epoxy alcohol **11** (Scheme VI). Treatment with potassium hydroxide in aqueous dioxane produces a roughly 6:1 mixture of enantiomers. (36, 37) The major isomer in this case is the result of epoxide migration, while the minor isomer is the result of direct addition of hydroxide at the terminal carbon. However, mild acid treatment results in direct opening at the terminal position without migration, preserving the high enantiomeric purity of the substrate.

Scheme VI.
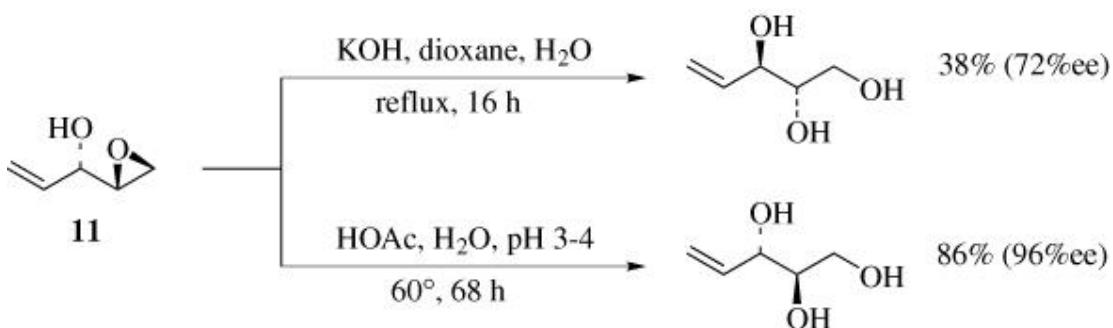
In the special case of pseudo-symmetrical epoxy alcohols with only one stereocenter (necessarily at C-2), nucleophilic opening both with and without epoxide migration gives the same product (Scheme VII). This special degeneracy has been exploited in syntheses involving glycidol (R = H). (38, 39)

Scheme VII.
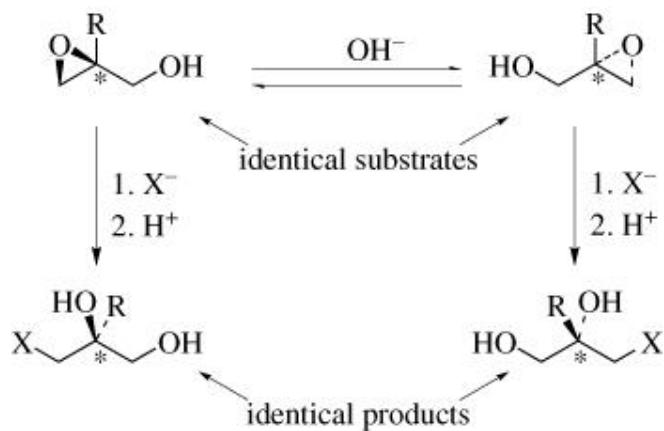
The regioselectivity of in situ epoxide formation can also play an important role in dictating the stereochemical outcome of epoxide migration. (14, 40) For example, treatment of bromodiol **12** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gives the cis-disubstituted epoxy alcohol **13** exclusively (Scheme VIII).

(41) Had the primary alcohol displaced the bromide, the outcome would have been completely different. Note that DBU is not effecting epoxide migration itself. Indeed, the observed product is only slightly favored at equilibrium relative to its rearranged counterpart. (3, 42) Such kinetic selectivity for disubstituted over primary epoxide formation prior to epoxide migration is well documented in the carbohydrate literature. (43-45)

Scheme VIII.
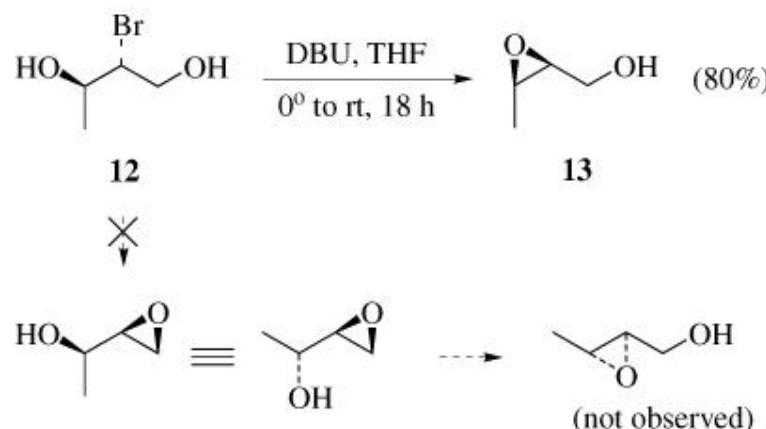
2.1.4. Epoxide Migration Under Nonbasic Conditions

Despite the fact that complex mechanisms involving "epoxide migration" under acidic conditions have occasionally been proposed, (46-52) work with carbohydrates has demonstrated conclusively that epoxide migration under acidic conditions is not generally observed. (53, 54) However, a recent report of epoxide migration under nonbasic conditions involves treatment of *meso* diol **14** with 1–2 mol% of the chiral cobalt(III) complex (*R,R*)-**15** (Eq. 8) to give 1,2-diol **16** in high yield and enantiomeric purity. (55) This result suggests that catalytic kinetic resolution of epoxy alcohols might be effected with chiral epoxide migration catalysts.

(8)
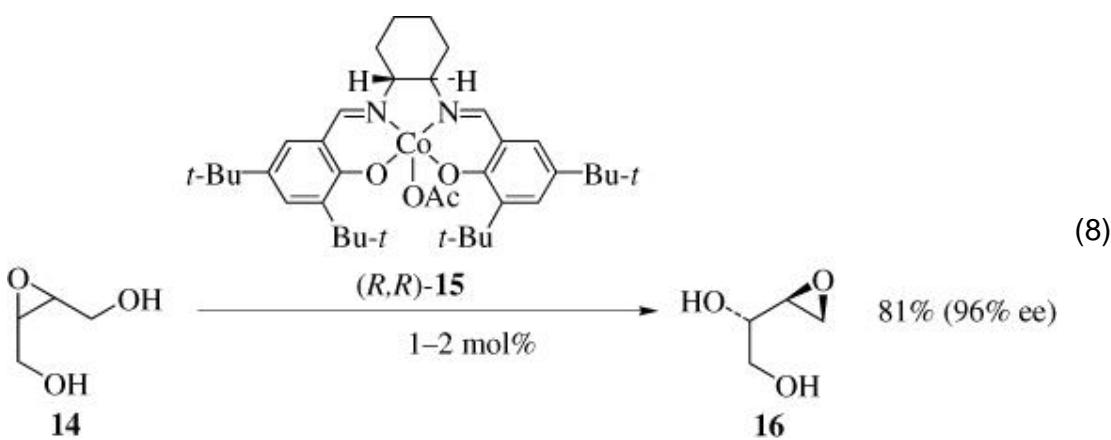
2.1.5. Nucleophilic Trapping in Situ

Many examples of in situ nucleophilic trapping of epoxide migration products have been reported, and many of these are intramolecular, such as illustrated in Schemes III and IV. A related example (Eq. 9) involves treatment of dibromide **17** with aqueous potassium hydroxide. (45) Within 30 minutes at 20°, **17** is converted to bicyclic ether **18** in over 70% yield, presumably via intermediates **19** and **20**. Note that both epoxide openings are favored *exo*-openings. (56) Since all four stereocenters in the substrate take part in the epoxide migration, all end up inverted.

(9)
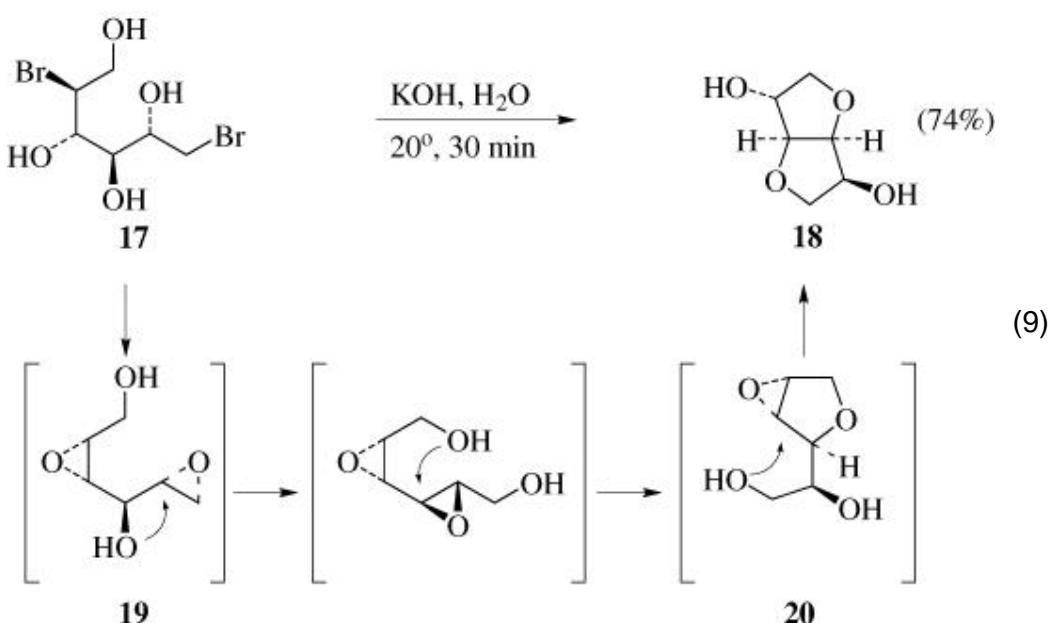
2.1.6. Electrophilic Trapping in Situ

Electrophilic trapping of epoxy alcohols after epoxide migration involves selective reaction of the hydroxy group of one of the equilibrating isomers (Scheme II). Specific reactions are discussed below, in the context of the scope of epoxide migration.

2.2. Aza-Payne Rearrangements

The proposed mechanisms for aza-Payne rearrangements are considerably more varied than those for epoxide migration because of two factors. First, with the added nitrogen atom, there are two distinct directions of reaction—"forward" (toward aziridine) and "reverse" (toward oxirane). Second, variation of the aziridine nitrogen substituent significantly affects the mechanism of the reaction.

Forward and reverse reactions carried out under basic conditions are presumed to follow a pathway analogous to Eq. 3. Forward reactions employing Lewis acids are presumed to be initiated by activation of the oxygen of the oxirane by the Lewis acid followed by aziridine formation.

Theoretical gas-phase calculations (MP2/6-31 + G* single-point energies at RHF/3-21 + G* optimized geometries, Figure III) (57) suggest that for the parent substrate, the aziridine isomer **21** lies approximately 5 kcal/mol in energy above the oxirane **22**. Deprotonation, however, would be expected to favor the aziridine by virtue of the lower energy of oxy anion **23** relative to aza anion **24**.

Figure III.
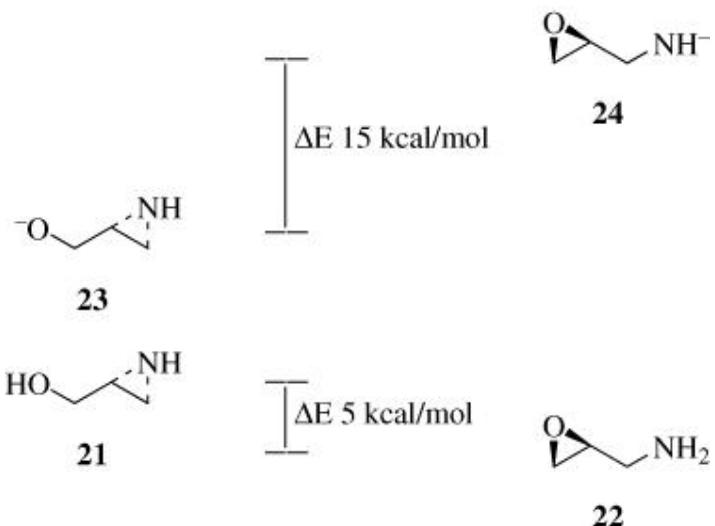
Experimentally it is observed that deprotonation of epoxy amines results in rearrangement to the aziridine. For example, deprotonation of oxirane **25** with *n*-butyllithium/potassium *tert*-butoxide (58) (Eq. 10) gives aziridine **26** in 85% yield after quenching. (57) A number of other bases, including sodium hydride, potassium hydride, and potassium *tert*-butoxide, were ineffective.
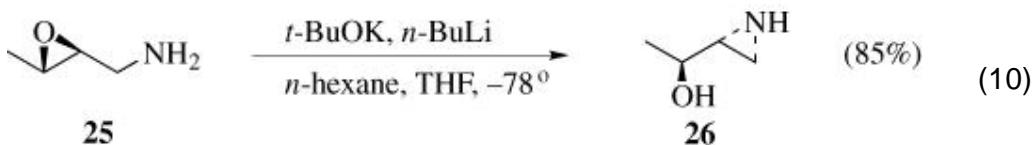
The equilibrium between epoxy amine and aziridine alcohol can also be driven

toward aziridine by complexation with titanium(IV), (59) boron trifluoride, (60) trimethylaluminum, (61) or trimethylsilyl triflate. (62) Examples include oxirane **27** rearranging to aziridine **28** upon treatment with titanium(IV) isopropoxide (Eq. 11), (59) 4-(*tert*-butoxycarbonyl)phenyl-protected ribopyranoside **29** rearranging to aziridine **30** upon treatment with boron trifluoride etherate in trimethylsilyl azide (Eq. 12), (60) and epoxy amine **31** rearranging to aziridine alcohol **32** upon treatment with butyllithium/trimethylaluminum (Eq. 13). (61) No evidence exists that these rearrangements under Lewis acid conditions are reversible equilibria. Rather, it appears that complexation with oxygen drives the reaction to the aziridine isomer. No detailed mechanistic or theoretical work has been done in this area.
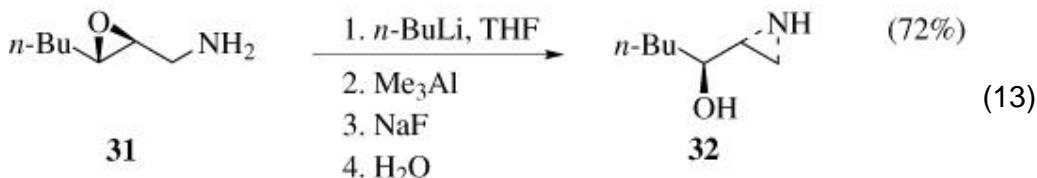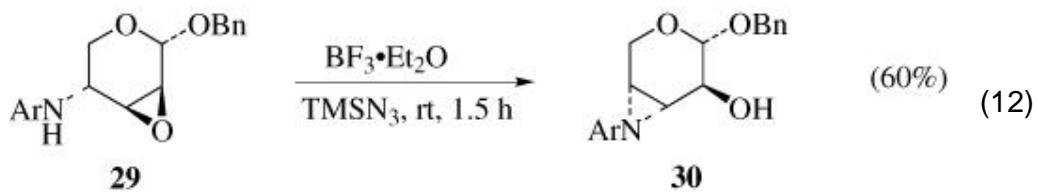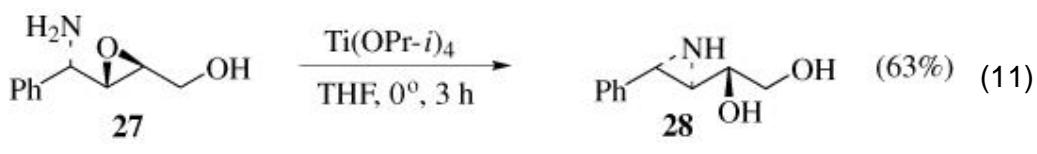

When trimethylsilyl triflate is employed in forward aza-Payne rearrangements of epoxy amines, in situ opening may be effected (Scheme IX). The formation of an aziridinium ion has been observed for the reaction of epoxy amine **33** using ^{1}H NMR spectroscopy. (62) Treatment of aziridinium ion **34** with methanolic K_2CO_3 regenerates epoxide **33**; treatment with a broad variety of amine nucleophiles leads to opening.

If the nitrogen is activated as a sulfonamide, then calculations suggest that the energy picture is considerably different (Figure IV). (57) Once again the more stable neutral species is the epoxide, **35**, rather than the aziridine, **36**.

However, now the more stable anion (at least in the gas phase) is predicted to be aza anion **37** rather than oxy anion **38**.

Figure IV.
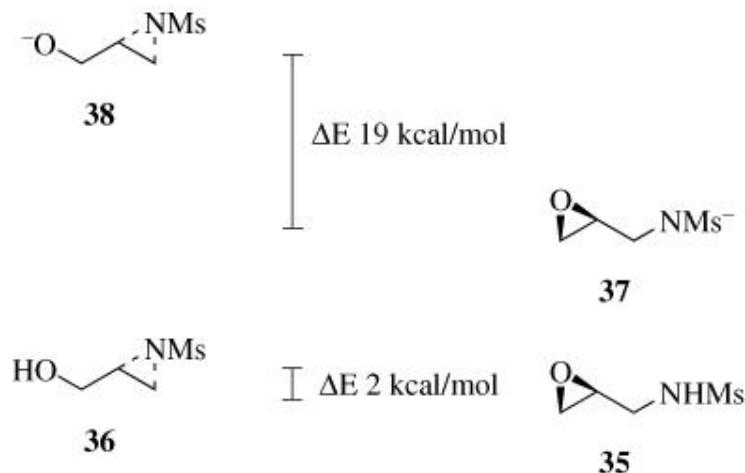
In practice, results for sulfonamides depend strongly upon substrate structure and conditions. In aqueous solution, where deprotonation is reversible, the structure of the substrate critically determines the equilibrium ratio. (57, 63) However, consistent with these calculations, use of irreversible hydride bases such as sodium hydride or potassium hydride in polar aprotic solvents (dichloromethane or tetrahydrofuran/hexamethylphosphoric triamide mixtures) leads to a preponderance of the oxirane. (57, 64)

In selected cases, however, brief treatment with refluxing aqueous sodium hydroxide converts epoxy sulfonamides into the aziridines (Eq. 14). (63) Structural factors are clearly at work here. No rearrangement was seen for primary sulfonamide **39** (Eq. 15); prolonged treatment led to decomposition.


(14)

(15)
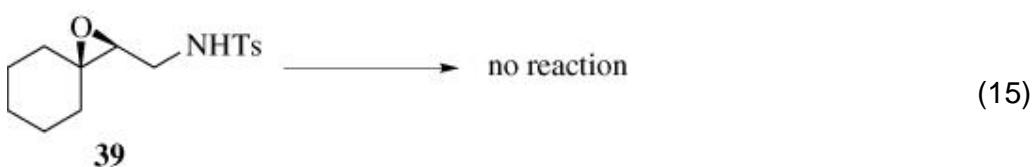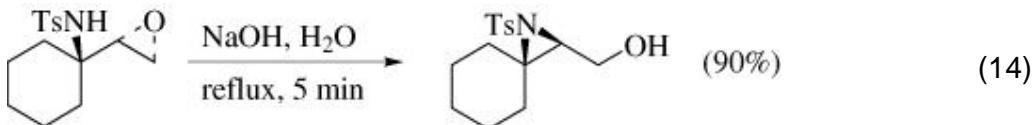
2.3. Thia-Payne Rearrangements

All reported thia-Payne rearrangements have been in the "forward" direction, starting with a 2,3-epoxy sulfide. Except for a single report, (65) these rearrangements have been carried out under Lewis-acidic conditions that have led to opening. Treatment, for example, of epoxide **40** with trimethylsilyl triflate (Eq. 16) produces an intermediate thiiranium salt (**41**), which is then opened with pyridine to form the pyridinium salt **42** in quantitative yield. (66)


(16)
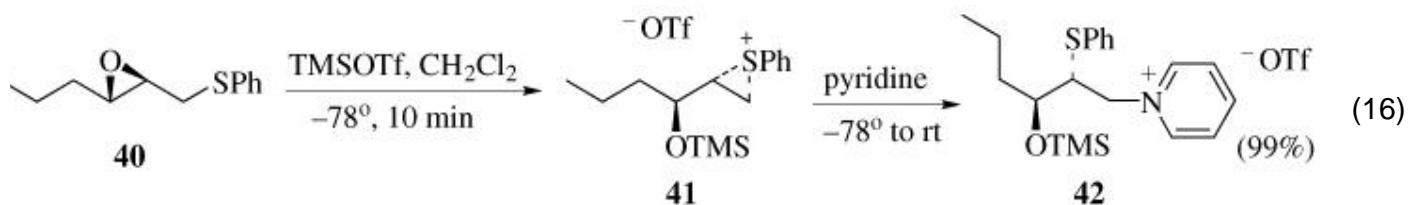
When aluminum reagents are used, both reduction and carbon-carbon bond forming reactions are made possible. (67, 68) However, the regiochemistry of opening with aluminum reagents is unlike that found in epoxide migrations and aza-Payne rearrangements, and it is sensitive to both substrate and reagent. For example, with trimethylaluminum, opening of epoxide **43** occurs at C-2 with retention (actually double inversion) exclusively to give alcohol **44** (Eq. 17). (67) Substrates prone to carbocation formation at C-3, such as epoxide **45**, undergo reactions that probably do not involve thiiranium intermediates (Eq. 18).


(17)

(18)
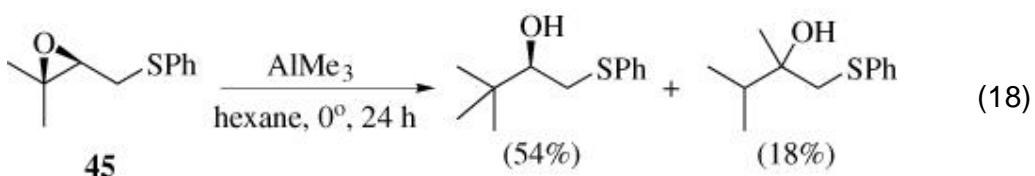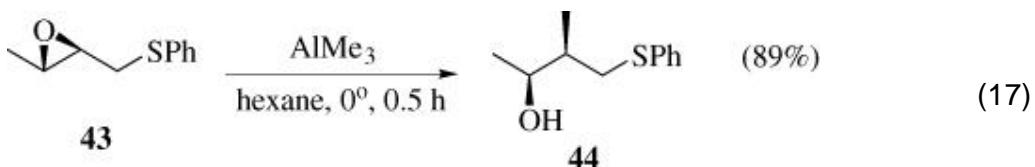
The proposed mechanism for the reaction of epoxy sulfides with trimethylaluminum (Scheme X) involves (a) complexation of the aluminum reagent with the epoxide oxygen, (b) formation of a thiiranium ion, and (c) opening by either the internally complexed aluminum species or a second equivalent of reagent. This reactivity appears to be unique to trimethylaluminum. The more active aluminum reagents, 1-hexenyl(diisobutyl)aluminum, diethyl(1-hexynyl)aluminum, and diisobutylaluminum hydride (DIBAL), all tend to open the thiiranium ion at the less substituted terminal position.
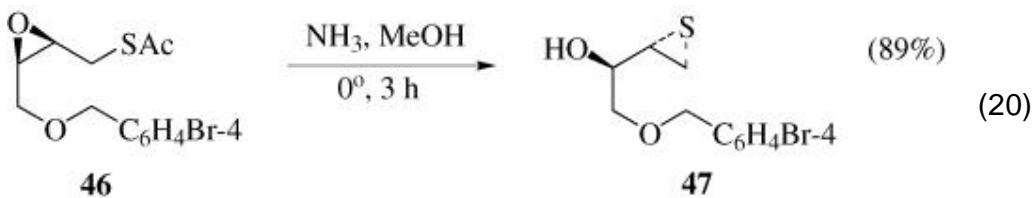
Scheme X.
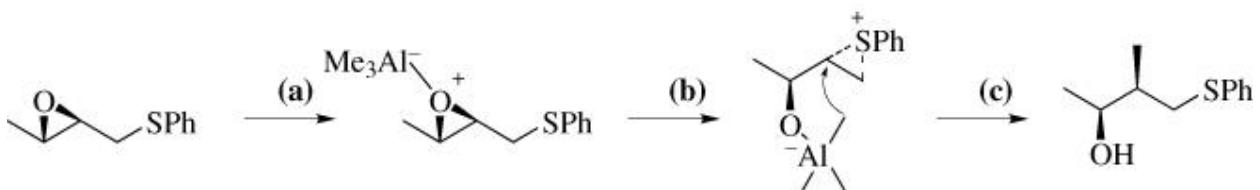
Excellent selectivities at C-2 have also been observed for opening of 2,3-epoxy sulfides with phenylborinic acid (Eq. 19). (69) Again, double inversion is observed.
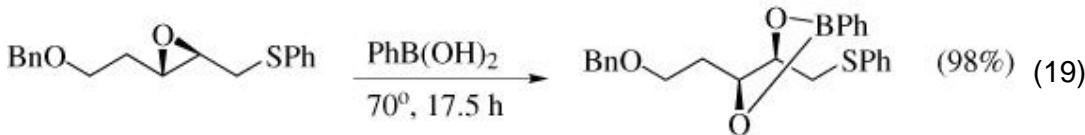
The single report of a thia-Payne rearrangement not involving a Lewis acid is the reaction of thioacetate **46** with ammonia to produce thiirane **47** in 89% yield (Eq. 20). (65)
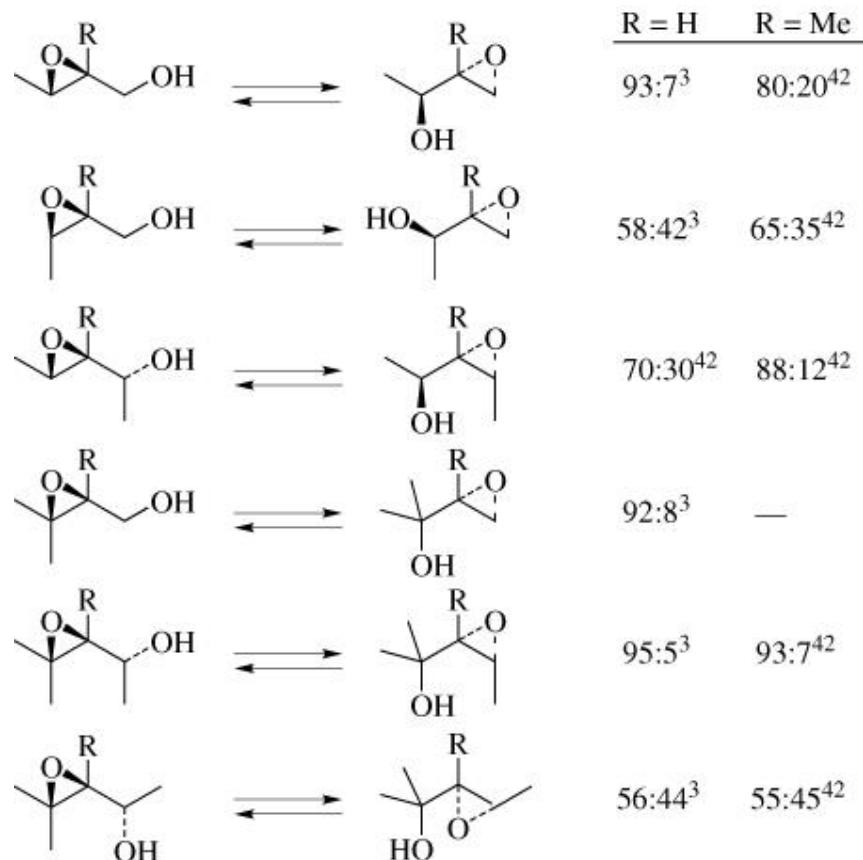
3. Scope and Limitations

In general, epoxide migration requires strongly basic conditions such as sodium hydroxide/water (3) or sodium methoxide/methanol. (54) Despite reports of their general inappropriateness, (3, 24) aprotic conditions such as butyllithium/lithium chloride/ tetrahydrofuran, (25) sodium hydride/tetrahydrofuran with (25) and without (26) [18]-crown-6, and lithium chloride/tetrahydrofuran (25) have been utilized with limited success. This narrow range of conditions places considerable limitations on the reaction.

The primary considerations in epoxide migration involve (a) direction of epoxide equilibration, (b) selectivity in epoxide opening by nucleophiles, and (c) selectivity in epoxy alcohol trapping by electrophiles. These subjects are discussed for epoxide migration, aza-Payne rearrangements, and thia-Payne rearrangements in this section. As will be seen, much research has focused on understanding the scope and limitations of epoxide migration in both cyclic and acyclic systems, and many generalizations have been made. In addition, many studies have shown that despite unfavorable thermodynamic preference for a desired epoxide, selectivity in opening can be achieved kinetically.

### 3.1. Direction of Epoxide Equilibration in Acyclic Systems

To a certain extent, the more stable of two isomeric acyclic epoxy alcohols is predictable based on the substitution pattern around the epoxide. Representative acyclic systems for which equilibrium has been approached from both sides under identical conditions (aqueous sodium hydroxide at room temperature) are shown in Figure V. The ratios, initially determined by gas chromatography, (3, 42) have been confirmed by NMR spectroscopy. (42, 70)

Figure V.

|	R = H	R = Me
	93:7[3]	80:20[42]
	58:42[3]	65:35[42]
	70:30[42]	88:12[42]
	92:8[3]	—
	95:5[3]	93:7[42]
	56:44[3]	55:45[42]

There is significant variability in the thermodynamic product ratios due to both steric and electronic effects. For example, whereas cis-disubstituted epoxide **48** and monosubstituted epoxide **49** establish only a 58:42 equilibrium ratio when treated with aqueous sodium hydroxide (Eq. 21), cis-disubstituted epoxide **50** and monosubstituted epoxide **51** establish a 5:95 equilibrium ratio (Eq. 22). (42)

$$\text{48} \quad \xrightarrow[\text{H}_2\text{O, rt, 1 h}]{\text{NaOH}} \quad \text{49} \tag{21}$$

58:42

$$(22)$$
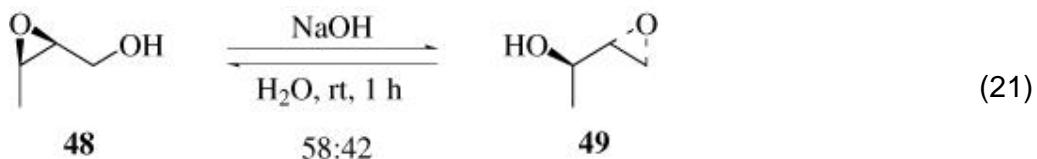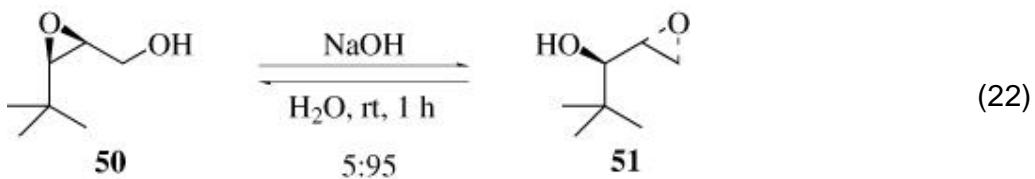
There is also evidence that vinyl and phenyl groups attached to the oxirane in one isomer lower its free energy relative to the other isomer, at least in comparison with simple alkyl substitution. Thus, vinyl epoxy alcohol **52** can be equilibrated to a 3:97 mixture with its 2,3-epoxy isomer by very careful isomerization with base (Eq. 23). (37) In comparison, isomerization of the saturated epoxy alcohol **53** gives a slightly lower selectivity (Eq. 24). (71)
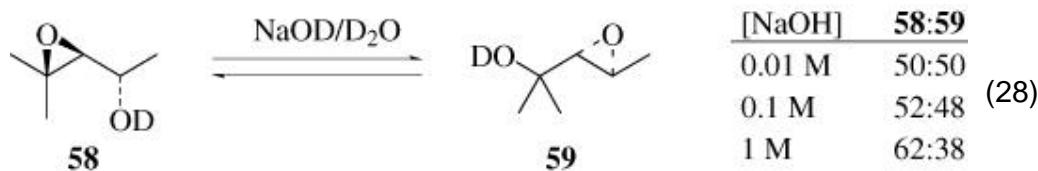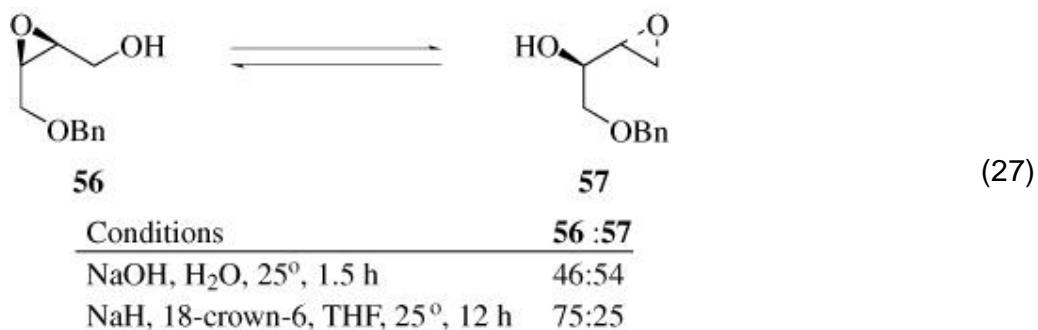

$$(23)$$

$$(24)$$
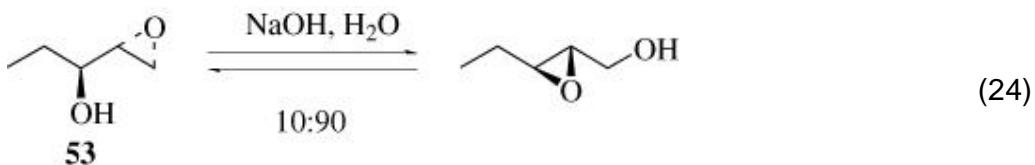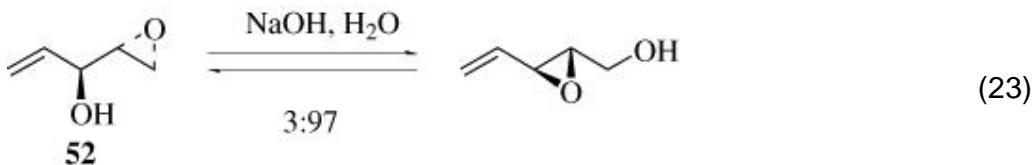
A strong effect of phenyl substitution is seen in comparing the equilibrations of epoxy alcohols **54** (70) and **55** (3) (Eqs. 25 and 26).

$$(25)$$

$$(26)$$
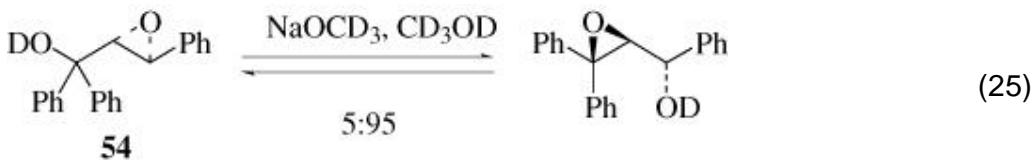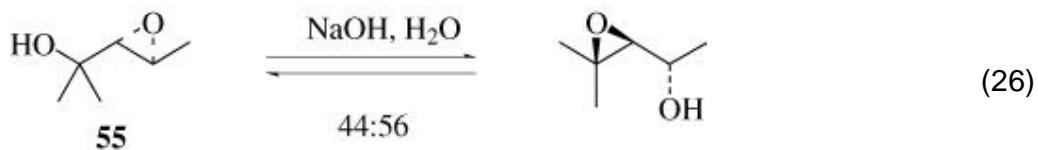
Generally only subtle effects of conditions on equilibrium ratios are observed. (70) However, the equilibrium ratio between epoxy alcohol isomers **56** and **57** (Eq. 27) using typical aqueous conditions is reversed using aprotic conditions. (25) The equilibrium is driven in the direction of the cis-disubstituted oxirane isomer **56** in this case. The equilibrium ratio for the isomerization of epoxy alcohol **58** to **59** (Eq. 28) is somewhat dependent upon base concentration. (70)

$$(27)$$

Conditions	56 :57
NaOH, H_2O, 25°, 1.5 h	46:54
NaH, 18-crown-6, THF, 25°, 12 h	75:25

[NaOH]	**58:59**
0.01 M	50:50
0.1 M	52:48
1 M	62:38

$$(28)$$

The following general observations relating to equilibrating acyclic epoxy alcohols have been reported:

1. An isomer with higher substitution around the oxirane is favored. (3, 42, 70)

2. A trans substituent on the epoxide is a stabilizing influence; a cis substituent is destabilizing. (3, 42, 70)

3. An isomer with a primary hydroxy group is favored. (42)

4. A substituent at C-2 has only secondary influence on the equilibrium. (42)

5. Resonance-donating substituents (such as phenyl (70) and allyl (37, 72)) on

the oxirane are stabilizing influences (relative to the other epoxide migration isomer, not to reactivity), while electron-withdrawing substituents (such as trifluoromethyl (73)) on the oxirane are destabilizing.

6. The concentration of base has little effect on equilibrium ratio. (70)

3.2. Direction of Epoxide Equilibration in Cyclic Systems

All reported equilibrium ratios for pyranoside epoxy alcohols where equilibrium was reached starting from both isomers under identical conditions are shown in Figure VI, although conditions vary among the five examples. Yields of isolated of pure regioisomers have been as high as 85%. (74) Note that any anomeric effect that might place the methoxy substituents in an axial orientation appears to be overshadowed substantially by the preference for equatorial hydroxyl. (That is, the methoxy group in each example is presumed to be equatorial as well, at least for predictive purposes). The situation is somewhat more complicated when the pyranoside is α -substituted (C-1 and C-5 substituents trans disposed), because in those cases simple conformational analysis appears to be of little help, and more subtle factors are involved. (75, 76)

Figure VI.
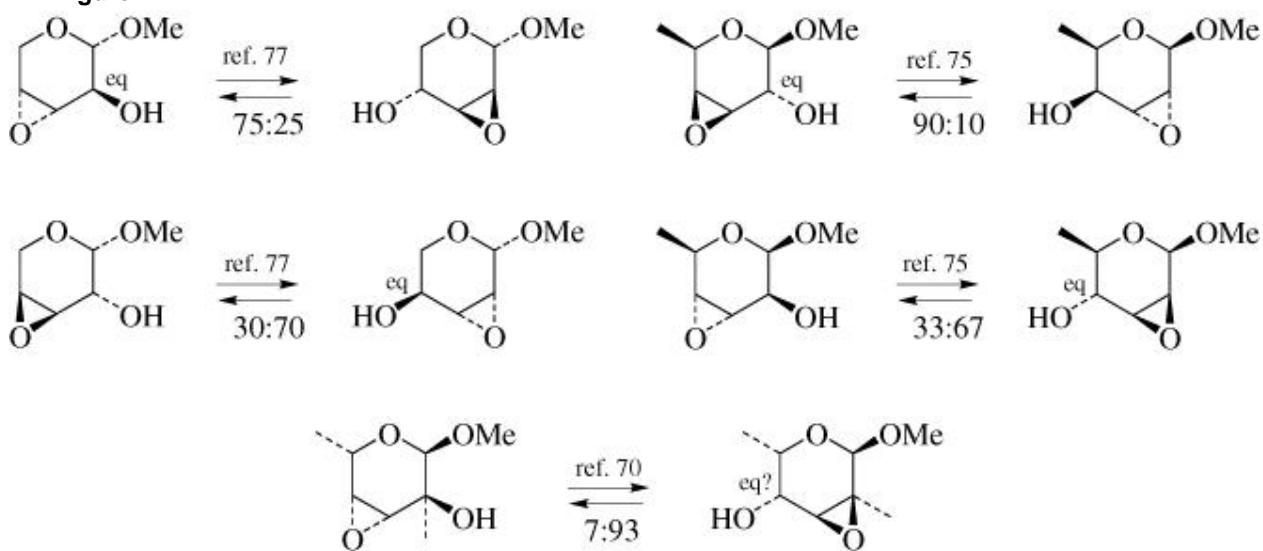
Three generalizations for pyranoside-based epoxide migrations have been made:

1. The favored epoxide is the one with more pseudoequatorial groups, with the anomeric center substituent generally assumed to be equatorial, provided that is possible. (78)

2. Substitution trends are similar in cyclic and acyclic systems, favoring trisubstituted oxirane isomers over disubstituted ones. (70, 79)

3. There is no evidence of significant through-space interactions such as

hydrogen bonding or lone-pair–lone-pair repulsions influencing the equilibrium ratio. (78)

Preference for the isomer with more equatorial groups is seen especially clearly for conformationally locked 1,6:3,4-dianhydro- β -D-*galacto*-hexopyranose **60**. Treatment of this compound with sodium hydroxide in methanol (Eq. 29) produces a 1:4 ratio of the starting material to its gulo isomer **61**. (80) Similarly, treatment of tosylate **62** with sodium hydroxide in water (Eq. 30) results in an 85% yield of isomer **63**. (81) In both cases, the favored isomer is the one with the pseudoequatorial hydroxy group.


(29)

(30)
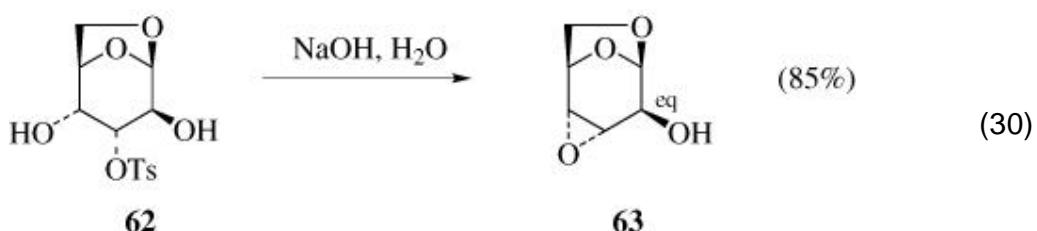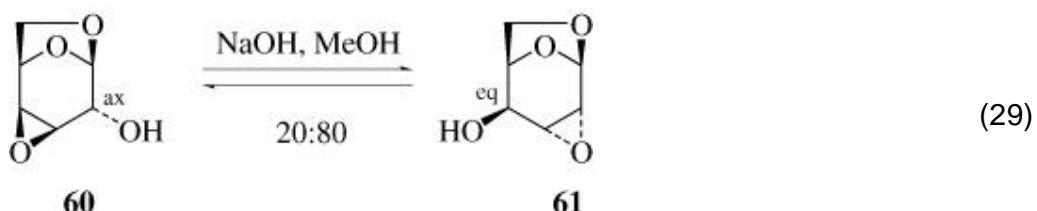
A dramatic reagent effect on epoxide migration in cyclic systems has been observed in one alkaloid synthesis (Eq. 31). (82) Attempts to reduce epoxy alcohol **64** with LiBHEt$_3$ instead resulted in epoxide migration to form isomer **65** in 80% yield, while attempts to reduce epoxy alcohol **65** with sodium borohydride instead resulted in epoxide migration to regenerate isomer **64** in 85% yield. No explanation of this unique result is provided, but it is probable that sodium borohydride in alcohol is effectively equilibrating the alcohols, while LiBHEt$_3$ under aprotic conditions involves irreversible deprotonation and equilibration favoring the primary alkoxide. This preference would be consistent with that observed for the equilibration of epoxide **56** using sodium hydride, as illustrated in Eq. 27

$$\text{(31)}$$
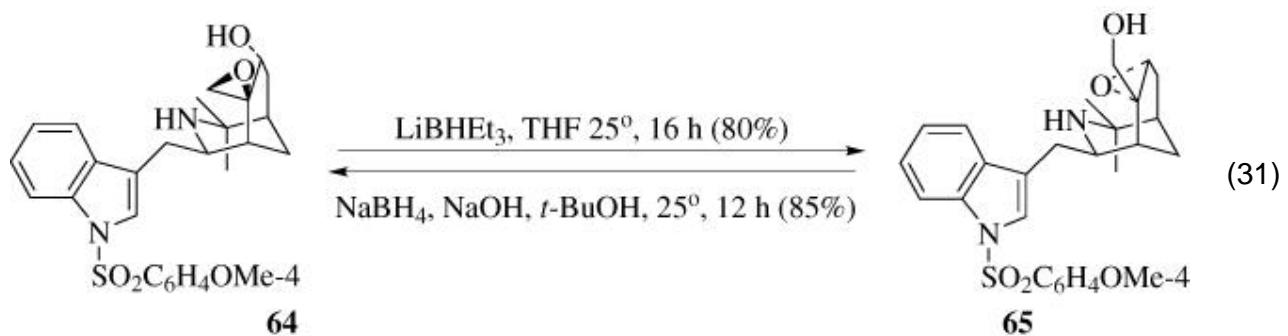
3.3. Selectivity of Epoxide Opening

Despite the fact that generally the more substituted epoxide is more stable, nucleophilic opening of a pair of equilibrating epoxy alcohols often can be engineered to occur primarily, if not exclusively, at the less substituted carbon of the less substituted epoxide, in accordance with the Curtin-Hammett principle (Figure II, above). Evidence suggests that in comparing monosubstituted, cis-disubstituted, and trans-disubstituted epoxy alcohols, although the order of stability is trans > cis > mono, (3, 42) the order with respect to the kinetics of epoxide opening is mono >> cis > trans. (31, 83)

Nucleophiles investigated include hydride, (4, 84) cyanide, (4, 85, 86) acetylide, (87-89)alkyl and alkenyl cuprates, (25, 90) amines, (91, 92) sulfonamides, (4) azide, (93-95) halides, (96, 97) phenythiolate, (31, 38, 98-102) tert-butylthiolate, (91-103) and numerous oxygen-based nucleophiles (for references, see Table III-D). Although yields have been moderate to excellent, regioselectivity has been mixed. Notable problems involve hydride (4, 84, 104) and acetylide (87-89) addition, for which the principal difficulty is competitive opening at C-2; amine addition, which is complicated by competitive opening at C-1, C-2, and C-3; (91) and phenylthiolate addition, which often exhibits low selectivity relative to opening at C-1 and C-3. (38) Generally, tert-butylthiolate is more selective than phenylthiolate. (91) The relative amount of opening of one isomer is reduced if that isomer has additional electron-withdrawing substituents vicinal to the oxirane. For example, opening of epoxide **66** (Eq. 32) with tert-butylthiolate is considerably more selective than opening of epoxide **67**.

|	R	% C-1 opening
66	CH_2OH	95
67	$n\text{-}C_7H_{15}$	66

$$\text{(32)}$$
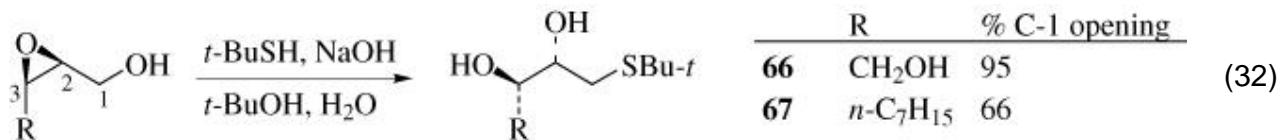
Where the alcohol or epoxide is allylic (36, 37, 105) or benzylic, (91) opening with and without epoxide migration often compete, even when hydroxide is the nucleophile. For example, the percent of opening of epoxide **68** (Eq. 33) at C-1 with diethylamine is considerably less than that for alkyl-substituted epoxide **69**. (91)

|	R	% C-1 opening
68	Ph	12
69	$n\text{-}C_7H_{15}$	80

(33)
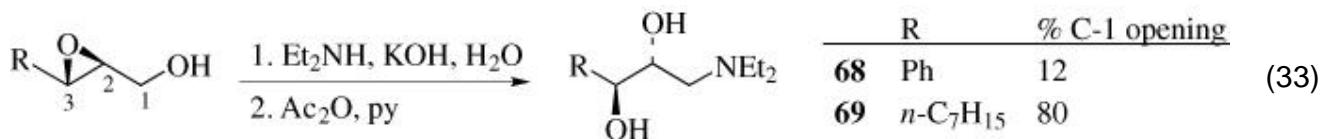
As noted above (Scheme VI), when the nucleophile is hydroxide, competitive opening at C-1 vs. C-3 can lead to a decrease in enantiomeric excess. For example, asymmetric epoxidation of divinylcarbinol (Scheme XI) gives only the product of epoxide migration (**52a**) when the original stoichiometric conditions reported for that reaction are used, including workup with sodium hydroxide. (106) When a nonbasic workup is used instead, (106) or the reaction is carried out using molecular sieves and a catalytic amount of titanium isopropoxide, (106, 107) then the unrearranged product **52 b** can be isolated in moderate yield. Rearrangement of **52b** to **52a** is effected by brief treatment with 0.5 M aqueous sodium hydroxide at room temperature. (37) No epoxide migration is observed when either epoxy alcohol isomer is opened with ammonia. (108, 109) The high regioselectivity of these vinylic epoxide openings stands in contrast to the reaction of *trans*-2,3-epoxyhexan-1-ol with amines, which leads to a complex mixture of isomers. (91)

Scheme XI.
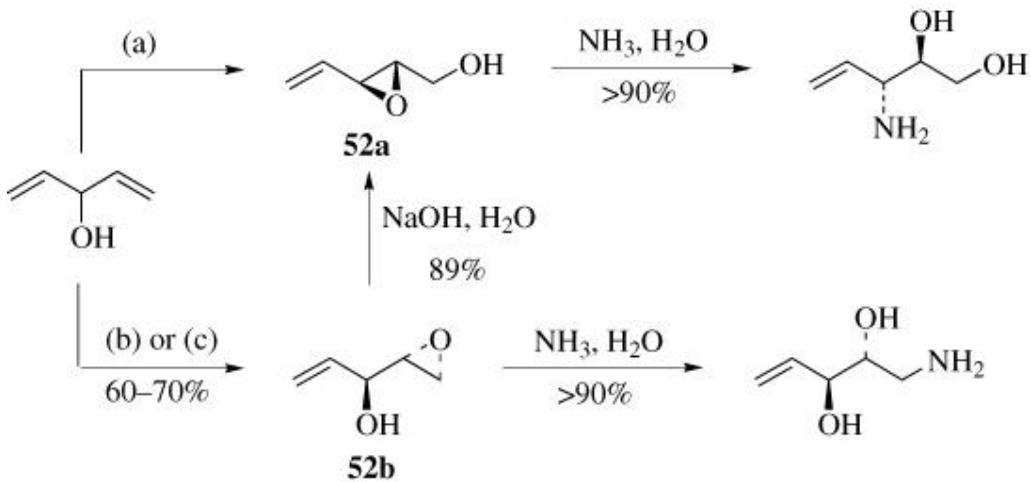
a: 1. Ti(OPr-i)$_4$ (1 eq), t-BuO$_2$H, L-(+)-DET, CH$_2$Cl$_2$, –20°, 3 d; 2. tartaric acid, NaOH, H$_2$O
b: 1. Ti(OPr-i)$_4$ (1 eq), t-BuO$_2$H, L-(+)-DET, CH$_2$Cl$_2$, –20°, 3 d; 2. H$_2$O/acetone, distillation
c: 1. Ti(OPr-i)$_4$ (0.1 eq), t-BuO$_2$H, L-(+)-DET, MS 4Å, CH$_2$Cl$_2$, –25°, 7 d; 2. distillation

In the conversion of hepoxilin (10S)-HxB$_3$ (**70**) into trioxilin (10R,11S,12S)-TrXB$_3$ (**71**), epoxide migration precedes opening at the allylic position when lithium hydroxide is used as the base (Eq. 34).

(34)
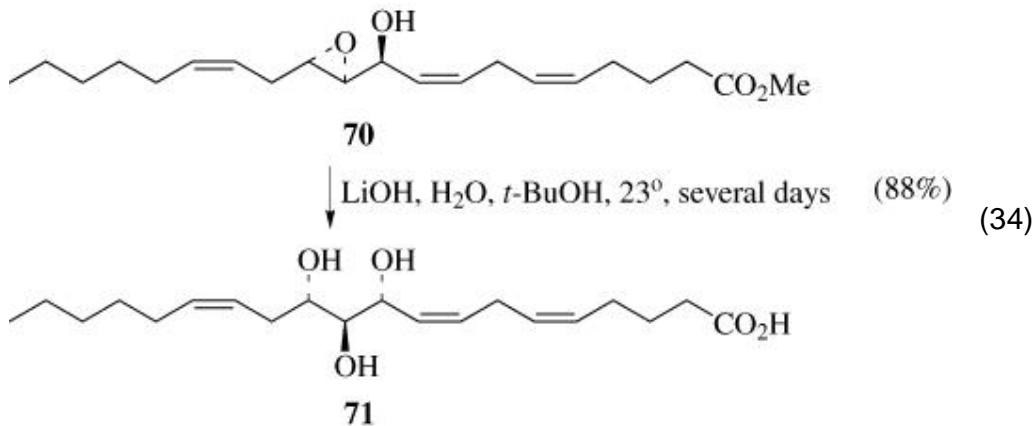
Where there is no allylic or benzylic activation of the epoxide, nucleophilic addition of hydroxide has been observed to occur with very high selectivity at the least substituted epoxide position. (31) Nonetheless, the reader is cautioned that reports of selective addition *of hydroxide ion* to racemic substrates can only be tentatively extrapolated to nonracemic cases, (110) since competitive addition in the racemic case has no observable effect, while competitive addition in the nonracemic case leads to a decrease in

enantiomeric excess (Scheme V).

In cyclic systems such as pyranosides, the regioselectivity of epoxide opening is highly biased toward axial addition to form a (possibly transient) diaxial species. Thus, for example, both 1,6:3,4-dianhydro-β-D-*galacto*-hexopyranose (60) and 1,6:2,3-dianhydro- β -D-*gulo*-hexopyranose (61) give the same 17:83 ratio of products, both of which result from a trans-diaxial opening of the epoxide (Eq. 35). (111) Since opening is slower than equilibration, it is simply fortuitous that the product ratio is similar to the equilibrium substrate ratio of 20:80. (80)


(35)
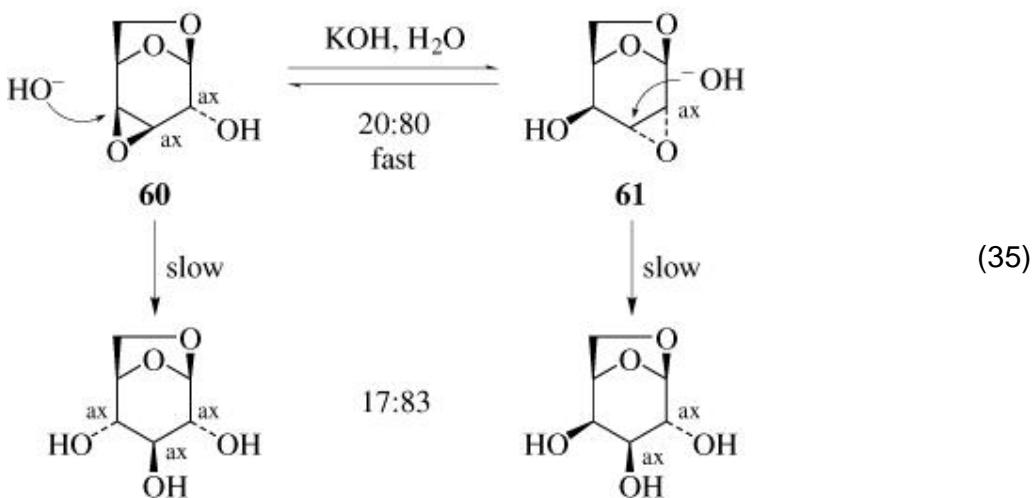
## 3.4. Epoxide Migration with Electrophilic Trapping in Situ

One might think that it would be possible to selectively remove one isomer of an epoxy alcohol equilibrium by kinetic trapping of the less substituted alcohol with electrophiles such as alkyl halides (Scheme II). However, the few results to date that bear on this question suggest otherwise. Part of the problem may be that the anhydrous aprotic conditions generally employed in alkylations and silylations are specifically the conditions that were found in Payne's original work (3) to *not* be conducive to epoxide migration.

The problem is almost certainly that alkylation and silylation are generally faster processes than epoxide migration, leading to no significant equilibration. Nonetheless, two reports do suggest that in certain highly biased cases such trapping is possible (Eqs. 36–38). Specifically, deprotonation of either tertiary alcohol 72 or 73 with sodium hydride in tetrahydrofuran leads to epoxide migration and alkylation of the primary alcohol, albeit in unspecified yield. (112) Silylation of 74 with trimethylsilyl chloride and imidazole followed by hydrolysis

effects its isomerization to the more highly substituted epoxide in 80% yield. (113)

(36)

(37)

(38)
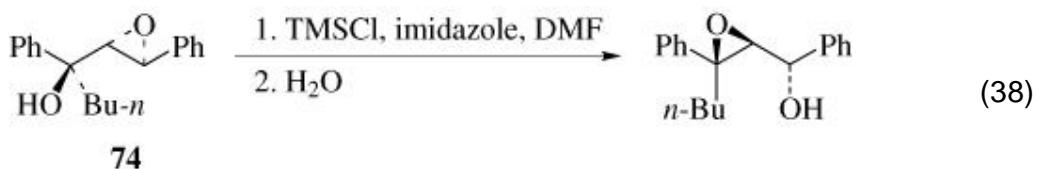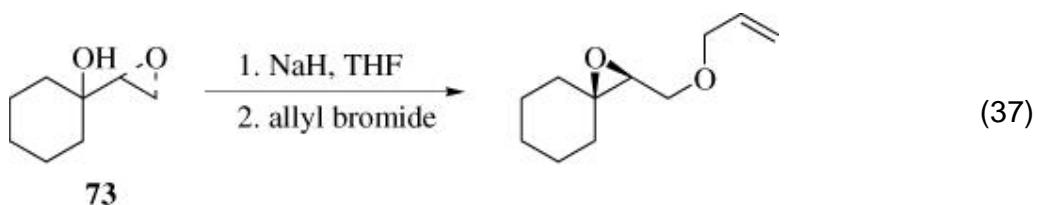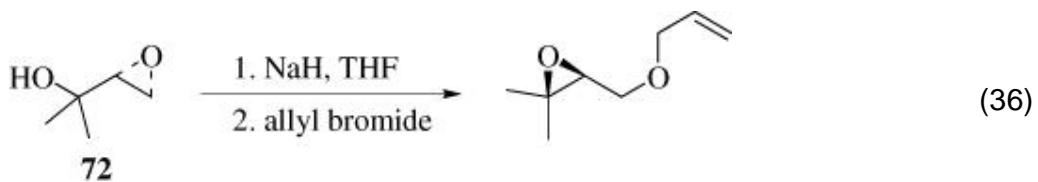
Much more generally successful has been the *intramolecular* electrophilic trapping of epoxide migration isomers. Examples include the reaction of epoxide **75** with potassium *tert*-butoxide to give diepoxide **76** (Eq. 39), (114) and the treatment of diepoxide acetate mixture **77** with aqueous sodium hydroxide to produce tetrahydrofuran **78** (Eq. 40). (115)
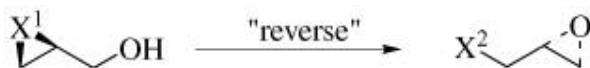

(83%) (39)

$$(66\%) \quad (40)$$
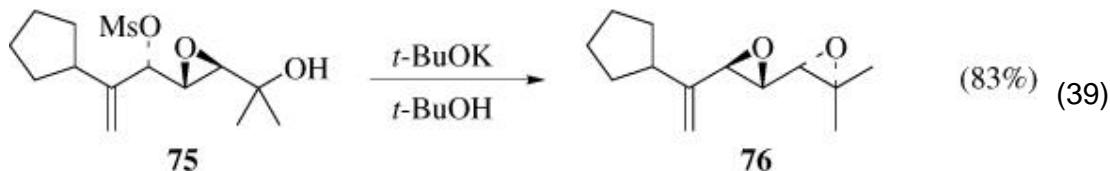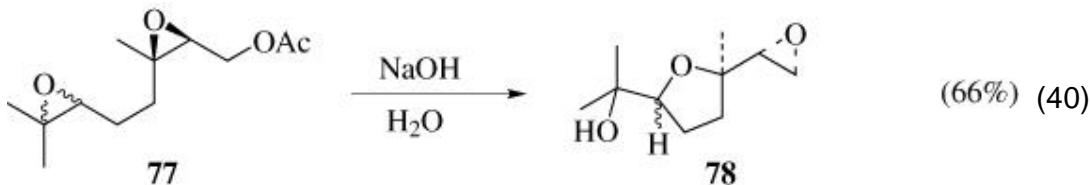
3.5. Rearrangement and Opening in Aza-Payne Systems

Conditions used for effecting equilibration in aza-Payne reactions are summarized in Eqs. 41 and 42.


X^1	Reagents Effecting Rearrangement Only	X^2	refs	
NH_2	n-BuLi/t-BuOK	NH	57, 59, 61	(41)
NHR	n-BuLi/AlMe$_3$, Ti(OPr-i)$_4$	NR	116	
NHR_2	RNH_2	NR_2^+	62	
NHAr	TMSOTf	NAr	60	
NHMs NHTs	BF$_3$•Et$_2$O, NaOH	NMs, NTs	63	

X^1	Reagents Effecting Rearrangement Only	X^2	refs	
NR_2^+	NaH, K$_2$CO$_3$	NR_2	62, 117	(42)
NMs	NaH	NHMs	57	
NTs	KH, NaH, NaOH, t-BuOLi, pyridine	NHTs	20, 57, 64, 118	

Considerable experimentation has gone into discovering the best conditions for the aza-Payne rearrangement when in situ opening is desired. Again we consider both the "forward" (Eq. 43) and the "reverse" (Eq. 44) sense of reaction. Here we see the exclusive use of Lewis-acidic conditions for forward rearrangement and opening, and the use of strongly basic conditions for reverse rearrangement and opening. Of these methods, by far the most explored involve treatment of 2,3-epoxy dialkylamines with trimethylsilyl triflate

(19), (62), (121) and treatment of *N*-tosyl-2-aziridinemethanols with potassium hydride. (20, 57, 124)
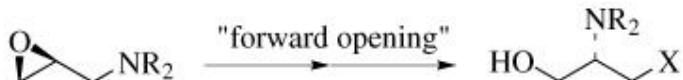
Rearrangement/Opening Reagents	X	refs	
SiO_2 / H_2O	OH	119	(43)
$BF_3 \cdot Et_2O$ / $NaBH_3CN$	H	119	
TMSOTf / amine	NH_2, NR_2	19, 62, 120, 121	
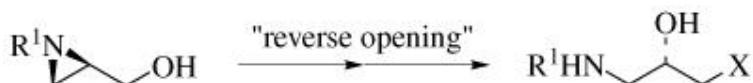
R^1	Rearrangement/Opening Reagents	X	refs	
H	KOH / H_2O	OH	122	
Ts	$MeCu(CN)Li \cdot LiBr$	Me	57, 64	
Ts	$BuCu(CN)Li \cdot 2LiCl$	Bu	57	(44)
Ts	KH / $Me_2Cu(CN)Li_2 \cdot 2LiBr$	Me	123, 124	
Ts	KH / $Bu_2Cu(CN)Li_2$	Bu	123, 124	
Ts	KH / Me_3SiCN, cat. $Yb(CN)_3$	CN	123, 124	
Ts	KH / $(R_2N)_2Cu(CN)Li_2$	NR_2	123, 124	
Ts	KH / $(Me_3Sn)_2Cu(CN)Li_2$	$SnMe_3$	123, 124	
Ts	KH / $(Me_3Si)_2Cu(CN)Li_2$	$SiMe_3$	123, 124	
Ts	KH / RSH	SR	123, 124	

When the nitrogen is activated as a sulfonate, treatment with potassium hydride in aprotic media drives the equilibrium "in reverse" toward the oxirane form, and opening by a variety of cuprate reagents occurs, as for epoxy alcohols, at the less substituted position. (25, 123, 124)

3.6. Rearrangement and Opening in Thia-Payne Systems

The scope and limitations of thia-Payne rearrangements have been little explored. Conditions used for rearrangement of epoxy sulfides to thiiranium salts with in situ opening are summarized in Equation 45. Note that, as discussed above, some aluminum reagents open the resultant thiiranium salt selectively at C-2.
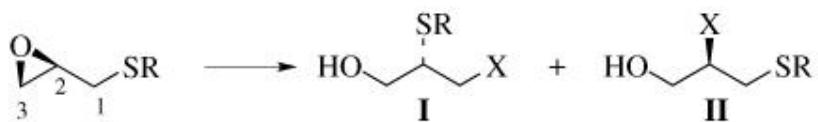
Rearrangement/Opening Reagents	X	Major Product	refs
$(i\text{-Bu})_2\text{AlH}$	H	**I**	67
Me_3Al	Me	**II**	67
Et_3Al	Et	**II**	67
$\text{Et}_2\text{AlC}\equiv\text{CBu-}t$	$\text{C}\equiv\text{CBu-}t$	**I**	67
$\text{Me}_2\text{AlC}\equiv\text{CTMS}$	$\text{C}\equiv\text{CTMS}$	**II**	68
PhB(OH)_2	OH	**I**	69
$\text{BF}_3\bullet\text{Et}_2\text{O} / \text{R}_2\text{NTMS}$	NR_2	**I**	66, 125
TMSOTf / RNH_2	NHR	**I**	126, 127
TMSOTf / RN=CHR'	NHR	**I**	66, 128
TMSOTf / TMS-imidazole	imidazolyl	**I**	66, 125
TMSOTf / pyridine	py^+	**I**	66
TMSOTf / (*O*)-TMS amide enolate	NHAc, NRAc	**I**	66, 125
TMSOTf / PhSTMS	SPh	**I**	129

4. Applications to Synthesis

4.1. Epoxide Migration in Acyclic Systems
4.1.1. Epoxide Migration Prior to Opening ("Payne Rearrangement Method")

A rare example of the isolation of an epoxide migration product in a natural product synthesis is found in the synthesis of (–)-borjatriol (Scheme XII). (130) A key transformation involves Payne rearrangement of epoxy alcohol mixture **79** to **80**. Without separation, this mixture was carried through to ketone **81**, which was ultimately converted into the target compound.

Scheme XII.
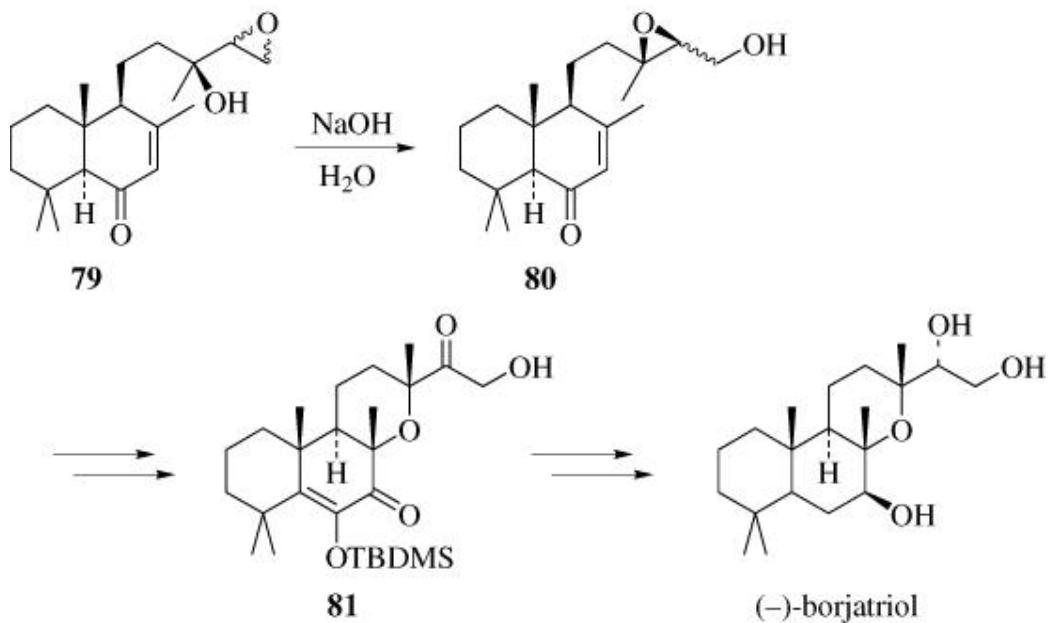
4.1.2. Nucleophilic Opening in Situ ("Payne Rearrangement/Opening Method")

One common use of epoxide migration in acyclic systems has been the transformation of an allylic alcohol into a 2,3-diol with addition of a nucleophile at C-1. The most direct route for this transformation is asymmetric epoxidation followed by epoxide migration with in situ nucleophilic opening (Scheme XIII). (4)
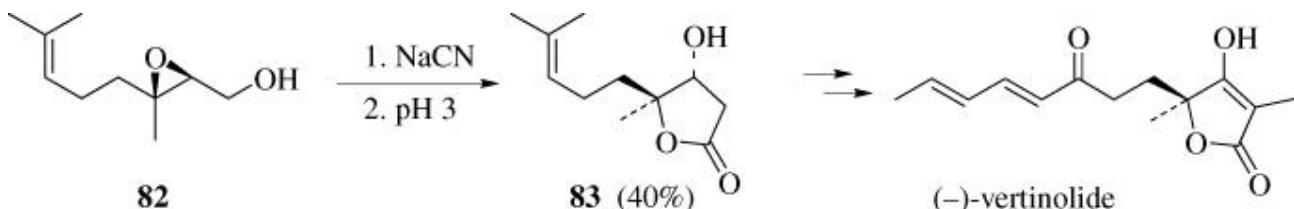
Scheme XIII.
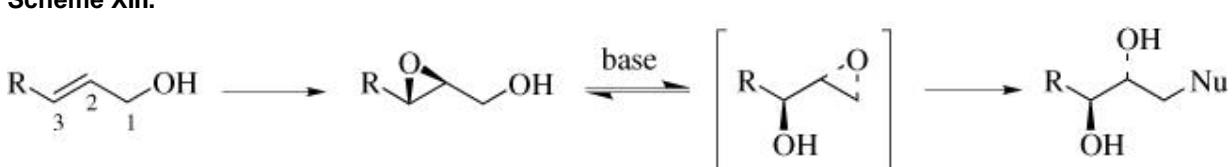
For example, asymmetric epoxidation of geraniol with L-(+)-diethyl tartrate gives epoxy alcohol **82** (Scheme XIV). Treatment of this compound with

sodium cyanide followed by mild acid hydrolysis leads to lactone **83**, an intermediate in the synthesis of (–)-vertinolide. (131)

Scheme XIV.

Although not particularly regioselective, in situ opening by alkynyllithium reagents in the presence of boron trifluoride etherate (89) has been used in the synthesis of lepidopteran pheromones (Scheme XV). (87) Even though regioselectivity was only 75:25 for C-1 vs. C-2 addition, Payne rearrangement/opening solved a difficult problem in this case, because the previously reported attempted synthesis of this class of compounds (132) using an alternative strategy was not successful.

Scheme XV.
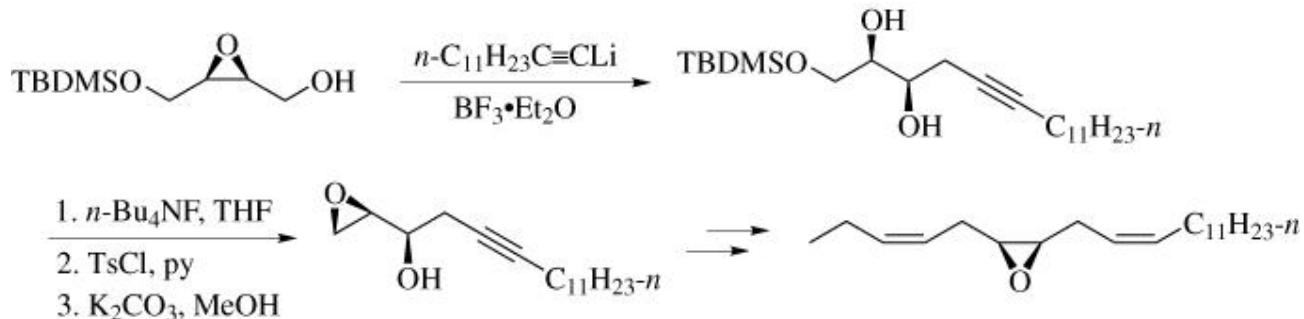
With hydroxide as the nucleophile, Payne rearrangement/opening has been used to synthesize all possible simple carbohydrate pentitols and hexitols (31) as well as a variety of 2-deoxyhexoses. (133) In all instances, regioselectivity for opening at C-1 is high because of the presence of an alkoxy substituent at C-4.

When the nucleophile is a thiolate, Payne rearrangement/opening is especially successful and has been used effectively in several natural product syntheses, including the syntheses of all possible simple tetritols (31) and hexoses. (99, 134) Here the strategy (Scheme XVI) was to carry out a Pummerer reaction (135) on the resultant phenyl thioether to give the aldehyde. Reduction with lithium aluminum hydride produces the tetritol; Wittig reaction extends the carbohydrate backbone by two carbons and sets the stage for another asymmetric epoxidation in the synthesis of the hexoses.

Scheme XVI.
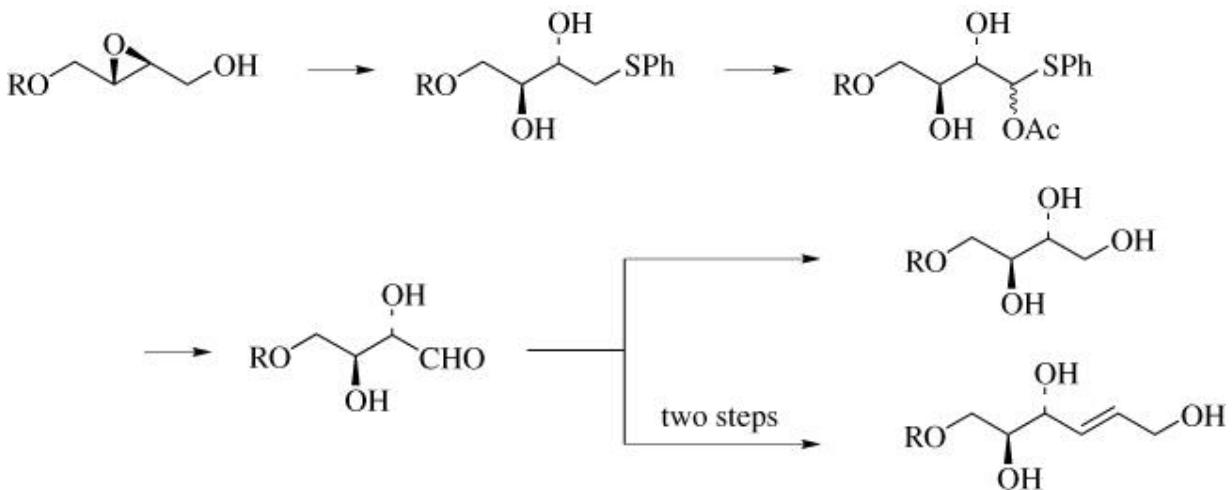
4.1.3. Three-Step Equivalent Sequence ("Diol-Sulfide Method")

Epoxide migration and opening can be carried out in separate steps in cases where competition with C-3 opening is a problem or where the basic conditions necessary for epoxide migration are not compatible with the required nucleophile (Eq. 46). (91) In this method, the initial epoxide migration/opening is carried out using a *tert*-butylthiolate nucleophile. Treatment of the isolated thioether with trimethyloxonium tetrafluoroborate (Meerwein's reagent) (136) and displacement of *tert*-butyl methyl sulfide under aprotic basic conditions produces the *less favorable* epoxide migration product cleanly. This epoxide is then opened in a separate step using aprotic conditions, thus avoiding concurrent epoxide migration back to the energetically more favorable isomer.
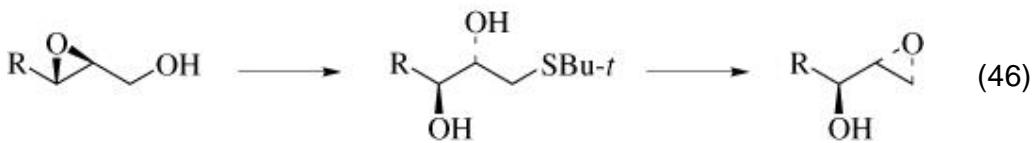

The advantages of the diol-sulfide method over the direct Payne rearrangement are that the steps involved are generally all high yielding, and isolation of the less favorable epoxide prior to opening allows the use of a broader range of nucleophiles, including hydride, acetylide, cyanide, methylcuprate, and azide. Thus, this method provides the synthetic chemist with a "back-up plan" when direct in situ opening is found to be unsuitable.

### 4.1.4. Intramolecularly Directed Chirality Inversion

A relatively unexploited use of epoxide migration in the synthesis of acyclic systems is based on the phenomenon that migration can lead to inversion of

multiple stereocenters. Indeed, in certain cases, all of the centers of a molecule may be inverted if opening by hydroxide or a hydroxide equivalent is employed. Whereas the inversion of all of the stereocenters in a molecule may seem contrary to the goal of synthesis, in fact exactly this strategy has been used to good effect in at least one case. (34) Thus, both enantiomers of leukotriene A$_4$ methyl ester are available from the same starting compound (Scheme XVII). (–)-LTA$_4$ is available from triol **84** directly. (137) Alternatively, activation of triol **84** as the 2,4,6-triisopropylphenylsulfonate and hydrolysis gives acid **85**. Treatment of this acid with sodium ethoxide in strictly anhydrous ethanol (so as to prevent opening by hydroxide) followed by acetylation gives lactone **86**, with both stereocenters inverted, in 88% yield. Conversion into the activated ester **87** allows for the formal synthesis of (+)-LTA$_4$ methyl ester.

Scheme XVII.
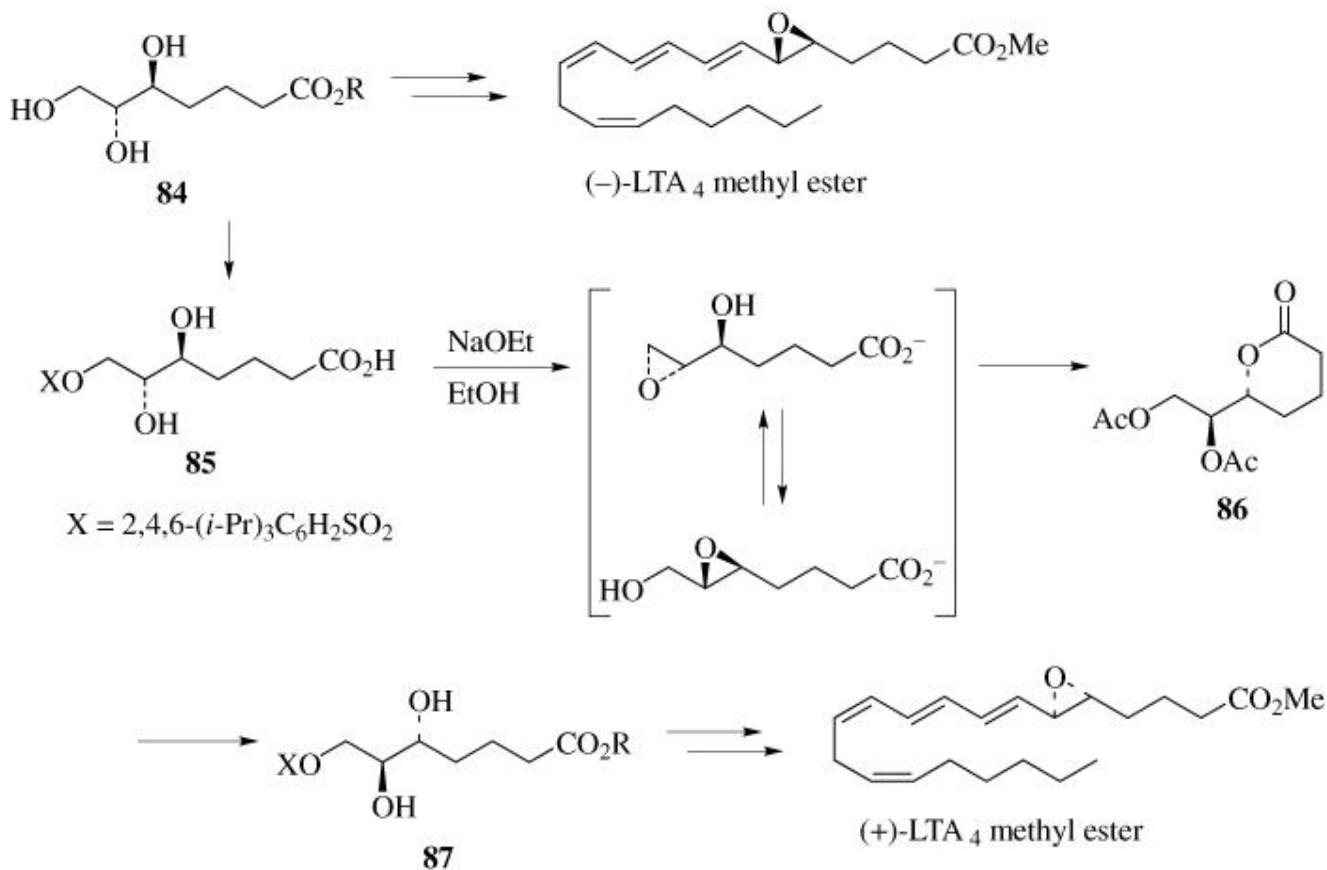
A second example involves the synthesis of tetrahydrofuran diol **89** from readily available dibromide **88** in 52% yield (Eq. 47). (45) Although not utilized to date in synthesis, this diol would seem to hold potential as a pseudo-C$_2$-symmetric ligand. (138, 139) Note that the α - and β -epoxides are identical compounds.

(52%) (47)
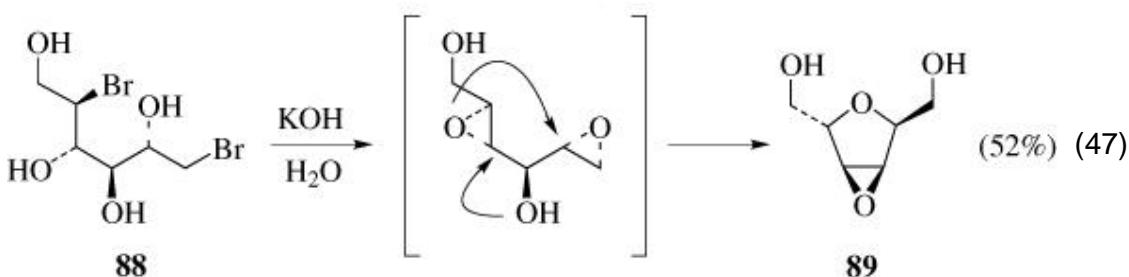
### 4.1.5. Epoxide Migration with Electrophilic Trapping in Situ

The last two steps in the total synthesis of spatol illustrate the in situ electrophilic trapping of an epoxide migration product (Eq. 48). Treatment of mesylate **90** with potassium *tert*-butoxide in *tert*-butyl alcohol gives spatol after oxidative removal of the *p*-methoxybenzyl protecting group. (114)



(48)
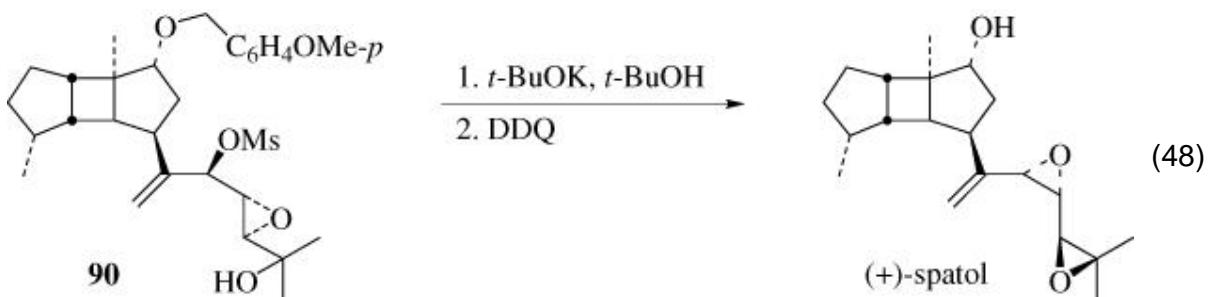
4.2. Epoxide Migration in Cyclic Systems

In the carbohydrate area, epoxide migration has not been used systematically except for the simple transformation of one known pyranose into another. Primary interest has been in understanding the chemistry of carbohydrates, with no specific synthetic goal in mind.

However, the lessons learned in the carbohydrate field have been applied to more complex syntheses. In particular, the preference for equatorial groups in pyranose systems was used in the synthesis of a derivative of gibberelin A_7 (Eq. 49). Upon treatment with base, iodohydrin **91** closes and rearranges to give migrated epoxy alcohol **92** in 63% yield. (140)

$$91 \xrightarrow{\text{KOH, H}_2\text{O}} 92 \quad (63\%) \quad (49)$$
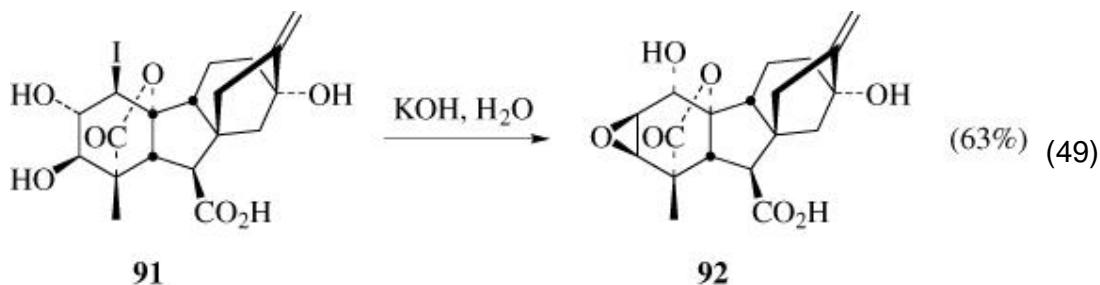
In a model study for the synthesis of taxinine (Scheme XVIII), the transformation of epoxy ketone **93** into enone **94** has been proposed to take place via a tandem aldol/Payne rearrangement. (141) No intermediates were isolated, and exposure of epoxide **93** to base in the absence of acetic anhydride led only to decomposition.

Scheme XVIII.
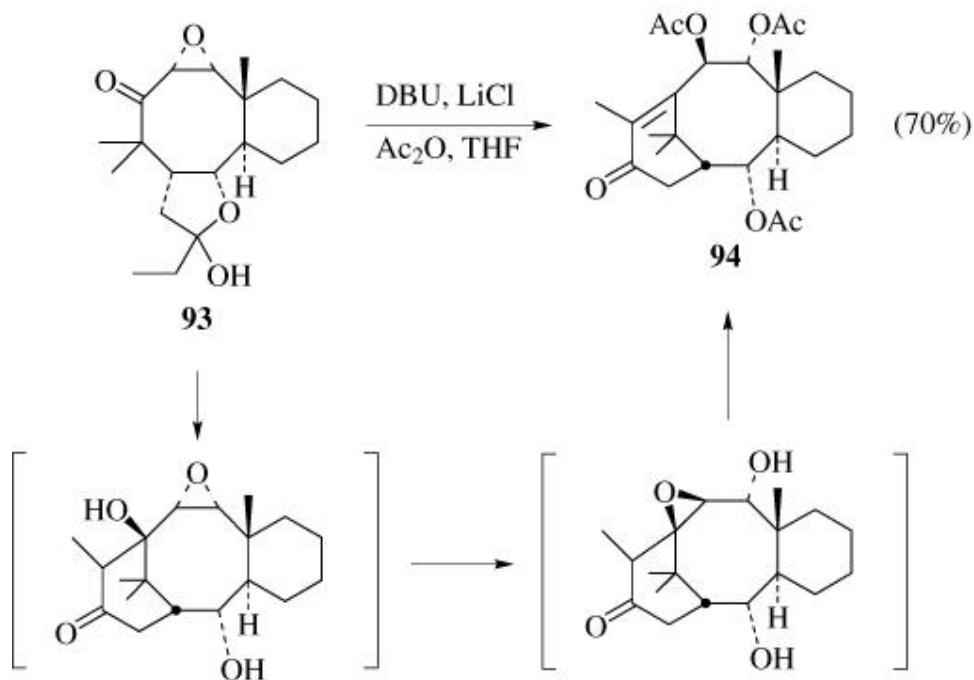
Unanticipated epoxide migration led to problems in the natural product isolation and surprises in the synthesis of epoxycyclohexenes **95** and **96** (Scheme XIX). These two compounds were not recognized to be distinct substances when isolated from the fungus *Chalara microspora*. (142) With almost identical 100 MHz NMR spectra, the presence of isomer **96** in the natural isolate was not initially noticed. However, when epoxide **95** was independently synthesized from (–)-methyl shikimate, it was discovered to

have an unexpectedly high optical rotation. (143, 144) It would appear that the natural isolate, with a rotation of +95°, was actually a 1:1 mixture of epoxy alcohols **95**, with a rotation of of +248°, and **96**, with a rotation of –54°. (145)

Scheme XXI.

(–)-methylshikimate   **95**   **96**   (–)-chorismic acid
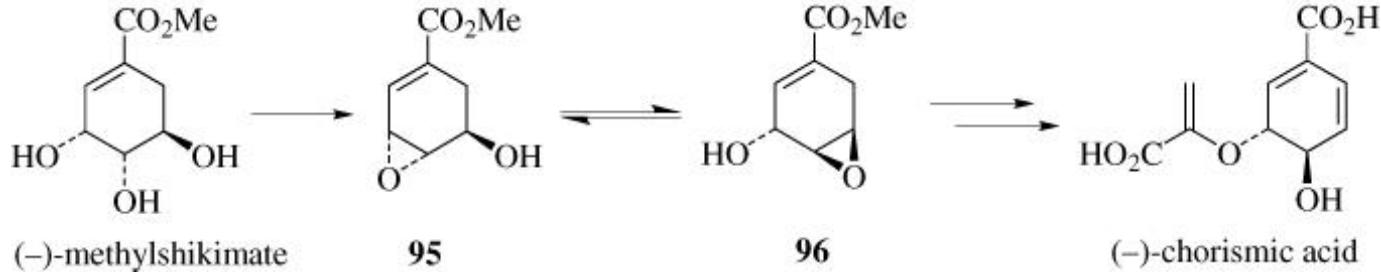
In this instance, epoxide migration could be prevented by using cold sodium methoxide in methanol for the synthesis of isomer **95**: Use of sodium methoxide in methanol at room temperature generates a 25:75 ratio of **95** to **96**. Since isomer **96** has been converted into (–)-chorismic acid independently, (145) its preparation from (–)-methyl shikimate constitutes a formal synthesis of (–)-chorismic acid from (–)-methyl shikimate.

4.3. Aza-Payne and Thia-Payne Rearrangements

Aza-Payne and thia-Payne rearrangements are new enough discoveries that only a few applications to synthesis have been described, and these mainly involve simple demonstrations of the method. For example, aza-Payne rearrangement of aziridine **97** with in situ opening by a cuprate reagent gives intermediate **98** (Scheme XX), which was used in a synthesis of dihydrosphingosine (**99**). (123, 124)

Scheme XX.
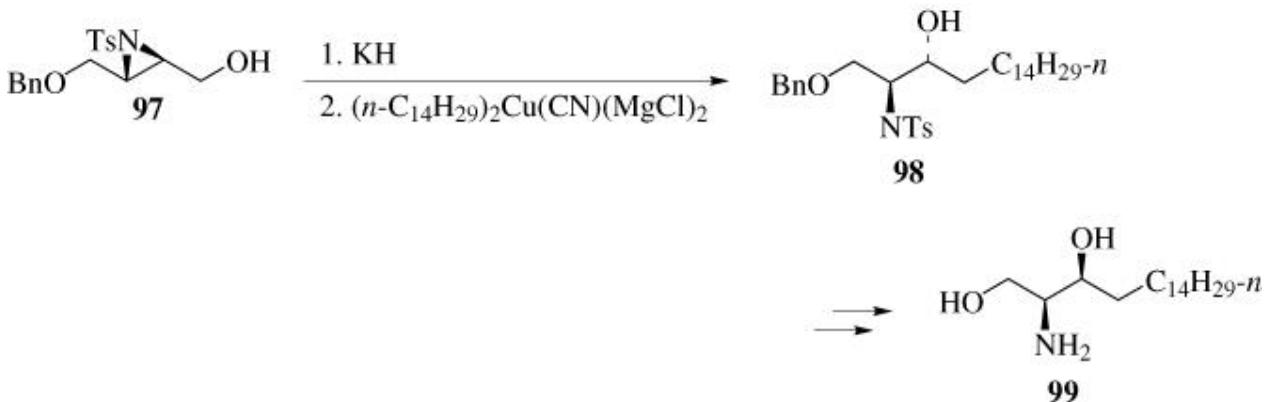
A recent application of the thia-Payne rearrangement has been reported. Thus, thia-Payne rearrangement of epoxide **100** (Scheme XXI) to thiirane **101** in 89% yield allowed for the synthesis of the novel nucleoside **102**, which was investigated for HIV-1 inhibitory activity. (65)
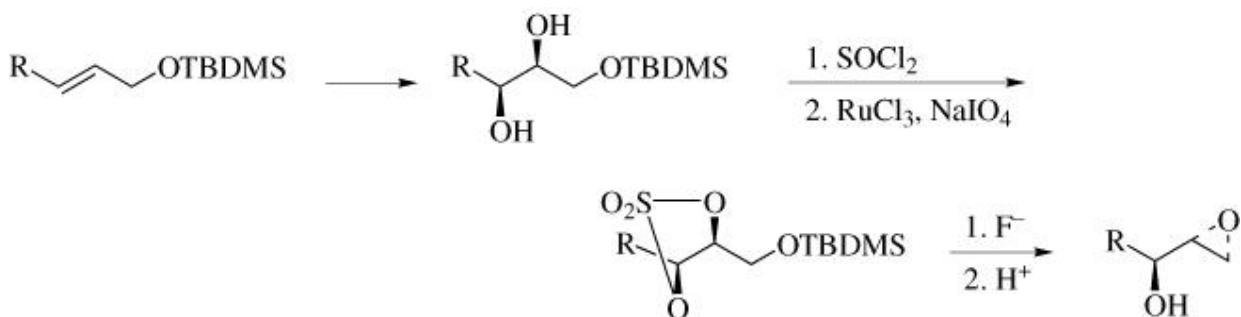
Scheme XXI.
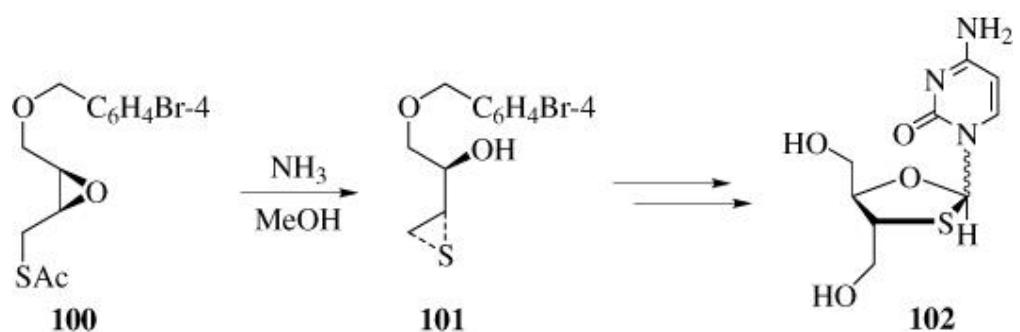
5. Comparison with Other Methods

5.1. Asymmetric Dihydroxylation Sequence I ("Cyclic Sulfate Method")

A method leading from allylic alcohols to 2,3-diols with nucleophilic opening at C-1 has been developed that involves 2,3-sulfates rather than 2,3-epoxides (Scheme XXII). (146, 147)

Scheme XXII.

This sequence begins with the initial asymmetric dihydroxylation (148-150) of an allylic silyl ether. Treatment of the resultant diol with sulfuryl chloride (151) or, preferably, thionyl chloride followed by oxidation (152, 153) generates a cyclic sulfate. This sulfate, when treated with fluoride in a nearly anhydrous solution followed by acidic hydrolysis, generates a terminal epoxide identical to that achieved by asymmetric epoxidation and epoxide migration. The cyclic sulfonate method has the advantage of avoiding the strongly basic conditions required for epoxide migration.

## 5.2. Asymmetric Dihydroxylation Sequence II ("C-3 Sulfonate Method")

A second alternative method involving asymmetric dihydroxylation has been developed in the area of pheromone synthesis (Scheme XXIII). (154) In this method, the triol from asymmetric dihydroxylation of an allylic alcohol is treated with sodium hydride and *N*-tosylimidazole (155) to provide the 1,2-epoxy-3-tosylate **103** directly. Coupling of this compound with an alkynyllithium reagent, treatment with potassium carbonate, and hydrogenation gives the target pheromone **104**.

Scheme XXIII.

103

104
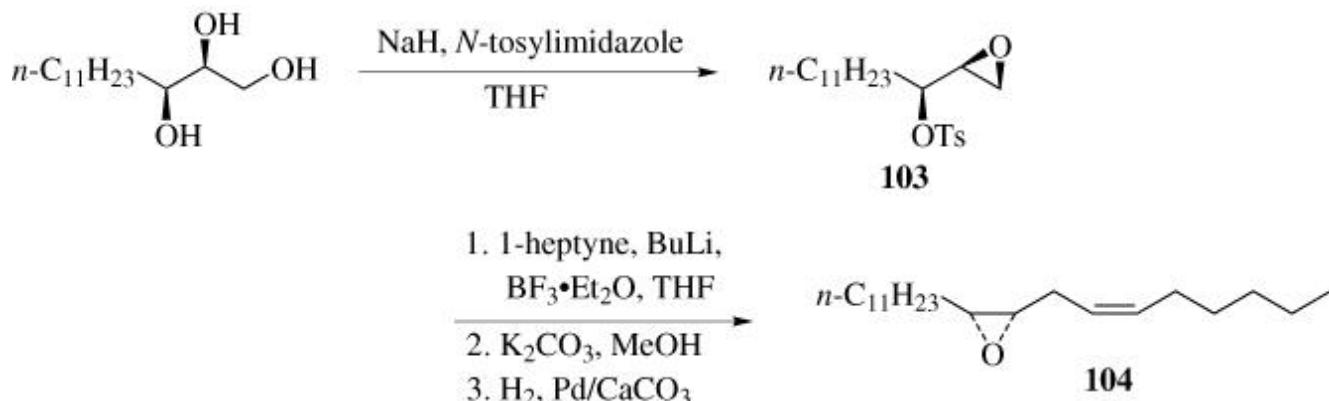
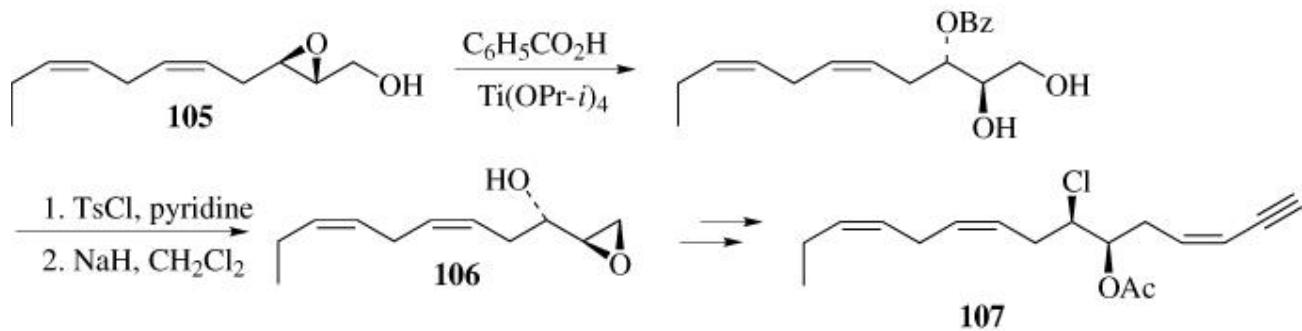### 5.3. C-2 Stereochemical Retention Sequence I ("Diol-Sulfonate Method")

Treatment of a 2,3-epoxy alcohol with an alkyl- or arylsulfonyl chloride followed by acid-catalyzed C-3 opening and sulfonate displacement using base (Eq. 50) is an alternative method of transposing epoxy alcohol functionality. (91) There is no inversion at C-2, and an epoxy alcohol of opposite relative configuration to that of epoxide migration is obtained.

(50)
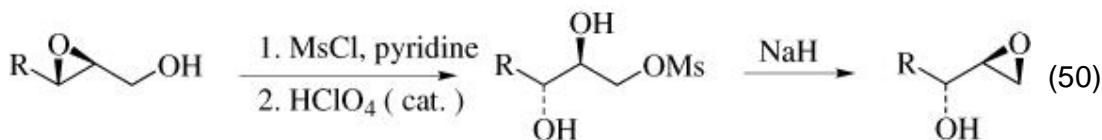
5.4. C-2 Stereochemical Retention Sequence II (Titanium-Mediated Opening)

A second method of transposing epoxy alcohol functionality without inversion at C-2 involves initial treatment of the product of asymmetric epoxidation with benzoic acid in the presence of titanium(IV) isopropoxide, (156) followed by C-1-selective sulfonylation and displacement. (157) For example, in the synthesis of laurediol-related polyene **107** (Scheme XXIV), epoxy alcohol **105** is converted into epoxy alcohol **106** in 60% yield by treatment with benzoic acid in the presence of titanium(IV) isopropoxide followed by tosylation and displacement. (158) Note that in this method, as in the diol-sulfonate method, it is C-3 that is inverted, not C-2.

Scheme XXIV.

5.5. C-2 Stereochemical Retention Sequence III (Lithium Salt Induced Double Inversion)

Several intriguing reports suggest that lithium salts can be used to transpose epoxy alcohol functionality without inversion at C-2 in only one or two steps. Treatment of epoxy alcohol **108** (Eq. 51) with lithium iodide in hot methanol gives rearranged epoxy alcohol **109** in 50% isolated yield, presumably by iodide addition at C-2 followed by displacement by the C-3 hydroxyl. (159) Similarly, treatment of 2,3-anhydropyranoside **110** (Eq. 52) with lithium bromide in refluxing 1,1,1-trichloroethane (which acts as a proton source for lithium alkoxides) gives bromodiol **111**, the product of opening at C-3 (pyranose numbering), displacement by the C-4 hydroxyl, and opening again at C-4. Treatment of this bromodiol with sodium methoxide gives the rearranged 3,4-anhydropyranoside **112** in 40% overall yield. (160)


(51)

(52)
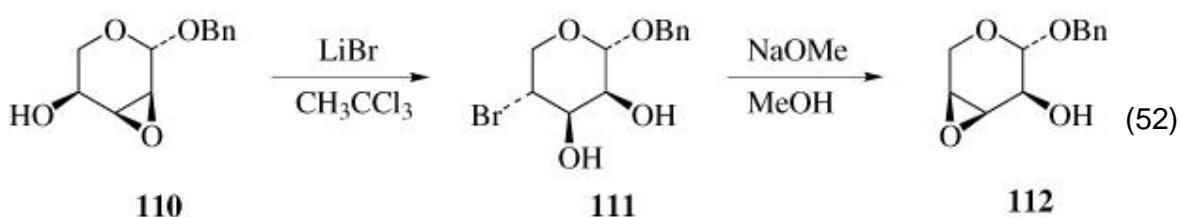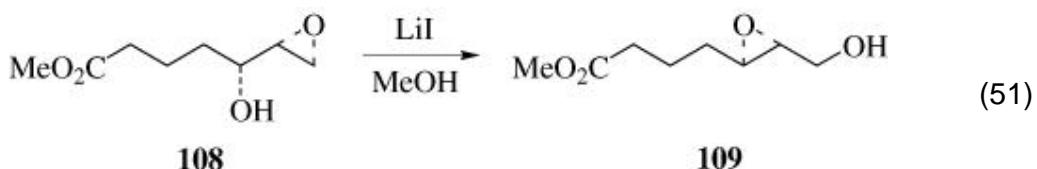
A similarly intriguing result involves the treatment of *trans*-2,3-epoxy alcohols with lithium iodide in hot dimethoxyethane, which results, effectively, in the

reverse of Eq. 52. A product analogous to **111** is isolated in moderate yield (Eq. 53). (161) Although the yields in these transformations, typically 65–85%, are not especially high, one must marvel at the complexity of the reaction, which almost certainly involves reversible addition of iodide at all three possible positions, C-1, C-2, and C-3. Ultimately, thermodynamic control leads to a preponderance of the primary iodide. The corresponding *cis*-2,3-epoxy alcohols are equally good substrates, and the product iododiols are excellent substrates for reduction, alkylation, and cuprate coupling reactions at C-1. (162)

$$\text{(65\%)} \quad \text{(53)}$$
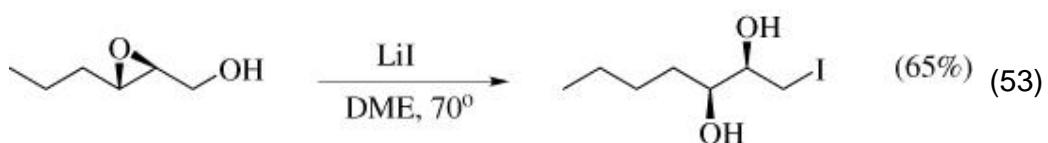
5.6. C-1-Directed C-2 Opening (Neighboring Group Assistance)

Finally, a strategy that effects the transformation of a 2,3-epoxy alcohol into a 1,3-diol with nucleophilic opening at C-2 is outlined in Eq. 54. Though outside the scope of this chapter and reviewed elsewhere, (13) this strategy is mentioned here as an alternative to epoxide migration.

$$\text{(54)}$$
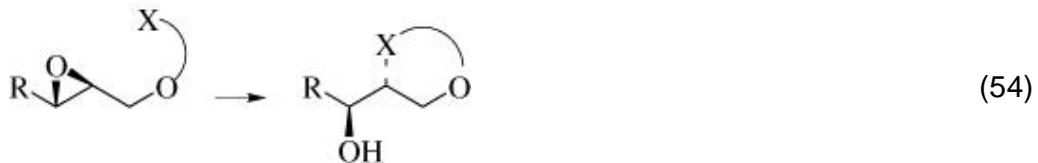
Examples include X = O using carbamates, (163-165) carbonates, (166) acetals, (167, 168) X = N using carbamates, (169) *N*-acylcarbamates, (170) and acetimidates, (171) and X = S using xanthates. (172, 173) C-1-Directed opening of cyclic sulfates has also been demonstrated, (174, 175) but as yet has been little explored.

6. Experimental Conditions

6.1. Epoxide Migration Without Opening

The classic conditions for epoxide migration are treatment of an epoxy alcohol or epoxy alcohol precursor with either aqueous barium hydroxide (2, 77) or sodium hydroxide (3) at room temperature. In the case of barium hydroxide, reactions are allowed to proceed for several hours; with sodium hydroxide, reactions are generally complete within 1 hour. (176) However, in many of these historically interesting examples yields are either low or not determined, and many represent crystallizations from complex mixtures. It is almost certain that substantial opening by hydroxide occurred. It now appears that the best way to effect epoxide migration without adventitious opening by hydroxide is the use of strictly anhydrous protic conditions such as freshly prepared sodium methoxide in methanol. (33, 34, 54, 177) Under these conditions migration is slower, and reactions typically run for at least 24 hours.

Other protic conditions that have been reported to be effective in specific cases include sodium sulfite (178) or potassium hydroxide (52, 179) in aqueous methanol, sodium hydroxide in acetone or *tert*-butyl alcohol, (73) lithium hydroxide in a two-phase water/ether system, (180) potassium *tert*-butoxide in *tert*-butyl alcohol, (181) potassium carbonate in hot isopropyl alcohol, (182) and brief treatment with room-temperature (32) or hot (183) aqueous potassium hydroxide.

Despite the fact that aprotic conditions were first reported to not effect epoxide migration, (3) several successful epoxide migrations utilizing aprotic bases have been reported. Conditions include sodium, potassium, or calcium hydride in tetrahydrofuran, (184) potassium *tert*-butoxide in dimethyl formamide, (185) and lithium diisopropyl amide (84) or *tert*-butyllithium (186) in tetrahydrofuran at –78°. In the case of *tert*-butyllithium, the system was sufficiently substituted that nucleophilic opening was strongly disfavored.

6.2. Epoxide Migration with Nucleophilic Opening in Situ

When in situ epoxide opening is desired, optimal conditions depend strongly on the nucleophile. Hydride addition has been effected using sodium borohydride in refluxing water/*tert*-butyl alcohol mixtures with only moderate yields and selectivity. (4) Lithium aluminum hydride in tetrahydrofuran has also been used in isolated cases. (84, 104) Cyanide addition has been accomplished in 30–60% yield using sodium cyanide in hot aqueous alcohol. (4, 85, 86, 131, 187) A variety of conditions for cuprate additions are tabulated in Table III-B.

In a detailed study of conditions for alkyl addition to *cis*-4-benzyloxy-2,3-epoxy-1-butanol (**113**, Eq. 55), it was found that addition

of lithium chloride enhances epoxide migration and leads to high yields and selectivities. (25, 90) For example, addition of methylcopper or lithium methyl(cyano)cuprate to epoxy alcohol **113** gives diol **114** in high yield only when lithium chloride is present. Reaction without lithium chloride or the use of more reactive cuprate reagents results in nonselective opening.

$$\text{(55)}$$
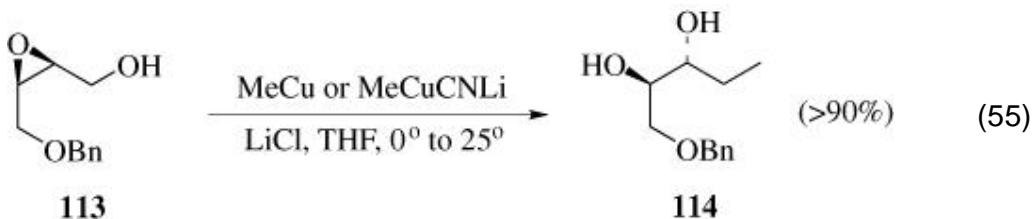
High yield and selectivity for the addition of azide to epoxy alcohol **113** result from using sodium azide in acetonitrile in the presence of lithium perchlorate. (93) Epoxide migration upon direct addition of amines has been attempted with only moderate success, as indicated in Table III-C, with yields of selected isomers ranging from 30–60%.

Where hydroxide addition is desired, use of excess aqueous potassium hydroxide and pH above 14 has been recommended. (14) Many studies have employed sodium, potassium, or lithium hydroxide in water or water/organic solvent mixtures, and most involve heating to 70–100°. Thiol addition has been carried out almost exclusively with thiophenol (31, 38, 99) or *tert*-butylthiol (91) in the presence of sodium hydroxide in aqueous *tert*-butyl alcohol or 1,4-dioxane. Heating is generally required.

6.3. Epoxide Migration with Electrophilic Trapping in Situ
Conditions for in situ electrophilic trapping of epoxy alcohols after epoxide migration have generally been standard conditions for epoxide migration: aqueous hydroxide (115, 188) or alcoholic potassium *tert*-butoxide. (114) However, as mentioned above (Eqs. 36–38), trapping of a primary alcohol over a tertiary one has been reported using allyl or benzyl bromide with sodium hydride in tetrahydrofuran, (112) and trapping of a secondary over a tertiary alcohol has been accomplished upon silylation. (113)

6.4. Aza-Payne Rearrangement
6.4.1. Forward Aza-Payne Rearrangement of 2,3-Epoxy Amines
Two reported procedures appear to be useful for the general transformation of a 2,3-epoxy amine into a 2-aziridinemethanol. Butyllithium/potassium *tert*-butoxide (58) in tetrahydrofuran at –78° is effective, (57) as is trimethylaluminum added to the lithium salt of the 2,3-epoxy amine (prepared

by treatment of the 2,3-epoxy amine with butyllithium). (61) In cases where both methods have been used on the same substrate, butyllithium/potassium *tert*-butoxide appears to give slightly better yields.

6.4.2. Forward Aza-Payne Rearrangement of N-Tosyl Epoxy Amines (63)

These transformations, only possible for highly biased substrates (*i.e.* tertiary sulfonamides), are carried out under typical epoxide migration conditions, namely 5% aqueous sodium hydroxide solution at room temperature or warmed briefly to reflux.

6.4.3. Reverse Aza-Payne Rearrangement of N-Tosyl-2-Aziridinemethanols (57)

The formation of an *N*-tosyl-2,3-epoxy amine from an *N*-tosyl-2-aziridinemethanol is best carried out using potassium hydride or sodium hydride in tetrahydrofuran or a mixture of tetrahydrofuran and hexamethylphosphoric triamide at reduced temperature. Yields are typically high, in the range 80–99%.

6.4.4. Forward Aza-Payne Rearrangement of 2,3-Epoxy Amines with Opening in Situ (62)

These reactions, using tertiary amine substrates, are performed using trimethylsilyl trifluoromethanesulfonate in dichloromethane at –78°. The epoxy amine is treated with the sulfonate for just a few minutes, then the nucleophile is added and the reaction is allowed to warm to room temperature and stirred for up to several days. Yields in the range 60–90% are typical.

6.4.5. Reverse Aza-Payne Rearrangement of N-Tosylaziridinemethanols with Addition in Situ (124)

These reactions, effective with a wide variety of cuprate reagents of the type $XCu(CN)Li \cdot LiBr$ or $X_2Cu(CN)Li_2$, are carried out in two steps. First the substrate is deprotonated in THF at –78° and allowed to warm to 0°. Then the reaction mixture is cooled again to –78° and treated with five equivalents of the cuprate reagent. Early procedures involving cuprate reagents directly without initial deprotonation by potassium hydride (57, 64) are no longer recommended. (20, 123, 124)Use of a higher-order cuprate reagent is critical; methyllithium and methylmagnesium bromide have been found to lead to complicated mixtures of products. For addition of cyanide, ytterbium cyanide/trimethylsilyl cyanide (189, 190) is effective. Yields are typically in the 80–95% range.

6.5. Thia-Payne Rearrangement
6.5.1. Thia-Payne Rearrangement of Epoxy Sulfides with Nucleophilic Opening at C-1 in Situ

These reactions are carried out much the same as for the forward aza-Payne rearrangement of 2,3-epoxy amines, with in situ opening using trimethylsilyl

triflate at low temperature. (66, 126, 127) Boron trifluoride etherate is an alternative Lewis acid for this transformation. (66, 125) Yields are typically in the range 50–80%. Reduction and acetylide addition using aluminum reagents involves treatment with two equivalents of reagent at 0° in hexane. (67)

6.5.2. Thia-Payne Rearrangement of Epoxy Sulfides with Nucleophilic Opening at C-2 in Situ

As mentioned above, recent reports indicate that trimethylaluminum (Eq. 17), (67) dimethyl(trimethylsilylethynyl)aluminum, (68) and phenylborinic acid (Eq. 19) (69) all react with 2,3-epoxy sulfides with opening at C-2. In the case of the aluminum reagent, reactions are carried out using two or three equivalents of reagent at 0° in hexane (67) or at –78° in dichloromethane. (68) Phenylborinic acid reactions are carried out with heating.

6.6. Prevention of Epoxide Migration

Over forty references to epoxide migration in the literature specifically describe substrates and conditions for which the reaction does *not* occur. In addition, over twenty of the cited examples in Tables I through IV are references to epoxide migrations as an unwanted side reaction. These numbers suggest that a brief discussion of the means available to prevent epoxide migration is in order. Table VII lists all substrates and associated conditions for which it was deemed by the original authors significant or unusual enough to relate their negative results. Many of these reactions (or nonreactions, as the case may be) are related to successful epoxide migrations of the same or similar substrate, and all of the tables have been cross-referenced for purposes of comparison.

Payne's study clearly showed that epoxide migration does not generally occur when the base used is sodium hydride in tetrahydrofuran. (3) What becomes clear from these additional reports is that weakly basic conditions, particularly amine or carbonate bases in tetrahydrofuran, methanol or water, rarely lead to rearrangement and can often be utilized to effect other changes in the system without effecting epoxide migration. Both aqueous potassium carbonate (32, 191, 192) and aqueous ammonia (43, 44) have been shown to effect epoxide opening without migration.

In the context of asymmetric epoxidation of acyclic allylic alcohols, epoxide migration was identified as a problem in the initial communication. (15) The difficulty arose from the strongly basic conditions used to hydrolyze the full equivalent of tartrate ester used in the reaction. However, with the use of distillation in the isolation of low molecular weight epoxy alcohols such as glycidol (193) and 4,5-epoxypent-1-en-3-ol (**11**, Scheme VI), (37, 106) and the discovery that inclusion of molecular sieves in the reaction mix allows the use of a ten- to twenty-fold decrease in the amount of tartrate ester, (16, 107, 194) the problem of epoxide migration in asymmetric epoxidation can now be largely avoided.

For carbohydrates, epoxide migration typically occurs upon formation of the epoxide from a 1,2-*trans*-hydroxy tosylate. Migration can be avoided completely if the base used for ring closure is the basic form of Amberlite 400 resin, (195) or if the addition of base is done slowly at high temperature. (74)

In terms of hydroxy protection, formyl groups (196) can be removed, and silylation, (196) acetylation, (53) tritylation, (53) benzylation, (197) and Mitsunobu inversion (165, 198, 199) can all be accomplished without migration.

Temperature can also be a critical factor in preventing epoxide migration. (53, 144) For example, with tosylate **115**, treatment with sodium methoxide (Scheme XXV) at low temperature produces unrearranged epoxide **116**, while treatment at room temperature produces the product of epoxide migration (**117**). (200)

Scheme XXV.
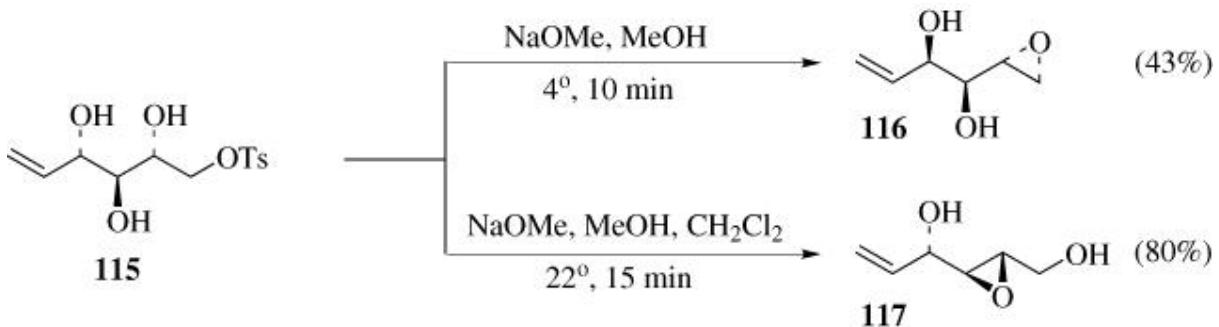
7. Experimental Procedures
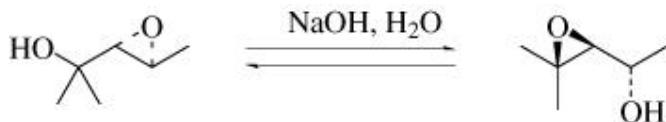
7.1.1. (±)-trans-2-Methyl-3,4-Epoxy-2-Pentanol and (2RS,3RS)-4-Methyl-3,4-Epoxypentan-2-ol (Epoxide Migration Using Aqueous Sodium Hydroxide) (3)

To 150 mL of 0.5 M aqueous sodium hydroxide previously cooled to about 5° was added 32.8 g (0.28 mol) of (±)-*trans*-2-methyl-3,4-epoxypentan-2-ol. The solution was allowed to warm to room temperature and remain there for 1 hour. After saturation with 100 g of ammonium sulfate, the solution was extracted with three 50-mL portions of chloroform. The combined chloroform extracts were washed with 25 mL of half-saturated aqueous ammonium sulfate, dried over magnesium sulfate, and concentrated on the steam bath to an internal temperature of 80–85°. Gas chromatographic analysis of the concentrate was made by means of a 2.5-m column packed with DC-710 on Fluoropak 80. The temperature was 100°, and a flow rate of 60 mL/min of helium was used. Emergence times of 9 and 15 minutes, respectively, were observed for the starting material (45%) and its isomer, (2*RS*,3*RS*)-4-methyl-3,4-epoxypentan-2-ol(55%).
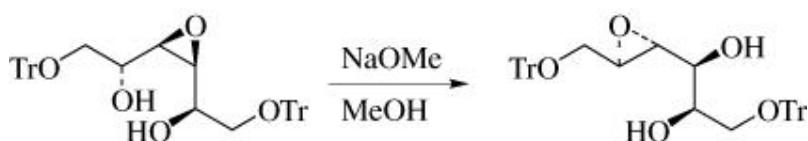
7.1.2. 2,3-Anhydro-1,6-Di-O-Trityl-D-Iditol (Epoxide Migration Using Sodium Methoxide in Methanol) (54)

To 25 mL of 0.2 M sodium methoxide in methanol was added 2.5 g (3.9 mmol) of 3,4-anhydro-1,6-di-*O*-trityl-D-altritol. After 18 hours at room temperature, the solution was heated to reflux for 1 hour. The products were examined by TLC using Kieselgel G that had been spread as a slurry with 2% boric acid. Water (30 mL) was added to the solution, and the product was isolated by extraction with chloroform. The resulting syrup (2.3 g) was crystallized from aqueous

methanol to give 2.1 g of the title compound (84%), mp 85°; [α]$_D$ +10.0° (*c* 10.1, CHCl$_3$).
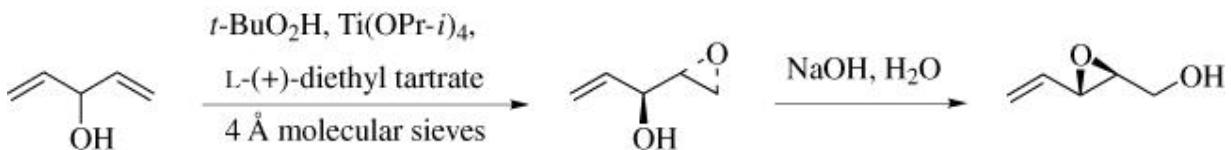
7.1.3. (2S,3S)-2,3-Epoxy-4-Penten-1-ol (Asymmetric Epoxidation with Epoxide Migration in Situ) (*37, 201*)

A mixture containing 15 g of activated powdered 4 Å molecular sieves in 450 mL of dichloromethane was cooled to –10°. To this vigorously stirred mixture was added 7.35 g (35.6 mmol) of L-(+)-diethyl tartrate and 8.44 g (29.7 mmol) of titanium(IV) isopropoxide. After cooling to –35°, the mixture was treated with 200 mL of a solution of *tert*-butyl hydroperoxide in dichloromethane (2.05 M, 410 mmol). After an additional 30 minutes stirring at –35°, a solution of 25.0 g (297 mmol) of divinylcarbinol in 20 mL of dichloromethane was added slowly over the course of 1 hour. After 7 days at –27°, the cold reaction mixture was slowly treated with 90 mL of a 16% w/w solution of acetic acid in water. The molecular sieves were removed by filtration, and the organic phase was removed and combined with five 40-mL dichloromethane extractions of the aqueous phase. After drying over sodium sulfate, the combined organic phases were concentrated and distilled in a 30-cm Vigreux column at water aspirator pressure (21 mmHg) to give 22.1 g of a colorless liquid, which by NMR spectroscopy was found to be 92% (3*S*,4*R*)-4,5-epoxy-1-penten-3-ol (the product of asymmetric epoxidation without epoxide migration) and 8% of a mixture of *tert*-butyl alcohol and *tert*-butyl hydroperoxide.

A solution of 2.10 g of a crude mixture prepared as described above (containing 19.9 mmol of unrearranged epoxy alcohol) in 30 mL of 0.5 M aqueous sodium hydroxide was stirred at room temperature for 45 minutes. After neutralization to pH 8 with ammonium chloride, the mixture was extracted four times with 30 mL of chloroform, and the combined organic phases were dried over sodium sulfate. Evaporation of solvent and Kugelrohr distillation (90–100°, 20 mmHg) provided a mixture containing 1.69 g of the title compound (85%) along with approximately 0.06 g of (3*S*,4*R*)-4,5-epoxy-1-penten-3-ol (3%), and 0.10 g of a mixture of *tert*-butyl hydroperoxide and *tert*- butyl alcohol; [α]$_D$ –54.0° (*c* 1.43, CHCl$_3$); IR (neat) 3600–3300, 3090, 2990, 2920, 2870 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.08 (dd, *J* = 2.3, 1.7 Hz, 1 H), 3.29 (br, 1 H), 3.39 (dddd, *J* = 7.5, 1.7, 1.5, 1.5 Hz, 1 H),

3.66 (dd, J = 12.5, 4.5 Hz, 1 H), 3.92 (dd, J = 12.5, 2.3 Hz, 1 H), 5.31 (ddd, J = 10.0, 1.5, 1.0 Hz, 1 H), 5.49 (ddd, J = 17.5, 1.5, 1.0 Hz, 1 H), 5.61 (ddd, J = 17.5, 10.0, 7.5 Hz, (1 H).

7.1.4. (2RS,3RS)-1-Benzyloxy-2,3-Pentanediol (Epoxide Migration with Cuprate Addition in Situ) (25)

A solution of methyl(cyano)cuprate (Solution A) was prepared as follows: to a suspension of 0.35 g (3.91 mmol) of copper(I) cyanide in 5 mL of tetrahydrofuran under argon at 0° was added dropwise over about 5 minutes 2.76 mL of a solution of methyllithium in ethyl ether (1.4 M, 3.86 mmol). The colorless solution was stirred for 10 minutes at 0°, warmed to 25° over 30 minutes, then cooled again to 0°. Separately, a solution of the lithium salt of (±)-*cis*-4-benzyloxy-2,3-epoxy-1-butanol (Solution B) was prepared as follows: to a solution of 0.5 g (2.58 mmol) of the epoxy alcohol and 0.90 g (21.4 mmol) of lithium chloride in 10 mL of tetrahydrofuran under argon at –78° was added dropwise 1.65 mL of a solution of *n*-butyllithium in hexane (1.56 M, 2.58 mmol). The solution was stirred for 5 minutes at –78°, allowed to warm to 0°, and then stirred at that temperature for 10 minutes. The reaction was effected by the addition of Solution A to Solution B via cannula at 0° followed by warming to room temperature over 2 hours. The reaction mixture was then stirred for a further 12 hours and then cautiously treated with 5 mL of saturated aqueous ammonium chloride. The mixture was stirred for 1–2 hours to aid removal of copper residues. Ethyl ether (20 mL) was then added, and the organic layer was separated. The aqueous phase was extracted twice with 20 mL of ethyl ether, and the combined organic phases were dried over magnesium sulfate, filtered, and concentrated to give 0.51 g of the title compound as a colorless oil (95%), IR (film) 3400, 3100, 3060, 3030, 2970, 2930, 2870, 1600, 1500, 1465, 1445, 1385, 1370, 1320, 1285, 1210, 1180, 1120, 1100, 1075, 1030, 1020, 980, 905, 830, 750, 730, 710, 695 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.37–1.53 (m, 2 H), 3.20 (br s, 2 H), 3.40–3.65 (m, 4 H), 4.48 (s, 2 H), 7.29 (s, 5 H).
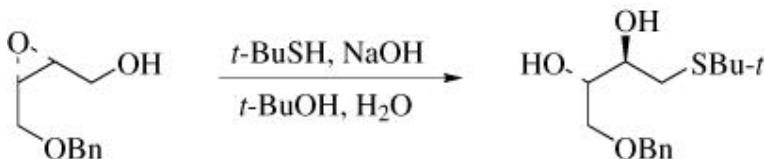
7.1.5. (2S,3R)-1-Benzyloxy-4-tert-Butylthio-2,3-Butanediol (Epoxide Migration with Nucleophilic Opening in Situ by tert-Butyl Thiol) (91)

The solvents required for this reaction were deoxygenated prior to use by the rapid passage of nitrogen through the solvent for not less than 30 minutes. A solution of 3.02 g (1.56 mmol) of (2R,3S)-4-benzyloxy-2,3-epoxy-1-butanol in 7.8 mL of *tert*-butyl alcohol and 7.8 mL of 0.5 M aqueous sodium hydroxide was immersed in a preheated oil bath at 70°. The reaction mixture was stirred vigorously as a dropwise addition of a solution of 0.176 g (0.220 mL, 1.96 mmol) of *tert*-butyl thiol in 2 mL of *tert*- butyl alcohol was conducted over a period of 40 minutes. During this time the oil bath temperature rose to 78°. Stirring was continued for 20 minutes after the dropwise addition was complete. The reaction mixture was then cooled to room temperature and neutralized with saturated aqueous ammonium chloride. Sufficient water was added to clarify the aqueous phase, and the phases were then separated. The aqueous phase was extracted five times with dichloromethane, and the combined organic phases were washed with saturated aqueous ammonium chloride, dried over sodium sulfate, concentrated, and the residue was dried under high vacuum. Flash chromatography gave 0.276 g of the title compound as an oil (62%), $[\alpha]_D$ −10.6° (c 1.98, CHCl$_3$); $[\alpha]_D$ +5.8 (c 0.80, EtOH); IR (NaCl) 3400, 3090, 3070, 3030, 2960, 2930, 2900, 2870, 1455, 1365, 1100, 740, 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.32 (s, 9 H), 2.61–2.85 (m, 3 H), 2.92 (d, J = 4.1 Hz, 1 H), 3.64 (m, 2 H), 3.81 (m, 1 H), 4.54, 4.58 (AB, J_{AB} = 12 Hz, 2 H), 7.25–7.41 (m, 5 H).
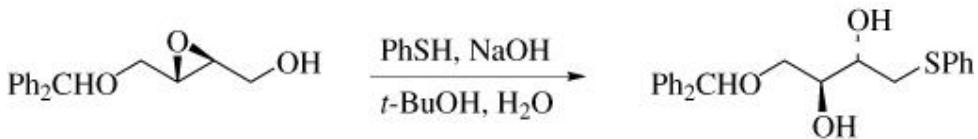
7.1.6. (2S,3S)-1-Benzhydryloxy-4-Phenylthio-2,3-Butanediol (Epoxide Migration with Nucleophilic Opening in Situ by Thiophenol) (99)

To a vigorously stirred refluxing mixture of 8.075 g (29.87 mmol) of (2S,3S)-4-benzhydryloxy-2,3-epoxy-1-butanol in 150 mL of *tert*-butyl alcohol

and 150 mL of 0.5 M aqueous sodium hydroxide was added via syringe over a period of 3 hours a solution of 4 mL (38.8 mmol) of thiophenol in 40 mL of *tert*-butyl alcohol. The reaction mixture was cooled to room temperature, and the two phases were separated. The organic phase was concentrated and diluted with 150 mL of dichoromethane, and the aqueous phase was extracted with portions of dichloromethane. The combined organic phases were washed successively with 1 M aqueous sodium hydroxide, water, and brine. Drying over sodium sulfate and concentration gave a crude solid, which was recrystallized from dichloromethane/hexane to give 8.070 g of the title compound as white needles (71%), mp 76–77.5°; [α]$_D$ +43.4° (*c* 1.15, ethanol); IR (KBr) 3400, 2900 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ2.55 (d, *J* = 5.1 Hz, 1 H), 2.71 (d, *J* = 4.1 Hz, 1 H), 2.99 (dd, *J* = 13.9, 8.6 Hz, 1 H), 3.33 (dd, *J* = 13.9, 3.6 Hz, 1 H), 3.61 (dd, *J* = 9.6, 5.8 Hz, 1 H), 3.68 (dd, *J* = 9.6, 3.8 Hz, 1 H), 3.77–3.88 (m, 2 H), 5.38 (s, 1 H), 7.20–7.40 (m, 15 H).
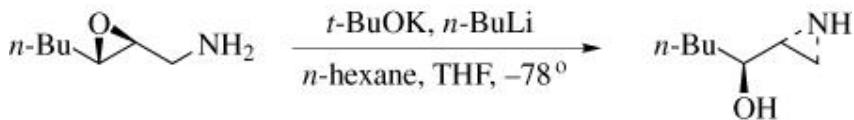
7.1.7. (2R, α S)- α -Butyl-2-Aziridinemethanol. (Forward Aza-Payne Rearrangement of an Epoxy Amine Using Super Base (58)) (57)

To a stirred solution of 505 mg (4.5 mmol) of potassium *tert*-butoxide in 5 mL of tetrahydrofuran under argon at –78° was added dropwise 2.76 mL of a solution of *n*-butyllithium in hexane (1.63 M, 4.5 mmol), and the mixture was stirred for 10 minutes. To this mixture was added with stirring a solution of 388 mg (3.0 mmol) of (2*S*,3*S*)-2,3-epoxyheptylamine in 3 mL of tetrahydrofuran. Stirring was continued for 90 minutes. With vigorous stirring, the reaction was quenched at –78° with 4 mL of saturated aqueous ammonium chloride. The inorganic salts were removed by filtration through Celite, and the Celite was washed twice with 40 mL of ethyl ether. The combined organic solutions were dried over magnesium sulfate and concentrated under reduced pressure to give 328 mg of the title compound as a colorless solid (85%). Recrystallization from ethyl ether/*n*-hexane (1:5) gave colorless crystals, mp 65°; [α]$_D$ +39.9° (*c* 1.69, CHCl$_3$); IR (CHCl$_3$) 3450, 3330 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.92 (m, 3 H), 1.28–1.43 (m, 4 H), 1.45–1.57 (m, 3 H), 1.61 (d, *J* = 3.6 Hz, 1 H), 1.72 (d, *J* = 5.9 Hz, 1 H), 2.14 (ddd, *J* = 5.9, 3.6, 3.6 Hz, 1 H), 3.63 (m, 1 H).
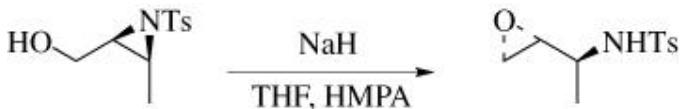
7.1.8. (2S,3R)-N-Tosyl-3,4-Epoxy-2-Butylamine (Reverse Aza-Payne Rearrangement of an N-Tosyl-2-Aziridinemethanol Using Sodium Hydride) (57)

To a stirred suspension of 24 mg (1 mmol) of sodium hydride in a mixture of 2 mL of tetrahydrofuran and 0.33 mL of hexamethylphosphoric triamide under argon at –40° was added a solution of 60.3 mg (0.25 mmol) of (2S,3S)-3-methyl-1-tosyl-2-aziridinemethanol in 2 mL of tetrahydrofuran. The mixture was allowed to warm to room temperature, and stirring was continued for 2 hours. The reaction mixture was cooled to –78° and quenched with 2 mL of 5% aqueous citric acid with stirring. The mixture was extracted with ethyl acetate, and the extract was washed successively with saturated citric acid, brine, 5% aqueous sodium hydrogen carbonate, and brine. After drying over magnesium sulfate and concentration, flash chromatography (silica, 1:3 ethyl acetate/n-hexane) gave 56 mg of the title compound as a crystalline mass (92%). Crystallization from ethyl ether gave colorless crystals, mp 102–103°; [α]$_D$ +9.9° (c 0.88, CHCl$_3$); IR (CHCl$_3$) 3385, 1602, 1335, 1152, 1092 cm^{-1}; ^{1}H NMR (300 MHz CDCl$_3$) δ 1.14 (d, J = 6.9 Hz, 3 H), 2.43 (s, 3H), 2.69 (m, 2 H), 2.92 (m, 1 H), 3.60 (dddd, J = 15.5, 13.8, 6.9, 2.9 Hz, 1 H), 4.55 (d, J = 8.5 Hz, 1 H), 7.29–7.32 (m, 2 H), 7.73–7.82 (m, 2 H).
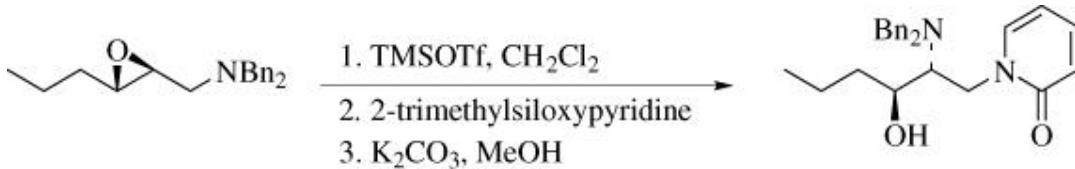
7.1.9. (2RS,3SR)-2-Dibenzylamino-1-(2-Pyridon-1-yl)-3-Hexanol (Aza-Payne Rearrangement of a Tertiary Epoxy Amine with in Situ Nucleophilic Opening by an Amide Equivalent) (62)

To a solution of 0.30 g (1.02 mmol) of (±)-trans-N,N-dibenzyl-2,3-epoxyhexylamine in 6 mL of dichloromethane under nitrogen at –78° was added 0.27 g (0.24 mL, 1.15 mmol) of trimethylsilyl trifluoromethanesulfonate. After 10 minutes, 0.34 g (2.04 mmol) of 2-trimethylsiloxypyridine was added, and the solution was allowed to warm to room temperature and stirred for 5 days. To the solution were added 9 mL of

methanol and 0.80 g (5.8 mmol) of potassium carbonate, and the mixture was stirred an additional 12 hours. The solvent was removed in vacuo, and the residue was purified by column chromatography (flash silica, 85:15 ethyl acetate/petroleum ether) to give 0.37 g of the title compound as a colorless viscous oil (93%), IR (thin film) 3480–3180, 2940, 2900, 2880, 1650, 1570, 1540, 1450, 1245, 1140, 1065, 840, 750, 700 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, J = 6.9 Hz, 3 H), 1.25–1.44 (m, 4 H), 2.91–2.92 (m, 1 H), 3.16 (d, J = 6.9 Hz, 1 H), 3.68 (d, J = 14.1 Hz, 2 H), 3.80 (dd, J = 13.5, 6.3 Hz, 1 H), 3.93 (d, J = 14.1 Hz, 2 H), 4.03–4.06 (m, 4H), 4.59 (dd, J = 13.5, 5.7 Hz, 1 H), 6.21 (t, J = 6.6 Hz, 1 H), 6.51 (d, J = 9.0 Hz, 1 H), 7.21–7.38 (m, 12 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.02, 19.18, 38.46, 47.65, 54.56, 61.19, 69.79, 106.26, 120.84, 127.00, 128.33, 128.38, 138.78, 139.55, 163.14.

7.1.10. (2S,3S)-2-[(4-Methylphenyl)sulfonamido]-3-Pentanol (Reverse Aza-Payne Rearrangement of an N-Tosyl-2-Aziridinemethanol with Cuprate Addition in Situ) (124)

To a stirred suspension of 40 mg (1 mmol) of potassium hydride in 2 mL of tetrahydrofuran under argon at –78° was added 121 mg (0.5 mmol) of (2S,3S)-3-methyl-1-tosyl-2-aziridinemethanol in 2 mL of tetrahydrofuran. The mixture was allowed to warm to 0°, and stirring was continued for 1 hour. To the mixture cooled to –78° was added by syringe 6 mL of a solution of Me$_2$Cu(CN)Li$_2$· 2LiBr in a 1:1 mixture of tetrahydrofuran and ether (0.42 M, 2.5 mmol), prepared from 224 mg (2.5 mmol) of copper(I) cyanide and 3.3 mL of a solution of methyllithium/lithium bromide in ethyl ether (1.5 M, 5 mmol). The mixture was stirred at –78° for 30 minutes. With vigorous stirring at –78°, the reaction was quenched with 4 mL of a 1:1 mixture of saturated aqueous ammonium chloride and 28% aqueous ammonium hydroxide. The mixture was extracted with a 4:1 mixture of ethyl ether and dichloromethane. Evaporation, drying, and flash chromatography (silica, 1:2 ethyl acetate/n-hexane) gave 128 mg of the title compound as a crystalline mass (99%). Crystallization from ethyl ether/n-hexane (3:1) gave colorless crystals, mp 90°; [α]$_D$ –3.3° (c 0.546, CHCl$_3$); IR (CHCl$_3$) 3550, 3400, 1598 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ0.88 (t, J = 7.4 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.44 (m, 2 H), 1.80 (br, 1 H), 2.43 (s, 3 H), 3.21–3.37 (m, 2 H), 4.78 (m, 1 H), 7.29–7.31 (m, 2 H), 7.75–7.79 (m, 2 H).
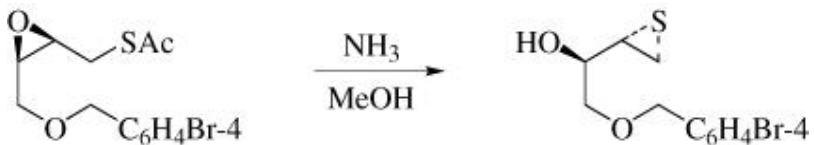
7.1.11. (2R,3S)-1-(4-Bromobenzyloxy)-3,4-Epithio-2-Butanol (Thia-Payne Rearrangement of an Epoxy Thioacetate) (65)

To a solution of 4.60 g (13.9 mmol) of (2R,3R)-S-acetyl-4-[(4-bromobenzyl)oxy]-2,3-epoxy-1-butanethiol in 120 mL of methanol at 0° was added 12 mL of a saturated solution of ammonia in methanol. The reaction mixture was stirred at 0° for 3 hours, diluted with dichloromethane, washed with water, dried, filtered, and evaporated. Column chromatography (1:9 ethyl acetate/toluene) gave 3.57 g of the title compound as a colorless oil (89%), ^{1}H NMR (250 MHz, CDCl$_3$) δ 2.20 (d, J = 8.0 Hz, 1 H), 2.40 (dd, J = 5.6, 0.8 Hz, 1 H), 2.44 (dd, J = 6.5, 0.8 Hz, 1 H), 3.26 (ddd, J = 6.5, 5.6, 4.0 Hz, 1 H), 3.53 (dd, J = 9.5, 5.8 Hz, 1 H), 3.61 (dd, J = 9.5, 5.6 Hz, 1 H), 3.85 (ddd, J = 8.0, 5.7, 4.0 Hz, 1 H), 4.57 (s, 2 H), 7.2–7.5 (m, 4 H); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 21.2, 38.1, 69.6, 72.8, 74.1, 121.7, 129.3, 131.6, 136.9.
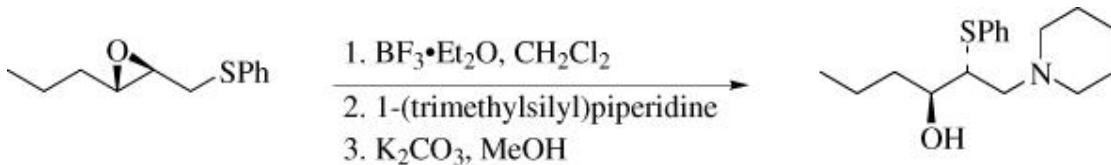
7.1.12. (2RS,3SR)-2-Phenylthio-1-Piperidino-3-Hexanol (Thia-Payne Rearrangement of an Epoxy Sulfide with Nucleophilic Opening in Situ Using a Silyl Amine) (66)

To a solution of 100 mg (0.48 mmol) of (±)-trans-2,3-epoxyhexyl phenyl sulfide in 2 mL of dichloromethane at –78° was added 68 mg (0.48 mmol) of trimethylsilyl trifluoromethanesulfonate. After 10 minutes, 76 mg (0.48 mmol) of 1-(trimethylsilyl)piperidine was added, and the solution was stirred for an additional 10 minutes at –78°. The solution was allowed to warm to 0° and stirred at that temperature overnight. Potassium carbonate (227 mg, 1.64 mmol) and 3 mL of methanol were added, and the mixture was stirred for 2 hours at room temperature. The mixture was concentrated, redissolved in 10 mL of dichloromethane, and washed twice with 2 mL of water. The aqueous washings were back-extracted four times with 5 mL of dichloromethane, and

the combined dichloromethane solutions were dried over magnesium sulfate, filtered, and concentrated. Flash chromatography using 15 g of kieselgel and a 1:8:1191 mixture of aqueous ammonia (specific gravity 0.880), ethanol, and dichloromethane gave 56 mg of the title compound as a yellow oil (40%), IR (thin film) 3660–3040, 3080, 3060, 2960, 2940, 2860, 2820, 1580, 1480, 1460, 1440, 1380, 1350, 1310, 1270, 1190, 1155, 1135, 1110, 1090, 1070, 1040, 1030, 990, 965, 860, 740, 690 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, J = 7.0 Hz, 3 H), 1.20–1.70 (m, 9 H), 1.90–2.03 (m, 1 H), 2.17–2.43 (m, 2 H), 2.43–2.67 (m, 2 H), 2.73 (AB, △ v = 6.8, J = 10.4 Hz, 2 H), 3.16 (dt, J = 10.4, 4.6 Hz, 1 H), 3.73 (dt, J = 11.5, 4.6 Hz, 1 H), 7.21–7.34 (m, 3H), 7.39 (d, J = 7.5 Hz, 2 H).

8. Tabular Survey

Reactions involving epoxide migration are grouped in Tables I–;IV. Aza-Payne rearrangements are presented in Tables V-A and V-B; thia-Payne rearrangements are collected in Table VI. Table VII is a collection of observations by authors specifically identifying substrates and conditions for which epoxide migration did not occur.

Tables I-A and I-B both present epoxide migrations in acyclic systems. Here *acyclic system* refers specifically to those structures for which the epoxide itself is not a part of a fused ring system in either isomer. Table I is separated into two parts: reactions where the substrate itself underwent the reaction (Table I-A) and reactions where the epoxy alcohol undergoing migration was generated in situ (Table I-B). Epoxide migration in *cyclic systems* (the epoxide is part of a fused ring system in one or both isomers) are similarly presented in Tables II-A and II-B.

In Tables I-A and II-A, the major isomer is tabulated in the first column and the minor in the second so as to allow a quick comparison of the effect of substituents on isomer ratio. Where one set of conditions favored one isomer and another set of conditions favored the other isomer, this organization requires two separate entries with switched major/minor isomers. The isomer ratios given here may or may not be true equilibrium ratios. In some cases they are simply ratios based on isolated yield.

Tables III-A through III-E present epoxide migrations which were followed by in situ nucleophilic addition. This includes reduction by hydride (Table III-A), addition of carbon-based nucleophiles including cuprates, acetylides, and cyanide (Table III-B), addition of nitrogen-based nucleophiles (amines, azide, and sulfonamides, Table III-C), addition of oxygen-based nucleophiles including hydroxide and alkoxides (Table III-D), and addition of thiols and halides (Table III-E).

Table IV presents epoxide migrations that involve in situ electrophilic trapping, either intra- or intermolecular.

Aza-Payne reactions are catalogued in Tables V-A (simple rearrangements) and V-B (rearrangement with in situ opening of the aziridine or aziridinium ion). In Table V-A the oxirane isomer is in the first column and given the designation **I**, while the aziridine isomer is in the second column as **II**. The starting isomer is then identified as either oxirane (**I**) or aziridine (**II**), and for the purposes of this chapter, "forward aza-Payne" reaction is thus from **I** to **II**.

Table VI presents all thia-Payne rearrangements reported to date. All start with the oxirane, all except one of which involve in situ opening of a presumed thiirane intermediate.

Table VII is somewhat of a departure from traditional *Organic Reactions* format in that it is a comprehensive collection of cases where the title reaction was specifically reported *not* to occur. This table is cross-referenced to the other tables to help the reader identify the sometimes subtle differences between successful and unsuccessful epoxide migration. It includes both reactions for which mild conditions allowed for synthetic transformations in the presence of a potentially migrating epoxide and reactions for which slight changes in substrate stereochemistry or regiochemistry led to surprisingly different epoxide behavior. Table VII does not include alicyclic systems bearing hydroxy and epoxide groups in a cis configuration, where migration is inherently impossible.

In all tables, entries are organized first by increasing number of carbons *in the contiguous carbon system containing the migrating heterocycle*, then by *total number of hydrogen atoms*. This organization was chosen so as to place related entries as close together as possible. Structural formulas have been normalized to emphasize the migration of interest. In particular, although many of the references are to the carbohydrate literature, all carbohydrates have been recast in a standard organic acyclic or alicyclic notation. The choice of this notation was made so as to allow a general overview of the reactions without a major distinction between carbohydrates and noncarbohydrates and to avoid two specific problems: the assumptions of conformation implicit in more standard carbohydrate notation and the odd sort of depiction required for representing *trans*-epoxides in Fischer projections. As much as possible, pyranose systems have been explicitly named so that those readers familiar with carbohydrate chemistry can make identifications quickly.

The following abbreviations are used in the tables:

(*R,R*)-**15**	See Eq. 8
Ac	acetyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
DBN	1,5-diazabicyclo[3.4.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate

DET   diethyl tartrate
DMAP   4-(dimethylamino)pyridine
DMF   dimethylformamide
DMSO   dimethyl sulfoxide
DMTS   dimethylthexylsilyl
EE   ethoxyethyl
HMPA   hexamethylphosphoric triamide
LDA   lithium diisopropylamide
Ms   methanesulfonyl
py   pyridine
TBDMS   *tert*-butyldimethylsilyl
TBDPS   *tert*-butyldiphenylsilyl
Tf   trifluoromethanesulfonyl
THF   tetrahydrofuran
THP   tetrahydropyranyl
TMS   trimethylsilyl
Tr   trityl
Ts   *p*-toluenesulfonyl

Table 1-A. Epoxide Migration in Acyclic Systems

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Table 1-B. Epoxy Alcohol Formation in Situ and Epoxide Migration in Acyclic Systems

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Table 2-A. Epoxide Migration in Cyclic Systems

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Table 2-B. Epoxy Alcohol Formation in Situ and Epoxide Migration in Cyclic Systems

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Table 3-A. Epoxide Migration with Reduction in Situ

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Table 3-B. Epoxide Migration with C-Nucleophile Opening in Situ

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Table 3-C. Epoxide Migration with N-Nucleophile Opening in Situ

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Table 3-D. Epoxide Migration with O-Nucleophile Opening in Situ

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Table 3-E. Epoxide Migration with Halide and S-Nucleophile Opening in Situ

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Table 4. Epoxide Migration with Electrophilic Trapping in Situ

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Table 5-A. Aza-Payne Rearrangements

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Table 5-B. Aza-Payne Rearrangements with Nucleophilic Opening in Situ

[View PDF](#)

Table 6. Reactions Involving Thia-Payne Rearrangements

[View PDF](#)

Table 7. Conditions not Leading to Epoxide Migration

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TABLE 1-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
		I or II	NaOH, H₂O, rt, 1 h	93:7	(—)	3
		I or II	"	90:10	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	58:42	(—)ᵃ	3
		I or II	"	58:42	(—)	42
		II	(R,R)-15 (1–2 mol%), CF₃CH₂OH, rt, 6 h	80:20	I (81)	55
		I	NaOH, H₂O, rt, 3 h	60:40	II (38)	65
		II	KOH, H₂O, THF, reflux, 1.5 h	90:10	(—)	30
		I	NaH, THF, 18-crown-6, 25°, 12 h	75:25	(—)	25
		I	BuLi, LiCl, THF, 25°, 4 h	70:30	(—)	25
		I	KOH, H₂O, THF, reflux, 2.5 h	50:50	(—)	30
		II	NaOH, H₂O, 25°, 1.5 h	54:46	(—)	25
		II	BuLi, LiCl (2 eq), THF, 25°, 12 h	60:40	(—)	25
		II	NaOH, H₂O, THF, reflux, 2 h	60:40	I (60)	202
		II	NaOD, D₂O, 0°, 45 min	77:23	(—)	37
		II	NaOD, D₂O, 0°, 2 h	90:10	(—)	37
		II	NaOD, D₂O, rt, 30 min	97:3	(—)	37
		II	NaOH, H₂O, rt, 30 min	97:3	(89)ᶜ	37
		II	NaOH, H₂O, –10°	—	I (89)	72
		II	NaOH, H₂O, 22°, 1 h	90:10	(74)	71
		II	NaOD, D₂O	93:7	(—)	70
		I or II	NaOH, H₂O, rt, 1 h	92:8	(82)ᵃ	3
		I or II	"	90:10	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	70:30	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	65:35	(—)	42

C₄

C₅

48

49

TABLE I-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (*Continued*)

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
		I or II	NaOH, H$_2$O, rt, 1 h	80:20	(—)	42
		II	NaOH, H$_2$O, *t*-BuOH	—	(—)	203
		I	NaH, THF, rt	77:23	(96)	26
		I	NaH, THF, rt	—	I (96)[g]	26
		I	NaOD, D$_2$O, rt, 1 h	52:48	(—)	70
		I or II	NaOH, H$_2$O, rt, 1 h	56:44	(—)	3
		I or II	"	56:44	(—)	42
		I	NaOD, D$_2$O, rt, 1 h	>95:5	(—)	70
		I or II	NaOH, H$_2$O, rt, 1 h	95:5	(—)	3
		I or II	"	95:5	(—)	42
		I	NaOH, H$_2$O, rt, 1 h	88:12	(—)	42
		I	NaOH, H$_2$O, 20°, 0.2 h	57:43	(—)	83
		I	NaOH, H$_2$O, 20°, 0.2 h	90:10	(—)	83
		II	NaOH, H$_2$O, 20°, 0.2 h	93:7	(—)	83
		II	NaOH, H$_2$O, 20°, 0.2 h	55:45	(—)	83
		II	NaOH, H$_2$O, *t*-BuOH, 60°, 45 min	—	I (69)	204

C$_6$

TABLE 1-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (*Continued*)

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
		II	1. NaOMe, MeOH, rt, 18 h 2. reflux, 1 h	—	I (84)	54
		II	NaOH, THF, rt	—	I (79)	133
		I or II	NaOH, H₂O, rt, 1 h	88:12	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	95:5	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	55:45	(—)	42
		I or II	NaOH, H₂O, rt, 1 h	93:7	(—)	42
		II	DBN, MeOH, 90°	—	I (20)	159
		II	NaOMe, MeOH	—	I (50)	159
		I	NaOD, D₂O, rt, 1 h	50:50	(—)ᵃ	24
		II	KOH, H₂O, DMSO, 130–140°, 15 min	—	I (78)	183
		II	K₂CO₃, MeOH, rt, 24 h	—	I (71)	177
		II	K₂CO₃, MeOH, rt, 24 h	—	I (74)	177
		II	NaOH, H₂O	>90:10	(—)	205
		I	NaOH, H₂O	98:2	(—)	205

TABLE 1-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (Continued)

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
		I	NaOH, H₂O	92:8	(—)	205
		II	NaOH, H₂O, rt, 1 h	94:6[h]	(64)	206
		I	Na₂SO₃, MeOH, H₂O, rt, 12 h	60:40	(—)	178
C₁₀		II	NaOH, H₂O, rt, 6 h	95:5	I (93)	207
		I	NaOMe, MeOH, reflux, 4 h	70:30	(—)	92
		II	K₂CO₃, MeOH, rt, 24 h	—	I (79)	177
C₁₁		II	K₂CO₃, MeOH, rt, 24 h	—	I (73)	177
		II	K₂CO₃, MeOH, rt, 24 h	—	I (74)	177
		II	PhSLi, THF	—	I (42)[e,f]	208
C₁₂		II	NaOH, t-BuOH, H₂O, rt, 2 h	>300:1	(81)	73
		II	NaOH, acetone, H₂O, rt, 1 h	>300:1	(87)	73
C₁₃		II	K₂CO₃, MeOH, rt, 24 h	—	I (73)	177
		II	LiC₂Me, BF₃·Et₂O, THF, −70°, 3 h	—	I (72)	209
C₁₄		II	NaOH, t-BuOH, H₂O, rt, 6 h	>155:1	(86)	73

TABLE I-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (Continued)

	Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture		Refs.
					I:II	Yield (%)	
C_{15}	(structure, Ph, OH)	(structure, Ph, OH, O)	II	t-BuOK, DMF, rt, 1 h	—	I (85)	185
C_{16}	(structure, Ph, Ph, OH, O)	(structure, HO, Ph, Ph, O)	II	KOH, MeOH, H₂O, rt, 3 h	—	I (82)ᶜ	179
C_{18}	(structure, OH, O, OH)	(structure, OH, OH, O)	II	NaOH, H₂O, t-BuOH	—	I (91)ᵈ	210
C_{20}	(structure, O, OH, HO)	(structure, OH, O, HO)	II	K₂CO₃, MeOH, rt	—	I (80)	181
	(structure, OH, O, HO)	(structure, OH, O, HO)	II	t-BuOK, t-BuOH, 30–40°	—	I (89)ᵈ	181
	(structure, O, OH)	(structure, O, OH)	II	NaOH, H₂O, t-BuOH, rt, 3 h	—	I (95)	130
	(structure, O, OH)	(structure, O, OH)	II	NaOH, H₂O, t-BuOH, rt, 3 h	—	I (95)	130
C_{21}	(structure, Ph, O, C₆H₄Cl-2, Ph, OH)	(structure, HO, O, C₆H₄Cl-2, Ph, Ph)	II	KOH, MeOH, rt, 15 h	—	I (95)	1
	(structure, Ph, O, Ph, Ph, OD)	(structure, DO, O, Ph, Ph, Ph)	II	NaOCD₃, CD₃OD	95:5	I (—)	70
	(structure, Ph, O, Ph, Ph, OH)	(structure, HO, O, Ph, Ph, Ph)	II	KOH, H₂O, MeOH, rt, 2 days	—	I (>60)	211

TABLE 1-A. EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (Continued)
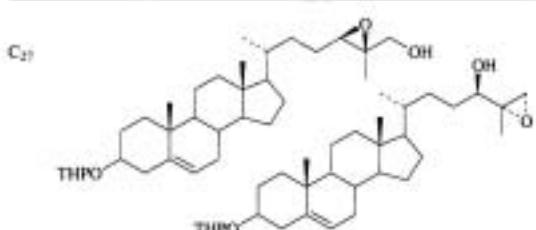
	Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture		Refs.
					1:II	Yield (%)	
C_{27}			II	K_2CO_3, i-PrOH, reflux, 2 h	—	I (84)	182
			II	K_2CO_3, i-PrOH, reflux, 2 h	—	I (85)	182

[a] See also Table VII under the same carbon count.

[b] The isomer ratio is based on isolated yield.

[c] The product was accompanied by the opening of I by PhS⁻ (II: RSPh = 42:58).

[d] Both isomers were 1:1 mixtures of stereoisomers at the position marked with an asterisk.

TABLE 1-B. EPOXY ALCOHOL FORMATION IN SITU AND EPOXIDE MIGRATION IN ACYCLIC SYSTEMS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C4	Bu4NF, CH2Cl2, 25°, 20 h	**I:II = 2:1**	25
C5	1. Ti(OPr-i)4 (1 eq), t-BuO2H, L-(+)-DET, CH2Cl2, –20° 2. tartaric acid, NaOH, H2O	(—)[b]	106
C6		I II III[a]	212

Conditions	X	I (%)	II (%)	III (%)
NaOMe, MeOH, rt, 24 h	OMe	52	14	31
PhSH, H2O, 0°, 1.5 h	SPh	17	20	—
t-BuSH, H2O, 0°, 0.3 h	SBu-t	67	24	—
1. NaN3, acetone, H2O, –22°, 10 h 2. rt, 10 h	N3	16	1	26
Et2NH, H2O, 45°, 17 h	NEt2	—	—	37
1. morpholine, THF, rt, 24 h 2. 60°, 48 h	(morpholine)	—	7	10

TABLE 1-B. EPOXY ALCOHOL FORMATION IN SITU AND EPOXIDE MIGRATION IN ACYCLIC SYSTEMS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Ti(OPr-*i*)₄ (100 mol%), *t*-BuO₂H, L-(−)-DET, CH₂Cl₂, −20°	I:II = 50:50 (—)[b]	213
	KOH, H₂O, 20°, 10 min	(62)[a,b] (38)[a,b]	45
	1. NaOH, H₂O, pH > 12.6 2. Na₂CO₃, EtOAc	(24)	214
C₃		I[a,b] II[a,b]	32
	KOH, H₂O, rt, 5 min KOH, H₂O, rt, 15 min KOH, H₂O, rt, 18 h	**I:II** 100:0 2:1 0:100	
	NaOMe, MeOH, CH₂Cl₂, 22°, 15 min	(80)[b]	200
	NaOMe, MeOH, CH₂Cl₂, 22°, 15 min	I II[a] I:II = 50:50 (74)[b]	200

[a] This was the product of epoxide migration.
[b] See also Table VII under the same carbon count.

TABLE 2-A. EPOXIDE MIGRATION IN CYCLIC SYSTEMS

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
C₅ α-D-arabino	α-D-lyxo	I	Ba(OH)₂, H₂O, rt, 5 h	73:27ᵃ	(71)	77
		II	"	75:25ᵃ	(84)	77, 176
β-L-lyxo	β-L-arabino	I	Ba(OH)₂, H₂O, rt, 5 h	67:33ᵃ	(82)	77
		II	"	70:30ᵃ	(83)	77
C₆ β-D-gulo	β-D-galacto	I	NaOH, EtOH, H₂O	—	(—)	215
		II	NaOH, MeOH	80:20	(—)	80
		II	Ba(OH)₂, H₂O, rt, 5 h	90:10	(—)	2
α-L-arabino	α-L-lyxo	II	NaOCD₃, CD₃OD, rt, 2 h	90:10	(—)	70, 79
β-D-manno	β-D-altro	I or II	NaOMe, MeOH, rt 16–20 h	67:33	(—)	75
		II	NaOMe, MeOH, reflux, 1 h	—	I (79)	74
β-D-galacto	β-D-gulo	I or II	NaOMe, MeOH, rt, 15 h	—	I (70)	75
		I or II	NaOMe, MeOH, rt, 16–20 h	90:10	(—)	
α-D-gulo	α-D-galacto	II	0.01 M NaOH, H₂O, 42°, 2.5 h	—	I (13)ᵇ	216
		II	0.01 M NaOH, H₂O, 42°, 1.5 h	55:45		76
α-D-gulo	α-D-galacto	II	NaOMe, MeOH, rt, 1 h	55:45ᵃ	(83)	176, 217
α-D-gulo	α-D-galacto	II	NaOMe, MeOH, rt, 1 h	55:45ᵃ	(78)	217

TABLE 2-A. EPOXIDE MIGRATION IN CYCLIC SYSTEMS (Continued)

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture		Refs.
				I:II	Yield (%)	
α-D-manno	α-D-altro	I	NaOMe, MeOH, rt 1.5 h	—	I (85)	74
C$_7$		I	LiOEt, EtOH, 60°, 7 h	—	(—)^c	218
		II	"natural product isolation"	50:50	(—)	143, 144
		II	NaOMe, MeOH, rt	50:50	(—)^d	219
		II	NaOMe, MeOH, rt	70:30	(—)	143, 144
		II	NaOMe, MeOH, 50°, 25 min	75:25	(—)	143, 144
α-D-manno	α-D-altro	I	NaOCD$_3$, CD$_3$OD, rt, 2 h	57:43	(—)	70, 79
α-D-galacto	α-D-gulo	II	NaOCD$_3$, CD$_3$OD, rt, 4 h	92:8	(—)	70, 79
α-L-gulo	α-L-galacto	I or II	NaOCD$_3$, CD$_3$OD, rt, 2 h	93:7	(—)	70, 79
C$_{11}$		I or II	LDA	100:0	(—)	84
		I or II	LDA	100:0	(—)	84
		II	BuLi, THF, −78° to rt, 1h	80:20	(90)	186
C$_{12}$		II	NaOD, DMSO-d$_6$, rt, 2 h	2:1	(—)	220
		I	NaOH, H$_2$O, rt, 5 h	2:1	(—)	220
C$_{13}$		II	LiOH, H$_2$O, Et$_2$O, 23°, 4 h	—	I (90)	180

TABLE 2-A. EPOXIDE MIGRATION IN CYCLIC SYSTEMS (Continued)

Major Isomer (I)	Minor Isomer (II)	Initial Isomer	Conditions	Final Mixture I:II	Yield (%)	Refs.
C_{14}		II	NaH, THF, 40°, 9.5 h	86:14[a]	(71)	184
		II	CaH₂, THF, 50°, 5 h	90:10[a]	(65)	
		II	KH, THF, 40°, 6.5 h	69:31[a]	(100)	184
C_{15}		II	LiOH, H₂O, Et₂O, 23°, 4 h	—	I (73)	180
C_{16}		II	LiOH, H₂O, Et₂O, 23°, 4 h	—	I (82)	180
C_{18}		I	KOH, H₂O	74:26[d]	(92)	140
C_{20}		II	LiBHEt₃, THF, 25°, 16 h	—	I (80)	82
		II	NaBH₄, NaOH, s-BuOH, 25°, 12 h	—	I (85)	82
C_{27}		II	KOH, MeOH, reflux, 1.5 h	—	(68)	50, 52
		II	"	—	(76)	50, 52

[a] The isomer ratio is based on isolated yield.
[b] The product was isolated as the acetate.
[c] Additional products due to decomposition were identified.
[d] See also Table VII under the same carbon count.

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₅		**I** + **II**ᵃ	221

		X	I (%)	II (%)
	Me₂NH, H₂O, 25°, 15 h	Me₂N	—ᵇ	12ᵇ
	piperidine, 90°, 0.5 h	(piperidine) N	34	20
	morpholine, 25°, 13 h	(morpholine) N	—	46

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(structure, OMe)	1. MeLi, THF, Et₂O, −78° 2. H₂O, HOAc, −25°	β-D-ribo (35) + α-L-lyxo (22) + α-L-arabino (19)ᵈ	70
α-D-xylo	NaOMe, MeOH, 55–60°, 1 h	α-D-lyxo (67) + α-D-arabino (15)ᵃ	77
α-D-xylo	NaOMe, MeOH, rt, 1.5 h	β-L-arabino (87) + β-L-lyxo (—)ᵃ	77
α-D-xylo	NaOMe, MeOH, rt, overnight	α-D-lyxo (75) + α-D-arabino (16)ᵈ	176
β-L-arabino	NaOMe, MeOH, rt, 6 h	β-L-lyxo (52) + β-L-arabino (9)ᵃ	77
C₆ (structure)	1. EtMgBr, THF, −70 to −15°, 12 d 2. NH₄Cl, H₂O	(37)ᵇ	222
(structure, OMe)	1. MeLi, THF, Et₂O, −78°	α-D-allo (I)ᵇ + α-D-gulo (II)ᵇ + α-D-galacto (III)ᵃ	70

		I (%)	II (%)	III (%)
	2. HOAc, −78°	42	47	6
	2. HOAc, −25°	37	34	26
	2. H₂O, 0°	49	6	40

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(structure, OMe)	1. MeLi, THF, Et₂O, −78° 2. H₂O, HOAc, −25°	α-L-talo (38) + α-L-galacto (22) + α-L-gulo (20)ᵃ	70

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	BuLi, THF	(26) + (7)[a]	223
	NaOMe, CHCl₃, MeOH	(0) + (60)[a] + (0)[a]	224
β-D-altro	NaOMe, MeOH, reflux, 4 h NaOH, H₂O, rt, 24 h	(20) (85) β-D-altro	78, 81 78, 81
β-D-gulo	1. NaOMe, CH₂Cl₂ 2. LiAlD₄, THF	(75)	225
	Ba(OH)₂, H₂O, rt, 5 h	(6)[h]	226
β-D-gluco	NaOMe, MeOH, rt, 12 h	β-D-manno (—) + β-D-altro (85)[c]	227
α-D-gluco	NaOMe, MeOH, reflux, 90 min	α-D-manno (I) + α-D-altro (II)[a] I:II <1:9	(68–72)	228
α-D-manno	NaOH, H₂O, rt, 18 h	(46)[b] α-D-manno	74
β-D-gluco	NaOMe, MeOH, rt, 16 h	β-D-manno (40) + β-D-altro (21)[a]	75
β-D-galacto	NaOMe, MeOH, rt, 6 h	β-D-gulo (initially) + β-D-galacto (strongly preferred)[a]	75

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
β-D-gluco	NaOMe, MeOH	β-D-manno (major) + β-D-altro (minor)[a]	229
β-D-gluco	NaOMe, MeOH, rt, 6 h	β-D-manno (65) + β-D-altro (29)[a]	230
	NaOMe, MeOH, CHCl₃	(10)[b] + (15)[a] + (10)[a]	224
	NaOMe, MeOH, CHCl₃	(12)[a] + (21) + (15)[a] + (12)[a] + (0)[a]	224
α-D-gluco	NaOH, H₂O, reflux, 1.5 h	α-D-galo (—)[a] + α-D-galacto (—)[a] (46)	231, 232
	1. NaOMe, CH₂Cl₂, MeOH, 50° 2. acetylation	(65) + (<10)[a]	233

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaOMe, MeOH, reflux, 2 h	(40) + (15)[a]	96
C₇	1. NaOMe, MeOH, 0°, 30 min 2. 50°, 35 min	(15)[b] + (46)[c] + (28)[c]	143, 144
	NaOMe, MeOH, THF, reflux	(33)[b] + (48)[c]	234
C₁₂	MeMgI, THF, Et₂O, rt, 3 d	(11) + (70)[c]	84
		I + II[a] + III[a]	84

	I:II:III
MeLi, LiCl, THF, rt, 4 d	57:43:0
MeLi, THF, rt, 4 d	47:53:0
MeLi, ether, rt 10 d	49:35:16
MeMgI, THF, rt, 3 d	0:100:0

	Conditions	Products		
	RLi, THF, 0°	I + II[a]		104

R	I (%)	II (%)
Me	77	15
Bu	—	—

 I + II[a]   84, 235

X	I:II
H	84:16
Me	86:14
n-Bu	70:30
s-Bu	24:76
t-Bu	0:100

Conditions	
NaBH₄, THF, rt, 3 d	H 84:16
MeLi, THF, rt, 1 h	Me 86:14
n-BuLi, THF, rt, 1 h	n-Bu 70:30
s-BuLi, THF, rt, 1 h	s-Bu 24:76
t-BuLi, THF, rt, 1 h	t-Bu 0:100

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

M(CH₂)₈OTBDMS, THF

M	I (%)	II (%)	236
BrMg	40	24	
Li	0	89	

84

X	I:II
NaBH₄, THF, rt, 3 d	H	71:29
LiAlH₄, THF, rt, 1 h	H	65:28
MeLi, THF, rt, 1 h	Me	100:0
n-BuLi, THF, rt, 1 h	*n*-Bu	0:100
s-BuLi, THF, rt, 1 h	*s*-Bu	0:100
t-BuLi, THF, rt, 1 h	*t*-Bu	0:100
PhLi, THF, rt, 1 h	Ph	74:26

PhMgBr, THF

(51)

237

C₁₄

1. 5% K₂CO₃, MeOH, rt, 3 h
2. Ac₂O, py

(61)

184

1. Bu₄NF, THF
2. Ac₂O, py

184

I (%)	II (%)
rt, 0.5 h	77	11
rt, 20 h	35	25
40°, 8 h	30	26

C₁₈

KOH, H₂O, rt, 6 h

(63)

140

TABLE 2-B. EPOXY ALCOHOL FORMATION IN SITU AND EPOXIDE MIGRATION IN CYCLIC SYSTEMS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	I (%)	II (%)	III (%)
K₂CO₃, MeOH, rt, 4 h	16	75	—
KOH, H₂O, rt 2 h	—	80	5

140

C₁₉

LiAlH₄, THF, 0° to rt, 1.5 h

(86)   (1)   (8)ᵃ

238

KMnO₄, CuSO₄

(39)

239

C₂₆

KOH, MeOH, H₂O, rt, 70 min

(31)   (62)ᵃ

240

ᵃ This was a product of epoxide migration.
ᵇ See also Table VII under the same carbon count.

TABLE 3-A. EPOXIDE MIGRATION WITH REDUCTION IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs
C_4	NaBH$_4$, NaOH, H$_2$O, t-BuOH, reflux	(70)	4
C_5	NaBH$_4$, NaOH, H$_2$O, t-BuOH, reflux	(15) + (39)[a]	4
	NaBH$_4$, NaOH, H$_2$O, t-BuOH, reflux	(60)	4
	NaBH$_4$, NaOH, H$_2$O, t-BuOH, reflux	(67)	4
C_{10}	NaBH$_4$, NaOH, H$_2$O, t-BuOH, reflux	(24) + (53)[a]	4

C_{11}–C_{14}

 I + II[a]

R	I:II	(%)	
LiAlD$_4$, THF, rt, 1 d	Me	0:100	48	84
LiAlD$_4$, THF, rt, 4–6 d	Me	63:37	92	104
LiAlD$_4$, THF, rt, 4–6 d	n-Bu	51:49	90	104

C_{15}	NaOMe, MeOH	(23)	241

C_{18} LiAlD$_4$, THF, rt, 1 d   I + II[a] 104

R	I:II	(%)
n-C$_8$H$_{17}$	53:47	87
CH$_2$(CH$_2$)$_7$OTBDMS	45:55	77
CH$_2$C≡CC$_3$H$_{15}$-n	65:35	81

[a] This was a product of epoxide migration.

TABLE 3-B. EPOXIDE MIGRATION WITH C-NUCLEOPHILE OPENING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_4 4-BrC$_6$H$_4$ ... OH	1. NaCN, EtOD, D$_2$O, reflux, 8 h 2. HCl 3. toluene, reflux	4-BrC$_6$H$_4$ ... OH (60)	85
BnO ... OH	1. NaCN, MeOH, H$_2$O, dioxane, 80° 2. H$^+$	BnO ... OH (35)	4
... OH OBn	1. NaCN, EtOH, H$_2$O, reflux, 8 h 2. toluene, azeotrope	BnO ... OH (38)	187

RM, LiCl, THF, 0 to 25°

R—I + II + III[a]   25, 90

R	RM	I:II:III	(%)
Me	MeCu	1:1:50	94
Me	MeCuCNLi	1:1:50	95
Me	Me$_2$CuLi	2:3:1	95
Bu	BuCuCNLi	1:1:50	90
Ph	PhCu•DMS	1:1:50	92
CH$_2$=C(CH$_3$)	[CH$_2$=C(CH$_3$)]$_2$CuCNLi$_2$	1:1:20	86

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
... OH OTBDMS	RC≡CLi, BF$_3$•Et$_2$O, −70°, 1 h	I + II[a]	87

R	I (%)	II (%)
n-C$_5$H$_{11}$	40	40
n-C$_8$H$_{17}$	32	51
n-C$_{11}$H$_{23}$	19	59

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_5 DMTSO ... OH	RC≡CLi, BF$_3$•Et$_2$O, −30°, 1 h	DMTSO ... + DMTSO ... R = n-C$_6$H$_{10}$ (17) (75)[a]	88
C_6 ... OH	PhC≡CLi, BF$_3$•Et$_2$O, −78°, 30 min	HO ... + HO ... (47) (34)[a]	89

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TABLE 3-B. EPOXIDE MIGRATION WITH C-NUCLEOPHILE OPENING IN SITU (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	RC≡CLi, BF$_3$·Et$_2$O, −78°, 30 min	**I** + **II**[c]	89

R	I:II	II (%)
n-C$_5$H$_{11}$	19:81	81
Ph	28:72	77

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_8$	1. BuLi, LiCl, THF, −78° 2. MeCu(CN)Li, 0°, 5 min 3. rt, 16 h	(60)	25, 90
	1. BuLi, LiCl, THF, −78° 2. (MeLi)$_{1.2}$CuCN, 0°, 30 min 3. rt, 4 days	(29) + (62)[a]	25
C$_9$	1. NaCN, EtOH, H$_2$O, reflux, 16 h 2. toluene, azeotrope	(65)	86
C$_{10}$	1. NaCN, EtOH, H$_2$O, reflux, 16 h 2. toluene, azeotrope	(56)	86
	1. NaCN, EtOH, H$_2$O, reflux, 5.5 h 2. TsOH, benzene, reflux, 1 h	(40)	131
	RC≡CLi, BF$_3$·Et$_2$O, −78°, 30 min	**I** + **II**[c]	89

R	I:II	II (%)
n-C$_5$H$_{11}$	20:80	87
Ph	45:55	94

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	n-C$_5$H$_{11}$C≡CLi, BF$_3$·Et$_2$O, −78°, 30 min	(50) + (50)	89

TABLE 3-B. EPOXIDE MIGRATION WITH *C*-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$ *n*-C$_{10}$H$_{21}$ ⬭ OH	HC≡CLi, BF$_3$•Et$_2$O, −78°	*n*-C$_{10}$H$_{21}$ ... OH ŌH (18) + *n*-C$_{10}$H$_{21}$ ... OH ŌH (57)^a	89
C$_{15}$ OTBDMS	C$_2$H$_2$, *n*-BuLi, BF$_3$•Et$_2$O, THF, −78 to −40°	OH ŌH OTBDMS (72)	242

^{a} This was a product of epoxide migration.

TABLE 3-C. EPOXIDE MIGRATION WITH *N*-NUCLEOPHILE OPENING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₄	1. Me₂NH, KOH, H₂O, rt 2. Ac₂O, py	 I:II:III = 4:21:75 (89)	91
	1. Et₂NH, KOH, H₂O, reflux 2. Ac₂O, py	(45)ᵇ	91
	NaN₃, LiClO₄, MeCN	(89)ᶜ	93
	NaNHTs, H₂O, dioxane, 60°	(61)	4
	1. Et₂NH, KOH, H₂O, reflux 2. Ac₂O, py	(64)ᵇ	91

TABLE 3-C. EPOXIDE MIGRATION WITH *N*-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C5	NaN3, *n*-C16H33NMe3Br, 1,4-dioxane, H2O, 100°	(52)	94
C6	1. NH3, KOH, H2O 2. Ac2O, py	(<30)	91
	1. Me2NH, Me4NOH, H2O, rt 2. Ac2O, py	I:II:III = 19:7:74 (94)	91
C7	NaN3, DMF, H2O, reflux, 14 h	(30) (25)[a]	95
C9	1. Et2NH, KOH, H2O, rt 2. Ac2O, py	(86) (12)[a]	91
C10	1,2,4-triazole, *t*-BuOK, *t*-BuOH, 70°, 15 h	(59)	92
	1. Me2NH, KOH, H2O, rt 2. Ac2O, py	I:II:III = 20:7:73 (94) III[a] (55)	91
	1. Et2NH, KOH, H2O, reflux 2. Ac2O, py	(63)[b]	91

[a] This was a product of epoxide migration.

[b] This was the yield of purified product. Significant amounts of other isomers were present in the crude mixture.

[c] See also Table VII under the same carbon count.

TABLE 3-D. EPOXIDE MIGRATION WITH *O*-NUCLEOPHILE OPENING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₃	1-Naphthol, NaOH, *t*-BuOH, H₂O	(54)	38
C₄	NaOH, H₂O, *t*-BuOH, reflux	(—)	243
	NaOH, H₂O, *t*-BuOH, 80°, 1 h	(70–80)	244
	NaOH, H₂O, *t*-BuOH, 80°, 1 h	(70–80)	244
C₅	KOH, H₂O, rt	I + II* + III* + IV + V	245
	KOH, H₂O, dioxane, reflux, 16 h	I + II* I:II = 14:86	36, 37
	NaOH, H₂O, *t*-BuOH, 70°, 15 h	(79)	31
	NaOH, H₂O, *t*-BuOH, 70°, 15 h	(75)	31
	NaOH, H₂O, *t*-BuOH, 70°, 15 h	(75)	31

time	I (%)	II (%)	III (%)	IV (%)	V (%)
5 min	43	18	0	14	24
15 min	23	28	0	12	37
2 h	0	12	25	13	50
24 h	0	7	20	12	61
48 h	0	0	0	15	85

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOH, H₂O, *t*-BuOH, 70°, 15 h	(78)	31
C₆ β-D-manno	KOH, H₂O, 100°, 5 h	(—)ᵃ β-D-manno	111
β-D-galo	KOH, H₂O, 100°, 5 h	β-D-galacto (I) + β-D-gluco (II)ᵃ I:II 83:17 (—)	111
β-D-galacto	KOH, H₂O, 100°, 5 h	β-D-gluco (I) + β-D-galacto (II)ᵃ I:II 17:83 (—)	111
dextran sulfate	NaOH, H₂O, 100°, 5 h	(—) α-D-manno	246, 247
C₆	1. KOH, H₂O, rt 2. Ac₂O, HClO₄	(48)	191
	1. KOH, H₂O, rt 2. Ac₂O, HClO₄	(44)	191
	1. KOH, H₂O, rt 2. Ac₂O, HClO₄	(56)	192
	1. KOH, H₂O, rt 2. H₂SO₄, MeOH 3. Ac₂O, py	(30) + (22) + (8)ᵃ	192

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TABLE 3-D. EPOXIDE MIGRATION WITH *O*-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaOMe, rt, 24 h 2. reflux, 5 h 3. Ac₂O, py	(—)	2
	1. Ba(OH)₂, rt 2. 100°, 3 h 3. Ac₂O, py	(21)ᵈ + (9)ᵈ	2
	NaOH, H₂O, 100°, 1.5 h	(27)ᵈ + (53)ᵈ	54
	KOH, H₂O, 20°, 20 h	(5)ᶜ + (52)ᵈ	45
	KOH, H₂O, 20°, 30 min	(74)	45
	1. Me₃SCHCONEt₂, THF, 0°, 2 days 2. rt, 1 day	(70)ᶜ + (16)ᵉ	248
	NaOH, t-BuOH, reflux, 24 h	(80)	249
	1. NaOMe, MeOH, rt, 48 h 2. Ac₂O, py	(23)	250
	NaOH, H₂O, 80°, 6 h	(20) + (68)ᵉ	35
I + II, I:II = 57:43	NaOMe, MeOH, 70°, 15 h	IIIᵈ + IVᵈ (—), III:IV = 34:66	83

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
I + **II** I:II = 90:10	NaOMe, MeOH, 70°, 15 h	**III**[a] + **IV**[a] III:IV = 55:45	(—) 83
I + **II** I:II = 7:93	NaOMe, MeOH, 70°, 15 h	**III**[a] + **IV**[a] III:IV = 18:82	(—) 83
I + **II** I:II = 45:55	NaOMe, MeOH, 70°, 15 h	**III**[a] + **IV**[a] III:IV = 63:37	(80) 83
C$_7$	1. KOH, H$_2$O, rt 2. Ac$_2$O, py	(47)	32
	1. NaOH, H$_2$O, t-BuOH, reflux 2. Ac$_2$O, py	(18)[a] + (36)[a,b]	133
	1. NaOH, H$_2$O, t-BuOH, reflux 2. Ac$_2$O, py	(45)	133
BnO	1. NaOH, H$_2$O, t-BuOH, 70°, 24 h 2. Ac$_2$O, Et$_3$N, DMAP	(65)	133
	1. NaOH, H$_2$O, t-BuOH, 70°, 24 h 2. Ac$_2$O, Et$_3$N, DMAP	(60)	133
EEO	1. NaOH, H$_2$O, t-BuOH, reflux 2. HCl 3. Ac$_2$O, py	(66)	133
	1. NaOH, H$_2$O, t-BuOH, reflux 2. HCl 3. Ac$_2$O, py	(66)	133
OEE	1. NaOH, H$_2$O, t-BuOH, reflux 2. HCl 3. Ac$_2$O, py	(73)	133
	1. NaOH, H$_2$O, t-BuOH, reflux 2. HCl 3. Ac$_2$O, py	(97)	133

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	KOH, DMSO, H_2O, 12 h	(50)	251
	NaOH, H_2O, 1,4-dioxane, 70°, 40 h	(63)	252
	1. NaOH, EtOH, H_2O 2. acetylation	 I:II = 16:84 (—)	34
	1. NaOEt, EtOH, rt, 18 h 2. OH⁻, H_2O, EtOH, rt, 1 h 3. Ac_2O, py	II (88)	33, 34
C₈	1. NaOEt, EtOH, rt, 24 h 2. OH⁻, H_2O, EtOH, rt, 1 h 3. Ac_2O, py	(68)	33
	NaOH, H_2O, 1,4-dioxane, 70°, 24 h	(37)	253
	NaOH, H_2O, 1,4-dioxane, 70°, 24 h	(64)	254, 255
	NaOH, H_2O, 1,4-dioxane, 70°, 18 h	(52)	254
	KOH (0.1%), MeOH, rt, 30 days	(54)	248
	KOH (0.1%), MeOH, rt, 30 days	(12)	248
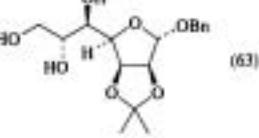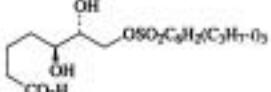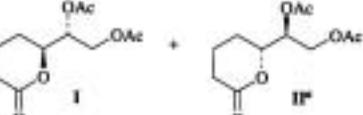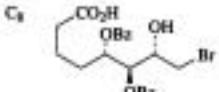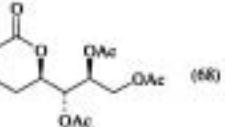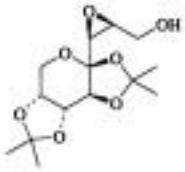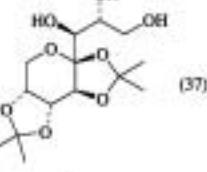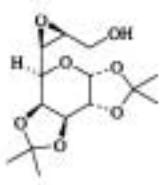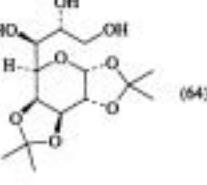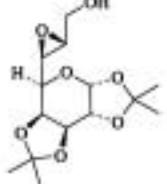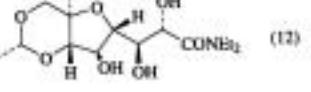
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TABLE 3-D. EPOXIDE MIGRATION WITH *O*-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	KOH (0.1%), MeOH, rt, 11 days	(—)[c]	248
	NaOH, dioxane, 70°	(—)	256
2:1		2:1	
C$_9$	KH, BnOH, THF	(91)	257
C$_{10}$	NaH, BnOH, 100°, 4 h	(>83)	92, 258
	NaOH, H$_2$O, 1,4-dioxane, 100°	(—)	259
	NaOH, H$_2^{18}$O, 1,4-dioxane, 100°	meso (38)[c] *dl* (38)[c]	259
	NaOH, H$_2$O, 1,4-dioxane, 70°, 24 h	(7) (44)[d]	260
	NaOH, H$_2$O, 1,4-dioxane, 70°, 24 h	(10) (41)[c]	260, 261

TABLE 3-D. EPOXIDE MIGRATION WITH O-NUCLEOPHILE OPENING IN SITU (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOH, H$_2$O, 1,4-dioxane, 70°, 22 h	(63)	260, 261
C$_{14}$	NaOH, H$_2$O, 80°, 1 h	(15)	262
C$_{16}$	KOH, H$_2$O, DMSO, 110°, 2 h	(12)	263
C$_{20}$	LiOH, t-BuOH, H$_2$O, 23°, 9 days	R = Me (78) R = H (—)	105
	LiOH, t-BuOH, H$_2$O, 23°, 2 days	R = Me (88) R = H (—)	105
	LiOH, MeOH, H$_2$O, 23°, 3.5 h	R = Me (67) R = H (—)	105

[a] This was a product of epoxide migration.

[b] See also Table VII under the same carbon count.

[c] The absolute configuration was not determined. The structure as shown arises from epoxide migration to the 3,4-position followed by nucleophilic opening by the C-1 oxygen. Alternatively, formation of the 1,2-epoxide followed by nucleophilic opening by the C-4 oxygen would give the enantiomer.

TABLE 3-E. EPOXIDE MIGRATION WITH HALIDE AND S-NUCLEOPHILE OPENING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₃	PhSH, NaOH, t-BuOH, H₂O	(93)	38
C₄	PhSH, NaOH, t-BuOH, H₂O	I + II + III[a] I:II:III = 29:7:64 (85)	38
	PhSH, NaOH, t-BuOH, H₂O	(87)	38
	t-BuSH, NaOH, t-BuOH, H₂O, 70–80°, 1–2 h	(85)	91
	PhSH, NaOH, H₂O, 1,4-dioxane, 65°, 3 h	(68)[b]	31
	PhSH, NaOH, t-BuOH, H₂O, reflux, 3 h	(52)	98
	t-BuSH, NaOH, t-BuOH, H₂O, 70–80°, 1–2 h	(81)	91
	PhSH, NaOH, H₂O, 1,4-dioxane, 65°, 3 h	(81)	31
	PhSH, NaOH, t-BuOH, H₂O, reflux, 3 h	(71)	99
C₅	i-PrSH, NaOH, t-BuOH, EtOH, H₂O, rt, 12 h	(—)	264
	PhSH, NaOH, t-BuOH, H₂O	(64)	38
	t-BuSH, NaOH, t-BuOH, H₂O, 70–80°, 1–2 h	(88)	91
	t-BuSH, NaOH, t-BuOH, H₂O, 70–80°, 1–2 h	(84)	91

TABLE 3-E. EPOXIDE MIGRATION WITH HALIDE AND *S*-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PhSH, NaOH, *t*-BuOH, H$_2$O, 100°, 3 h	(—)	100, 134
	PhSH, NaOH, *t*-BuOH, H$_2$O, 100°, 3 h	(—)	100, 134
	1. *t*-BuSH, NaOH, *t*-BuOH, H$_2$O 2. NaH, Me$_3$OBF$_4$, CH$_2$Cl$_2$, 2,6-di-*tert*-butylpyridine	(57)	265
	PhSH, NaOH, *t*-BuOH, H$_2$O	(69)	265
C$_6$	KSPh, KOH, H$_2$O, 25°, 8 h	(88)	101
	KHF$_2$, 2-methoxyethanol, reflux	(19)^a + (12)^a	97
	t-BuSH, NaOH, *t*-BuOH, H$_2$O, 70–80°, 1–2 h	(75)	91
	PhSH, NaOH, *t*-BuOH, H$_2$O, reflux, 3 h	(79)	99
	PhSH, NaOH, *t*-BuOH, H$_2$O, reflux, 3 h	(86)	99
	PhSH, NaOH, *t*-BuOH, H$_2$O, reflux, 3 h	(72)	99
	PhSH, NaOH, *t*-BuOH, H$_2$O, reflux, 3 h	(63)	99
	LiI, Et$_2$O, 3–4 days	(37)	96

TABLE 3-E. EPOXIDE MIGRATION WITH HALIDE AND S-NUCLEOPHILE OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10} n-C_7H_{15} epoxide OH	t-BuSH, NaOH, t-BuOH, H_2O, 70–80°, 1–2 h	n-C_7H_{15} — OH, SBu-t **I** + n-C_7H_{15} — OH, SBu-t, OH **II** + n-C_7H_{15} — SBu-t, OH **III**[a] (47) I:II:III = 32:9:59	91
C_{11} C_8H_{17}-n epoxide OH	PhSH, NaBH$_4$, EtOH, rt, 2 h	HO, C_8H_{17}-n, HO, SPh (81)	102
C_{13} epoxide OH, $C_{10}H_{21}$-n	t-BuSH, NaOH, t-BuOH, H_2O, 70–80°, 1–2 h	HO, OH, SBu-t, $C_{10}H_{21}$-n (65)[c]	91
C_{15} epoxide OH, $C_{12}H_{25}$-n	t-BuSH, NaOH, t-BuOH, H_2O	HO, OH, SBu-t, $C_{12}H_{25}$-n (81)	103

[a] This was a product of epoxide migration.

[b] Approximately 15% of a mixture of other isomers was also isolated.

[c] Approximately 32% of a mixture of other isomers was also isolated.

TABLE 4. EPOXIDE MIGRATION WITH ELECTROPHILIC TRAPPING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_5$	1. NaH, THF 2. RBr	R=Bn, CH$_2$CH=CH$_2$ (—)	112
C$_6$ β-D-galacto	1. NaH, THF, rt, 5 h 2. BnBr, NBu$_4$I, rt, 12 h	β-D-galacto (10) + BnO β-D-gulo (70)^e	80
C$_8$ 4-ClC$_6$H$_4$	1. MeMgBr 2. KOH, MeOH	(—)	188
	1. NaH, THF 2. MeI or allyl bromide	R=Me, CH$_2$CH=CH$_2$ (—)	112
C$_{10}$	NaOH, H$_2$O, rt, 2 h	(54)	115
	NaOH, H$_2$O, rt, 2 h	(66)	115

TABLE 4. EPOXIDE MIGRATION WITH ELECTROPHILIC TRAPPING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃	1. MsCl, py 2. t-BuOK, t-BuOH, rt, 1 h	(83)	114
	1. MsCl, py 2. t-BuOK, t-BuOH, rt, 1 h	(80)	114
	t-BuOK, t-BuOH, rt, 1 h	(55)	114
C₁₆	1. TBDMSCl, imidazole, DMF 2. H₂O	(69)	113
C₁₈	KOH, MeOH, rt	(75)	188
C₁₉	1. TMSCl, imidazole, DMF 2. H₂O	(80)	113
C₂₀	1. Zn(OTs)₂, DEAD, PPh₃, CH₂Cl₂ 2. t-BuOK, DMF	(46)	114
	1. Zn(OTs)₂, DEAD, PPh₃, CH₂Cl₂ 2. t-BuOK, t-BuOH	(68)	114
	1. Ms₂O, DMAP, CH₂Cl₂ 2. t-BuOK, t-BuOH, rt, 1 h	(73)	114
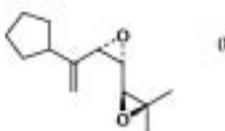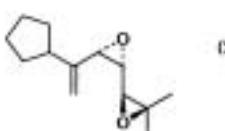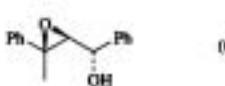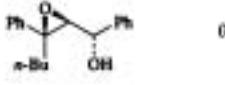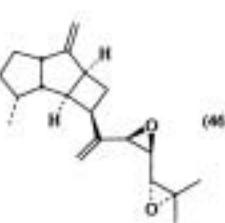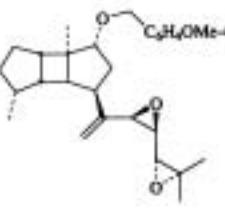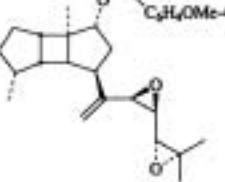
TABLE 4. EPOXIDE MIGRATION WITH ELECTROPHILIC TRAPPING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Me₂O, DMAP, py, CH₂Cl₂ 2. *t*-BuOK, *t*-BuOH 3. DDQ	(51)	266
	1. Zn(OTs)₂, DEAD, PPh₃, benzene 2. *t*-BuOK, DMF 3. DDQ, CH₂Cl₂	(58)	266

ᵃ This was a product of epoxide migration.

TABLE 5-A. AZA-PAYNE REARRANGEMENTS

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
C₃		II	NaH, THF, HMPA, rt 1 h	—	I (65)	57
C₄		I	n-BuLi, AlMe₃, THF, −80 to 0°	—	II (69)	61
		I	t-BuOK, n-BuLi, n-hexane, THF, −78°	—	II (85)	57
		II	NaH, THF, HMPA, 0°, 2 h	—	I (80)	57
		II	KH, CH₂Cl₂, 0°, 4 h	—	I (77)	57
		II	KH, CH₂Cl₂, 0°, 4 h	—	I (76)	57
		II	NaH, THF, HMPA, −78° to rt, 18 h	—	I (92)	64
		II	KH, CH₂Cl₂ or toluene, 0°, 1 h	—	I (99)	57
		II	NaOH, t-BuOH, H₂O, 0°, 18 h	70:30	(—)	57
		II	NaH, THF, HMPA, −78° to rt, 18 h	—	I (87)	64
		II	KH, THF, HMPA, 0°, 30 min	—	I (92)	57
		II	KH, THF, HMPA, 0°, 1 h	—	I (95)	57

TABLE 5-A. AZA-PAYNE REARRANGEMENTS *(Continued)*

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
NHTs, OBn	NTs, OBn	II	NaH, THF, HMPA, rt, 2 h	—	I (97)	57
NHTs, OTBDPS	NTs, OTBDPS	II	t-BuOLi, THF, HMPA	—	I (95)	20

C₅

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
α-D-lyxo	α-D-arabino	Iᵃ	RNH₂, DMF, rt, 5 h			116

RNH₂

CO₂Me, NH₂			88:12	(89)
BocN(H)...CO₂Bn, NH₃			82:18	(55)

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
β-L-lyxo	β-L-arabino	Iᵃ	RNH₂, DMF, rt, 5 h			116

RNH₂

CO₂Me, NH₂			87:13	(68)
BOCN(H)...CO₂Bn, NH₃			83:17	(52)

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
4-BocC₆H₄N(H), OBn, α-D-lyxo	4-BocC₆H₄N, OBn, OH, α-D-arabino	I	BF₃•Et₂O, TMSN₃, rt, 1.5 h	—	II (60)	60
4-BocC₆H₄N(H), OBn, β-L-lyxo	4-BocC₆H₄N, OBn, OH, β-L-arabino	I	BF₃•Et₂O, TMSN₃, rt, 1.5 h	—	II (53)	60
NHTs, CO₂Et, TBDMSO	NTs, HO, CO₂Et, TBDMSO	II	Py, DMSO	—	I (64)	118

C₆

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
NBn₂	NBn₂⁺ OTf⁻, OTMS	I	TMSOTf, CDCl₃, −40° to rt	0:100	(—)	62
N-piperidine	N⁺ OTf⁻, OTMS	I	TMSOTf, CDCl₃, −40° to rt	0:100	(—)	62
NBn₂	NBn₂⁺ OTf⁻, TMSO	I	TMSOTf, CH₂Cl₂, −78°	0:100	(—)ᵇ	62

TABLE 5-A. AZA-PAYNE REARRANGEMENTS (Continued)

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture I:II	Yield (%)	Refs.
		I	TMSOTf, CDCl₃, –40° to rt	0:100	(—)	62
		II	K₂CO₃, MeOH	100:0	I (87)	
C₇		I	n-BuLi, AlMe₃, THF, –80 to 0°	—	II (72)	61
		I	t-BuOK, n-BuLi, n-hexane, THF, –78°	—	II (85)	57
		I	n-BuLi, AlMe₃, THF, –80 to 0°	—	II (75)	61
		I	t-BuOK, n-BuLi, n-hexane, THF, 0°, 3 h	—	II (40)	57
		II	KH, THF, 0°, 2 h	—	I (88)	57
C₈		I	t-BuOK, n-BuLi, n-hexane, THF, –78°	—	II (96)	57
		II	NaOH, t-BuOH, H₂O, 0°, 18 h	98:2	(100)	57
		II	KH, THF, rt, 18 h	—	I (99)	
		I	NaOH, H₂O, brief heating	—	II (90)	63
C₉		I	n-BuLi, AlMe₃, THF, –80° to 0°	—	II (73)	61
		I	t-BuOK, n-BuLi, n-hexane, THF, –78°	—	II (80)	57
		I	n-BuLi, AlMe₃, THF, –80° to 0°	—	II (78)	61
		II	KH, THF, HMPA, 0°, 1.5 h	—	I (91)	57
		II	KH, THF, HMPA, 0°, 1.5 h	—	I (94)	57
		II	NaOH, t-BuOH, H₂O, 0°, 18 h	39:61	(100)	57
		I	NaOH, H₂O, reflux, 5 min	—	II (85)	63
		I	NaOH, H₂O, reflux, 5 min	—	II (81)	63
		I	NaOH, H₂O, reflux, 5 min	—	II (80)	63

TABLE 5-A. AZA-PAYNE REARRANGEMENTS (*Continued*)

Oxirane (I)	Aziridine (II)	Initial Compound	Conditions	Final Mixture		Refs.
				I:II	Yield (%)	
		II[c]	NaH, MeI, THF, 0°, 12 h	—	I (14)	117
C₁₀		I	Ti(OPr-i)₄, THF, 0°, 3 h	—	II (63)	59
		I	t-BuOK, n-BuLi, n-hexane, THF, −78°	—	II (88)	57
		I	NaOH, H₂O, reflux, 5 min	—	II (93)	63

[a] The starting material in this reaction was the 4-*O*-triflate, which was displaced by the amine to produce I directly and II indirectly.

[b] The product was contaminated by azetidinium salt formed by reaction at C-3.

[c] The starting material in this reaction was the free base, which was treated with methyl iodide to form II in situ.

TABLE 5-B. AZA-PAYNE REARRANGEMENT WITH NUCLEOPHILIC OPENING IN SITU

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₄ (TsN epoxide-OH structure)	1. KH, THF, 0°, 1 h	(OH, NHTs, X structure)	124
		X (%)	
	2. Me₂Cu(CN)Li₂·2LiBr, THF, Et₂O, −78°, 0.5 h	Me 90	
	2. n-Bu₂Cu(CN)Li₂, n-hexane, THF, −78 to 0°, 2 h	n-Bu 88	
	2. PhSH, THF, rt, 2 h	SPh 88	
	2. t-BuSH, THF, rt, 2 h	SBu-t 59	
	1. KH, THF, 0°, 1 h 2. Me₃SiCN, Yb(CN)₃ (cat.), THF, hexane, rt, 3 h 3. n-Bu₄NF, THF, 0°, 15 min	(OH, NHTs, CN structure) (86)	124
	MeCu(CN)Li·LiBr, THF, Et₂O, −78° to rt, 18 h	(OH, NHTs structure) (39) + (OH, NHTs structure) (53)	57, 64
	n-BuCu(CN)Li·2LiCl, n-hexane, THF	(OH, NHTs structure) (91)	57

TABLE 5-B. AZA-PAYNE REARRANGEMENT WITH NUCLEOPHILIC OPENING IN SITU (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KH, THF, 0°, 1 h		123, 124

		X	(%)	
	2. Me₂Cu(CN)Li₂•2LiBr, THF, Et₂O, −78°, 0.5 h	Me	99	
	2. n-Bu₂Cu(CN)Li₂, n-hexane, THF, −78 to 0°, 2 h	n-Bu	89	
	2. (n-Bu₃Sn)₂Cu(CN)Li₂, THF, hexane, −10°, 1 h	n-Bu₃Sn	68	
	2. (n-Bu₂N)₂Cu(CN)Li₂, THF, hexane, 0°, 1.5 h	n-Bu₂N	91	
	2. PhSH, THF, rt, 2 h	SPh	91	
	2. s-BuSH, THF, rt, 2 h	SBu-t	70	

	1. KH, THF, 0°, 1 h			
	2. Me₃SiCN, Yb(CN)₃ (cat.), THF, hexane, rt, 3 h	(90)		123, 124
	3. n-Bu₄NF, THF, 0°, 15 min			

	1. KH, THF 0°, 1 h	(58)	123
	2. (Me₃Si)₂Cu(CN)Li₂		

	MeCu(CN)Li•LiBr, THF, Et₂O, −78° to rt, 18 h	(55) + (36)	57, 64

	n-BuCu(CN)Li•2LiCl, n-hexane, THF	(41)	57

| | 1. KH, THF, 0°, 1 h | | |

		X	(%)	
	2. Me₂Cu(CN)Li₂•2LiBr, THF, Et₂O, −78°, 0.5 h	Me	99	124
	2. Bu₂Cu(CN)Li₂, THF, Et₂O, −78 to 0°, 2 h	n-Bu	91	123, 124
	2. (n-C₁₄H₂₉)₂Cu(CN)Li₂, THF, −78°, 2 h	n-C₁₄H₂₉	93	124
	2. (n-Bu₂N)₂Cu(CN)Li₂, THF, hexane, 0°, 1.5 h	n-Bu₂N	88	123, 124
	2. PhSH, THF, rt, 2 h	SPh	94	123, 124
	2. s-BuSH, THF, rt, 2 h	SBu-t	95	123, 124
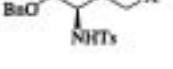
	1. KH, THF, 0°, 1 h			
	2. Me₃SiCN, cat. Yb(CN)₃, THF, hexane, rt, 3 h	(95)		123, 124
	3. n-Bu₄NF, THF, 0°, 15 min			

TABLE 5-B. AZA-PAYNE REARRANGEMENT WITH NUCLEOPHILIC OPENING IN SITU (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KH, THF, 0°, 1 h		123, 124
	2. Me₂Cu(CN)Li₂•2LiBr, THF, Et₂O, −78°, 0.5 h	X (%) Me 98	
	2. (n-C₁₄H₂₈)₂Cu(CN)Li₂, THF, −78°, 2 h	n-C₁₄H₂₉ 90	
	2. (n-Bu₃Sn)₂Cu(CN)Li₂, THF, hexane, −10°, 1 h	n-Bu₃Sn 42	
	2. (n-Bu₂N)₂Cu(CN)Li₂, THF, hexane, 0°, 1.5 h	n-Bu₂N 88	
	2. PhSH, THF, rt, 2 h	SPh 92	
	1. KH, THF, 0°, 1 h 2. TMSCN, Yb(CN)₃ (cat), THF, hexane, rt, 3 h 3. n-Bu₄NF, THF, 0°, 15 min	(85)	124
	1. TMSOTf, CH₂Cl₂, −78° 2. morpholine, −78° to rt 3. K₂CO₃, MeOH, rt	(59)	62
	1. TMSOTf, CH₂Cl₂, −78° 2. [pyridine-OTMS], −78° to rt 3. K₂CO₃, MeOH, rt	(79)	62
	1. TMSOTf, CH₂Cl₂, −78° 2. H₂N-CO₂Me, −78° to rt 3. K₂CO₃, MeOH, rt	(74)	19, 121
	1. TMSOTf, CH₂Cl₂, −78° 2. morpholine, −78° to rt 3. K₂CO₃, MeOH, rt	(61)	62
C₆ β-D-manno	KOH, H₂O, 90–100°, 6 h	(32) β-D-manno	122
	1. TMSOTf, CH₂Cl₂, −78° 2. [pyrimidine-OTMS], −78° to rt 3. K₂CO₃, MeOH, rt	(79)	62
	1. TMSOTf, CH₂Cl₂, −78° 2. NH₃ (l)	R = Bn (65) R = allyl (54)	62

Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.

1. TMSOTf, CH₂Cl₂, –78°
2. HNX, –78° to rt
3. K₂CO₃, MeOH, rt

HNX	R = allyl (%)	R = Bn (%)	
H₂NPr-i	47	47	62, 120
H₂NBu	—	44	62, 120
HN-(allyl)₂	88	67	62
HN (piperidine)	66	60	62, 120
HN O (morpholine)	90	92	62, 120
HN MeO₂C (proline ester)	—	87	19, 121
H₂N CO₂Me	77	86	19, 121
H₂N CO₂Bu-t	84	88	19, 121
H₂N CO₂Me	85	90	19, 121
H₂N CO₂Me, Ph	91	88	19, 121

1. TMSOTf, CH₂Cl₂, –78°
2. (2-TMSO pyridine), –78° to rt
3. K₂CO₃, MeOH, rt

R = Bn	(93)	62, 120
R = allyl	(83)	62, 120

1. TMSOTf, CH₂Cl₂, –78°
2. (TMSO-pyrimidine-OTMS), –78° to rt
3. K₂CO₃, MeOH, rt

R = Bn	(89)	62, 120
R = allyl	(91)	62, 120

1. TMSOTf, CH₂Cl₂, –78°
2. morpholine, –78° to rt
3. K₂CO₃, MeOH, rt

(58) 62

1. TMSOTf, CH₂Cl₂, –78°
2. H₂N CO₂Me, –78° to rt
3. K₂CO₃, MeOH, rt

R = Bn	(62)	19, 121
R = allyl	(57)	19, 121

C₉ | TsN Ph OH |

1. KH, THF, 0°, 1 h

X	(%)	
2. Me₂Cu(CN)Li₂·2LiBr, THF, Et₂O, –78°, 0.5 h	Me 93	123, 124
2. PhSH, THF, rt, 2 h	SPh 64	124

124

125

TABLE 5-B. AZA-PAYNE REARRANGEMENT WITH NUCLEOPHILIC OPENING IN SITU (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KH, THF, 0°, 1 h 2. TMSCN, Yb(CN)₃ (cat.), THF, hexane, rt, 3 h 3. n-Bu₄NF, THF, 0°, 15 min	(67)	123, 124

	1. KH, THF, 0°, 1 h	

	X	(%)	
2. Me₂Cu(CN)Li₂·2LiBr, THF, Et₂O, −78°, 0.5 h	Me	75	124
2. n-Bu₂Cu(CN)Li₂, n-hexane, THF, −78 to 0°, 2 h	Bu	94	123, 124
2. (n-Bu₃Sn)₂Cu(CN)Li₂, THF, hexane, −10°, 1 h	n-Bu₃Sn	52	123, 124
2. (n-Bu₂N)₂Cu(CN)Li₂, THF, hexane, 0°, 1.5 h	n-Bu₂N	94	123, 124
2. PhSH, THF, rt, 2 h	SPh	89	124

	1. KH, THF, 0°, 1 h 2. TMSCN, Yb(CN)₃ (cat.), THF, hexane, rt, 3 h 3. n-Bu₄NF, THF, 0°, 15 min	(85)	123, 124

	SiO₂ chromatography	(33)	119

	NaBH₃CN, BF₃·Et₂O, THF, reflux	I + II	119

NR₂	I (%)	II (%)
morpholine	0	48
indole	14	0
Ph-N-Me	0	48
4-MeC₆H₄-N-Me	27	27
3-MeOC₆H₄-N-Me	0	65
Ph₂CH-N-H	17	39

C₁₈			
	NaBH₃CN, BF₃·Et₂O, THF, reflux, 3.5 h	(37)	119

a This was the product of an aza-Payne rearrangement.

TABLE 6. REACTIONS INVOLVING THIA-PAYNE REARRANGEMENTS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₃	1. AlMe₃, hexane, 0°, 30 min 2. Ac₂O, DMAP, py	(72)	67
C₄	1. AlMe₃, hexane, 0°, 1 h 2. Ac₂O, DMAP, py	(89)	67
	NH₃, MeOH, 0°, 3 h	(89)	65
	Me₂AlC≡CTMS, CH₂Cl₂, –78°, 10 min	(14) + (80)	68
	PhB(OH)₂, 70°, 20 h	(100)	69
	PhB(OH)₂, 70°, 3 h	(99)	69
C₅	PhB(OH)₂, 70°, 17.5 h	(98)	69
	PhB(OH)₂, 70°, 13.5 h	(97)	69
C₆	1. AlMe₃, hexane, 0°, 0.6 h 2. Ac₂O, DMAP, py	(34)	67
	1. TMSOTf, CH₂Cl₂, –78°, 10 min 2. , 0°, 72 h 3. K₂CO₃, H₂O, rt, 3 h	(70)	66, 128
	1. TMSOTf, CH₂Cl₂, –78°, 10 min 2. H₂N....CO₂Me, –78°, 4–24 h 3. NaHCO₃, H₂O, rt 4. AcOH, MeOH, rt, 3h	(53)	126, 127
	1. (i-Bu)₂AlH, hexane, 0°, 1 h 2. Ac₂O, DMAP, py	(86)	67

TABLE 6. REACTIONS INVOLVING THIA-PAYNE REARRANGEMENTS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. AlMe₃, hexane, 0°, 1 h 2. Ac₂O, DMAP, py	(SPh structure) (92)	67
	1. AlEt₃, hexane, 0°, 1 h 2. Ac₂O, DMAP, py	(SPh structure) (86)	67
	Et₂AlC≡CBu-t, hexane, 0°, 2 h	(8) + (70)	67
	Me₂AlC≡CTMS, CH₂Cl₂, −78°, 10 min	(9) + (82)	68
	1. TMSOTf, CH₂Cl₂, −78° 2. py, −78° to rt	(99)	66
(epoxide-SR¹ substrate)	1. TMSOTf, CH₂Cl₂, −78°, 10 min 2. nucleophile, −78 to 0°, 1–3 days 3. K₂CO₃, MeOH, rt, 45 min	(product OH, X)	66, 125

nucleophile	X	R¹ = Me	R¹ = Ph	R¹ = Bn
(pyridine-TMSO)	(pyridinone)	85	81	—
(pyrimidine-OTMS, TMSO)	(uracil)	81	75	53
(imidazole-NTMS)	(imidazole)	33	39	—
(TMSN, OTMS)	NHAc	54	58	51
(Me, TMSN, O)	NMeAc	44	55	—

TABLE 6. REACTIONS INVOLVING THIA-PAYNE REARRANGEMENTS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. BF₃·Et₂O, CH₂Cl₂, –78°, 10 min 2. TMSX, –78 to 0°, 3 days 3. K₂CO₃, MeOH, rt, 45 min		66, 125

X	R¹ = Me (%)	R¹ = Ph (%)
N-piperidine	47	40
N-morpholine	44	—
N-pyrrolidine	37	33

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. TMSOTf, CH₂Cl₂, –78°, 10 min 2. H₂N‑CO₂Bu-t, –78°, 4–24 h (R²) 3. NaHCO₃, H₂O, rt 4. AcOH, MeOH, rt, 3 h		126, 127

R²		R¹ = Me (%)	R¹ = Ph (%)
Me	(ala)	54	48
i-Bu	(leu)	54	58
PhCH₂	(phe)	49	—

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. TMSOTf, CH₂Cl₂, –78° 2. TMSSPh, –78°, 2 days 3. NEt₃, –78°, 1 h 4. K₂CO₃, MeOH, rt, 2 h		129

R	(%)
Me	30
i-Bu	70
n-Bu	64
Ph	46

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Me₂AlC≡CTMS, CH₂Cl₂, –78°, 10 min	(16) + (77)	68
	1. TMSOTf, CH₂Cl₂, –78°, 10 min 2. R‑N≡C₆H₄OMe-4, 0°, 72 h 3. K₂CO₃, MeOH, rt, 3 h		66, 128

R	(%)
i-Pr	57
Ph	66
Bn	46

	1. AlMe₃, hexane, 0°, 1 h 2. Ac₂O, DMAP, py	(92)	67
	1. AlEt₃, hexane, 0°, 2 h 2. Ac₂O, DMAP, py	(40) + (43)	67
	PhB(OH)₂, 70°, 21 h	(98)	69

TABLE 6. REACTIONS INVOLVING THIA-PAYNE REARRANGEMENTS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. TMSOTf, CH$_2$Cl$_2$, –78°, 10 min 2. nucleophile, –78 to 0°, 1–3 days 3. K$_2$CO$_3$, MeOH, rt, 45 min		66, 125

nucleophile	X	R = Me (%)	R = Ph (%)
(pyrimidine, N=/N, OTMS, TMSO)	(uracil, N, O, NH, O)	68	55
TMSN, OTMS	NHAc	44	40

	1. TMSOTf, CH$_2$Cl$_2$, –78°, 10 min 2. H$_2$N–CO$_2$Bu-t, –78°, 4–24 h 3. NaHCO$_3$, H$_2$O, rt 4. AcOH, MeOH, rt, 3 h		
		R = Me (44) R = Ph (43)	126, 127 126, 127

| | 1. TMSOTf, CH$_2$Cl$_2$, –78°
2. TMSSPh, –78°, 2 days
3. NEt$_3$, –78°, 1 h
4. K$_2$CO$_3$, MeOH, rt, 2 h | | 129 |

R	(%)
Me	50
i-Bu	56
n-Bu	33
Ph	55

C$_7$

	AlMe$_3$, hexane, 0°, 30 min	(96)	67

	1. AlMe$_3$, hexane, 0°, 0.6 h 2. Ac$_2$O, DMAP, py	(91)[b]	67

C$_8$

	1. AlMe$_3$, hexane, 0°, 30 min 2. Ac$_2$O, DMAP, py	(90)	67

C$_9$ n-C$_8$H$_{17}$ ... SPh

	Me$_2$AlC≡CTMS, CH$_2$Cl$_2$, –78°, 10 min	(13) + (74)	68

	PhB(OH)$_2$, BF$_3$•Et$_2$O, 60°, 48 h	(30) + (70)	69

[a] This was a product of the thia-Payne rearrangement.
[b] A roughly 3:1 mixture of diastereomers was retained throughout the reaction.

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION[a]

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
C$_4$	K$_2$CO$_3$, MeOH, 0° to rt, 8 h DBU, THF 0° to rt, 18 h	(65) (80)	I-B	41 41
	NaN$_3$, LiClO$_4$, NH$_4$ClO$_4$, MeCN, MeOH	(23) + (61)	III-C	93
C$_5$	Et$_2$NH, H$_2$O, 50°, 4 h	(32)	II-B	221
	EtMgBr, THF, –70° to rt	(80)	II-B'	267
	1. Ti(OPr-i)$_4$ (1 eq), t-BuO$_2$H, L-(+)-DET, CH$_2$Cl$_2$, –20° 2. acetone (aq.), distillation	(50–60)	I-B	106
	NH$_3$, H$_2$O, rt, 2–3 d (R)-H$_2$NCH(Me)Ph, 100°, 27 h		III-C	108 109

		R	(%)
		H	100
		(R)-CH(Me)Ph	90

| | R^{1}R^{2}NH, Ti(OPr-i)$_4$, CH$_2$Cl$_2$,
rt, 1–4 d | | III-C | 109 |

R^1	R^2	(%)
H	Bn	50
H	i-Pr	74
H	(R)-CH(Me)Ph	90
H	t-Bu	91
H	Ph	76
i-Pr	i-Pr	83
Bn	Bn	87

	R^{1}R^{2}NH, rt, 2–4 d		III-C	109

R^1	R^2	(%)
H	H	77
H	(S)-CH(Me)Ph	80
Me	Me	98

| | BnBr, NaH, n-Bu$_4$NI, THF, –10°
BnBr, NaH, n-Bu$_4$NI, THF, rt | (80)
(—) | I-A | 268
197 |
| | 4-MeOC$_6$H$_4$CH$_2$Br, NaH, THF, 0° | (94) | IV | 269 |

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[g]	Refs.
	R^1R^2N, rt, 1 d		III-C	270, 271

R^1	R^2	(%)
H	H	78
H	(R)-CH(Me)Ph	93
H	(S)-CH(Me)Ph	78

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table	Refs.
	NH_3 (l), −78° to rt NH_3, H_2O, rt, 2 d	(100) (100)	III-C	108, 271 270
	R^1R^2N, rt, 1–5 d		III-C	108, 270

R^1	R^2	(%)
H	Bn	83
H	(R)-CH(Me)Ph	96
H	(S)-CH(Me)Ph	91
H	i-Pr	90
H	t-Bu	100
H	Ph	90
Me	Me	96
i-Pr	i-Pr	74

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table	Refs.
	Imidazole, Ti(OPr-i)₄, CH_2Cl_2, rt, 5 d	(54)	III-C	270
	NaH, THF, 10°, 1.5 h	—[f]	I-A	3
	BnNH₂, Et₃Al, CH_2Cl_2, 25[a]	(—)	III-C	272
	PdCl₂(PhCN)₂, C_6H_6, reflux, 6–48 h	(50)	—	273
	TBDMSCl, imidazole, DMF, 35°, 50 min	(93)	II-A	196
	TBDMSCl, imidazole, DMF, 35°, 50 min	(98)	II-A	196
	NaOH, DMF, H_2O, rt	(78)	II-A	196
	NaOH, DMF, H_2O, rt	(86)	II-A	196

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
	NaOH, H₂O, *t*-BuOH	+ other isomers (88)	I-A	274
C₆ β-D-altro	KOH, H₂O, 100°, 5 h	(—) β-D-manno	III-D	111
	n-BuLi	not (—)	II-B	275
	1. EtMgBr, THF, −70°, 15 min 2. NH₄Cl, H₂O	+ (16)	II-B	222
	1. MeLi, THF, Et₂O, −78° 2. H₂O, HOAc, −25°	+ α-D-talo (80) α-D-manno (11)	II-B	70
	Ti(OPr-*i*)₄ (5 mol%), *t*-BuO₂H, L-(−)-DET, CH₂Cl₂, −20°	(78)	I-B	213
	1. Ag₂O, I₂, THF, ¹⁸OH₂ 2. DBU, CH₂Cl₂, THF, rt. 24 h	(72)	I-B	276
	1. Ag₂O, I₂, THF, ¹⁸OH₂ 2. DBU, CH₂Cl₂, THF, rt. 24 h	(70)	I-B	276
	K₂CO₃, H₂O, 20°, 9 days	+ (31)[c] (69)	I-B	45
	NH₃, H₂O, rt, 3 h	(69)	III-D	43
	1. NH₃, H₂O, rt, 2 h 2. HCl	•HCl (55)	III-D	44
	Ac₂O, py, rt, 24 h	(97)	II-A	53

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
	TrCl, py, rt, 40 h	(85)	II-A	53
	NaH, 4-MeOC₆H₄CH₂Br	(84)	I-A	277, 278
	1. Me₂SCHCONEt₂, THF, 0°, 2 days 2. rt, 1 d	(69)	III-D	248
β-D-gluco	Amberlite IRA 400 OH⁻, MeOH, rt, 5 min	(98) β-D-galacto	II-B	195
β-D-gluco	Amberlite IRA 400 OH⁻, MeOH, rt, 15 min	(95) β-D-manno	II-B	195
β-D-gluco	Amberlite IRA 400 OH⁻, MeOH, rt, 15 min	(98) β-D-galacto	II-B	195
	1. DEAD, Ph₃P, 4-O₂NC₆H₄CO₂H 2. NaOMe, MeOH, rt, 25 min	(65)	I-B, IV	165
1L-chiro	NaOMe, MeOH, rt, 4 h / Deacidite FF (OH form) resin, MeOH, H₂O, 75–80°, 1h	(60) / (33) 1L-myo	II-B / II-B	279 / 226
1L-myo	NaOMe, DMSO, MeOH, rt, 2 h	(56) 1L-chiro	II-B	279
α-D-manno	NaOH, H₂O, 80°, dropwise	(79) α-D-altro	II-B	74

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
α-D-gluco	NaOMe, MeOH, CHCl₃, 0°, 5 h	(74) α-D-galacto	II-B	53
α-D-gluco	NaOMe, MeOH, CHCl₃, 0°, 5 h	(81) α-D-galacto	II-B	53
C₇	NaH or K₂CO₃, THF or MeOH	—[d]	II-A	219
	K₂CO₃, H₂O, rt, 24 h	(72) + (28)	I-B	32
	1. DEAD, Ph₃P, 4-O₂NC₆H₄CO₂H 2. NaOMe, MeOH, rt, 25 min	(76)	I-B, IV	165
	NaOMe, MeOH, 0°, 30 min	(87)	II-B	143, 144
	MeO⁻, 0°	(70)	II-B	280
	MsCl, py, 0°, 18 h	(91)	I-A, IV	281
β-D-manno	NaSMe, MeOH, reflux, 2 h	(65) β-D-gluco	III-E	282
	NaOMe, MeOH, 4°, 10 min	(43)	I-B	200
	NaOMe, MeOH, 4°, 10 min	(50)	I-B	200

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
	NaH, THF, reflux, 2 h	—[a]	I-A	24
	NaOMe, MeOH, THF, 0°	(87)	II-B	234
	K₂CO₃, MeOH, 23°, 2 h	(98)	I-B	283, 284
	NaBH₄, H₂O, Et₂O, rt, 30–45 min	(55)	I-B	285
	NaH, BnBr, THF, rt, 1.5 h	(73)	I-A	286
	KOH (0.1%), MeOH, rt, 66 days	—[a]	III-D	248
	1. DEAD, Ph₃P, 4-NO₂-C₆H₄CO₂H, rt, 12 h 2. NaOMe, MeOH, rt, 45 min	(55)	I-A	198
	Unspecified cuprate reagents	—[d]	III-B	287
	Base	—[d]	I-A	288
	LiAlH₄ or PhLi, THF, rt	(90) R=H, Ph	II-B	84
	RLi, THF, –20°, rapid addition		II-B	104
	RLi, THF, –20°, rapid addition			
	RZnBr, THF			
	MeLi, THF, rt, 1 h	(—)	II-B	84

R	(%)
n-C₈H₁₇	83
CH₂(CH₂)₇OTBDMS	95
CH₂C≡CC₉H₁₁-n	82

TABLE 7. CONDITIONS NOT LEADING TO EPOXIDE MIGRATION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Related Table[b]	Refs.
C_{11}	PhSLi, THF	(83)	I-A	208
	PhSLi, THF	(83)	I-A	208
C_{12}	BnBr, *t*-Bu₄NI, NaH, THF, 25°, 1 h	(80)	IV	289
C_{14}	Unspecified bases	—[d]	I-A	290
C_{16}	*t*-BuOK, *t*-BuOH, reflux, 4 h	(72)	I-A	179
C_{18}	1. BnNCO, Et₃N, CH₂Cl₂, rt 2. NaH, THF, rt, 5 h	I:II = 58:42 (85)	IV	169
C_{20}	K₂CO₃, MeOH, rt	—[e] (—)	I-A	181
C_{21}	MeNH₂, TsOH (cat.), 130°, 4 d	(58)	III-C	181

[a] Entries include only those reports for which the lack of epoxide migration was specifically noted.

[b] Other conditions leading to epoxide migration can be found in this table under the same carbon count.

[c] Compare 2,3-epoxycyclohexanone, Table II-B.

[d] No reaction was evident.

[e] For this product, the authors propose the opening of epoxide I, below, at C-2 and C-5, without epoxide migration.
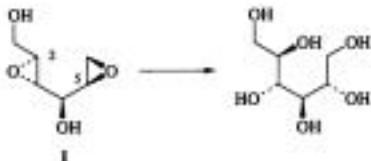
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The Intramolecular Heck Reaction

J. T. Link, Abbott Laboratories, Abbott Park, IL

1. Introduction

Since the discovery of the Heck reaction, (1, 2) the process has gained widespread acceptance within the synthetic community both as a practical tool and a research area. (3-15) The intramolecular Heck reaction has enjoyed a similar renaissance, particularly within the last decade. (16) The reaction has emerged as a reliable method for efficiently constructing small, medium, and large rings and is outlined in generic form in Eq. 1 (**1**®**2** and/or **3**). Since the reaction occurs under mild and nearly neutral

$$(1)$$
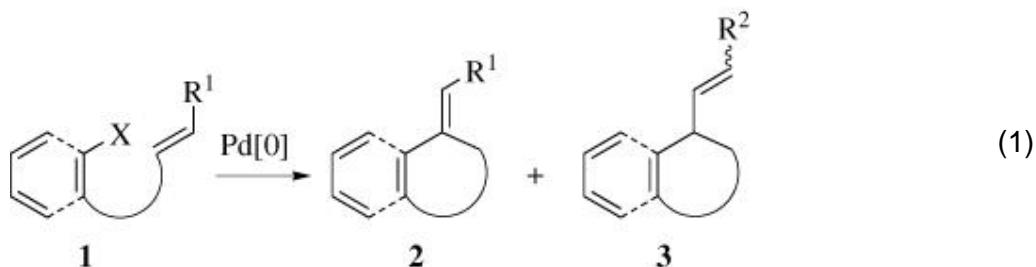
conditions, the functional group tolerance is high. Tandem reactions, which are initiated by intramolecular Heck reactions, have been developed allowing for multiple ring formations, cyclization and intermolecular coupling, and a multitude of other ever-expanding possibilities. Furthermore, congested tertiary and quaternary centers can be efficiently constructed diastereoselectively or enantioselectively during the ring-forming reaction. The numerous advances in reaction technology and capability have led to frequent application of the reaction in complex molecule synthesis and combinatorial library preparation. (17, 18) For the purposes of this review, the intramolecular Heck reaction is defined as the palladium[0]-catalyzed intramolecular coupling of an aryl or alkenyl halide or perfluorosulfonate with an alkene, alkyne, allene, or arene.

2. Mechanism and Stereochemistry

The mechanism of the Heck reaction is an active area of research. Precise mechanistic details vary substantially depending upon catalyst, substrate, additives, and reaction conditions. The introduction given here is designed to give the chemist a basic understanding of the currently accepted mechanisms to aid in the rational selection and optimization of reaction conditions. For more detailed analyses, several reviews on the mechanistic forefront of the Heck reaction have been published. (19, 20)

2.1. Neutral Pathway of the Heck Reaction

Two mechanistic manifolds are invoked to explain the majority of intramolecular Heck reactions. (21-28) Alkenyl and aryl halides **4** commonly react via the "neutral pathway" (Scheme 1). The catalytically active palladium species **5** typically has two phosphine ligands, and oxidatively adds into the carbon-halogen bond. The reactivity order for the formation of palladium complex **6** (and often for the overall reaction) is X = I > Br >> Cl. Ligand exchange by decomplexation of a phosphine ligand and coordination of the pendant unsaturated group (in this case alkene) provides complex **7**. Syn insertion of the alkene yields the σ -bonded alkylpalladium intermediate **8**. Syn β -hydride elimination provides product **9** and a hydrido palladium complex **10**, which is converted by a stoichiometric amount of base into the catalytically active palladium complex **5**. One notable feature of the neutral mechanism is that one of the phosphine ligands leaves the palladium coordination sphere during the course of the reaction. For asymmetric reactions, which commonly employ chiral bidentate phosphines, this is commonly invoked as an explanation for the loss of enantioselectivity often observed in reactions postulated to occur via the neutral pathway.
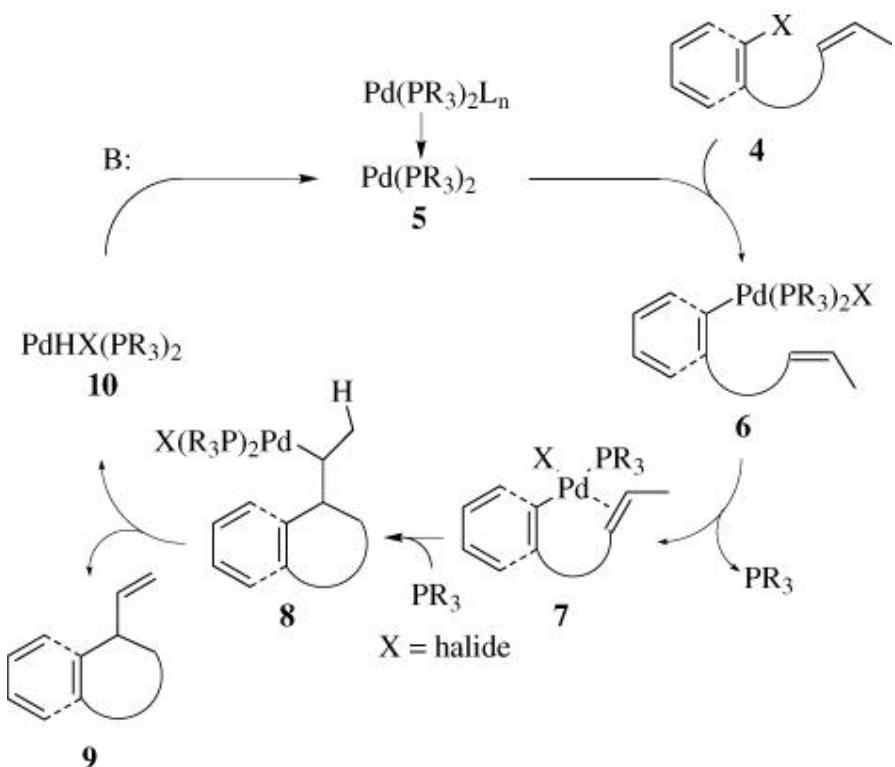
Scheme 1.

2.2. Cationic Pathway of the Heck Reaction

Aryl and vinyl perfluorosulfonates **4** (X = Tf (trifluoromethylsulfonyl), Nf (non-aflate)) react via the "cationic pathway" of the Heck reaction (Scheme 2). After oxidative addition of the palladium complex **5** into the carbon triflate bond, cationic intermediate **11** is obtained. Coordination of the pendant unsaturated group (in this case alkene) then provides complex **12**. Insertion yields the σ-bonded palladium complex **13**, which after β-hydride elimination gives the product **9** and a hydrido-palladium complex **14**. As in the neutral case, a stoichiometric amount of base converts the hydridopalladium triflate complex **14** back into the catalytically active palladium complex **5**. In this mechanistic pathway, both phosphines remain complexed to palladium during the entire reaction. For this reason, most asymmetric reactions use the cationic pathway.

Scheme 2.

OTf

4

B: → Pd(PR₃)₂ **5**

HPd(PR₃)₂OTf **14**

$[R_3P{-}Pd{-}PR_3]^{+}$ OTf⁻ **11**

9

$[(R_3P)_2Pd{-}CH{-}CH_2{-}H]^{+}$ OTf⁻ **13**

$[R_3P{-}Pd{-}PR_3]^{+}$ OTf⁻ **12**
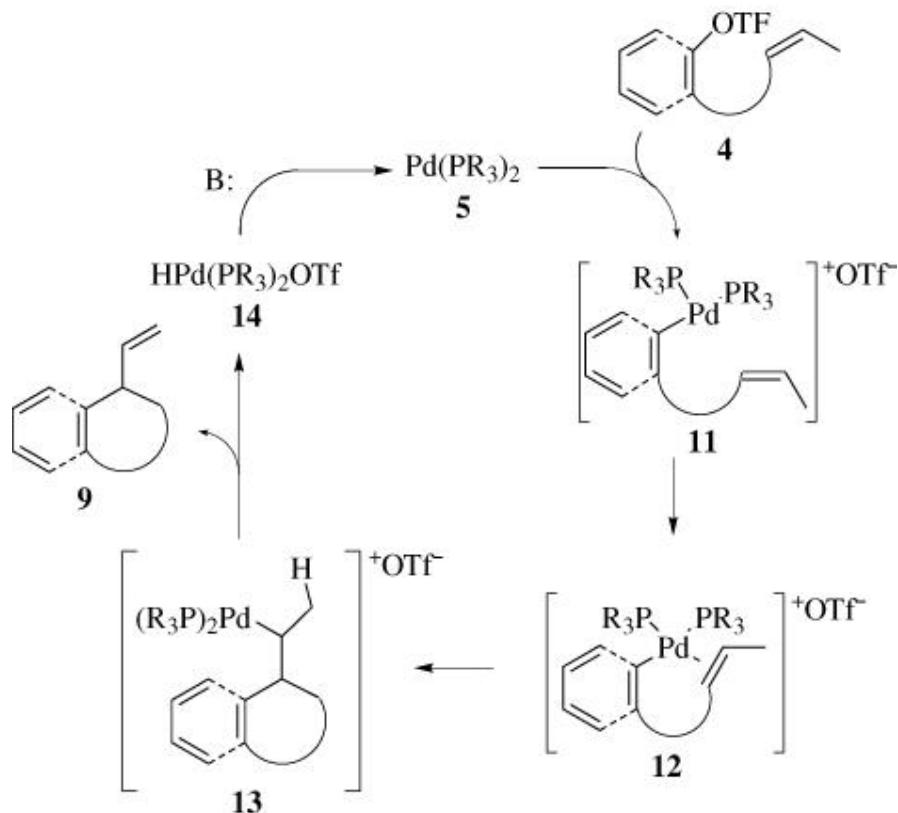
Reaction conditions have been developed to allow vinyl and aryl halides to undergo reaction via the "cationic pathway". (24, 29, 30) Addition of silver (31, 32) or thallium salts (33) to the reaction mixture accomplishes this task. Vinyl and aryl triflates can also be directed into the "neutral manifold" by the addition of tetrabutylammonium halide salts. (34)

2.3. Insertion

Alkenes undergo suprafacial insertion into palladium carbon σ -bonds. (35, 36) Depending upon the geometry (enforced by the substrate structure), the alkene can approach the palladium-carbon σ -bond by two limiting relative orientations (Eq. 2). In the eclipsed orientation, the palladium-carbon σ -bond approaches the alkene in the plane of the alkene π -bond en route to the insertion product. If the approach is somewhat out of plane, a twisted orientation leads to the insertion product.

(2)
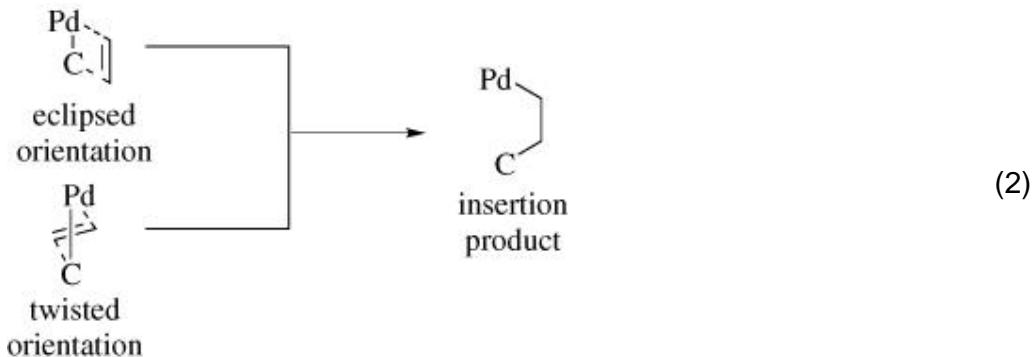
Cyclization of substrates that can access either insertion orientation has been conducted (Eq. 3). (37) For example, aryl iodide **15** upon treatment with a catalyst derived from palladium acetate and triphenylphosphine, in the presence of silver carbonate, yields cyclic either **16** in good yield. The diastereoselectivity of the reaction, which presumably proceeds via the cationic pathway, is greater than 20 : 1.

(3)
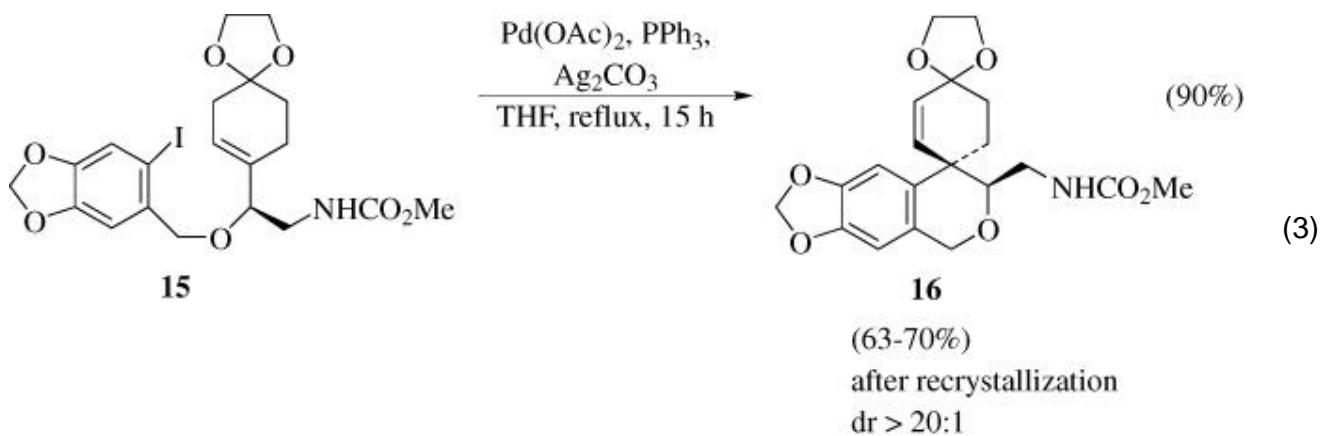
The two potential competing cyclization conformers with the carbamate group disposed equatorially are **17** and **18** (Scheme 3). In boat conformer **17**, the carbonpalladium bond and alkene are aligned in an eclipsed orientation. Insertion, followed by β -hydride elimination, yields the observed diastereomer **16**. Chair conformer **18** places the carbon-palladium σ -bond and alkene in a twisted orientation. No product was observed from this conformer. Examination of this reaction indicates a preference for an eclipsed conformation; however, even in closely related systems, the trend erodes.
Scheme 3.

eclipsed boat **17**   twisted-chair **18**

major product **16**   minor product
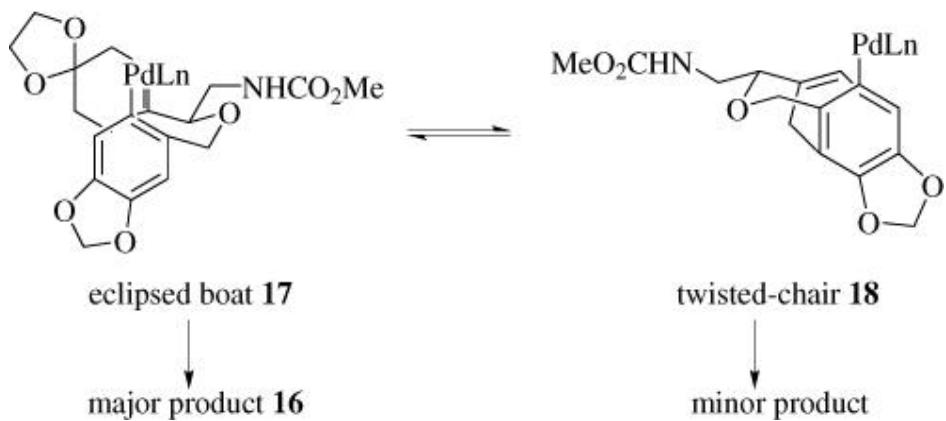
Aryl iodides **19a** and **19b** are closely related to cyclization precursor **15** (Eq. 4). (38) Reaction of carbamate **19a** yields **20a** as a 1.4:1 mixture of diastereomers under the same reaction conditions. Although the major product has the same relative stereochemistry as **16**, a significant amount of the diastereomer derived from a twisted chair conformer analogous to **18** is isolated. Under identical reaction conditions a number of substrates cyclize similarly, with tosylate **19b** giving the most diastereoselective reaction. The results indicate the potential for the twisted orientation and show that subtle variations in structure can play an important role in the intramolecular Heck reaction.

$$\text{(4)}$$

	R
19a	NHCO$_2$Me
19b	OTs

	dr
20a	1.4:1
20b	2.5:1
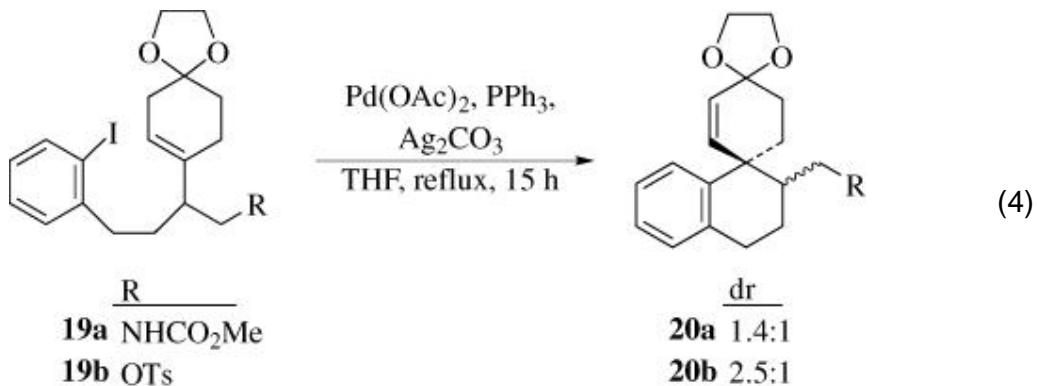
2.4. Pentacoordinate Palladium Intermediates

Detailed studies of the intramolecular Heck reactions of anilino amides have revealed an additional mechanistic possibility. (34) When the bidentate ligand (*R*)-BINAP is employed, iodoamide **21** cyclizes to oxindole **22**, which upon enol ether cleavage and reduction provides alcohol **23** enantioselectively in 91% ee (Eq. 5). Such a highly enantioselective reaction occurring via the neutral pathway is unusual.

$$(5)$$
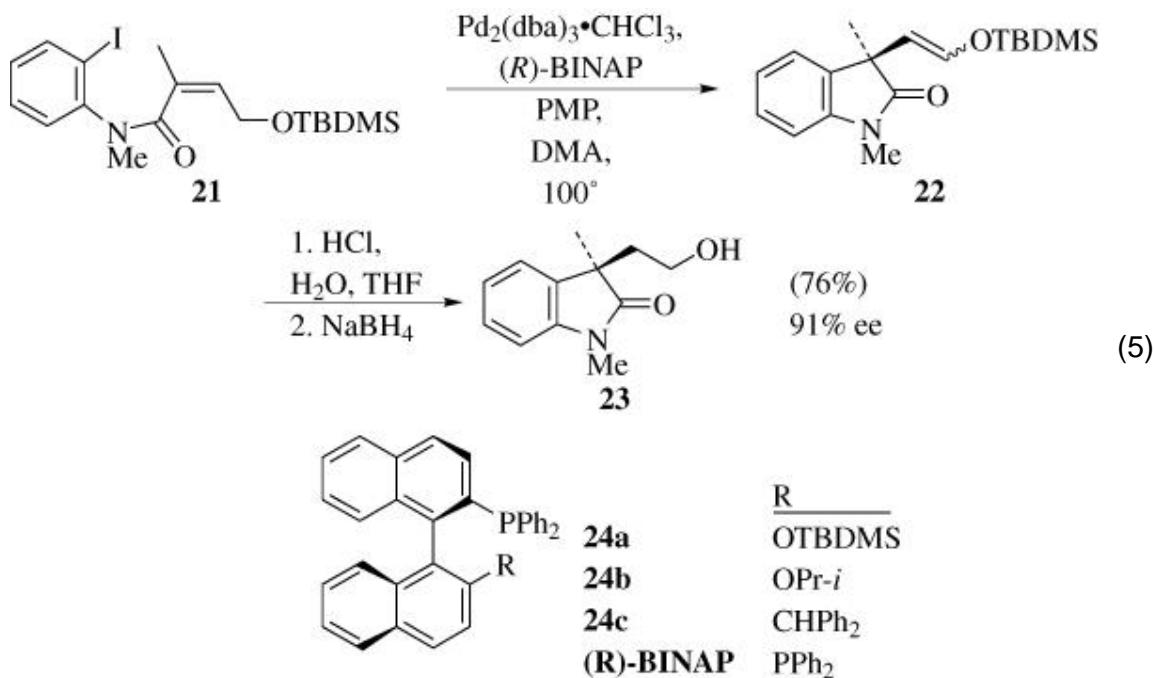
In the neutral pathway, oxidative addition of a bidentate palladium species yields complex **27** (Scheme 4). Ligand dissociation (**27®28**) and insertion (**28®30**) then deliver the cyclized intermediate **30**. Enantioselectivity is usually low for these processes. This observation has been rationalized by the loss of rigidity of intermediate **28** with only one phosphine coordinated during the insertion event. Experimentally, it was determined that the catalytic species is a monomeric Pd-BINAP complex. In addition, neither oxidative addition nor β-hydride elimination is believed to be the enantioselective step. Experimental support for oxidative addition not being the enantioselective step was found when iodides were discovered to react with different enantioselectivity in the presence of silver salts. The possibility that β-hydride elimination is the enantioselective step was ruled out since the geometry of the double bond of the substrate affects the enantioselectivity of the process. To determine if the normal neutral pathway could be responsible, the reaction was conducted with monodentate phosphine BINAP mimics **24a**, **24b**, and **24c** (Eq. 5). Intramolecular Heck reactions with these ligands occur with low and opposite enantioselectivities compared to those with BINAP and at much increased rates. These experiments suggested that the path **25®27®28®30** is not in operation. Two additional alternatives were considered. The dissociation of X from the palladium coordination sphere and replacement by the alkene (**27®29**) were also ruled out by the differing results obtained under cationic conditions. Another possibility is the associative generation of **29** via the pentacoordinate

intermediate **31**. In this event, the conversion of **27**®**31** or **31**®**29** could be the enantiodiscriminating step. Although migratory insertion from complex **31** directly to σ -bonded palladium intermediate **30** has not been disproven, it has been deemed unlikely.

Scheme 4.

Neutral Pathway
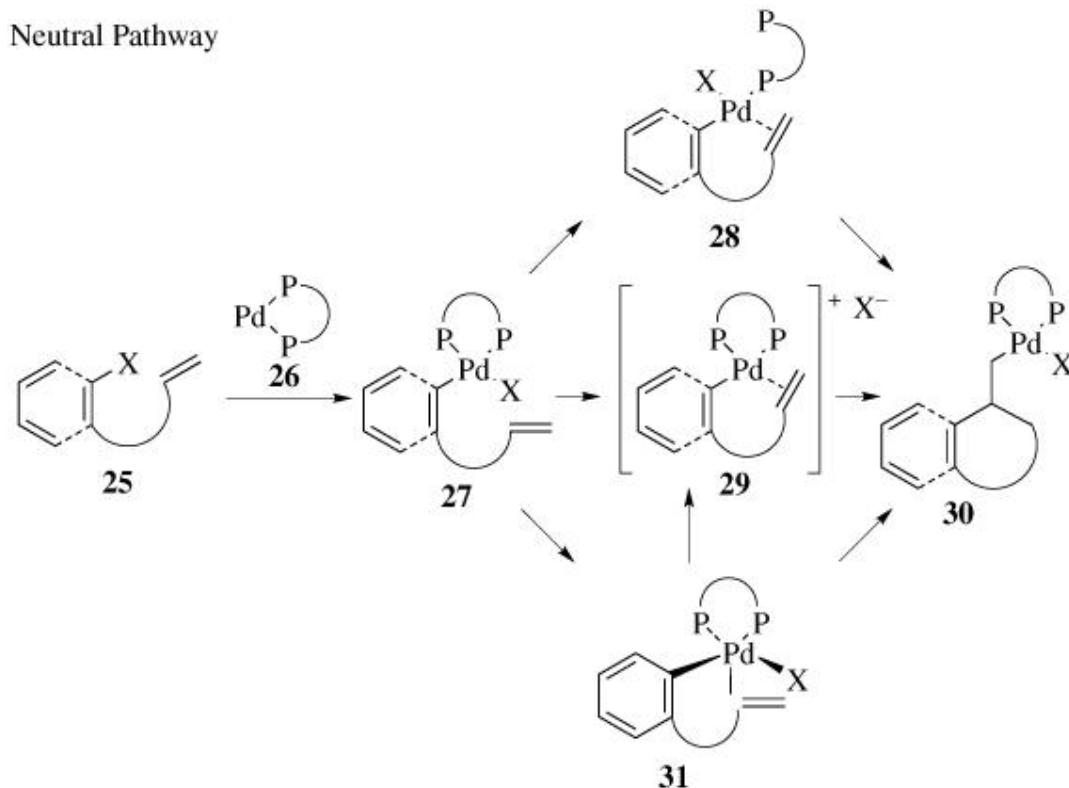
2.5. Anionic Mechanism

Recently, a new catalytic cycle involving anionic Pd[0] and Pd[II] intermediates has been proposed (Scheme 5). (39, 40) The catalytic cycle is thought to arise from the mixture of the common Heck precatalysts Pd(OAc)$_2$ and phosphines. Their combination yields palladium complex **33**. Reduction of **33** with triphenylphosphine (which produces triphenylphosphine oxide) provides anionic complex **34**, which undergoes oxidative addition with substrate **32** to yield the short-lived pentacoordinate complex **35**. Loss of X⁻ then yields an equilibrating mixture of complex **36** and cationic complex **37**. Further reaction of **36** yields cyclized adduct **38**, which after β -hydride elimination yields product **39** and hydridopalladium complex **40**. Deprotonation of **40** with base yields the anionic complex **34** ready to initiate another turn of the catalytic cycle. This mechanism provides an attractive rationale for the effect of many additives like KOAc in Heck reactions.

Scheme 5.

Anionic Mechanism

Pd(OAc)$_2$ + nPPh$_3$

↓

Pd(OAc)$_2$(PPh$_3$)$_2$

33

B + PPh$_3$ → OPPh$_3$ + BH$^+$

B: → [Pd(PPh$_3$)$_2$OAc]$^-$

34

32

HPd(OAc)(PPh$_3$)$_2$

40

$$\left[\text{PdXOAc(PPh}_3)_2 \right]^-$$

35

→ X$^-$

39

Pd(OAc)L$_2$

38
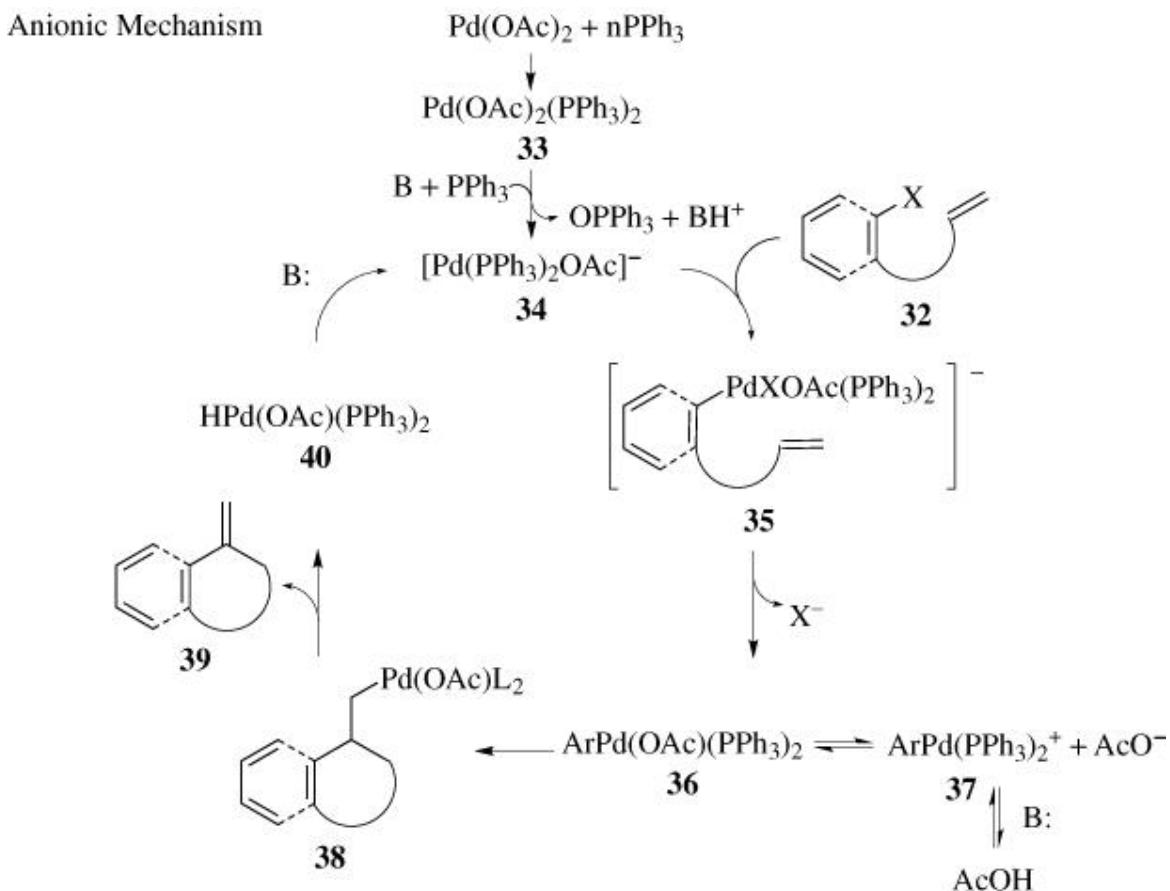
← ArPd(OAc)(PPh$_3$)$_2$ ⇌ ArPd(PPh$_3$)$_2$$^+$ + AcO$^-$

36 **37**

B:

AcOH

2.6. Phosphapalladacycles

Phosphapalladacycles have been introduced as catalysts for the Heck reaction (Scheme 6). (41, 42) These air-stable, yellow solids are generated by heating phosphines like P(C$_6$H$_4$Me–2)$_3$ with Pd(OAc)$_2$ to provide the phosphapalladacycles (e.g. **42a** and **42b**) via cyclometallation. (43, 44) Many earlier examples of Heck reactions in the presence of Pd(OAc)$_2$ and P(C$_6$H$_4$Me–2)$_3$ are potentially mediated by *trans*-di(μ -acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (**42a**; HBC; Herrmann-Beller catalyst). These catalysts deliver excellent turnover numbers (TON) and turnover frequencies (TOF) and have good thermal stability. The precise mechanism for participation of these catalysts in Heck reactions has yet to be delineated. However, initial studies indicate the involvement of a Pd[0] complex rather than a Pd[II]/Pd[IV] catalytic cycle. Studies with 1-bromo-4-chlorobenzene and α -methylstyrene implicate the Pd[0] species **43**, which upon oxidative addition gives complex **44**. (45)

Scheme 6.

	R^1	R^2
41a	H	C_6H_4Me-2
41b	Me	mesityl

2.7. Substitution Reactions

Intramolecular Heck reactions that result in the substitution of an alkenyl or aryl group for an alkenyl proton during cyclization are termed substitution reactions (Eq. 6). The reaction (**45**→**46**) also changes the olefin geometry because of the reaction mechanism. Intramolecular Heck cyclization of precursor **45** after cis-carbopalladation yields σ -bonded palladium intermediate **47**. Bond rotation to allow for syn β -hydride elimination provides complex **48** en route to the substitution product **46**. In some examples, alkene geometry changes are not observed. Presumably, olefin isomerization by palladium [II] salts present in the reaction mixture or anti elimination explains these results.

(6)

2.8. Stereogenic Center Formation

When the reacting alkene **49** is substituted (R ^{1} H), the intramolecular Heck reaction (**49**®**50**) forms a quarternary center (Eq. 7). In this case, β -hydride elimination must occur toward the terminal allylic carbon. Intramolecular Heck reactions can be diastereoselective or enantioselective depending upon substrate and catalyst. Asymmetric reactions typically employ bidentate phosphines of which BINAP is most frequently selected. When R = H, a mixture of the substitution product and products containing a tertiary stereocenter (**50**) are usually obtained. Allylsilanes can be employed to control the regiochemistry of β-elimination (vide infra) yielding a tertiary stereocenter as in **50** (R = H).

$$(7)$$

2.9. Aromatic Substrates

Arenes also participate in the intramolecular Heck reaction as illustrated by the conversion of arene **51** into cyclized biaryl **52** (Eq. 8). Mechanistically, these reactions differ from alkene reactions and are thought to occur via reductive elimination of intermediate **53**. Intermediate **53** could arise from an intramolecular electrophilic aromatic substitution or a Pd [IV] intermediate. There is little experimental support for either reaction pathway, thus inviting mechanistic studies to better understand these transformations. Some alkenyl substrates may also react via a similar mechanism. (46)

$$(8)$$

2.10. Other Termination Pathways

Syn β -hydride elimination is the most common termination step for Heck reactions. Many examples of anti β -hydride elimination have also been documented. (47) Several additional synthetically useful termination pathways for σ -bonded palladium intermediates have been identified. Many, including anion capture and carbonylation, are discussed in the Tandem Reactions Section. By appropriate selection of silyl substrate and reaction conditions, β -silane elimination can occur in preference to β -hydride elimination. These reactions will be discussed in the Asymmetric Reactions Section. β -Alkoxy elimination is uncommon, but has been observed when the alkoxy group is at the anomeric position of a sugar. (48-53) Vinyl bromide **54** is cyclized to glycal **55** in moderate yield, by a process formally requiring a syn β -alkoxy elimination (Eq. 9). (48, 49, 51) Interestingly, the isomeric vinyl bromide **56** reacts similarly to give enol ether **57** (Eq. 10). (53) This reaction formally requires an anti β -alkoxy elimination. Mechanistically it has been proposed that coordination of the anomeric oxygen to the σ-bound palladium insertion product leads to oxonium ion formation en route to the product. (49)

3. Scope and Limitations

3.1. Potential Substrates

Substrates for the intramolecular Heck reaction are typically aryl or vinyl halides or perfluorosulfonates. Iodides, bromides, and triflates make up the majority of the documented examples. One strategy to activate typically unreactive aryl chlorides results in the cyclization of chloride **58** to the substitution product **59** (Eq. 11). (54) Formation of the electron-withdrawing chromium tricarbonyl complex increases the

$$\text{58} \quad \xrightarrow[\text{CH}_3\text{CN, 23°, 24 h}]{\text{Pd(OAc)}_2,\ \text{PPh}_3,\ \text{Et}_3\text{N}} \quad \text{59} \quad (85\%) \tag{11}$$

reactivity of the substrate, leading to an efficient reaction under mild conditions (room temperature). Recently, ligands have been discovered that efficiently promote intermolecular Heck reactions of chlorides. (55) Use of these catalysts may provide for reactions of vinyl and aryl chlorides without having to resort to other activation strategies. Several unsaturated groups, including alkenes, alkynes, allenes, and arenes, also participate in the reaction. The connecting tether can vary in length and composition. Four- through 27-membered rings have been formed and a wide array of functionality is tolerated.

3.2. Isomerization

The intramolecular Heck reaction frequently creates a new alkene, which can isomerize under typical conditions. The isomerization presumably occurs by readdition of the hydrido palladium complex to the alkene followed by β-hydride elimination (or possibly from catalysis by palladium [II] complexes). One example, in which the isomerization is exploited, is the conversion of aryl bromide **60** into indole **61** (Eq. 12). (56) Addition of silver or thallium salts to the reaction mixture typically reduces the amount of isomerization. (32) For example, iodide **62** can be converted into the substitution product **63** without formation of the indole (Eq. 13). (57)

$$O_2N \text{--} \underset{\underset{\text{OBn}}{|}}{\text{Br}} \text{--} \overset{\overset{\text{allyl}}{}}{\underset{\text{H}}{N}} \xrightarrow[\text{DMF, rt, 24 h}]{\substack{Pd(OAc)_2, \\ n\text{-}Bu_4NBr, Et_3N}} O_2N \text{--}\underset{\text{OBn}}{\text{indole}}\text{--}\text{Me} \quad (96\%) \quad (12)$$

60 → **61**

$$MeO \text{--}\underset{\text{SO}_2\text{Ph}}{\overset{I}{N}}\text{--allyl} \xrightarrow[\text{DMF, rt, 5 h}]{\substack{Pd(OAc)_2, PPh_3, \\ Ag_2CO_3}} MeO\text{--}\underset{\text{SO}_2\text{Ph}}{N}\text{--indoline} \quad (80\%) \quad (13)$$

62 → **63**

3.3. Allylic Stereocenters

Allylic stereocenters bearing leaving groups can undergo competitive reaction with palladium [0] complexes under typical Heck reaction conditions, owing to the formation of palladium π-allyl intermediates. For many substrates, such a pathway can be avoided by a judicious choice of protecting groups. For instance, the *tert*-butyldimethylsilyl-protected vinyl bromide **64** undergoes conversion into diene **65** (Eq. 14). (58-60) An allylic acetate would probably be reactive. One reactive

$$\xrightarrow[\text{CH}_3\text{CN, reflux}]{\substack{Pd(PPh_3)_4, \\ K_2CO_3}} \quad (92\%) \quad (14)$$

64 → **65**

allylic system is revealed by the conversion of aryl iodide **66** into tetracycle **67** (Eq. 15). (61) During this reaction, the N-O bridge is inverted, which has been rationalized by the formation of a palladium π-allyl intermediate followed by reclosure. Imaginative uses of this type of chemistry have led to tandem reactions. (62)

$$\text{(15)} \quad \mathbf{66} \xrightarrow[\text{CH}_3\text{CN, 80°, 18 h}]{\text{Pd/C (10\%) , Et}_3\text{N}} \mathbf{67} \quad (50\%)$$

3.4. 4-Exo Cyclization

The majority of intramolecular Heck cyclizations are exo, although many endo examples exist. The smallest ring that has been constructed is a cyclobutane although there are currently only a few examples. Nonaflate **68** undergoes a substitution reaction to provide diene **69** in moderate yield (Eq. 16). (63) Perhaps more impressive is the formation of two cyclobutanes in one reaction by the conversion of bis(nonaflate) **70** into tricycle **71** (Eq. 17). (63) Typically, intramolecular Heck reactions prefer a 5-endo pathway over 4-exo.

$$\text{(16)} \quad \mathbf{68} \xrightarrow[\text{DMF, 80°, 12 h}]{\text{Pd(OAc)}_2, \text{PPh}_3, \text{Et}_3\text{N}} \mathbf{69} \quad (52\text{-}65\%)$$

$$\text{(17)} \quad \mathbf{70} \xrightarrow[\text{DMF, 80°, 12 h}]{\text{Pd(OAc)}_2, \text{PPh}_3, \text{Et}_3\text{N}} \mathbf{71} \quad (\text{—})$$

3.5. 5-Exo Cyclization

5-Exo intramolecular Heck reactions are the most facile (Eq. 18). For this reason, the reaction is popular for constructing five-membered rings, particularly if acid-sensitive functional groups are present. It is commonly used to produce indoles, benzofurans, benzothiophenes, oxindoles, benzofuranones, and other heterocycles. One

$$(71\%) \quad (18)$$

example is the conversion of aryl iodide **72** into the substitution product carbacycle **73**. (64) Annulations typically produce a cis ring juncture. For example, vinyl iodide **74** is converted into the cis-fused bicycle **75** (Eq. 19). (65) Alkene isomerization in this

$$(77\%) \quad (19)$$

case is suppressed by Ag$_2$CO$_3$. Similarly, the cyclization of diol **76** produces a cis ring junction. (66) In this case β -hydride elimination yields an enol which tautomerizes to ketone **77**. These three examples also illustrate the wide functional group tolerance of the reaction, which leaves esters, nitriles, and alcohols as well as many other potentially labile groups unperturbed.

$$(67\%) \quad (20)$$

3.6. 6-Exo Cyclization
The formation of six-membered rings via a 6-exo intramolecular Heck reaction is also common (Eq. 21). One example of a substitution reaction is the conversion of aryl bromide **78** into tricycle **79**. (67) The conversion illustrates the ability of the reaction

$$(73\%) \quad (21)$$

78   **79**

to construct rings in a potentially sensitive system. Heck catalysts are typically stable at high temperatures, allowing the construction of strained systems. During the cyclization of **78** to **79**, both groups on the dioxolane ring must move into energetically unfavorable axial orientations. Another bridged system can be formed via the reaction of sulfonamide **80** to give tricycle **81** (Eq. 22). (68, 69) The intramolecular Heck reaction also efficiently constructs quaternary centers. Triflate **82** undergoes 6-exo cyclization to provide enol ether **83** by forming a 6-membered ring, a quaternary center, and converting a protected alcohol into a protected aldehyde in one step (Eq. 23). (70, 71)

$$(78\%) \quad (22)$$

80   **81**

$$(42\%) \quad (23)$$

82   **83**

As with the 5-exo reaction, 6-exo reactions typically deliver a cis ring juncture. For instance, aryl bromide **84** cyclizes to tetracycle **85** under the influence of the Herrmann-Beller catalyst **42a** (Eq. 24). (72, 73) An interesting example in which a trans ring juncture is formed predominantly is the cyclization of amide **86** (Eq. 25). Trans-fused tetracycle **87** is produced as the major product and cis-fused **88** as the minor product. (74)

$$(24)$$

87 β-vinyl group (65%)
88 α-vinyl group (3%)

$$(25)$$

3.7. 7-Exo Cyclization

Seven-membered rings are efficiently constructed by the intramolecular Heck reaction. Although not as facile as the formation of five- and six-membered rings, many high yielding examples of 7-exo cyclization have been documented. An example of a substitution reaction is the conversion of aryl iodide **89** into benzazepine **90** in high yield (Eq. 26). (75) Similarly, ether **91** cyclizes to tricycle **92** (Eq. 27). (76)

(96%) $$(26)$$

(84%) $$(27)$$

Again, a preference for cis ring junctures is observed as illustrated by the reaction of bromide **93** to yield pentacyclic amine **94** (Eq. 28). (77-79)

$$\text{(81\%)} \quad \text{(28)}$$

Intramolecular Heck reactions also are effective ways to build strained ring systems. An example of this is the conversion of vinyl iodide **95** into tricycle **96** (Eq. 29). (80) Hydroxyketone **96** is highly strained owing to its anti-Bredt alkene,

$$\text{(52\%)} \quad \text{(29)}$$

geminal dimethyl substituted bridge carbon, and five sp^2 hybridized centers in the seven-membered ring. Allenes are competent reaction partners for forming medium and large rings. (81, 82) Typically, as in intermolecular reactions, attack at the central sp-carbon of the allene is observed. One example is the reaction of iodide **97** to yield diene **98** (Eq. 30). (81, 82)

$$\text{(71\%)} \quad \text{(30)}$$

3.8. 8-Exo Cyclization

Medium-sized rings, including eight-membered, are suitable targets for the intramolecular Heck reaction (Eq. 31). The alkenyl examples arise from synthetic studies toward the natural product taxol® (vide infra). Allenes also participate (including cases in which the corresponding alkene is reluctant to react), as demonstrated by the conversion of aryl bromide **99** into styrene **100** (Eq. 31). (81, 82)

$$\text{(31)}$$

3.9. Macrocyclization

Large rings can also be synthesized by the intramolecular Heck reaction. Examples can be either exo or endo and are typically controlled by the electronics of the reacting partners rather than by the tether. For instance, enoate **101** undergoes 22-endo cyclization to cinnamate **102** (Eq. 32). (83) As with medium-sized rings, allenes are also good substrates as exemplified by the highly efficient reaction of allene **103** to styrene **104** (Eq. 33). (82) The reaction closes a 20-membered ring in 86% yield.

$$\text{(32)}$$

$$(86\%) \quad (33)$$

3.10. Endo Cyclization

Although most intramolecular Heck reactions are exo, the endo reaction can be used in a number of situations. 5-endo Reactions are typically preferred over 4-exo reactions. For example, enoate **105** undergoes reaction under Jeffery's conditions to yield indole **106** (Eq. 34). (84) Similarly, aziridinylquinone **107** cyclizes efficiently to tetracycle **108** (Eq. 35). (85) It is interesting that the reaction is effective with substrates that have different alkene polarization.

$$(46\%) \quad (34)$$

$$(96\%) \quad (35)$$

Although 5-exo cyclization is generally preferred over 6-endo, there are examples of efficient 6-endo reactions. One example is the closure of eneamide **109** to tricyclic lactam **110** (Eq. 36). (86) A related reaction

(**111** → **112**, Eq. 37) indicates that alkene electron polarization does not dominate the reaction. (**87**)

$$109 \quad \xrightarrow[\text{CH}_3\text{CN, reflux, 10 h}]{\begin{array}{c}\text{Pd(OAc)}_2, \text{PPh}_3,\\ \text{Et}_3\text{N}\end{array}} \quad 110 \quad (99\%) \qquad (36)$$

$$111 \quad \xrightarrow[\text{CH}_3\text{CN, 100}^\circ, \text{15 h}]{\begin{array}{c}\text{Pd(OAc)}_2, \text{P(tol-}o)_3,\\ \text{Et}_3\text{N}\end{array}} \quad 112 \quad (96\%) \quad (37)$$

As the ring size increases to medium and large rings, the intramolecular Heck reaction begins to behave more like the intermolecular reaction. For instance the 7, 8, and 9-endo closures of iodides **113** to bicyclic compounds **114** follow this trend (Eq. 38). (**88-90**) Interestingly, the yield of the reaction increases with increasing ring size.

$$113 \quad \xrightarrow[\begin{array}{c}n\text{-Bu}_4\text{NCl}\\ \text{mol sieves (3 Å)},\\ \text{DMF, 105-110}^\circ, \text{16 h}\end{array}]{\text{Pd(OAc)}_2, \text{NaHCO}_3,} \quad 114 \qquad (38)$$

n	
1	(55%)
2	(73%)
3	(86%)

3.11. Rearrangement

Several examples of intramolecular Heck reactions give a product that upon first inspection is the result of endo cyclization with a change in olefin geometry. For example, vinyl iodide **115** undergoes reaction to give diene **116** (Eq. 39). (91) The

$$
\begin{array}{c}
\textbf{115} \xrightarrow[\substack{\text{Et}_3\text{N, Et}_2\text{NH} \\ \text{DMF, 80}^\circ\text{, 8 h}}]{\text{PdCl}_2(\text{PPh}_3)_2,} \textbf{116} \quad (94\%)
\end{array}
\tag{39}
$$

$$
\textbf{117} \longrightarrow \textbf{118}
$$

reaction is not a violation of the rules governing these palladium-mediated reactions, but is actually a rearrangement. Upon 5-exo cyclization, **115** is converted into the neopentyl palladium intermediate **117**; 3-exo cyclization then yields cyclopropane **118**. Bond rotation, cyclopropane cleavage, and β-hydride elimination then provide product **116** in good yield. (91, 92)

The reaction has been observed in complex systems when a normal Heck reaction was anticipated. (93) In one case, 6-exo cyclization of vinyl iodide **119** yields palladium complex **121** (Eq. 40). Complexation with the neighboring carbamate is invoked to explain why rearrangement to polycycle **120** via cyclopropane formation/fragmentation occurs instead of β-hydride elimination.

$$(40)$$

3.12. Aromatic Cyclization

Although mechanistically different from alkenes and alkynes, aromatic groups also undergo intramolecular reactions. Halides (I, Br, Cl) and triflates are substrates, and the reaction creates a biaryl bond closing 5–7 membered rings. Aryl bromide **122** undergoes reaction to provide lactam **123** in nearly quantitative yield

$$(41)$$

(Eq. 41). (94-96) In addition to six-membered rings, five-membered ring examples are common as illustrated by the regioselective closure of triflate **124** to pentacyclic aromatic **125** (Eq. 42). (97) Seven-membered ring closures are rarer, but the cyclization of bis-indolemaleimide **126** to the hexacycle **127** proceeds efficiently (Eq. 43). (98)

$$(42)$$

(43)

126 → **127** (81%)

Phenolates are excellent substrates for the reaction although electron-deficient aromatic rings will also react. Furthermore, they often react regioselectively as in the conversion of iodide **128a** into tricycle **129** (Eq. 44). (99) The corresponding methyl ether **128b** gives a different regioisomer **130** and is a poor participant in the coupling reaction under identical conditions.

(44)

R
128a OH
128b OMe

	129	130
	(97%)	(0%)
	(0%)	(10%)

3.13. Tandem Reactions

s -Alkylpalladium complexes are capable of undergoing a broad range of chemistry in addition to β -hydride elimination. The intramolecular Heck reaction is one method for generating these complexes, whose rich chemistry leads to tandem reactions capable of producing complex products from simple starting materials in a predictable manner. (100-102) These reactions have also been termed domino reactions. (103, 104) As in the Heck reaction, σ -alkylpalladium complexes undergo alkene insertion reactions that can be exploited in an inter- or intramolecular sense. This versatility leads to multiple insertion pathways capable of forming rings and coupling fragments. For instance, generic precursor **131** under palladium catalysis yields the σ-alkylpalladium complex **132** (Eq. 45). Since **132** has no β -hydrogens,

(45)

no elimination takes place, and an intermolecular Heck reaction with an alkene yields product **133**. In order for this catalytic cycle to function efficiently, the cyclization of precursor **131** to intermediate **132** must be faster than the direct coupling of precursor **131** with the alkene. Thus, for many intramolecular Heck initiated tandem reactions, the first ring formed must be small (five- or six-membered), although in some cases medium-sized (seven- or eight-membered) rings can be formed. The second insertion can also be intramolecular, leading to the formation of two rings as in the conversion **131**→**134**→**135**. Alkynes are also effective relay partners. For example, alkyne **136** undergoes Heck cyclization to provide vinylpalladium intermediate **137** ready to undergo a second insertion reaction en route to tricycle **138** (Eq. 46). Many variations of these themes are possible and are detailed in the following sections and in the tables on multiple insertions.

(46)

Carbonylation is another reaction pathway available to σ -alkylpalladium complexes (Eq. 47). After carbon monoxide adds to the insertion product **139** to produce acylpalladium complex **140**, a variety of nucleophiles (XH) can react to provide products **141**. Nucleophiles (XH) include hydride equivalents, alcohols, amines, and soft carbanions (like malonate), leading to aldehydes,

esters, amides, and ketones, respectively. The nucleophilic X and pendant group R^1 can also be connected to provide an intramolecular reaction.

$$(47)$$

The intramolecular Heck reaction with a diene or allene can yield a π-allylpalladium intermediate that can trap soft nucleophiles or undergo other reactions. Reactions with dienes can generate π-allyl complexes in two different ways. Intramolecular Heck reaction of generic diene **142** (Eq. 48) can yield π-allyl intermediate

$$(48)$$

143 directly which, after capturing a nucleophile, yields alkene **144**. Alternatively, after Heck reaction of diene **145** (Eq. 49) yields σ-alkylpalladium complex **146**, β-hydride elimination and readdition provide π-allyl complex **147** that again can react with a soft nucleophile to deliver products **148**. Allenes are also effective

$$(49)$$

partners for inter- and intramolecular Heck reactions (Eq. 50). The intramolecular reaction of allene **149** yieldsπ-allyl complex **150**, which reacts wth nucleophiles to give products **151**. Allenes close to give small, medium,

and large rings at suitable rates to allow these types of tandem processes to occur.

$$(50)$$

Anionic capture is a term coined to describe the reaction of various anions, neutral molecules, and organometallics with σ-bonded alkylpalladium complexes (**152** → **153**; Eq. 51). (100, 101) Anions include hydride equivalents, cyanide, acetate, azide, TsNR, SO_2Ph, and malonates. Neutral species include amines, MeOH/CO, acrylates, and allenes. The organometallics include stannanes, boronic acids, and organozincs.

$$(51)$$

3.13.1. Multiple Insertions

3.13.1.1. Intermolecular Insertions

Intramolecular Heck reaction followed by an intermolecular Heck reaction is an effective one-pot method for constructing a ring and coupling two fragments. One example from a benzoprostacyclin synthesis is the reaction of iodide **154** (Eq. 52). (105) Treatment with palladium acetate under Jeffery's conditions leads to 5-exo cyclization and establishes the cis ring juncture. β -Hydride elimination is precluded by the neighboring hydroxy group, allowing for intermolecular Heck coupling with 1-octen-3-one to give tricyclic product **155**. The reaction closes a ring, sets two stereogenic centers, couples two

$$(52) \quad (42\%)$$

154 → **155**

fragments, and builds two carbon-carbon bonds. Vinyl bromide **156** (Eq. 53) undergoes a related reaction. (106) 5-exo Cyclization onto the pendant alkyne provides a vinylpalladium intermediate that undergoes an intermolecular reaction with methyl acrylate. Ring closure in similar systems is thought to occur by two different mechanisms: 6-endo insertion prior to β-hydride elimination or 6π electrocyclization. In both cases, oxidation gives the aromatic ring. In this case, the mechanism involving 6-endo insertion is thought to be operating.

$$(56\%) \quad (53)$$

156 → **157**

An example of an intramolecular Heck reaction followed by an intermolecular insertion followed by an intramolecular insertion is shown in Eq. 54. 5-exo Cyclization of aryl iodide **158** yields a vinylpalladium intermediate that reacts with norbornene. (107, 108) The σ-alkylpalladium intermediate **159** cannot β-hydride eliminate and undergoes a 3-exo reaction followed by β-hydride elimination to yield cyclopropane **160**. The reaction couples two fragments and assembles a tetrasubstituted

$$(54)$$

cyclopropane while controlling the relative configuration of each stereogenic center. Allene can also play a key role in tandem reactions. Intramolecular Heck reaction of ether **161** yields the corresponding 5-exo vinylpalladium adduct. Reaction with allene yields a π-allyl intermediate that is trapped by piperidine to give dienyl amine **162** (Eq. 55). (448)

$$(55)$$

3.13.1.2. Intramolecular Insertions
Multiple intramolecular insertions can be utilized to rapidly assemble a variety of polycyclic skeletons (Eq. 56). (109, 110) For example, amide

$$(56)$$

163 undergoes a 5-exo cyclization to yield a neopentyl σ-bonded palladium intermediate incapable of β-hydride elimination. (111) Subsequent 6-exo substitutive coupling then provides tricycle **164**, assembling one quaternary center and closing two rings in high yield. In a second example, sugar-derived

vinyl bromide **165** undergoes a tandem 5-exo; 5-exo coupling to give product **166** (Eq. 57). (50) The reaction closes

$$(79\%) \quad (57)$$

two five-membered rings, sets two ring junction stereocenters, and determines the final alkene geometry. One can also install a cyclopropane at a ring juncture using multiple insertions. For instance, treatment of vinyl triflate **167** under standard Heck conditions leads to 5-exo cyclization to a neopentyl intermediate, which undergoes 3-exo cyclization and β -hydride elimination to give cyclopropane **168** diastereoselectively (Eq. 58). (110)

$$(90\%) \quad (58)$$

Alkynes are effective relay units for multiple insertion reactions (Eq. 59). For example, vinyl iodide **169** undergoes a 6-exo intramolecular reaction with the alkyne. (112) Two additional 5-exo insertion steps close two five-membered rings, efficiently producing the tricyclic compound **170**. This "zipper" mode polycyclization

$$(90\%) \quad (59)$$

efficiently produces an angularly fused polycyclic network. (109, 110) Related cyclizations can be designed to build linearly or spiro-fused polycyclic networks. A different type of cyclization is illustrated by the reaction of **171** to tricycle **172** (Eq. 60). (113) A tandem 5-exo; 5-exo; 6-endo cyclization accounts for the reaction.

$$\text{(83\%)} \quad \text{(60)}$$

3.13.2. Carbonylation

Tandem Heck/carbonylation reactions are most effective when used to construct five- and six-membered rings. With larger rings, carbonylation competes with cyclization. Capture of the intermediate acylpalladium intermediate with alcohols yields esters efficiently. Thallium salts are not required, but have been shown to promote many reactions, including the 5-exo cyclization of sulfonamide **173** to indoline **174** (Eq. 61). (114) Similarly, the diastereoselective closure of amide

$$\text{(91\%)} \quad \text{(61)}$$

175, carbonylation, and intermolecular capture with methanol yields ester **176** efficiently (Eq. 62). (114) The reaction occurs across the less hindered face of the alkene. In both cases, a sterically congested neopentylpalladium intermediate is carbonylated effectively. The reaction also works with vinylpalladium intermediates, and the trapping alcohol can be a part of the substrate. Alkyne **177** undergoes 6-exo cyclization followed by carbonylation and primary alcohol capture to give bicyclic lactone **178** (Eq. 63). (115)

175 → 176 (86%) (62)

PdCl₂(PPh₃)₂, CO, TlOAc
MeOH, 65°, 21 h

177 → 178 (80%) (63)

PdCl₂(PPh₃)₂, CO, Et₃N
MeOH, 70°, 24 h

Amines can be used in the reaction in place of alcohols, leading to amides. For example, sulfonamide **179** undergoes 5-exo cyclization, carbonylation, and amine trapping to give indole **180** after olefin isomerization (Eq. 64). (101, 102) Some unisomerized material **181** is also obtained from the reaction. Intramolecular examples are also known, such as the conversion of aryl iodide **182** into the eight-membered ring lactam **183** (Eq. 65). (116)

179

Pd(OAc)₂, P(C₆H₄Me-2)₃, CO, proton sponge
CH₃CN, 60°, 18 h

180 (5%) +

181 (—)

(64)

182 → **183**   (45%)   (65)

The reaction can also be conducted in the presence of diphenylmethylsilane to yield aldehydes. For instance, aryl iodide **184** is converted into aldehyde **185** by this protocol (Eq. 66). (117) Intramolecular capture by soft carbon nucleophiles is also effective, as demonstrated by the reaction of diester **186** to give cyclopentanone **187** (Eq. 67). (116)

184 → **185**   (61%)   (66)

186 → **187**   (50%)   (67)

3.13.3. Aromatic Cyclization Termination
Aromatic groups also react intramoleculary with σ -bonded palladium intermediates. Thus, they can be used to terminate tandem reactions as in the

cyclization of aryl iodide **188**. 5-exo Cyclization followed by reaction with the furan derivative produces spirocycle **189** (Eq. 68). (118)

$$\text{(64\%)} \quad \text{(68)}$$

3.13.4. *p-Allylpalladium Intermediates*

Intramolecular Heck reactions that form π -allylpalladium intermediates allow for intriguing tandem reactions. In most examples, the resultant π -allylpalladium intermediates are used to trap nucleophiles inter- or intramolecularly. For example, in a total synthesis of (–)-morphine, intramolecular Heck reaction of substrate **190** presumably yields a π -allylpalladium intermediate that then reacts with the pendant phenol (Eq. 69). (119) Frequently,

$$\text{(56\%)} \quad \text{(69)}$$

nucleophiles attack π -allyl intermediates at the less substituted end of the allyl unit on the face opposite the palladium group. In this example, the intramolecular nature of the reaction allows for capture on the same face and at the more substituted end to give product **191**. In a related reaction, allene **192** undergoes a 7-exo reaction to yield a π -allyl intermediate that is then captured on the less substituted terminus by the phenol to give tricycle **193** (Eq. 70). (82)

$$\text{(70)}$$

As with many palladium-catalyzed reactions, the precise reaction conditions can have a substantial influence on the outcome of the reaction. For example, 6-exo cyclization of allene **194** and capture of the resultant π-allylpalladium intermediate occur with opposite regioselectivities under different reaction conditions (Eq. 71). (120, 121) In the presence of potassium carbonate, capture occurs at the less substituted end to give isomer **195**. Switching to Ag_2CO_3 reverses the selectivity, giving adduct **196**.

$$\text{(71)}$$

Carbon nucleophiles can also be accomodated by this type of tandem reaction. Allene **197** reacts and captures potassium diethyl malonate to give product **198** in 84% yield (Eq. 72). (82) This reaction is remarkable in the efficient closure of an eight-membered ring and nucleophile capture, both of which construct carbon-carbon bonds.

3.13.5. Reductive Cyclization

Alkene insertion followed by reduction of the resultant σ -bound palladium intermediate lead to a net reductive cyclization. Inclusion of reductants like sodium or potassium formate can divert a Heck reaction down this path.

$$(84\%) \quad (72)$$

For instance, treatment of amide **199** under standard Heck conditions with the additives formic acid and piperidine yields lactam **200** (Eq. 73). (122) The reaction is also

$$(65\%) \quad (73)$$

effective with alkynes as demonstrated by the conversion of alkynylsilane **201** into vinylsilane **202** (Eq. 74). (123) The reaction is noteworthy because of the fragility of exocyclic allylsilanes (and the reactivity of allylsilanes, vide infra). The reaction can be applied to some seven-membered ring cases as exemplified by the reaction **203→204** (Eq. 75). (124) Medium and large rings often do not perform well owing to competing triflate or halide reduction.

$$(72\%) \quad (74)$$

203 → **204** (60%) (75)

3.13.6. Capture

Capture of the σ -alkylpalladium adducts of intramolecular Heck reactions by other groups can lead to highly functionalized products. For example, 6-exo cyclization of ether **205** followed by cyanide anion capture gives benzopyran **206** (Eq. 76). (125) Two carbon-carbon bonds are formed in this reaction. The reaction can be intramolecular as illustrated by the 6-exo cyclization of alkynone **207**. (70, 71, 126) Capture of the pendantenol gives pentacyclic furan **208** (Eq. 77). The tandem reaction results in the net annulation of a furan.

205 $\xrightarrow[\text{toluene, }110°, 18\text{ h}]{\begin{array}{c}\text{Pd(OAc)}_2, \text{PPh}_3,\\ \text{18-crown-6, KCN}\end{array}}$ **206** (62%) (76)

207 $\xrightarrow[\text{DMF, rt, 8 h}]{\begin{array}{c}\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3,\\ \text{K}_2\text{CO}_3\end{array}}$ **208** (72%) (77)

3.13.7. Organometallic Capture

Organometallic reagents can also be captured efficiently. Suzuki coupling of boronic acids and related reagents with the σ -alkylpalladium complexes derived from insertion reactions can be quite efficient. Ring closure rates in these reactions are critical since direct coupling prior to ring closure can occur. Typically, five- and six-membered ring cases are most effective. Triflate **209** undergoes a diastereoselective 5-exo Heck reaction to produce a neopentyl σ -alkylpalladium intermediate. Tandem Suzuki coupling with 3-nitrophenylboronic acid yields ester **210** in high yield (Eq. 78). (127, 128) 6-exo Closures are also effective as

shown by the conversion of iodide **211** into oxacycle **212** (Eq. 79). (128) Lactam **213** also undergoes a 6-exo closure and Suzuki coupling with sodium tetraphenylborate to produce tetracycle **214** (Eq. 80). (128) As expected, syn-carbopalladation followed by Suzuki coupling with retention of configuration explains the stereochemical result.

Vinyl, alkynyl, allyl, aryl, and other stannanes also participate in organometallic capture reactions. Tandem intramolecular Heck/Stille reactions are again effective in reactions where five- and six-membered rings are formed. Vinyl bromide **215**, when treated with tetrakis(triphenylphosphine)palladium,

undergoes 5-exo closure to provide a vinylpalladium intermediate. Stille cross-coupling with an alkynyl stannane yields dienyne **216** in good yield (Eq. 81). (129) Another 5-exo cyclization example

is the reaction of iodoamide **217** with tri-*n*-butyl(vinyl)tin to yield lactam **218** stereoselectively (Eq. 82). (130, 131) The reaction occurs on the less hindered face of the alkene, and Stille coupling occurs with retention of configuration.

Alkylzinc reagents are rapidly gaining popularity amongst synthetic chemists because of their functional group tolerance and cross-coupling capacity. (132a), (b) Heck reaction with subsequent coupling allows these reagents to be used in a tandem reaction. One example is the 5-exo cyclization reaction of alkynyl iodide **219** to provide a vinylpalladium intermediate. Cross coupling with PhZnCl yields indoline **220** in moderate yield (Eq. 83). (132)

3.13.8. Heck/Diels-Alder Reactions

Intramolecular Heck reactions of vinyl halides and triflates frequently form dienes, which are substrates for Diels-Alder reactions. Frequently the two reactions are conducted in a one-pot process because of the instability of some of the dienes and the efficiency of both the intramolecular Heck and Diels-Alder reactions. One example is the reaction of vinyl bromide **221** in the presence of *tert*-butyl acrylate (Eq. 84). (133) 5-exo Intramolecular Heck reaction provides an exocyclic diene that reacts regioselectively with the acrylate to produce cyclopropane **222**. Alkynes and quinones also can be employed as Diels-Alder partners, as demonstrated by the reactions of **223** → **224** (Eq. 85) (133) and **225** → **226** (Eq. 86). (133)

3.14. Diastereoselective Reactions

The intramolecular Heck reaction can be highly diastereoselective depending upon substrate structure. Two types of diastereoselective reactions have already been mentioned. In the first, a stereocenter in the chain between the reacting aryl iodide and alkene imparts selectivity (Eqs. 3, 4, and Scheme 3). A second type of diastereoselective reaction is observed when the cyclization creates a ring junction. Typically cis junctures are formed preferentially (Eqs. 10, 20, 21, 24, 28, 40, 52, 57). Chiral auxiliaries have been employed to take advantage of diastereoselective reactions to produce enantiomerically pure products. In one case, the chiral auxiliary is appended to the tether linking the reacting aryl iodide and alkene. (134) Cyclization of aryl iodide **227** delivers lactam **228** diastereoselectively (Eq. 87). (134) In a second example, sulfoxide **229** cyclizes to cyclopentane **230** (Eq. 88). (135) The factors by which the sulfoxide attached to the reacting alkene influences the reaction are still under investigation. In both cases, the chiral auxiliary (proline-derived pyrrolidine and aryl sulfoxide, respectively) can be removed, albeit inefficiently under conditions that may not be broadly applicable.

Stereocenters on the reacting halide or triflate can affect the reaction diastereoselectivity just as those on the tether and reacting unsaturated group. For instance, vinyl triflate **231** undergoes 6-exo cyclization to form a quaternary center yielding the diastereomeric enol ethers **232** and **233** (Eq. 89). (136) When the reaction is conducted under conditions that presumably favor

the neutral pathway with the monodentate ligand triphenylphosphine, an unselective reaction favoring tricycle **232** is observed. However, when the bidentate ligand dppp is employed under cationic conditions, diastereomer **233** is the major product of a more selective and efficient reaction.

	232	233
Pd(OAc)$_2$, PPh$_3$, KOAc, TPAB, DMSO, 85°, 14 h	(35%)	(23%)
Pd(OAc)$_2$, dppp, K$_2$CO$_3$, toluene, 100°, 7 h	(5%)	(85%)

(89)

Examples of several types of diastereoselective tandem reactions are known. Aryl chloride chromium complex **234** reacts under carbonylative conditions to give indane **235** in high diastereoselectivity (Eq. 90). (54) In product **235**, the newly formed stereocenter orients the ester on the face opposite the Cr(CO)$_3$ group. In a related

example, the bulky silyl ether **236** undergoes tandem 6-exo cyclization/carbonylation to yield tetralins **237** and **238** (Eq. 91). (137) ester **237**, in which the ester and bulky OTBDMS group are on opposite faces of the

newly-closed six-membered ring, is the major product. Tandem 5-exo;6-exo cyclization of aryl iodide **239** occurs diastereoselectively (Eq. 92). (101, 114, 128, 138, 139) Trapping by carbonylation or Suzuki reaction provides products **240a** and **240b**, respectively.

$$(91)$$

$$(92)$$

R		
a CO$_2$Me	PdCl$_2$(PPh$_3$)$_2$, CO, TlOAc, MeOH, 65°	(43%)
b Ph	Pd$_2$(dba)$_3$, TFP, NaBPh$_4$, anisole, 110°, 24 h	(63%)

3.15. Asymmetric Reactions

The asymmetric intramolecular Heck reaction is a powerful method for synthesizing enantiomerically enriched polycycles. (71, 140-143) Furthermore, it is one of the most effective methods for building quaternary centers. (144) The reaction typically employs bidentate phosphines, and BINAP is often the most effective ligand. Typically, the substrates and reaction conditions are selected to ensure the reaction occurs via the cationic pathway. For bidentate phosphines this is critical because it guarantees that both phosphines will remain bonded to palladium during the catalytic cycle and therefore be more able to impart asymmetric information throughout the course of the reaction. For instance, *E*-alkenyltriflate **241** undergoes reaction in the presence of a palladium complex derived from (*R*)-BINAP and Pd$_2$dba$_3$· CHCl$_3$ (Eq. 93). (145) Tetralin **242** is obtained in 95% yield and 51% ee as an 84:11 *E*:*Z* mixture. *Z*-Alkenyltriflate **243** cyclizes similarly with higher enantioselectivity to enol ether tetralin **244** in 87% yield and 93% ee as a 21:3 *E*:*Z* mixture (Eq. 94). (145)

Both reactions employ triflates as precursors, so presumably occur under cationic conditions.

$$Pd_2(dba)_3 \cdot CHCl_3,$$
$$(R)\text{-BINAP, } K_2CO_3$$
$$THF, 70°, 48 \text{ h}$$

(95%)
51% ee
E:Z 84:11 (93)

241

242

$$Pd(OAc)_2,$$
$$(R)\text{-BINAP, } K_2CO_3$$
$$THF, 60°, 48 \text{ h}$$

(87%)
93% ee
E:Z 21:3 (94)

243

244

Most asymmetric intramolecular Heck reactions are more effective under cationic rather than neutral conditions. In order to induce halides such as iodide **245** to react via this pathway, the reaction is conducted in the presence of a silver or thallium salt (Eq. 95). (146, 147) Cyclization in the presence of Ag_3PO_4 and a catalyst derived from (R)-BINAP yields tetracycle **246** in 81% yield and 71% ee. Cyclization of iodide **245** under conditions that favor the neutral pathway delivers tetracycle **247** (the enantiomer of **246**) using the same ligand. The latter reaction is surprisingly enantioselective (66 %ee) given that it probably occurs via the neutral pathway. Pentacoordinate intermediates are potentially involved.

(95)

An example of kinetic resolution using an intramolecular Heck reaction is the conversion of racemic triflate **248** into enol ethers **249** and **250** (Eq. 96). (136) In the presence of a catalyst derived from Pd(OAc)$_2$ and (*R*)-Tol-BINAP, enol ether **249** is produced in modest yield and in 96% ee. Unfortunately, the starting triflate **248** could not be recovered.

(96)

3.15.1. Asymmetric Tandem Reactions

Asymmetric tandem reactions offer the potential for constructing multiple bonds and introducing new functionality into substrates enantioselectively. An example from polyene cyclization is the conversion of aryl triflates **251a-d** into tetracycles **252a-d** (Eq. 97). (148) The reaction occurs via a

	R^1	R^2				yield	% ee	
a	H	H	(S)-BINAP		a	(88%)	71	S
a	H	H	(R)-BINAP		b	(83%)	71	R
c	H	Me	(R)-BINAP		c	(83%)	90	R
d	Me	H	(R)-BINAP		d	(71%)	96	R

(97)

tandem 6-exo;6-endo cyclization pathway under reaction conditions that favor the cationic pathway. The first carbon-carbon bond built in the reaction forms a quaternary center and the enantioselectivity for some substrates like **251d** is excellent. Reductive cyclization of iodide **253** also constructs a quaternary center in modest yield and moderate enantioselectivity (Eq. 98). (149)

3.15.2. Group-Selective Cyclizations

Substrates that cyclize via the reaction of one of two equivalent groups are termed group selective reactions. In the presence of an asymmetric catalyst, the reaction can be induced to occur preferentially with one group, leading to enantiomerically enriched products. Again, substrates and reaction conditions are selected to drive the reaction to the "cationic" manifold. Iodide **255**,

(98)

		yield	% ee
(R)-BINAP	a	(42%)	81
(S)-BINAP	b	(35%)	80

in the presence of a silver salt, reacts to give diene **256** (Eq. 99). (150) Differentiation of the two enantiotopic alkenes is efficient, giving ester **256** in 72% yield and 86%

(72%) 86% ee (99)

ee. Triflate **257** undergoes cyclization to enone **258** in 76% yield and 86% ee (Eq. 100). (151, 152) In this case, β -hydride elimination yields an enol that tautomerizes to the corresponding ketone. Pivalate **258** and related substrates are useful for preparing enantioenriched cis-decalins, which are complementary to enantioenriched trans-decalins typically prepared by Robinson annulation.

(76%) 86% ee (100)

Tandem group-selective asymmetric reactions are also potentially capable of assembling a wide array of molecules. One example is the cyclization of triflate **259** (Eq. 101). (153-155) The 5-exo asymmetric closure yields a π -allylpalladium intermediate that is regio- and stereoselectively trapped with NaCH(SO$_2$Ph)$_2$ as well as other nucleophiles. The product sulfone **260** is obtained in 83% yield and 94% ee and is the result of two carbon-carbon bond formations. One generates a quaternary center enantioselectively, and the other constructs an allylic center diastereoselectively.

$$(101)$$

3.15.3. Allylsilane Termination

Allylsilanes are useful terminators for intramolecular Heck reactions. (31, 156, 157) They can be used to effectively direct the regioselectivity of σ-alkylpalladium intermediate elimination. Depending on reaction conditions, β-hydride or β-silane elimination can occur. For example, cyclization of cis-allylsilane **261** provides both the products of β-silane elimination **262** and β-hydride elimination **263** (Eq. 102). (158, 159) Under reaction conditions that favor the neutral pathway, β-silane elimination is the primary result, and benzazepine **262** is obtained in 70% yield. In the presence of a silver salt, under conditions that favor the cationic manifold, β-hydride elimination occurs preferentially to deliver benzazepine **263** as the major product in 72% yield.

$$(102)$$

	262	263
Pd(OAc)$_2$, PPh$_3$, KOAc, NPr$_4$Br, DMF, 80°, 6 h	(70%)	(4%)
Pd$_2$(dba)$_3$, PPh$_3$, Ag$_2$O, DMF, 80°, 24 h	(4%)	(72%)

One potential limitation of the asymmetric cyclization of substrates like iodides **264** is the potential for achiral product formation. 7-exo Cyclization can be followed by β-hydride elimination of the newly formed stereocenter to yield a styryl product with no stereogenic center. Since the rate of β-silane elimination can be greater than β-hydride elimination, the use of allylsilanes allows for the asymmetric cyclization of substrates that build tertiary centers. For example, cis-allylsilane **264a** undergoes reaction to give benzazepine **265** in 71% yield and 92% ee (Eq. 103). (158, 159) The trans-allylsilane **264b** cyclizes to

benzazepines **265** and **266**. Interestingly, β -hydride elimination product **266** is the major product and is formed in 91% ee. Both reactions are conducted under conditions that favor the cationic pathway. This fact helps explain the high enantioselectivity, but it is interesting that so much β -silane elimination product is observed.

(103)

	R^1	R^2		265	266
a	H	CH$_2$SiMe$_3$	(+)-TMBTP, 68 h	(71%) 92% ee (*S*)	(0%)
b	CH$_2$SiMe$_3$	H	(*R*)-BITIANP, 24 h	(21%) 60% ee (*S*)	(66%) 91% ee (*S*)

4. Applications to Synthesis

Intramolecular Heck reactions have been employed extensively to solve a variety of synthetic challenges. Chief among them have been natural product synthesis and the creation of libraries on solid supports.

4.1. Total Synthesis of Natural Products and Other Complex Molecules

Complex molecule synthesis provides a challenging testing ground for synthetic methods. One example of the use of the intramolecular Heck reaction in natural product synthesis comes from a total synthesis of (±)-FR900482. (160) Aryl iodide **267** undergoes a 6-exo substitutive cyclization to tetracycle **268** (Eq. 104). The reaction

$$\text{Pd(PPh}_3)_4, \text{Et}_3\text{N} \quad \text{CH}_3\text{CN}, 90°, 18 \text{ h}$$

267   **268** (93%)   (104)

illustrates the functional group tolerance of the reaction. The slightly basic reaction conditions allow both the potentially sensitive allylic ketal and aziridine to survive. Many of the catalyst systems employed in the Heck reaction are stable at high temperatures, allowing cyclizations from high energy conformers. For example, in the reaction of aryl iodide **269**, the aromatic group must assume an axial orientation over the decalin ring system in order to react to provide polycyclic **270** in a synthesis of (–)-morphine. (161)

$$\text{Pd(O}_2\text{CCF}_3)_2(\text{PPh}_3)_2, \quad \text{PMP} \quad \text{tol}, 120°$$

269   **270**   (60%) (105)

Intramolecular Heck reactions are among the most powerful methods for constructing quaternary centers embedded in a variety of ring systems. One example that assembles two adjacent quaternary centers comes from the total

syntheses of *meso*- and (–)-chimonanthine (Eq. 106). (162) Treatment of diamide **271** with

$$\text{271} \xrightarrow[\text{DMA, 100°}]{\text{Pd(PPh}_3)_2\text{Cl}_2, \text{Et}_3\text{N}} \text{272} \quad (71\%) \quad (106)$$

Pd(PPh$_3$)$_2$Cl$_2$ under typical Heck conditions delivers (bis)oxindole **272** stereoselectively in good yield. In the first of two sequential 5-exo diastereoselective intramolecular Heck reactions, the tetrasubstitued alkene reacts to form an oxindole and the second establishes the ring system *en route* to *meso*-chimonanthine. The remote protected alcohols control the stereoselectivity of the reaction. The corresponding trans-acetonide **273** reacts under similar conditions to give (bis)oxindole **274** stereoselectively (Eq. 107). (162) In this case, the relative configuration of the quaternary centers is different, ultimately leading to (–)-chimonanthine. The factors governing stereoselectivity have not yet been described.

$$\text{273} \xrightarrow[\text{DMA, 100°}]{\text{Pd(PPh}_3)_2\text{Cl}_2, \text{Et}_3\text{N}} \text{274} \quad (90\%) \quad (107)$$

The reaction has been used to construct medium-sized rings in a number of natural product syntheses. A 7-exo intramolecular Heck cyclization has been used to assemble CP-263,114. Iodofuran **275** undergoes reaction to yield bicyclo[4.3.1]undecenone **276** in good yield (Eq. 108). (163) The reaction sets a cis-ring juncture,

$$(108)$$

closes a 7-membered ring, and occurs despite opposing alkene polarization. Eight-membered rings can also be closed by the reaction. From a total synthesis of Taxol®, vinyl triflate **277** undergoes 8-exo cyclization to diene **278** (Eq. 109). (164, 165) The reaction assembles a strained ring system in the presence of the oxetane, which could be destroyed by other ring closure methods.

$$(109)$$

In an approach to diazonamide A, an intramolecular Heck macrocyclization is a key step. A 13-endo closure of aryl iodide **279** under cationic conditions yields macrocycle **280** (Eq. 110). (166, 167) The unprotected phenol in precursor **279** plays an important role in the reaction. The corresponding methyl ether cyclizes less efficiently.

$$(110)$$

The intramolecular Heck reaction can play additional roles in drug discovery and in the bulk synthesis of complex molecules. The reaction has been utilized to assemble camptothecin. (168, 169) Related synthetic efforts to produce potential anticancer agents have identified GI47211 (a salt of piperazine **282**) as an interesting candidate. (170) Cyclization of aryl halide **281** to the potential anticancer agent **282** occurs in good yield, as do reactions of the corresponding iodide and chloride (Eq. 111). Cyclization of aryl bromide **281** was performed on a 125-g. scale.

(111)

Intramolecular Heck cyclization of an aromatic substrate has been employed in a total synthesis of gilvocarcin M (Eq. 112). (171, 172) Cyclization of aryl iodoester **283**

(112)

yields lactone **284** in 90% yield. The reaction allows for the synthesis of other A-ring substituted gilvocarcins because the ester bond is formed late in the synthetic sequence prior to Heck ring closure. The reaction is also notable

since the iodide is activated for closure despite the electron-donating methoxy and bulky carboxy groups that flank it.

The intramolecular Heck reaction also plays a role in materials synthesis, including polycyclic aromatic hydrocarbons. Palladium-catalyzed intramolecular arylation of aryl bromide **285** yields polycycle **286** in very good yield (Eq. 113). (173) Three carbon-carbon bonds and three oxidative aromatization steps efficiently construct the product.

$$\text{285} \quad \xrightarrow[\text{DMF, 130°, 24 h}]{\begin{array}{c}\text{Pd(OAc)}_2,\\ \text{K}_2\text{CO}_3,\ \text{BnMe}_3\text{NBr}\end{array}} \quad \text{286} \quad (71\text{-}79\%)$$

(113)

Tandem reactions can be powerful in natural product synthesis. In a synthesis of (–)-scopadulcic acid, alkenyl iodide **287** undergoes a polyene cyclization in the presence of Ag_2CO_3 to give tricycle **288** after deprotection (Eq. 114). (174) A 6-exo cyclization sets the quaternary center and provides a neopentyl σ-palladium intermediate, which undergoes a 5-exo reaction to give the ring system.

$$\text{287} \quad \xrightarrow[\begin{array}{c}\text{2. TBAF, THF, rt}\end{array}]{\begin{array}{c}\text{1. Pd(OAc)}_2,\ \text{PPh}_3,\\ \text{Ag}_2\text{CO}_3,\ \text{THF,}\\ \text{65°, 18 h}\end{array}} \quad \text{288} \quad (90\%)$$

(114)

4.2. Intramolecular Heck Reactions on Polymer Supports

The intramolecular Heck reaction can be used with substrates that are attached to solid supports. This strategy offers an excellent method for building libraries of heterocycles. (175) For example, aryl iodides **289** attached to a Rink amide or Rink amide AM resin undergo 5-exo cyclization and isomerization to give indoles **290** in good yield after cleavage from the solid support (Eq. 115). (176) A reductive cyclization reaction has been performed on iodoaryl amides **291** attached to a Wang resin to give benzazepines **292** (Eq. 116). (177)

Macrocyclization reactions are often performed on polymer supports in order to prevent intermolecular reaction. Aryl iodide **293** undergoes palladium-catalyzed reaction to give an example of a 20-endo intramolecular Heck reaction (Eq. 117). (178) Cyclization of aryl iodide **293**, followed by cleavage from the solid support, delivers macrocycle **294**. In this case, cyclization of the corresponding acid in solution is also successful, but relatively slow.

1. Pd(OAc)$_2$, PPh$_3$,
   Et$_3$N, n-Bu$_4$NCl,
   DMF, H$_2$O, 37°, 4 h

2. AcOH, TFE,
   CH$_2$Cl$_2$, rt, 40 min

(117)

293

P^3 = 2-chlorotrityl resin

NHMtr

HO$_2$C

(30%)

294

5. Comparison with Other Methods

The closest competing methodology to the intramolecular Heck reaction is radical cyclization. (179-181), (182a) Although both methods typically give efficient exo ring closure, radical cyclizations (usually mediated by n–Bu$_3$SnH) are often reductive. Heck reactions are generally not reductive, but can be run under reductive conditions. Both reactions employ vinyl and aryl halides as precursors, although triflates are not typical radical substrates. Radical cyclization substrates can be primary, secondary, or tertiary alkyl halides, which are not substrates for palladium-mediated cyclizations. Both methodologies allow the chemist to perform related tandem reactions including multiple alkene insertions. One difference between the reactions arises from the termination events. In radical cylizations, chain termination is usually reductive leading to a reductive cyclization. In the Heck reactions, β -hydride elimination is the usual outcome, although additives can lead to a reductive cyclization. One drawback of radical cyclization is the use of stoichiometric quantities of n–Bu$_3$SnH, which can be difficult to separate from the reaction products, is toxic, and poses disposal challenges. Newer reagents like (Me$_3$Si)$_3$SiH overcome some of these limitations. (182, 183) There are several examples of substrates that have been cyclized by both radical and intramolecular Heck reactions. (105, 184-189) In some cases, one reaction is superior, but they can also give complementary results. For instance, cyclization of aryl bromide **295** under standard radical cyclization conditions gives the 5-exo reductive product tetracyclic lactone **296** as the major product (Eq. 118). (190, 191) The minor product, lactone **297**, results from a 6-endo cyclization. Exposure of aryl bromide **295** to typical Heck reaction conditions yields the 6-endo product **298**. Interestingly, cyclization of the alkene isomer of **295** by both radical and reductive Heck procedures yields lacone **296** efficiently.

$$n\text{-Bu}_3\text{SnH, AIBN, C}_6\text{H}_6, \text{reflux}$$

296 (49%) +

297 (29%)

$$\text{Pd(PPh}_3)_2\text{Cl}_2, \text{PPh}_3, \text{K}_2\text{CO}_3, \text{DMF, } 90°, 5\ \text{h}$$

298 (75%)

295

R = 3,4,5-trimethoxyphenyl

(118)

6. Experimental Conditions

6.1. Palladium Complexes

A variety of palladium(0) and palladium(II) complexes are common precatalysts for the Heck reaction. Palladium(0) precatalysts include $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(dba)_2$, and $Pd_2(dba)_3 \cdot CHCl_3$. These complexes are commercially available. However, they can be prepared in higher purity and lower cost by standard procedures. (10) $Pd(PPh_3)_4$ should be stored cold in an inert atmosphere and is stable in air for a short time. In solution, the complex is readily oxidized, so inert atmosphere conditions should be employed. The dibenzylideneacetone complexes are air stable, making them attractive catalyst precursors. Stoichiometric quantities of phosphines are typically added to make the active catalyst. Both phosphine structure and the phosphine/palladium ratio affect catalyst structure and performance. The activity of the catalyst is generally higher with low phosphine/palladium ratios, while catalyst stability is often higher at high phosphine/palladium ratios. High-activity systems often employ two equivalents of phosphine per palladium and have modest stability. More robust systems use four or more equivalents of phosphine per palladium.

Palladium(II) precatalyst complexes include $Pd(OAc)_2$, $PdCl_2(CH_3CN)$, $Pd(PPh_3)_2Cl_2$, $Pd[(allyl)Cl]_2$, $Pd(PCy_3)_2Cl_2$, and $Pd(PPh_3)_2(O_2CCF_3)$. The precatalysts are air stable and commercially available. In the first two cases, phosphine ligands are added in varying ratios. Phosphines and water are the reductants which typically reduce the palladium (II) precatalysts generating $Pd(PPh_3)_2$ (Eq. 119). (192, 193)

Reduction of Pd[II] to Pd[0] by a phosphine

$$Pd(OAc)_2 + H_2O + 3\ PPh_3 + 2\ Et_3N \xrightarrow[40°]{C_6H_6} Pd(PPh_3)_2 + OPPh_3 + 2\ Et_3NHOAc \qquad (119)$$

Three equivalents of phosphine per equivalent of $Pd(OAc)_2$ is a common catalyst cocktail since palladium acetate is the cheapest source of palladium. If a phosphine is not present, a tertiary amine commonly serves as a reductant (Eq. 120). (194) After amine coordination, β -hydride elimination provides a hydridopalladium complex which, after reductive elimination of HX, provides the Pd(0) catalyst. Catalyst activity can differ depending upon the counterion of the palladium salt used in the reaction.

Reduction of Pd[II] to Pd[0] by an amine

$$R_2NCH_2R' + PdX_2 \longrightarrow \begin{bmatrix} R_2N-CHR^1 \\ | \quad\quad | \\ Pd \quad H \\ | \\ X \end{bmatrix} X \longrightarrow [R_2^+N{=}CHR^1]X^- + PdHX \longrightarrow Pd[0] + HX \tag{120}$$
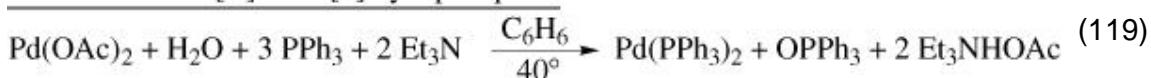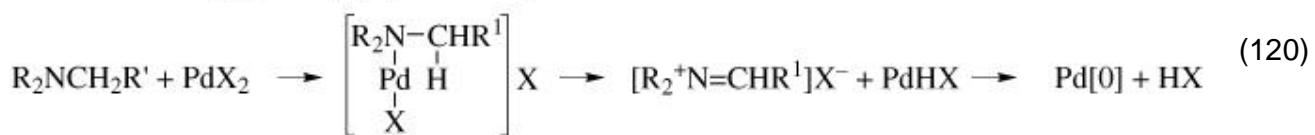
Most of the intramolecular Heck reactions reported to date use 5–20 mole percent of catalyst. Although many of these reactions have not been optimized with the goal of minimizing catalyst loadings, studies of recently developed high-stability catalysts indicate that substantially lower loadings are possible. Two such examples are the phosphapalladacycles (for details see the Mechanism and Stereochemistry section) typified by **42a** and catalyst **299** (Strs-1). (195, 196)

6.2. Ligands

Many phosphines have been used to prepare catalysts for the intramolecular Heck reaction. Achiral phosphines include PPh_3, $P(tol{-}o)_3$, TFP, PCy_3, 2-(di-*tert*- butylphosphanyl)-biphenyl (**300**) (197), dppe, dppp, dppb, and dppf. $AsPh_3$ has also been used in a few examples. For most substrates, PPh_3 and/or $P(tol{-}o)_3$ are suitable. PCy_3 has been found to be effective for aromatic cyclizations of aryl chlorides and may be more broadly applicable to reactions of aryl and vinyl chlorides. (198-200) Bidentate phosphines are utilized when the monodentate ligands are ineffective or to modify diastereoselectivity. Typically they are used with triflates or other substrates manipulated to react via the cationic pathway. Intramolecular Heck reactions can also be carried out in aqueous media. (201-204) In order to increase catalyst solubility, sulfonated versions of phosphines like TPPTS or dibenzofurans **301** and **302** have been employed. (205, 206)

Tol Tol
P
O O
Pd Pd
O O
P
Tol Tol

42a

R$_2$P—Pd—PR$_2$
TFA
R = o-C$_5$H$_9$

299

P(Bu-t)$_2$

2-(di-$tert$-butylphosphanyl)-
biphenyl
300

Ph$_2$P—

SO$_3$Na

O

301

P

SO$_3$Na

O

3

302
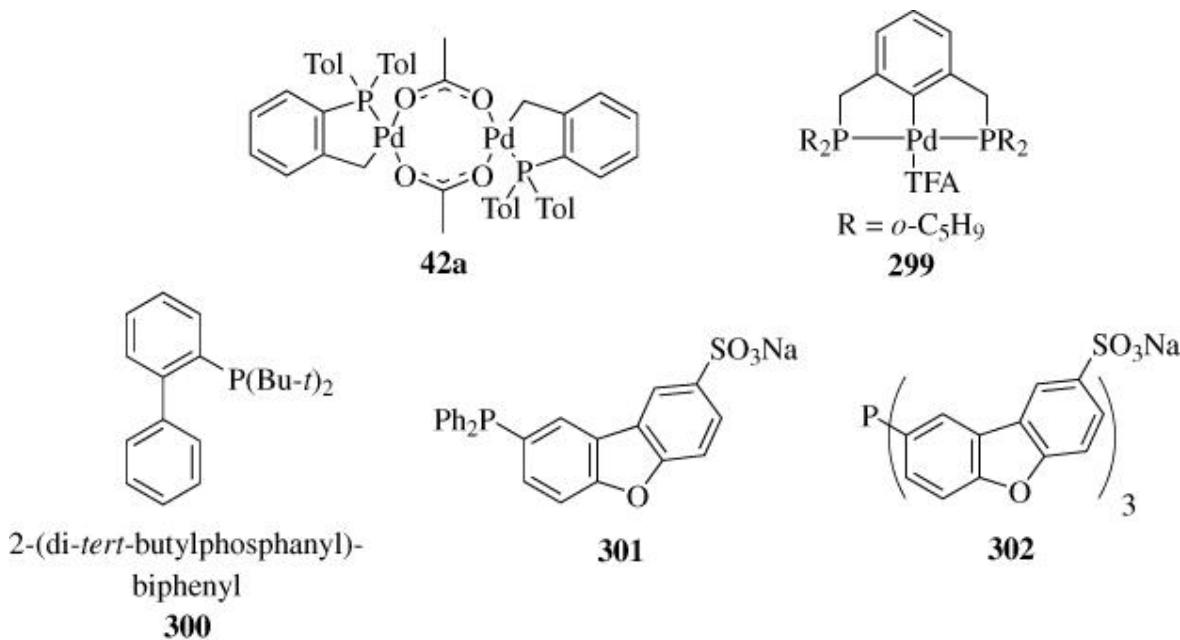
Asymmetric intramolecular Heck reactions employ chiral phosphines. BINAP ((R) isomer **303**, Strs-2) is most commonly employed, and both antipodes as well as the racemate are commercially available. It typically gives high enantioselectivities. Related ligands (R)-Tol-BINAP (**304**), (R)-BINAPAS (**305**) (207), and (R)-BINAs (**306**) (208) can be utilized to optimize a reaction if BINAP does not give the desired level of selectivity. Other biarylphosphines, which have not been as widely used, include (+)-TMBTP (**307**), (R)-BITIANP (**308**), and (R)-MeO-BIPHEP (**309**). Other ligands include the dppf relative (R)-(S)-BPPFOH (**310**) and the alkylphosphines (S,S)-BCPM (**311**), (R,R)-CHIRAPHOS (**312**), and (R,R)-DIOP (**313**). Bidentate (P,N) chiral phosphinooxazolines (exemplified by ligand **314**) have also been developed and show advantages in some systems. (209, 210) Because oxygen oxidizes phosphines to phosphine oxides in the presence of palladium, Heck reactions should be conducted under an inert atmosphere (nitrogen or argon). (211) This is particularly important for asymmetric reactions where catalyst degradation can result in loss of enantioselectivity.

6.3. Bases
A stoichiometric amount of base is required for the intramolecular Heck reaction, and frequently multiple equivalents are employed. Inorganic bases include NaOAc,
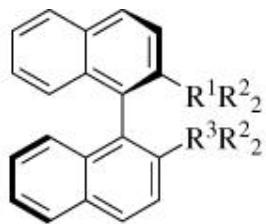
	R¹	R²	R³
303 (+)-(R)-BINAP	P	Ph	P
304 (R)-Tol-BINAP	P	tolyl	P
305 (R)-BINAPAs	As	Ph	P
306 (R)-BINAs	As	Ph	As
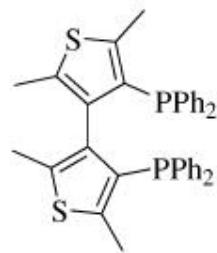
307 (+)-TMBTP
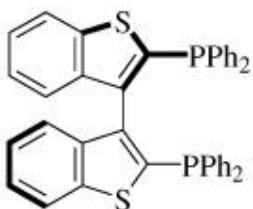
308 (R)-BITIANP
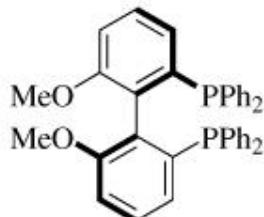
309 (R)-MeO-BIPHEP
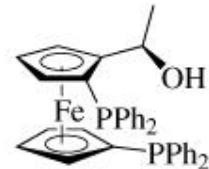
310 (−)-(R,S)-BPPFOH
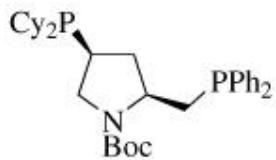
311 (−)-(S,S)-BCPM
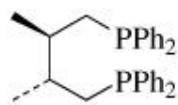
312 (R,R)-CHIRAPHOS
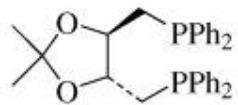
313 (R,R)-DIOP
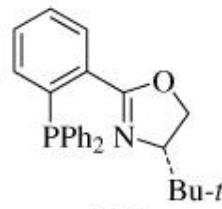
314 phosphinooxazoline

NaHCO$_3$, Li$_2$CO$_3$, Na$_2$CO$_3$, K$_2$CO$_3$, CaCO$_3$, and K$_3$PO$_4$. Potassium carbonate is perhaps the most frequently used. Soluble bases include bases such as Et$_3$N, i–Pr$_2$NEt, n–Bu$_3$N, PMP, Proton Sponge®, and TMEDA. The highly hindered base PMP has been utilized in asymmetric intramolecular Heck reactions. Other bases such as NaOBu-t or KOBu-t have been used less frequently. Aromatic cyclizations have employed DBU and NaOPiv, while Cs$_2$CO$_3$ has been particularly effective with phenol aromatic cyclization substrates.

6.4. Additives

Additives have substantial effects on the Heck reaction. They can shift the basic mechanistic pathways (neutral versus cationic versus anionic pathways) altering product yields and selectivities, as well as having other subtler effects. Silver (31, 32) (Ag$_2$CO$_3$, Ag$_3$PO$_4$, AgOTf, AgOAc, Ag$_2$O , AgNO$_3$, and silver-exchanged zeolite) and thallium (33) (Tl$_2$CO$_3$, TlOAc, and TlNO$_3$) salts

are probably the most common additives. They often increase the rate of reaction, lower reaction temperatures, minimize alkene isomerization, modify regioselectivity, and alter enantioselectivity. Many of these changes in the reaction occur because of a change in mechanism since they drive reactions of halides down the cationic pathway. Halide salts (NaCl, LiCl, KCl, NaBr, TBAC, TBAB, TBAI, BnEt$_3$NCl, Pr$_4$NBr , and Et$_4$NCl) can divert reactions of triflate precursors from the cationic to the neutral pathway. (34) In some cases, this change can improve enantioselectivity. Halide salts can also divert a reaction down the anionic pathway, however the consequences of this shift have not been well studied.

Alcohols like *t*-BuOH and pinacol have been used as additives in asymmetric intramolecular Heck reactions. Catalyst stability studies indicate that pinacol (as well as NaOAc) prevents the oxidation of the catalytically active Pd(0) species in DCE. (152) *N,O*-bis(trimethylsilyl)acetamide (BSA) has been shown to be a useful additive during the cyclization of a secondary amide. (212) It may be in situ silation of the amide during the intramolecular Heck reaction that assists the cyclization. The temporary protection of other functionalities during Heck reactions with this reagent can be envisioned.

6.5. Jeffery's Conditions
The solid-liquid phase-transfer conditions reported by Jeffery are routinely employed. (213-216) Tetrabutylammonium chloride (TBAC) or bromide (TBAB) is added in stoichiometric amounts and frequently increases reaction rates, allowing for lower reaction temperatures. It has been proposed that the ammonium halides stabilize the catalytic species by halide coordination, shift the equilibrium between the hydridopalladium complex and the catalytically active Pd(0) species toward the latter, and shunt the reaction down the anionic pathway. Future mechanistic investigations in this area should prove interesting.

6.6. Solvents and Reaction Temperatures
Common solvents for the intramolecular Heck reaction are polar aprotic solvents like THF, DMF, NMP, DMA, and CH$_3$CN . Toluene, C$_6$H$_6$, DCE, EtOH, and H$_2$O are also used on occasion. Perfluorous biphasic solvent systems can also be utilized. Recently the first examples of fluorous-phase synthesis using a triarylphosphine bearing a perfluoroalkyl side chain were reported. (217) Reaction temperatures vary between room temperature and reflux in these high-boiling solvents. The catalyst's stability to these thermal conditions allows for the formation of strained ring systems. High pressure conditions that increase catalyst lifetime and can alter selectivity have also been successfully applied to the reaction. (218) Microwave radiation has been used to drive some cyclizations which fail under thermal conditions. (219, 220)

6.7. Polymer Supports

Polymer supports have been used in intramolecular Heck reactions in two different ways. Several reactions using a polymer-supported catalyst have been performed. (217, 221) This development might allow for the simple recovery and reuse of the catalyst. Reactions of substrates attached to the polymer support has also allowed for the preparation of libraries of heterocycles. (175) A number of polymer supports and linkers have been demonstrated to be compatible with the Heck reaction conditions (see Table 6).

7. Experimental Procedures
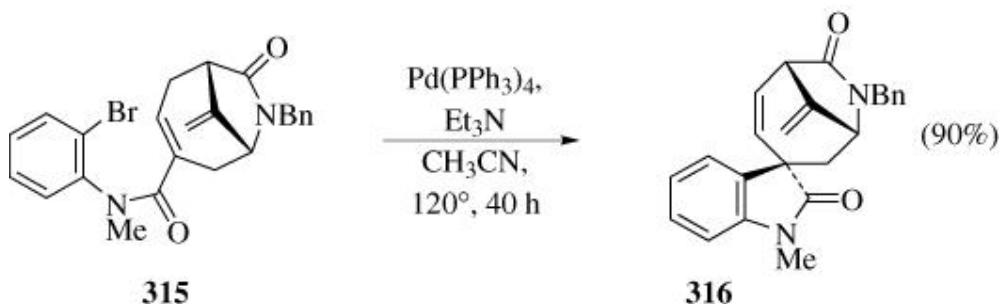
7.1.1. N-Methylspirooxindole (316) (5-Exo Intramolecular Heck Reaction) (222, 223)

A solution of amide **315** (0.365 g, 0.809 mmol), Pd(PPh$_3$)$_4$ (0.187 g, 0.162 mmol), and triethylamine (1.12 mL, 8.08 mmol) in MeCN (8 mL) in a sealed tube was heated slowly to 120°. After stirring for 40 hours, the reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was chromatographed (loaded with CH$_2$Cl$_2$) to give the title product **316** (0.270 g, 90%) as a colorless oil; R_f 0.42 (EtOAc/petroleum ether 10:1); [α]^{22}$_D$ +14.9 (c, 1.0, CHCl$_3$); IR 3027, 2930, 1712, 1673, 1608, 1492, 1343, 1248 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.33–7.21 (m, 6 H), 7.07 (dd, J = 7.3, 16.4 Hz, 1 H), 7.00 (t, J = 7.5 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.30 (dd, J = 8.7, 11.4 Hz, 1 H), 5.32 (d, J = 15.7 Hz, 1 H), 5.04 (s, 1 H), 4.95 (s, 1 H), 4.93 (d, J = 11.1 Hz, 1 H), 4.17 (s, 1 H), 3.98 (d, J = 15.7 Hz, 1 H), 3.62 (d, J = 8.7 Hz, 1 H), 3.17 (s, 3 H), 2.56 (dd, J = 3.5, 15.5 Hz, 1 H), 2.06 (dd, J = 2.8, 15.5 Hz, 1 H); ^{13}C NMR (100 MHz) δ 177.4, 172.9, 147.8, 142.2, 136.5, 132.2, 131.6, 128.8, 128.4, 128.2, 127.7, 127.1, 123.7, 122.9, 107.9, 105.9, 61.0, 54.7, 49.9, 44.4, 38.2, 26.4; HRMS Calcd. for C$_{24}$H$_{22}$N$_2$O$_2$: 370.1681. Found: 370.1692.

283 → 284 (90%)
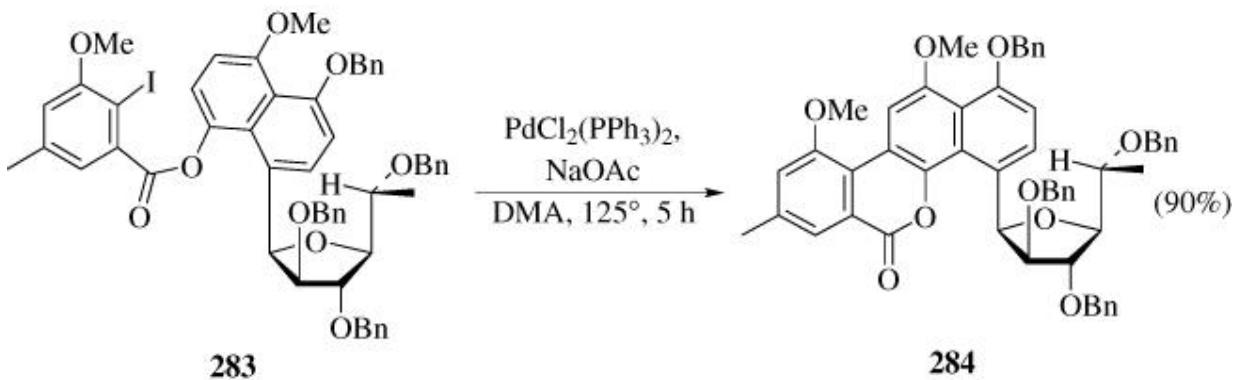
7.1.2. 1-(Benzyloxy)-10,12-dimethoxy-8-methyl-4-(2,3,5-tri-O-benzyl- α -D-fucofuranosyl)-6H-benzo[d]naphtho[1,2-b]pyran-6-one [Gilvocarcin M Tetrabenzyl Ether] (284) (Aromatic Cyclization) (171, 172)

A yellow suspension of naphthyl benzoate **283** (303 mg, 0.312 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (57 mg, 0.081 mmol), and NaOAc (79 mg, 0.96 mmol) in DMA (45 mL) was heated at 125° for 5 hours. After the solution was cooled to room temperature, the resulting dark brown suspension was diluted with Et$_2$O, and the mixture was washed successively with 2 N HCl and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/2 to 6/4) to afford gilvocarcin M tetrabenzyl ether (**284**) (235 mg, 89%) as a yellow oil, which crystallized by concentrating from hexane-Et$_2$O as a yellow foam: mp 37–45°; R_f = 0.35 (hexane/EtOAc 7/3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.45 (s, 1 H), 8.14 (d, J = 8.3 Hz, 1 H), 7.85 (s, 1 H), 7.60–7.63 (m, 2 H), 7.23–7.49 (m, 13 H), 7.16 (s, 1 H), 7.11 (d, J = 8.3 Hz, 1 H), 6.84–6.88 (m, 3 H), 6.71–6.74 (m, 2 H), 6.25 (d, J = 3.4 Hz, 1 H), 5.22 (s, 2 H), 5.11 (d, J = 3.4 Hz, 1 H), 4.92 (d, J = 11.7 Hz, 1 H), 4.77 (d, J = 12.2 Hz, 1 H), 4.74 (d, J = 12.2 Hz, 1 H), 4.53 (d, J = 11.7 Hz, 1 H), 4.20 (d, J = 12.0 Hz, 1 H), 4.12 (dd, J = 6.4, 4.6 Hz, 1 H), 4.07 (s, 3 H), ca. 4.07 (1 H, concealed in the singlet peak), 4.03 (d, J = 12.0 Hz, 1 H), 3.99 (s, 3 H), 3.94 (dq, J = 6.4, 6.4 Hz, 1 H), 2.51 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.4, 157.2, 154.8, 153.2, 141.5, 139.8, 138.4, 138.1, 137.5, 129.2, 128.41, 128.38, 128.29, 128.25, 127.8, 127.7, 127.6, 127.5, 127.3, 127.09, 127.06, 126.1, 124.9, 122.4, 122.2, 122.1, 118.8, 118.1, 114.4, 110.4, 104.8, 86.4, 85.3, 82.4, 82.3, 75.3, 71.8, 71.7, 71.5, 71.3, 56.8, 56.3, 21.6, 16.3; IR (KBr) 2920, 2850, 1720, 1610, 1590, 1485, 1450, 1370, 1330, 1300, 1270, 1240, 1225, 1135, 1065, 1025, 960, 845, 785, 735, 700 cm^{-1}; [α]^{23}$_D$ –220° (c 1.2, CHCl$_3$); Anal. Calcd. for C$_{54}$H$_{50}$O$_9$: C 76.94; H, 5.98. Found: C, 76.83; H, 6.05.

1. Pd(OAc)$_2$, PPh$_3$,
   Ag$_2$CO$_3$, THF,
   65°, 18 h
2. TBAF, THF, rt

287 → **288** (90%)
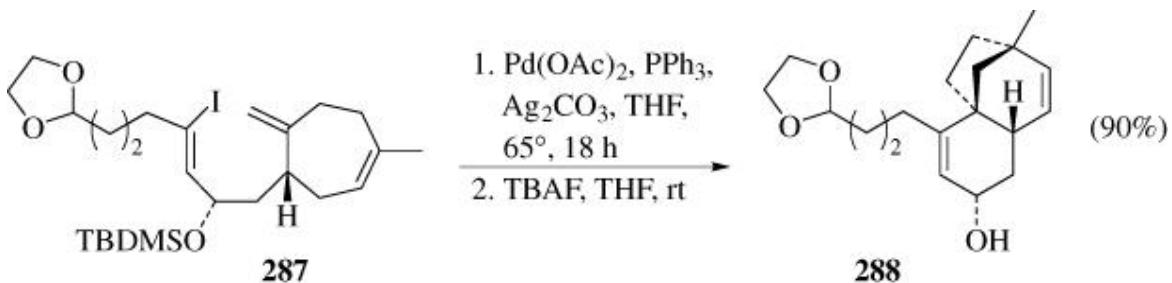
7.1.3. (2S,4 α S,7S,9 αS)-4-[4-(1,3-Dioxolanyl)butyl]-7-methyl-1,2,5,6,7,9a-hexahydro-4a,7-methano-4aH-benzocyclohepten-2-ol (288) (Tandem 6-Exo;5-exo Intramolecular Heck Reaction) (174)

A solution of vinyl iodide **287** (740 mg, 1.35 mmol) in THF (75 mL) was degassed (Ar, evacuate-refill), and Ph$_3$P (107 mg, 0.41 mmol), Ag$_2$CO$_3$ (410 mg, 1.5 mmol), and Pd(OAc)$_2$ (46 mg, 0.20 mmol) were added. The resulting suspension was stirred at room temperature for 15 minutes and then heated at 65° in a sealed tube for 12 hours. A black suspension resulted after 10–20 minutes at 65°. After GC analysis of a filtered aliquot showed that the reaction had not proceeded to completion, additional Ph$_3$P (107 mg, 0.41 mmol), Ag$_2$CO$_3$ (411 mg, 1.49 mmol), and Pd(OAc)$_2$ (46 mg, 0.20 mmol) were added, and the black suspension was stirred in a sealed tube at 65° for an additional 6 hours. The suspension was then cooled to room temperature and filtered through a plug of silica gel (1.5 cm × 12 cm, EtOAc), and the filtrate was concentrated to give the crude product as a yellow oil. This sample was dissolved in THF (4 mL), and TBAF (1.0 M solution in THF, 2.0 mL) was added. The resulting solution was maintained at room temperature for 20 hours and quenched with saturated aqueous NH$_4$Cl (20 mL). The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 20 mL), the combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated, and the residue was purified by flash chromatography (4:1 hexanes-EtOAc) to provide 370 mg (90%) of tricyclic allylic alcohol **288** as a pale yellow oil: R_f = 0.25 (5:1 hexanes-EtOAc); [α]^{24}$_D$ +49.5, [α]^{24}$_{577}$ +53.9, [α]^{24}$_{546}$ +61.6, [α]^{24}$_{435}$ +109, [α]^{24}$_{405}$ +133 (c 1.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.53 (d, J = 9.5 Hz, 1 H), 5.32 (br s, 1 H), 5.19 (dd, J = 9.5, 1.6 Hz, 1 H), 4.87 (t, J = 4.5 Hz, 1 H), 4.33 (t, J = 7.5 Hz, 1 H), 4.00–3.83 (m, 4 H), 2.50 (d, J = 13.3 Hz, 1 H), 2.52–1.25 (m, 15 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.3, 137.2, 127.7, 125.0, 104.4, 68.4, 64.8, 47.3, 46.4, 45.2, 42.4, 41.3, 34.0, 33.6, 32.4, 30.6, 23.9, 22.8; IR (film) 3390, 1652 cm^{-1}; HRMS (EI) m/z 304.2042 (calcd. for C$_{19}$H$_{28}$O$_3$: 304.2038).

317 → **318** (71%) + **319** (5%)
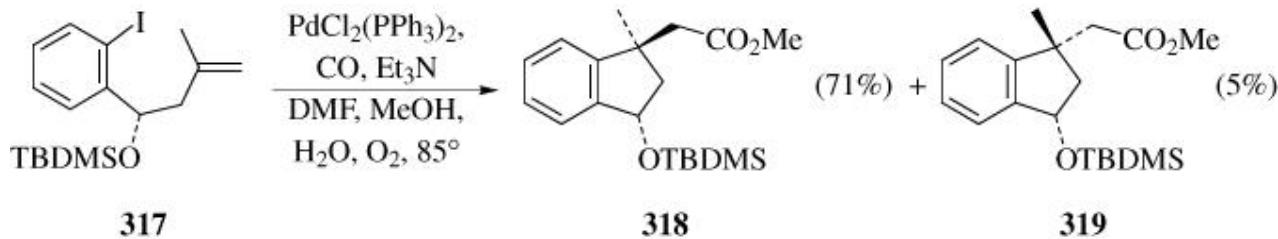
7.1.4. (1R,3S)-1-(tert-Butyldimethylsilyloxy)-3-methyl-3-methoxycarbonyl methyl)indane (318) (6-Exo;Carbonylative Tandem Intramolecular Heck Reaction) (137)

A mixture of iodide **317** (217 mg, 0.54 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (18 mg, 0.027 mmol), triethylamine (0.3 mL, 2.2 mmol), and H$_2$O (0.11 mL) in a 2:1 mixture of DMF/MeOH (3.3 mL) was stirred under 1 atm of CO at 85°. The yellow reaction mixture turned black, and then slowly turned back to its original yellow color. This mixture was then exposed to air for 20–30 seconds, flushed with CO, and stirred until it turned black over 0.5 to 1 hour. The reaction mixture was concentrate, the residue was diluted with Et$_2$O, washed with H$_2$O , dried over MgSO$_4$, filtered, and concentrated. Analysis by NMR spectroscopy indicated that the title product **(318)** was formed in 76% yield as a 94:6 mixture of diastereomers. Chromatography on silica gel (98/2 n-pentane-Et$_2$O) afforded 135 mg (74%) of isomer **318**: ^{1}H NMR δ 7.1–7.4 (m, 4 H), 5.27 (t, $J = 6.7$, Hz, 1 H), 3.60 (s, 3 H), 2.66 (dd, $J = 13.0$, 6.8 Hz, 1 H), 2.52 (d, $J = 13.9$ Hz, 1 H), 2.42 (d, $J = 13.9$ Hz, 1 H), 1.85 (dd, $J = 13.0$, 6.6 Hz, 1 H), 1.47 (s, 3 H), 0.94 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR δ 172.03, 148.57, 144.59, 128.04, 127.34, 124.25, 122.53, 74.22, 51.26, 49.53, 45.84, 44.43, 27.47, 25.87, 18.19, –4.42, –4.61; IR (neat) 1736 cm^{-1}. The following signals were discernible for the minor isomer **319**: ^{1}H NMR δ 3.66 (2, 3 H), 2.1–2.4 (m, 2 H); ^{13}C NMR δ 128.12, 124.42, 122.53, 122.28, 74.42, 46.11, 26.69.

243 → **244** (87%) 93% ee E:Z 21:3
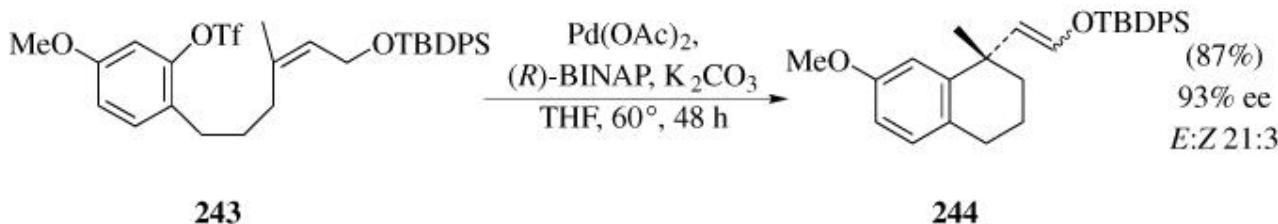
7.1.5. Tetralin *244* (6-Exo Asymmetric Intramolecular Heck Reaction) (*145*)

To a mixture of Pd(OAc)$_2$ (36 mg, 0.16 mmol), (*R*)-BINAP (243 mg, 0.39 mmol), and K$_2$CO$_3$ (962 mg, 6.96 mmol) was added triflate **243** (1.41 g, 2.32 mmol) in THF (40 mL). The resulting mixture was degassed through three freeze-pump-thaw cycles, stirred at 60° for 48 hours, diluted by the addition of saturated NH$_4$Cl , and extracted with Et$_2$O. The organic layer was washed with brine, dried (Na$_2$SO$_4$), and concentrated to give an oily residue, which was purified by flash chromatography (SiO$_2$, 0.5% EtOAc in hexane) to give title product **244** (954 mg, 90%, trans:cis = 21:3) as a colorless oil. The trans isomer: IR (neat) 2930, 1650, 1110 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.62–7.69 (m, 4 H), 7.32–7.44 (m, 6 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.70 (d, *J* = 2.6 Hz, 1 H), 6.62 (dd, *J* = 8.2, 2.6 Hz, 1 H), 6.16 (d, *J* = 12.3 Hz, 1 H), 5.24 (d, *J* = 12.3 Hz, 1 H), 3.69 (s, 3 H), 2.63 (t, *J* = 6.4 Hz, 2 H), 1.51–1.73 (m, 4 H), 1.24 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (CDCl$_3$) δ157.4, 144.2, 140.8, 135.5, 133.1, 129.8, 129.7, 128.6, 127.7, 123.7, 113.1, 111.9, 55.1, 38.5, 37.9, 29.4, 29.2, 26.6, 19.3, 19.2; MS *m*/*z* 399 (M$^+$-*tert*-Bu), 175 (base peak); Anal. Calcd. for C$_{30}$H$_{36}$O$_2$Si : C, 78.90; H, 7.95, Found: C, 78.65; H, 8.12; [α]^{24}$_D$ –5.89 (*c* 0.81, CHCl$_3$) (90% ee). The cis isomer: IR (neat) 2930, 1650, 1110 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ7.62–7.69 (m, 4 H), 7.33–7.42 (m, 6 H), 6.99 (d, *J* = 2.7 Hz, 1 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 8.1, 2.7 Hz, 1 H), 5.99 (d, *J* = 5.2 Hz, 1 H), 4.58 (d, *J* = 5.2 Hz, 1 H), 3.77 (s, 3 H), 2.71–2.80 (m, 2 H), 2.23–2.36 (m, 1 H), 1.77–1.91 (m, 4 H), 1.56 (s, 3 H), 0.94 (s, 9 H); ^{13}C NMR (CDCl$_3$) δ157.8, 147.2, 137.8, 147.2, 137.8, 135.4, 132.6, 128.6, 129.9, 129.6, 128.1, 127.7, 119.6, 113.0, 111.5, 55.2, 38.6, 37.0, 31.5, 29.6, 26.3, 20.0, 18.9; MS *m*/*z* 456 (M$^+$), 399 (M$^+$-*tert*-Bu, bp).

8. Tabular Survey

The tables are organized according to increasing carbon count including protecting groups and other abbreviated structures. The tables cover examples of the intramolecular Heck reaction up to October 15, 2000. The tables themselves are organized by the ring size of cyclization and whether the cyclization is exo or endo. Table 1 contains the examples of exo cyclization (4–8-exo plus exo-macrocyclization). Table 2 contains examples of endo cyclizations (5–8-endo plus endo-macrocyclizations). Both the exo and endo macrocyclization sections are grouped by the size of the ring formed in the reaction and then by carbon count. Table 3 covers 5- to 7-membered ring forming aromatic cyclizations. Table 4 consists of tandem reactions grouped by ring sizes formed in the reaction (4–8 plus macrocyclization) and by the type of reaction terminating event. Asymmetric reactions are covered in Table 5 and polymer supported cyclizations on polymer supports are the subject of Table 6. Footnotes within the polymer symbol indicate the solid support used in the reaction. When a reaction was reported using several protocols only the highest yielding one is listed, however references are given for all reports.

The following abbreviations are used in the tables:

18-C-6	18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane)
Ala	alanine
(*S*,*S*)-BCPM	(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
(*R*)-BINAP	(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
(*S*)-BINAP	(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINAPAs	2-diphenylarsino-2′-diphenylphosphino-1,1¢-binaphthyl
BINAs	2,2′-bis(diphenylarsino)-1,1′-binaphthyl
(*R*)-BITIANP	(*R*)-(+)-2,2′-bis(diphenylphosphino)-3,3′-dibenzo[*b*]thiophene
BOC	*tert*-Butoxycarbonyl
(*R*)-(*S*)-BPPFOH	(*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol
BSA	*N,O*-bis(trimethylsilyl)acetamide
Camphorsultam	10,2-camphorsultam
Cbz	benzyloxycarbonyl
(*R,R*)-CHIRAPHOS	(2*R*,3*R*)-(+)-bis(diphenylphosphino)Butane
Cy	cyclohexyl
dba	dibenzylideneacetone
DBS	dibenzosuberyl

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
(+)-DIOP	(+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
(*R,R*)-DIOP	(–)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
(*S,S*)-DIOP	(+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMA	*N,N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dmphen	2,9-dimethyl-1,10-phenanthroline
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomer ratio
ee	enantiomeric excess
Gly	glycine
HBC	Herrmann-Beller catalyst {trans-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)} (**42a**)
HMPA	hexamethylphosphoric triamide
kbar	kilobar
Leu	leucine
MEM	methoxyethoxymethyl
(*R*)-MeO-BIPHEP	(*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)-bis(diphenylphosphine)
Mts	mesitylsulfonyl (2,4,6-trimethylphenylsulfonyl)
Mesityl	2,4,6-trimethylphenyl
mol sieves	molecular sieves
MOM	methoxymethyl
Ms	methanesulfonyl
Mtr	4-methoxy-2,3,6-trimethylbenzenesulfonyl
Nf	nonaflate
NMI	*N*-methylimidazole
NMP	*N*-methylpyrrolidine
Pd/C	palladium on carbon
Phe	L-phenylalanine

Phth	phthalimide
Piv	pivaloyl
PMB	4-methoxybenzyl
PMP	1,2,2,6,6-pentamethylpiperidine
P^n	polymer (type denoted in footnote n)
Pro	L-proline
Proton Sponge®	1,8-bis(dimethylamino)naphthalene
PS	polystyrene
SEM	2-(trimethylsilyl)ethoxymethyl
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCNE	tetracyanoethylene
TDS	thexyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TFP	trifurylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
(+)-TMBTP	(+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
tol	toluene
(*R*)-Tol-BINAP	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TPAB	tetrapropylammonium bromide
TPPTS	3,3′,3″-phosphinetriyltribenzenesulfonate
tr	trace
Ts	tosyl
THP	2-tetrahydropyranyl

Table 1. Exo-Cyclizations

[View PDF](#)

Table 2. Endo Cyclizations

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Table 3A. 5-Aromatic Cyclizations

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Table 3B. 6-Aromatic Cyclizations

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Table 3C. 7-Aromatic Cyclizations

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Table 4. Tandem Reactions

[View PDF](#)

Table 5. Asymmetric Cyclizations

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Table 6. Cyclizations on Polymer Supports

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TABLE 1. EXO CYCLIZATIONS
A. 4-EXO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18-22}	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 80°, 12 h		63
R			
Allyl		(52-65)	
Bn		(52-65)	
C_{22}	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 80°, 12 h	(—)	63
C_{26}	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 80°, 12 h	(56)	63

TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)				Refs.
C_{7-15}	CH$_3$CN, 80°	**I** + **II**				
R^1 R^2 R^3			**I**	**II**	Alkene Isomers of **II**	
H H H	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$		(37)	(30)	(0)	225, 226
CO$_2$Et CO$_2$Et H	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, 4 h		(7)	(67)	(0)	225, 226
CO$_2$Et CO$_2$Et H	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, 1 h		(37)	(30)	(0)	225, 226
Me COPh H	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, 35 h		(52)	(21)	(0)	225, 226
Me COPh H	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, 2 d		(23)	(58)	(0)	225, 226
COMe COMe H	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, 2.3 h		(54)	(20)	(15)	225, 226
COMe COMe H	Pd(PPh$_3$)$_4$, PPh$_3$, K$_2$CO$_3$, 1.25 h		(38)	(26)	(34)	225, 226
CO$_2$Me H Me	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, 18 h		(55)	(39)	(0)	226
CO$_2$Me H Me	Pd(PPh$_3$)$_4$, PPh$_3$, K$_2$CO$_3$, 12 h		(61)	(28)	(0)	226
C_8	Pd$_2$(dba)$_3$•CHCl$_3$, dppb, Ag$_3$PO$_4$, DMF	(55) + (12)				227
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, tol. 100°, 18 h	(65)				66
	Pd(OAc)$_2$, PPh$_3$, CH$_3$CN, 80°, 2.5 h	(63) + (11)				226

TABLE 1. EXO CYCLIZATIONS (Continued)
B. 5-EXO CYCLIZATIONS (Continued)

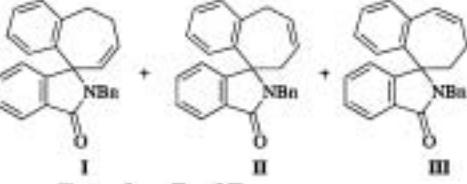| Substrate	Conditions	Products(s) and Yield(s) (%)	Refs.

C_{9-15}

R^1	R^2	R^3	R^4	R^5		Temp	Time	I	II	
H	H	H	H	H	Pd(OAc)$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	48 h	(0)	(47)	228
H	H	H	H	H	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF	reflux	36 h	(15)	(45)	76
H	H	Me	H	H	Pd(OAc)$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	48 h	(0)	(83)	228
H	Me	H	H	H	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF	reflux	36 h	(20)	(61)	76
H	H	CO$_2$Me	H	H	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF	reflux	36 h	(0)	(68)	76
H	H	Me	Me	H	Pd(OAc)$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	48 h	(0)	(76)	228
H	H	Me	H	Me	Pd(OAc)$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	48 h	(0)	(40)	228
COMe	H	Me	Me	H	Pd(OAc)$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	24 h	(0)	(42)	228
H	H	Ph	H	H	Pd(CH$_3$CN)$_2$Cl$_2$, Na$_2$CO$_3$, NaO$_2$CH, n-Bu$_4$NCl, DMF	80°	48 h	(0)	(81)	228

		R	Temp	Time		
Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN		H	140°	15 h	(70)	229
		Ph	160°	65 h	(35)	

C_{9-13}

R^1	R^2	R^3	R^4	R^5	R^6		Temp	Time		
H	H	Br	H	H	H	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(60)	230
H	H	I	H	H	H	Pd(OAc)$_2$, Na$_2$CO$_3$, n-Bu$_4$NBr, DMF	25°	24 h	(97)	230, 231
H	H	I	H	H	H	Pd(OAc)$_2$, A, Et$_3$N, CH$_3$CN, H$_2$O	40°	19 h	(97)	207
H	H	I	H	H	H	Pd(OAc)$_2$, A, Na$_2$CO$_3$, H$_2$O	80°	18 h	(60)	207
H	H	I	H	H	H	Pd(OAc)$_2$, TPPTS, Et$_3$N, CH$_3$CN, H$_2$O	25°	—	(97)	207
Me	H	Br	H	H	H	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(77)	230
H	H	I	Me	H	H	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN	reflux	—	(92)	75, 230
H	H	I	H	Me	H	Pd(OAc)$_2$, Et$_3$N, n-Bu$_4$NBr, DMF	80°	24 h	(73)	231
H	H	I	COMe	H	H	Pd(OAc)$_2$, NaOAc, n-Bu$_4$NBr, DMF	80°	24 h	(90)	231
H	H	I	H	Me	Me	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(73)	230
CO$_2$Et	H	Br	H	H	H	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(50)	230
H	H	I	CH$_2$CH=CH$_2$	H	H	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(87)	230
OMe	OMe	Br	H	H	H	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN	110°	72 h	(66)	230

C_9

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 48 h		(67)		66

C_{10}

Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 80°, 4 h		(69)		82

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C[10-17]

Pd(OAc)$_2$, P(tol-o)$_3$,
Et$_3$N, CH$_3$CN

R^1	R^2
H	H
NHCH$_2$CH=CH$_2$	H
NHBn	H
H	CH$_2$CH=CH$_2$

Temp	Time	I	II	III
75°	15 h	(31)	(0)	(0)
95°	18 h	(43)	(26)	(0)
65°	15 h	(49)	(23)	(0)
105°	25 h	(14)	(0)	(24)

232

C[10-15]

R
H
COCH=CH$_2$

Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N,
CH$_3$CN, 105°

	Time	
air	15 h	(36)
	5.2 h	(34)

232

C[10-16]

1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_3$SnH,
   THF, 0°, 1 h
2. Et$_4$NCl·H$_2$O,
   CH$_3$CN, reflux

R^1	R^2	
H, H	O	(85)[a]
O	NMe	(72)
H, H	NSO$_2$Ph	(66)

233

C[11-19]

Pd(OAc)$_2$, n-Bu$_4$NBr,
K$_2$CO$_3$, DMF

R^1	R^2	R^3	R^4	R^5
H	Br	Bn	H	H
Cl	Br	Bn	H	H
H	Br	allyl	H	H
H	Cl	H	H	H
H	Cl	H	(CH$_2$)$_2$CH=C(CH$_3$)$_2$	Me
H	Cl	H	H	CH$_2$OBn
H	Br	H	Ph	H

Temp	Time	
80°	30 min	(83)
80°	30 min	(26-32)
80°	30 min	(97)
100°	2 h	(67)
100°	2 h	(57)
100°	2 h	(43)
80°	30 min	(65)

234

C[11]

Pd(OAc)$_2$, PPh$_3$,
K$_2$CO$_3$, n-Bu$_4$NCl,
DMA, 100°, 15 h

(60)

235

Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$,
EtOH, DMF, 80°, 3 h

(50) *E:Z* 79/21

82

Pd(PPh$_3$)Cl$_2$, Et$_3$N,
n-Bu$_4$NCl, DMF, H$_2$O, 80°

R	Time	
Br	(—)	(25)
I	2 d	(80)

176

Pd(OAc)$_2$, PPh$_3$, Et$_3$N,
CH$_3$CN, 70°

(88)

236

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$,
CH$_3$CN, 80°, 5 d

(77)

65

218

219

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{15-17}$

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, DMF, 25°, 3 h

(—) 237

R = Me, Bn

C$_{11}$

Pd(OAc)$_2$, P(tol-*o*)$_3$, CH$_3$CN

I + II

R		Temp	Time	I	II	
K$_2$CO$_3$	H	reflux	5 h	(86)	(<1)	239
Et$_3$N	H	100°	31 h	(15)	(60)	239
K$_2$CO$_3$	OH	reflux	2 h	(90)	(0)	238, 239

Pd(OAc)$_2$, dmphen, Ag$_2$CO$_3$, CH$_3$CN, AcOH

(78) + (10) 134

C$_{11-13}$

I + II

R^1	R^2			I	II	
Me	Me	Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, MeOH, CH$_3$CN, C$_6$H$_6$, reflux, 4 h		(23)	(60)	240
CH=CH$_2$CH=CH$_2$		"		(0)	(47)	
allyl	Me	"		(21)	(52)	
Me	Me	Pd(PPh$_3$)$_4$, CO, Et$_3$N, MeOH, CH$_3$CN, C$_6$H$_6$, 100°, 1–48 h		(28)	(12)	

C$_{11-24}$

Pd(OAc)$_2$, *n*-Bu$_4$NHSO$_4$

I + II + III

R^1	R^2	R^3		Temp	Time	I	II	III	
OEt	O	H	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	80°	—	(68)	(0)	(0)	49
H	O	TBDMS	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	80°	—	(66)	(0)	(0)	49
H	O	TBDMS	PPh$_3$, Et$_3$N, CH$_3$CN	80°	10 h	(65)	(7)	(0)	48
H	O	TBDMS	PPh$_3$, Et$_3$N, CH$_3$CN	80°	20 h	(42)	(28)	(0)	48
OEt	O	TBDMS	TFP, Et$_3$N, H$_2$O, CH$_3$CN	80°	4 h	(77)	(0)	(0)	49
OEt	O	TBDMS	PPh$_3$, Et$_3$N, CH$_3$CN	80°	15 h	(72)	(0)	(0)	48, 51, 53
OEt	O	TBDMS	PPh$_3$, Na$_2$CO$_3$, CH$_3$CN	80°	24 h	(39)	(13)	(0)	48
OEt	O	TBDMS	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	80°	—	(0)	(0)	(57)	49
OBu-*t*	O	TBDMS	PPh$_3$, Et$_3$N, CH$_3$CN	80°	24 h	(20)	(0)	(0)	48, 49
OC$_6$H$_4$NO$_2$-*p*	O	TBDMS	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	40°	27 h	(23)	(0)	(0)	51, 53
OC$_6$H$_4$(Bu-*t*)-*p*O		TBDMS	PPh$_3$, Et$_3$N, DMF	80°	24 h	(70)	(0)	(0)	51, 53
OC$_6$H$_4$(Bu-*t*)-*p*O		TBDMS	PPh$_3$, Et$_3$N, CH$_3$CN	80°	24 h	(35)	(0)	(0)	48, 49, 51
OEt	NTs	TBDMS	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	80°	—	(81)	(0)	(0)	49
OEt	C(CO$_2$Me)$_2$	TBDMS	PPh$_3$, Et$_3$N, H$_2$O, CH$_3$CN	80°	—	(80)	(0)	(0)	49

C$_{12}$

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 80°, 24 h

(47) 241

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, DMF, reflux, 6 h

(35) 242, 243

220

221

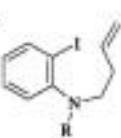TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, CH₃CN	(50)	64
	Pd(PPh₃)₄, Et₃N, CH₃CN	(71)	64
	Pd(PPh₃)₄, Et₃N, CH₃CN, 140–160°, 143 h	(51)ᵃ	229
	Pd(OAc)₂, PPh₃, Et₃N, Bu Et₃NCl	(—)	244
	Pd(PPh₃)₄, Et₃N, CH₃CN, THF, reflux, 16 h	(87)ᵇ	76
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 80°, 15 h	(60)	245

C₁₃₋₁₄

R¹	R²	R³	R⁴		Temp	Time	
H	F	F	CH₂	P(tol-*o*)₃, *i*-Pr₂NEt, KOAc	100°	18 h	(60)
H	H	OMe	CO	dppp, Et₃N, KOAc	130°	1 h	(47)
H	OMe	H	CO	dppp, *i*-Pr₂NEt, KOAc	120°	18 h	(95)
OMe	H	H	CH₂	dppp, Et₃N	100°	18 h	(95)

Ref. 246

	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN		54

R	Temp	Time	
H	80°	4 h	(78)
Me	23°	24 h	(85)

C₁₃

	Pd(PPh₃)₄, Et₃N, CH₃CN, THF, reflux, 20 h	(72) + (8)	247
	Pd(PPh₃)₄, Et₃N, THF, CH₃CN, 100°, 6 h	(68)	248

	Temp	Time	I	II	III		
K₂CO₃, DMF	100°	2 h	(36)	(31)	(25)		249
K₂CO₃, Et₄NCl, DMF	30°	2 h	(49)	(23)	(0)		249, 250
CH₃CN	—	—	(—)	(—)	(—)	I:II:III 1.45:1.27:1	33
TlOAc, CH₃CN	80°	4 d	(65)	(0)	(0)		33

	Pd(OAc)₂, PPh₃, TMEDA, 125°		350

R	Time	I	II	III
Cl	5 h	(tr)	(59)	(0)
Br	5 h	(43)	(0)	(15)
I	3 h	(20–24)	(47)	(4)

TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, THF, CH₃CN, 100°, 6 h	(50) + (30)	248
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 82°, 18 h	(91)	252
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 23°, 48 h	(55) + (16)	252
	Pd(OAc)₂, Na₂CO₃, NaO₂CH, n-Bu₄NCl, DMF, 80°, 48 h	(52)	228
	Pd(PPh₃)₄, LiCl, Et₃N, DMF, 90°, 18 h	(62) + (10)	253
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN	Temp Time reflux 24 h (67) rt 2-8 h (—)	254 38
	Pd(PPh₃)₂Cl₂, Et₃N, CH₃CN, C₆H₆, reflux, 4 h	(—)	240
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux	(79)	75

C_{15-19}

| | Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN | I + II + III | 226 |

R¹	R²
CO₂Et	Ph
CO₂Me	CO₂Me
CO₂Me	CO₂Me

Temp	Time	I	II+III
80°	6 h	(38)	(50)
30°	35 h	(45)	(0)
30°	3.5 h	(24)	(44)

C_{13}

	Pd(OAc)₂, PPh₃, Et₄NCl, K₂CO₃, CH₃CN, 80°, 3 h	(60)	249
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 90°, 45 min	(95)	255
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 90°, 90 min	(83)	134

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}	Pd(PPh₃)₄, Et₃N, THF, CH₃CN, reflux, 16 h	(50)	256
	Pd(OAc)₂		65

	Temp	Time	I	II
KOAc, n-Bu₄NCl, DMF	rt	24 h	(12)	(65)
PPh₃, Ag₂CO₃, CH₃CN	80°	72 h	(59)	(3)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, THF, CH₃CN, 100°, 6 h	(71)	248
C_{14-15}	Pd(PPh₃)₄, Et₃N, CH₃CN, THF, reflux, 24 h	 R CH₂ (58) (CH₂)₂ (73)	257
C_{14}	Pd(OAc)₂, PPh₃, Bu₄NCl, Et₃N, CH₃CN, H₂O, rt to 50°, 1 h	(42) + (32)	258
C_{16-20}	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, rt, 20-24 h	 R (±)-H (78) crude (41) after purification (±)-CO₂Et (64) (R)-CO₂Et (64)	259
C_{14-20}	Pd(OAc)₂, PPh₃, CH₃CN		252

R^1	R^2	R^5	R^4
Br	Me	H	H
Br	Bn	H	H
Br	SEM	H	H
I	Me	H	H
I	Me	H	H
Br	Me	n-Bu	H
Br	Me	H	Me

	Temp	Time	I	II	I:II
Et₃N	reflux	36 h	(85)	(85)	—
Et₃N	reflux	36 h	(68)	(68)	—
Et₃N	reflux	36 h	(70)	(70)	—
Et₃N	reflux	36 h	(—)	(0)	1:1
AgNO₃, Et₃N	reflux	3 h	(67)	(3)	—
Et₃N	82°	36 h	c		
Et₃N	82°	24 h	d		

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}	Pd(OAc)₂, Et₃N, CH₃CN		260

	Temp	Time	I	II
AsPh₃	80°	64 h	(0)	(74)
PPh₃, TlOAc	80°	19 h	(84)	(0)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 (60:40 E:Z)	Pd(OAc)₂, Na₂CO₃, NaO₂CH, n-Bu₄NCl, DMF, 80°, 48 h	(83)	228

TABLE 1. EXO CYCLIZATIONS (Continued)

B. 5-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PdCl$_2$, TPPTS, i-Pr$_2$NEt, CH$_3$CN, H$_2$O, 80°, 18 h	(50)	261
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 60°, 3 h	(83)	245
	Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, MeOH, CH$_3$CN, C$_6$H$_6$, reflux, 4 h	(72)	240
	Pd(PPh$_3$)$_4$, Et$_3$N, THF, CH$_3$CN, 100°, 6 h	(82)	248
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, rt, 10 h	(93)	254
	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, reflux, 40 min	(12)	242
	Pd(PPh$_3$)$_4$, Et$_3$N, THF, CH$_3$CN, 100°, 6 h	(77)	248
	Pd(OAc)$_2$, NaOAc, n-Bu$_4$NBr, DMF, 80°, 24 h	(97)	231
C$_{15-16}$	Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, 100°	R Time H 18 h (58) Me 29 h (22)	262
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, 115°, 24 h	(79)	107
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 80°, 72 h	(72) 1.2:1 dr	65
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 82°, 36 h	(83) + (3)	252
	Pd(PPh$_3$)$_4$, LiCl, Et$_3$N, DMF, 90°, 72 h	(48) * (32) + (2)	253
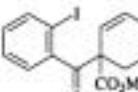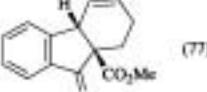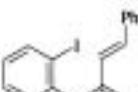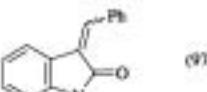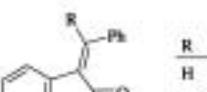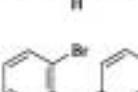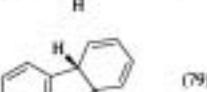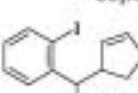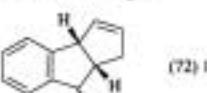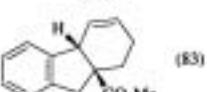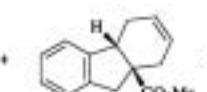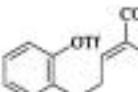
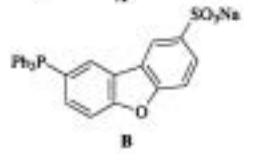TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{15-19}$	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°	<table><tr><td>n</td><td>R</td><td>Time</td><td></td></tr><tr><td>1</td><td>H</td><td>1.5 h</td><td>(50)</td></tr><tr><td>1</td><td>CO$_2$Et</td><td>2 h</td><td>(80)</td></tr><tr><td>2</td><td>H</td><td>3 h</td><td>(55)</td></tr><tr><td>2</td><td>CO$_2$Et</td><td>3 h</td><td>(37)</td></tr><tr><td>3</td><td>H</td><td>6 h</td><td>(75)</td></tr></table>	263
C$_{19}$	Pd(OAc)$_2$, PPh$_3$, KOAc, anisole, 145°, 22 h	CO$_2$Me (6) + CO$_2$Me (52) + CO$_2$Me (8)	68
	R$_2$P—Pd—PR$_2$ TFA R=cyclopentyl Na$_2$CO$_3$, NMP, 135°, 19 h	CO$_2$Me (42) + CO$_2$Me (42)	197
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 82°, 36 h	(84) + (6)	252
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 82°, 56 h	(45) + (13)	252
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 82°	<table><tr><td>R</td><td>Time</td><td>I</td><td>II</td></tr><tr><td>I</td><td>10 h</td><td>(31)</td><td>(51)</td></tr><tr><td>Br</td><td>56 h</td><td>(46)</td><td>(6)</td></tr></table> I + II	252
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, THF, reflux, 5 h	(60)	264
C$_{15-21}$ R^1 R^2 R^3 H H Me H H Bn OMe H Me NO$_2$ H Bn H NO$_2$ Me Br H Me	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 60-65° n-Bu$_4$NCl n-Bu$_4$NCl — — — —	<table><tr><td>Time</td><td></td></tr><tr><td>17 h</td><td>(59)^f</td></tr><tr><td>12 h</td><td>(62)^f</td></tr><tr><td>12 h</td><td>(75)^f</td></tr><tr><td>12 h</td><td>(77)^f</td></tr><tr><td>12 h</td><td>(65)^f</td></tr><tr><td>4 h</td><td>(77)^f</td></tr></table>	265
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, THF, rt, 96 h	(18)	264
	Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, DMF, 60-65°, 4 h	(85)	264

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TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

$C_{15,16}$

R^1	R^2
I	CO_2Me
Br	CO_2Me
I	CN

		Temp	Time	I+II	III
Pd(0), base		—	—	I (major)	(minor)
Pd(dppe), KH, 18-C-6, THF		55°	24 h	(42)	(34)
Pd(dppe), KH, 18-C-6, THF		25°	4 h	(30)	(45)

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C_{15}

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 80°, 20 h — (57) + (29) — 245

Pd(PPh₃)₄, Et₃N, THF, CH₃CN, 100°, 6 h — (67) + (7) — 248

Pd(PPh₃)₄, Et₃N, THF, CH₃CN, 100°, 6 h — (52) + (35) — 248

K₂CO₃, CH₃CN — I + II + III — 267

Pd(OAc)₂, PPh₃ HBC		Temp	Time	I	II	III
		80°	60 h	(52)	(14)	(0)
		88°	96 h	(24)	(0)	(27)

Pd(OAc)₂, PPh₃, Et₃N — I + II — 268

		Solv	Temp	Time	I	II
		tol	80°	3 h	(84)	(9)
		THF	65°	3 h	(71)	(18)

C_{15-25}

Pd(OAc)₂, PPh₃, Et₃N, Bu₄NHSO₄, H₂O, CH₃CN — I + II — 51, 53

R
H
OEt
OC₆H₄NO₂-*p*
OC₆H₄(Bu-*t*)-*p*

		Temp	Time	I	II
		50°	17 h	(51)	(0)
		80°	10 h	(0)	(57)
		40°	29 h	(30)	(0)
		50°	53 h	(32)	(0)

C_{16}

Pd(OAc)₂, n-Bu₄NBr, Et₃N, DMF, rt, 24 h — (96) — 56

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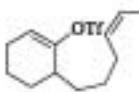TABLE 1. EXO CYCLIZATIONS (*Continued*)
B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 1 h

(23) + (30)

249

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, DMF, rt, 5 h

(80)

57

C$_{16-23}$

Pd(OAc)$_2$(PPh$_3$)$_2$, *n*-Bu$_3$N, DMF, 80°

R	Time	
Me	1 h	(73)
(CH$_2$)$_2$COCH$_3$	1.5 h	(30)
(CH$_2$)$_2$CO$_2$CH$_3$	1.5 h	(70)
CH$_2$C$_6$H$_{11}$	1.5 h	(65)
Pr-*i*	1 h	(90)
(CH$_2$)$_2$Ph	1 h	(84)
CH(CH$_3$)COCH$_3$	1 h	(93)
Bn	1 h	(55)

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C$_{16}$

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 9 h

(52) + (<10)

250

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 9 h

" (23) + (23) + (6)

263

C$_{16-21}$

R^1	R^2	R^3
N(Ac)CH$_2$CH=CH$_2$	Br	Ac
H	Me	Ac
N(Ac)CH$_2$CH=CH$_2$	Me	Ac
H	Me	CH$_2$CH=CH$_2$

Pd(OAc)$_2$, P(tol-*o*)$_3$, Et$_3$N, CH$_3$CN

I II

Temp	Time	I	II
—	—	(64)	(0)
80°	20 h	(89)	(0)
105°	2 h	(76)	(21)
105°	5 h	(78)	(0)

232

C$_{18}$

Pd(OAc)$_2$, PPh$_3$, anisole

I II III

	Temp	Time	I	II	III
KOAc	140°	30 h	(8)	(30)	(42)
TlOAc	120°	15 h	(60)	(14)	(tr)
AgOAc	136°	12 h	(14)	(61)	(4)

33, 68

Pd(PPh$_3$)$_4$, Ag$_2$CO$_3$, CH$_3$CN, 50°, 5 h

(44)

259

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Ph$_3$P, Ag$_2$CO$_3$, THF, 120-130°	(70)	270
	PdCl$_2$, TPPTS, i-Pr$_2$NEt, CH$_3$CN, H$_2$O, 12 h		261

For the second substrate:

R	Temp	
Br	70°	(77)
I	80°	(68)

C$_{16-25}$

Pd(OAc)$_2$, CH$_3$CN

R^1	R^2	R^5		Temp	Time	I		II
H	H	C$_6$H$_4$NMe$_2$-2	dppp or dppf, Ag$_2$CO$_3$	60°	—	(54) 92:8		(0)
CO$_2$Et	H	C$_6$H$_4$NMe$_2$-2	PPh$_3$, Ag$_2$CO$_3$	rt	24 h	(84) 98:2		(14)
CO$_2$Et	H	C$_6$H$_4$NMe$_2$-2	dppf, Ag$_2$CO$_3$	rt	24 h	(78) 98:2		(2)
CO$_2$Et	Me	C$_6$H$_4$NMe$_2$-2	dppp or dppf, Ag$_2$CO$_3$	60°	—	(70) >98:<2 5:1 E:Z		(0)

Ref: 136

C$_{16}$

Pd(PPh$_3$)$_4$, LiCl, Li$_2$CO$_3$, THF, reflux, 3 h

 (82) + (16)

Ref: 253

 I + II

	Temp	Time	I	II	
Pd(OAc)$_2$, KOAc, n-Bu$_4$NCl, DMF	rt	5 h	(25)	(59)	65
Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN	25°	8 d	(34)	(23)	65

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 85°, 5.5 h

 (27)^f

Ref: 271

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 1 h	(30) + (23)	249
	Pd(OAc)$_2$, 25°	I + II	65
	KOAc, *n*-Bu$_4$NCl, DMF	Time I II 5 d (45) (16)	
	PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN	3 d (53) (3)	
	Pd(PPh$_3$)$_4$, Et$_3$N, THF, CH$_3$CN	(68)	64
C$_{17}$	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, reflux, 30 min	I + II	272
		I II (31) (17)	
	AgNO$_3$	(96) (0)	
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 100°, 1 h	(59)	249
	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, tol, 107°, 12 h	(66)	273
	Pd$_2$(dba)$_3$, (+)-DIOP, Ag$_3$PO$_4$, NMP, 80°, 6 h	(91)	147
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 130°, 24 h	(43)	270
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF, reflux, 6 h	(40) + (40)	247
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 120°, 24 h	R Br (48) I (72)	270

238

239

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, AgNO$_3$, CH$_3$CN, reflux	(—) >95% de	135
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, AgNO$_3$, CH$_3$CN, reflux	(—) >95% de	135
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 60-65°, 72 h	(58)	265
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 60-65°, 12 h	(83)	265
	Pd(OAc)$_2$ KOAc, n-Bu$_4$NCl, DMF PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN,	 <table><tr><td>Temp</td><td>Time</td><td>I</td><td>II</td></tr><tr><td>80°</td><td>6 h</td><td>(27)</td><td>(61)</td></tr><tr><td>25°</td><td>8 d</td><td>(34)</td><td>(23)</td></tr></table>	65
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF, reflux, 10 h	(69) + (17)	247
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, n-Bu$_4$NHSO$_4$, H$_2$O, CH$_3$CN, 80°	(50)	49
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 60-65°, 16 h	(81)	265
C$_{18-25}$ 	Pd(OAc)$_2$(PPh$_3$)$_2$, TlOAc, CH$_3$CN, 80°	 <table><tr><td>R</td><td>Time</td><td></td></tr><tr><td>Me</td><td>1.5 h</td><td>(66)</td></tr><tr><td>Ph</td><td>6 h</td><td>(73)</td></tr><tr><td>Cl</td><td>23 h</td><td>(58)</td></tr><tr><td>F</td><td>23 h</td><td>(75)</td></tr><tr><td>COPh</td><td>4 h</td><td>(75)</td></tr></table>	274
C$_{18}$ 	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°, 7 h	(34)	249
	Pd(PPh$_3$)$_2$(OAc)$_2$, NaOAc, n-Bu$_4$NBr, 4Å mol sieves, DMF, 80°	(64) + (12)	275
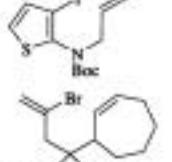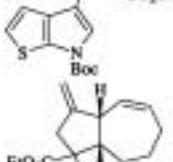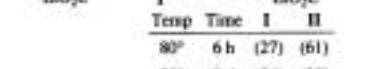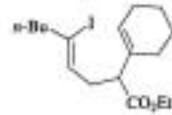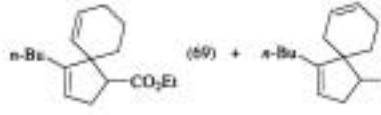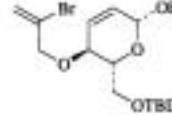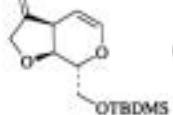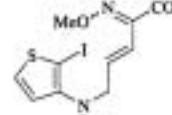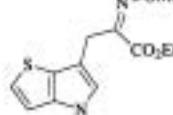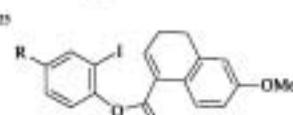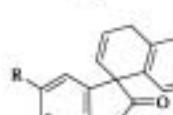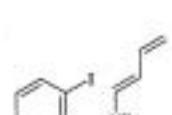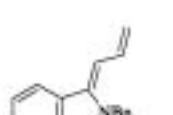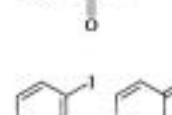
TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, K₂CO₃		249, 250
	DMF Et₄NCl, CH₃CN	 Temp Time I II 100° 1 h (64) (16) 80° 1 h (83) (8)	
C₁₈₋₁₉ R / CH / N	K₂CO₃, CH₃CN, 80° Pd(PPh₃)₄, 16.5 h Pd(OAc)₂, PPh₃, 9 min	 (86) (90)	225, 226
C₁₈	Pd(OAc)₂P(tol-*o*)₂, *n*-Bu₃N, tol, 120°, 48 h	(74) + (18)	276
	Pd(OAc)₂, PPh₃, *n*-Bu₃N, CH₃CN, 70°, 6 h	(48)	251
	Pd(OAc)₂, P(tol-*o*)₃, Et₃N, CH₃CN, reflux, 3 h	(89)	277
	Pd(OAc)₂, PPh₃, K₂CO₃, Et₄NCl, DMF, 110°, 2-4 h	(70)	69
	HBC, Et₃N, DMF, 110°, 4 h	(16)	278
	Pd(OAc)₂(PPh₃)₂, TlOAc, CH₃CN, 80°, 2.5 h	(85) 1.7:1 dr	274
	Pd(OAc)₂, (S)-BINAP, K₂CO₃, Et₄NCl, CH₃CN, reflux	(—) 48% de	135
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux, 48 h	(64) + (—)	280

TABLE 1. EXO CYCLIZATIONS (Continued)

B. 5-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, CH₃CN	I + II + III	279

	Temp	Time	I	II	III	I+II+III
TFP, Et₃N	80°	19 h	(—)	(—)	(—)	(79)
K₂CO₃	100°	168 h	(0)	(0)	(54)	(54)
(R)-BINAP, Et₃N, cyclohexane	80°	20 h	(0)	(54)	(—)	(—)
PPh₃, TlOAc, Et₃N	80°	17 h	(79)	(0)	(0)	(79)

C₁₈₋₂₁

| | Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, rt, 24 h | I + II | | 136 |

R	I	dr	II
t-Bu	(59)	83:17	(1)
p-tol	(98)	54:46	(2)

C₁₉

| | | I + II | | |

	Temp	Time	I	II
Pd(OAc)₂, KOAc, DMF	80°	—	(14)	(57)	274
Pd(OAc)₂(PPh₃)₂, TlOAc, CH₃CN	80°	9 h	(86)	(0)	274

C₁₉₋₂₂

| | Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN | I + II | | 250, 263 |

	n	R	Temp	Time	I	II
—	1	H	80°	2.4 h	(60)	(0)
Et₄NCl	1	CO₂Et	80°	2 h	(70)	(0)
Et₄NCl	2	H	45°	72 h	(53)	(14)
Et₄NCl	3	H	45-50°	48 h	(71)	(0)
Et₄NCl	4	H	45-50°	48 h	(75)ᶠ	(0)

C₁₉

| | Pd(OAc)₂, PPh₃, Bu₄NHSO₄, Et₃N, H₂O, CH₃CN, 80°, 15-24 h | | | 50, 460 |

R	
(CH₂)₂CH=CH₂	(78)
CH₂C(CH₃)=CH₂	(72)

C₂₀

| | Pd(OAc)₂(PPh₃)₂, TlOAc, CH₃CN, 80°, 2.5 h | (75) 1.8 : 1 dr | 274 |

| | Pd(OAc)₂, PPh₃, CH₃CN, 80°, 18 h | I + II | 33 |

	I	II	I:II
—	(—)	(—)	4:1
AgOAc	(43)	(0)	(—)
TlOAc	(—)	(—)	18:1

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. S-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, rt, 24 h	(45) + (15)	259
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 60–65°, 12 h	(20) + (70)	265
	Pd(PPh$_3$)$_4$, LiCl, Li$_2$CO$_3$, THF, reflux, 3 h	(91)	253

C$_{21}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$(PPh$_3$)$_2$, TlOAc, CH$_3$CN, 80°, 24 h	(59)	274

C$_{21-27}$

R^1	R^2	R^3	R^4	Conditions	Temp	Time	I	II	Refs.
Me	Br	H	CH=CH$_2$	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	82°	—	(49-54)	(27-32)	281
MOM	I	OMe	CH=CH$_2$	Pd$_2$(dba)$_3$ CHCl$_3$, Ag$_3$PO$_4$, Et$_3$N, THF	reflux	—	(7)	(71)	283
SEM	Br	H	CH=CH$_2$	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	82°	—	(41)	(25)	281
SEM	Br	H	CH=CH$_2$	Pd$_2$(dba)$_3$, Et$_3$N, tol	110°	1 h	(71-85)	(9-10)	282
SEM	Br	H	CH=CH$_2$	Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, THF	66°	36 h	(2)	(75)	282
SEM	Br	H	Et	Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, THF	66°	36 h	(—)	(—)	282
Bn	Br	H	CH=CH$_2$	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	82°	—	(54)	(38)	281

C$_{21}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, (S)-BINAP, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, reflux	(—) 55% de	135

C$_{22}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 60°, 15 h	(80)	213

246

247

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, TlOAc, DMF, 130°, 24 h	(93)	284, 285
	PdCl₂(PhCN)₂, PPh₃	(60) + (13)	251
	Pd(OAc)₂, dppp, Et₃N, Ag₂CO₃, 80°, 2 h	(96)	286
	Pd(OAc)₂, PPh₃, CH₃CN	I + II	33
	Tl₂CO₃		

Temp	Time	I	I:II
—	—	(—)	1.8:1
80°	22 h	(78)	(—)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, rt, 24 h	(39)ᵇ 20:80 dr + (59)	136
	Pd(OAc)₂, dppf, Ag₂CO₃, CH₃CN, 60°, 5 h	(75)	136
	Pd(PPh₃)₂(OAc)₂, NaOAc, n-Bu₄NBr, DMF, 90°	(69–77)	275

C₂₃₋₂₅

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Et₄NCl, K₂CO₃, CH₃CN, 80°	I + II + III	

n	Time	I	II	III	
1	12 h	(87)	(0)	(0)	250, 263
2	10 h	(12)	(50)	(0)	263
3	24 h	(12)	(58)	(23)	263

C₂₈

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, CH₃CN, 120°, 40 h	(90)	223, 224

248

249

TABLE 1. EXO CYCLIZATIONS (*Continued*)
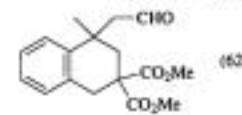B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Proton Sponge®, tol, reflux, 48 h	(57)	287

C₂₅

Pd(OAc)₂, PPh₃, CH₃CN, 80°

Time	I	II	I:III
Tl₂CO₃	4 h	(—)	(—) 5.75:1
TlOAc	46 h	(65)	(0) —

33

Pd(OAc)₂, DMF

	R	Temp	Time	
n-Bu₄Cl, Et₃N, DME	Br	80°	1 h	(76)
Et₃N	H	reflux	—	(81)

289
288

C₂₅₋₂₇

R
OH
OAc
OAc

Conditions	Temp	Time	I	II	
Pd(PPh₃)₄, Et₃N, CH₃CN	60°	18 h	(5)	(85)	290, 291
Pd(OAc)₂, Ag₂CO₃, DMF	20°	3 h	(0)	(90)	290, 291
Pd(OAc)₂, Ag₂CO₃, DMF	20°	3 h	(40)	(50)	291

C₂₉

Conditions	Temp	Time	I	II	
Pd(OAc)₂, NaOAc, n-Bu₄NCl, DMF	70°	30 min	(64)	(30)	292
Pd(PPh₃)₄, Et₃N, MeCN	65°	70 h	(10)	(70)	292

Pd(OAc)₂(PPh₃)₂, TlOAc, CH₃CN, 80°, 2 h

 (77)ʲ

274

TABLE 1. EXO CYCLIZATIONS (*Continued*)

B. 5-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, TlOAc, DMF, 130°, 2 d	(28)	293
C₃₃			
	Pd(OAc)₂(PPh₃)₂, TlOAc, CH₃CN, 80°, 9 h	(70)ᶠ	274
	1. Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux, 3 d 2. TBAF, THF, rt	I II (0) (—)	294
	1. Pd₂(dba)₃, Et₃N, C₆H₆, 110° 2. TBAF, THF, rt	(60) (30)	294
C₃₇			
	Pd(PPh₃)₂Cl₂, Et₃N, DMA, 100°	(90)	163
C₄₆			
	Pd(PPh₃)₂Cl₂, Et₃N, DMA, 100°	(71)	163
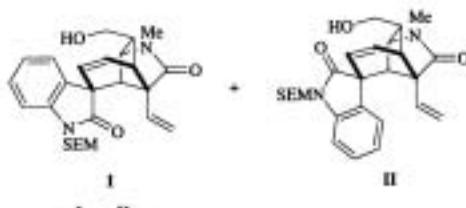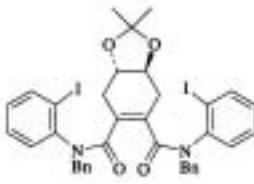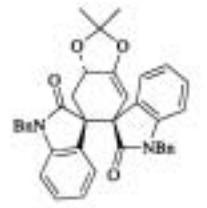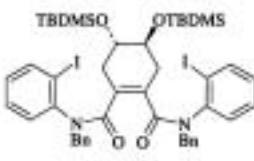
^a This compound is the major isomer in a mixture of alkenes.
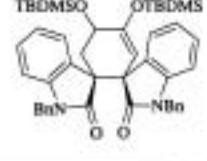
ᵃ This compound is the major isomer in a mixture of alkenes.

ᵇ The product mixture is predominantly composed of two isomers.

ᶜ This product is a 1.1:1 mixture of isomers I and II (75) + 10% of a structural isomer.

ᵈ The products (89) are an unassigned mixture of olefin and stereoisomers.

ᵉ The yields are for allylation to make the substrate followed by intramolecular Heck Reaction.

ᶠ Also formed is a mixture of diene isomers plus a triene without an OAc group (44%).

ᵍ An isomeric product of undetermined structure (5%) is also formed.

ʰ The minor diastereomer is shown.

ⁱ The product is a single diastereomer.

TABLE 1. EXO-CYCLIZATIONS *(Continued)*
C. 6-EXO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₀

Pd₂(dba)₃, PPh₃,
n-PrCOK, anisole,
PhCN, CO, 80°, 24 h

(85)

295

Pd(OAc)₂, PPh₃,
K₂CO₃, Et₄NCl,
DMF, 110°, 2-4 h

(78)

68, 69

Pd(PPh₃)₄,
K₂CO₃, n-Bu₄NCl,
xylene, 85°, 15.5 h

(83)

296

C₁₀₋₁₅

Pd(OAc)₂, Et₃N

I + II + III

243, 297, 298

R¹	R²	R³	R⁴		Temp	Time	I	II	III
NO₂	Br	O	CH₂	P(tol-o)₃	125°	30 min	(66)	(15)	(4)
NO₂	Br	CH₂	O	P(tol-o)₃	—	—	(76)	(20)	(0)
H	Br	O	CH₂	P(tol-o)₃	100°	48 h	(28)	(47)	(0)
H	Br	CH₂	O	P(tol-o)₃	100°	64 h	(21)	(48)	(0)
H	I	CH₂	O	PPh₃, CH₃CN	reflux	19 h	(92)	(tr)	(0)
NO₂	Br	CH₂	NAc	P(tol-o)₃	100°	5 min	(69)	(26)	(0)
NO₂	Br	CH₂	C(CO₂Me)₂	P(tol-o)₃	100°	5 min	(72)	(14)	(0)

C₁₀

$\dfrac{R^1}{H_2}$
O

n-Bu₄NCl, DMF, 24 h

231

R²	Temp	
Pd(OAc)₂, Na₂CO₃	H	80°	(39)
Pd(PPh₃)₄, Et₃N	OH	100°	(58)

C₁₀₋₁₁

Pd(OAc)₂, n-Bu₄NCl,
DMF, 24 h

231

R	Temp	
Na₂CO₃	H	25°	(92-97)
NaOAc	Me	80°	(55)

C₁₁

$\dfrac{R}{I}$
Br

Pd(OAc)₂, PPh₃, C₆H₆

I + II

299

	Temp	Time	I	II
Ag₂CO₃	rt	10 h	(43)	(40)
CH₃CO₂H	reflux	—	(10)	(0)

Pd(OAc)₂, PPh₃, Et₄NCl,
K₂CO₃, DMF, 120°, 4 h

(40)

68

Pd(PPh₃)₂Cl₂, K₂CO₃,
EtOH, DMF, 80°, 2 h

(66)

82

254

255

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, K₂CO₃, Bu₄NCl, DMF	(79)	171, 300
	Pd(OAc)₂, PPh₃, Et₄NCl, K₂CO₃, CH₃CN, 80°, 12 h	(45) + (45)	68
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 80°, 20 h	(74)	245
	Pd(OAc)₂, PPh₃, AgNO₃, Bu₄NCl, Et₃N, CH₃CN, 80°	(72)	301

C₁₀₋₁₃

| | | Pd(OAc)₂ | I + II | | | | 65 |

R¹	R²
H	CN
H	CN
H	CO₂Et
CH₂OH	CN
CH₂OH	CN

	Temp	Time	I	II
KOAc, n-Bu₄NCl, DMF	80°	4 h	(40)	(40)
PPh₃, Ag₂CO₃, CH₃CN	80°	5 d	(53)	(3)
PPh₃, Ag₂CO₃, CH₃CN	80°	4 d	(42)	(0)
KOAc, n-Bu₄NCl, DMF	25°	8 d	(41)	(2)
PPh₃, Ag₂CO₃, CH₃CN	25°	3 d	(46)	(2)

C₁₁₋₁₇

| | | K₂CO₃, n-Bu₄NCl, DMF, 90° | I + II | | 300, 302, 303 |

R¹	R²	R³	R⁴
H	CH	Br	Me
H	CH	I	Me
H	CH	I	Me
H	N	I	Me
H	N	I	Me
H	N	I	Me
H	N	I	Me
H	N	I	Me
Cl	N	I	Me
Cl	N	I	Me
H	CH	I	Ph
H	CH	I	Ph

	Time	I:II
Pd(OAc)₂, (PPh₃)₃RhCl	3 h	12.6:1
Pd(OAc)₂, (PPh₃)₃RhCl	2 h	18.4:1
Pd(OAc)₂	17 h	6.9:1
Pd(OAc)₂	24 h	(7):(72) (E)
Pd(OAc)₂, (PPh₃)₃RhCl	4 h	(68) 14.3:1 (Z)
Pd(OAc)₂, (PPh₃)₃RhCl	2 h	28.6:1
Pd(OAc)₂	16 h	7.7:1
Pd(OAc)₂(PPh₃)₂, (PPh₃)₃RhCl	—	1.1:1
Pd(OAc)₂, (PPh₃)₃RhCl	2.5 h	19.3:1
Pd(OAc)₂	9 h	6:1
Pd(OAc)₂, (PPh₃)₃RhCl	2.5 h	1:46.4
Pd(OAc)₂	7 h	1:8.7

C₁₁₋₁₅

| | Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux | | | 75 |

R	
Me	(94)
4-pentenyl	(81)

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO-CYCLIZATIONS (Continued)

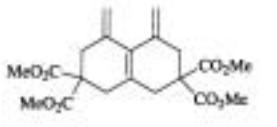| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-18}

R		Temp	Time	I	II	
H	CH_3CN	30-80°	—	(88)	(0)	68, 250, 252
Me	DMF	110°	1.5 h	(14)	(56)	68, 250
Me	DMF	120°	1.5 h	(15)	(59)	68
Ph	CH_3CN	—	—	(55)	(0)	68, 250

C_{12}

Pd(OAc)_2, H_2O, 95°
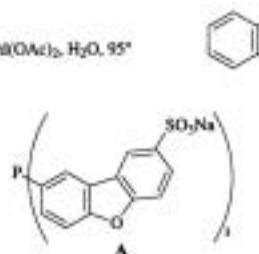
   207

Reag	Base	Solv	Time	
A	Et_3N	CH_3CN	24 h	(50)
A	Na_2CO_3	—	21 h	(50)
B	Et_3N	CH_3CN	24 h	(52)
B	Na_2CO_3	—	20 h	(50)

A

B

Pd(OAc)_2, PPh_3, Et_3N, CH_3CN, reflux, 24 h

   (81)   66

Pd(OAc)_2, PPh_3, Et_3N, toluene, 100°, 18 h

   (76)   66

C_{12-13}
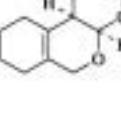
Pd(OAc)_2, PPh_3, K_2CO_3, Et_4NCl, DMF
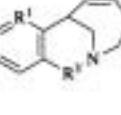
R^1	R^2	R^3	Temp	Time		
N	Cl	CO	150°	48 h	(45)	69
CH	I	SO_2	110°	2-4 h	(81)	
CH	I	CO	110°	2-4 h	(68)	

C_{12}

Pd(PPh_3)_2Cl_2, Et_3N, DMF, reflux, 55-60°, 5 h

 + +   304

(61)   (—)   (—)
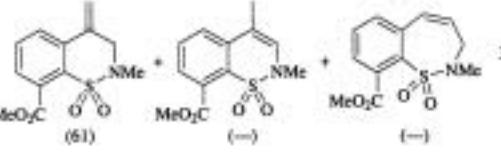
Pd(OAc)_2, dppe, Ag_2CO_3, CH_3CN, 60°, 5 h
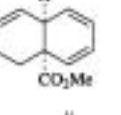
   (68)   305

Pd(OAc)_2, PPh_3, Et_3N, CH_3CN, 70°

   (80)   236

TABLE 1. EXO CYCLIZATIONS (Continued)
C. 6-EXO CYCLIZATIONS (Continued)

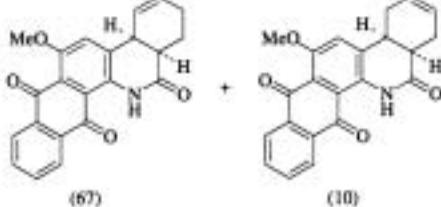| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13-14}

E or Z	R^1	R^2		I	II	III + IV
E	1	Me	Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(51)	(3)	(33)
E	1	Et	Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(49)	(13)	(23)
Z	1	Me	Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(46)	(6)	(35)
Z	1	Et	Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(35)	(12)	(23)
Z	1	i-Pr	Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(36)	(36)	(12)
Z	1	i-Pr	Pd(PPh₃)₄, Et₃N, CH₃CN, DMF, 10 kbar, 60°	(27)	(9)	(19)
Z	Br	Me	Pd(PPh₃)₄, Et₃N, CH₃CN, DMF, 10 kbar, 60°	(32)	(11)	(42)

Pd(OAc)₂, PPh₃, Et₃N, toluene, 100°, 48 h — (50) + (5) — 66

Pd(OAc)₂, PPh₃, CH₃CN, 80°, 23 h

Base	I	II	
K₂CO₃	(45)	(22)	225, 226
—	(47)	(19)	

C_{15-28}

Pd(OAc)₂, PPh₃, Et₃N, AgNO₃, 80°

R^1	R^2		I	II	
H	H	CD₃CN	(91)	(9)	307, 308
H	OBn	CD₃CN	(53)	(6)	307, 308
—OCH₂O—	OBn	CH₃CN, H₂O, 4 h	(70)	(6)	308, 309

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux, 1 h — (84) — 310, 311

C_{13}

6:1 E:Z

PPh₃, DMF — 159

	I:II
Pd(OAc)₂, KOAc, NPr₄Br	2.5:1
Pd₂(dba)₃, Ag₂O	4.1:1

TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	Temp	Time	I:II	I+II	
Et₄NCl, K₂CO₃	80°	85 min	1:9	(—)	242
TlOAc	reflux	15 min	3:1	(84)	312

Pd(OAc)₂, PPh₃, CH₃CN

Pd(OAc)₂, PPh₃, CH₃CN, reflux, 48 h

	I	II	
Et₃N	(56)	(22)	66
Ag₂CO₃	(54)	(0)	

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux, 24 h

(70)　　66

C₁₃₋₁₇

PdCl₂(PPh₃)₂, Et₃N, CH₃CN, reflux, 3-5 h

R	I	II	
H	(37)	(37)	76
t-Bu	(25)	(25)	

C₁₃₋₁₈

HBC, Et₃N, DMF, 80°, 4 h

R¹	R²
(CH₂)₂CH=CH₂	H
Me	H
Me	Me

I:II	III
(—)	(—)
(—)	(—)
3:1 (34)	(3)

C₁₃₋₁₄

Pd(OAc)₂, PPh₃, K₂CO₃, Et₄NCl, DMF, 110°, 2-4 h

R	
SO₂	(51)
CO	(71)

60

C₁₃₋₁₉

R¹	R²	R³	R⁴		Conditions	I	II	III	
I	H, H	Me	Me		Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(42)	(5)	(3)	314
I	O	Me	Me		Pd(OAc)₂, PPh₃, TPAB, KOAc, DMF, 80°	(58)	(2)	(7)	
Br	H, H	Boc	i-Pr		Pd(PPh₃)₂, Et₃N, CH₃CN, DMF, 10 kbar, 60°	(91)	(0)	(4)	

TABLE 1. EXO CYCLIZATIONS (*Continued*)
C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

1:3.4 *E/Z* — PPh₃, DMF

I + II (—) 159
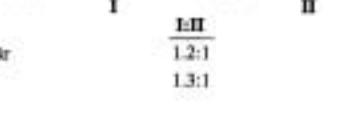
Pd(OAc)₂, KOAc, NPr₄Br — I:II 1.2:1
Pd₂(dba)₃, Ag₂O — 1.3:1

Pd(OAc)₂, PPh₃, Et₃N, 4 h
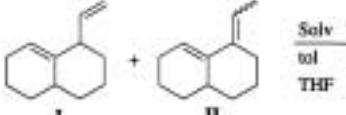
Solv	Temp	I	II	
tol	70°	(33)	(47)	268
THF	65°	(36)	(45)	

Pd(PPh₃)₄, Et₃N, CH₃CN, THF, reflux, 16 h — (97) 76

C₁₄
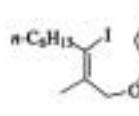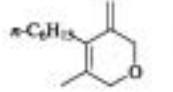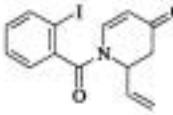
Pd(PPh₃)₂(OAc)₂, NaOAc, *n*-Bu₄NBr, 4 Å molecular sieves, DMF — (30) + (48) 275
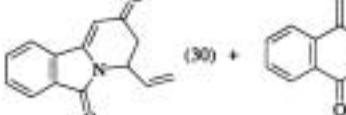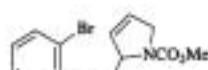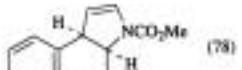
HBC, *n*-Bu₄NOAc, H₂O, DMF, CH₃CN, reflux, 2 h — (78) 315

C₁₄₋₁₅

Pd(OAc)₂, P(tol-*o*)₃, *n*-Bu₃N, DMF, 120°

R	I+II	
H	(79)	316
Me	(97)	

C₁₄₋₁₈
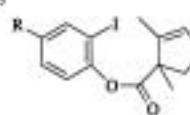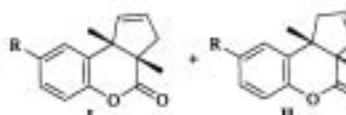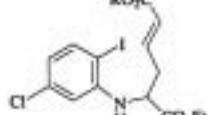
Pd(PPh₃)₄, Et₃N, DMF, 120°

R	Time		
H	3 h	(>70)	317
t-Bu	2 h	(85)	
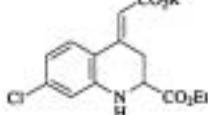
C₁₄
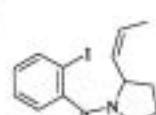
Pd(OAc)₂, PPh₃, TPAB, DMF, 80°, 8 h — I + II + III + IV 318

I, II, III, IV	I:II	(I+II):(III+IV)
(71)	9:1	7:1

Pd(OAc)₂, PPh₃, KOAc, TPAB, DMF, 80° — (61) + (5) + (5) 319
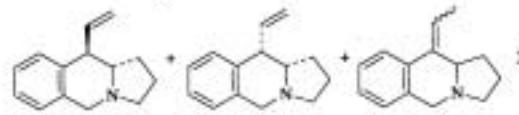
TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, CH$_3$CN, reflux, 19 h	(21) + (64)	76

C$_{14-18}$

		I II III	
R^1 R^2 R^3			
I O Me	Pd(OAc)$_2$, PPh$_3$, TPAB, KOAc, DMF, 80°	(60) (0) (0)	314
Br H, H Boc	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, DMF, 10 kbar, 60°	(57) (4) (9)	

C$_{16}$

| | Pd(OAc)$_2$, TPPTS, i-Pr$_2$NEt, CH$_3$CN, H$_2$O, 60°, 18 h | (40) + (40) | 261 |
| | Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 80°, 2 h | (23)^a | 82 |

| | Pd(OAc)$_2$, PPh$_3$, CH$_3$CN | I + II | 225, 226 |

Temp	Time	I	II
80°	14 h	(69)	(17)
— Et$_4$NCl	30°	36 h	(69)	(10)

C$_{14-17}$

| | Pd(OAc)$_2$, Ph$_3$P, K$_2$CO$_3$, CH$_3$CN, 80°, 5 h | | 320 |

R	
MOM	(58)
THP	(—)

C$_{15}$

| | Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, reflux, 1.5 h | (87) | 320 |

| | Pd(OAc)$_2$, P(tol-o)$_3$, Ag$_2$CO$_3$, DMF, reflux | (66) | 310 |

| | Pd(OAc)$_2$, PPh$_3$, Et$_3$N | I + II | 241 |

	Solv	Temp	Time	I	II
—	CH$_3$CN	—	—	(—)	(37-48)
—	DMF	80°	24 h	(55)	(0)
Cr(CO)$_6$ or [Cr(CO)$_3$naphthalene]	DMF	80°	24 h	(27)	(0)

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, dppe, Bu$_4$NOAc, PMP tol, 70°, 5 h	(50)	321
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, 140°, 48 h	(73)	67
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF, reflux, 6 h	(57) + (24)	247
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 110°, 5 h	(89)	322
	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, 80° AsPh$_3$ PPh$_3$, TlOAc	I + II	260
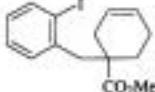
Time	I	II
120 h	(0)	(67)
50 h	(91)	(0)

C$_{15-22}$

Pd$_2$(dba)$_3$·CHCl$_3$, PPh$_3$ I + II   323,324
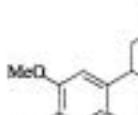
R
H
H
n-Pr
i-Pr
2-O$_2$NC$_6$H$_4$
Ph
4-MeOC$_6$H$_4$

	Solv	Temp	Time	I	II
K$_2$CO$_3$, Et$_4$NCl	DMF	120°	6 h	(17)	(35)
K$_2$CO$_3$, Et$_4$NCl	DMF	120°	5 h	(33)	(0)
K$_2$CO$_3$, Et$_4$NCl	DMF	120°	8 h	(26)	(42)
K$_2$CO$_3$, Et$_4$NCl	tol	120°	16 h	(30)	(60)
i-Pr$_2$NEt, DMF	DMF	100°	25 h	(65)	(0)
K$_2$CO$_3$, Et$_4$NCl	DMF	120°	3 h	(87)	(0)
K$_2$CO$_3$, Et$_4$NCl	DMF	120°	3 h	(76)	(9)

C$_{15}$

	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 23°, 30 h	(70) + (4)	252
	Pd(OAc)$_2$, PPh$_3$, AgNO$_3$, Et$_3$N, CH$_3$CN, reflux, 30 h	(76) + (8)	325
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF, reflux	I + II	247
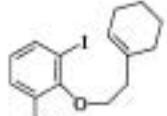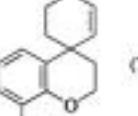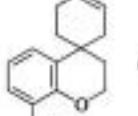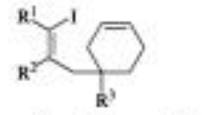
R^1	R^2	R^3
n-Bu	H	CO$_2$Me
H	n-C$_6$H$_{13}$	H

Time	I	II
6 h	(73)	(8)
2 h	(63)	(7)

TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, P(tol-*o*)₃, *n*-Bu₃N. DMF, 120°, 12 h	(93)	326
	PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, DMF, 85°, 50 h	(<3) (37) (17)	138, 327
	PPh₃, DMF, 65°		159

I II III

Pd(OAc)₂, KOAc, NPr₄Br, 3 h (26) (13) (31)
Pd₂(dba)₃, Ag₂O, 20 h (<1) (<1) (80)

C₁₅₋₁₆

 268

R		Solv	Temp	Time	I	II
I	Pd₂(dba)₃·CHCl₃, dppb, KOAc	DMF	80°	2 h	(54)	(2)
I	Pd₂(dba)₃·CHCl₃, dppb, Ag₃PO₄	DMF	80°	2 h	(39)	(18)
OTf	Pd(OAc)₂, PPh₃, Et₃N	tol	75°	2 h	(54)	(36) + double bond isomers (9)
OTf	Pd(OAc)₂, PPh₃, Et₃N	THF	50°	3 h	(55)	(26)

C₁₅₋₃₄

 328

I II
(53) (26)

R¹	R²		I	II
—C(Me)₂—		Pd₂(dba)₃·CHCl₃, dppb, Ag₃PO₄, CaCO₃, DMA		
TBDMS	TBDPS	Pd(OAc)₂, P(tol-*o*)₃, K₂CO₃, CH₃CN, reflux	(39)	(39)

C₁₆₋₃₅

 329

R¹	R²	R³		
H	I	H	Pd(OAc)₂	(58)
H	I	OMe	Pd(OAc)₂	(ca 58)
OMe	I	OMe	Pd(OAc)₂	(ca 58)
H	Pd(PPh₃)₂I	OMe	tol, reflux	(90)

C₁₈

 | Pd(OAc)₂, Na₂CO₃, *n*-Bu₄NCl, DMF, 110°, 24 h | (33)[b] | 231 |

 | Pd(PPh₃)₄, NaOAc, *n*-Bu₄NCl, DMF, 100°, 24 h | (39)[b] | 231 |

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{16}$	Pd(OAc)$_2$, PPh$_3$, i-Pr$_2$NEt, CH$_3$CN, reflux, 12 h	(91)	62
C$_{16-17}$	HBC, n-Bu$_4$NOAc, H$_2$O, CH$_3$CN, DMF, 110-120°, 3-7 h	$\begin{array}{ll} R & \\ CH_2 & (80) \\ (CH_2)_2 & (81) \end{array}$	79
C$_{16}$	PPh$_3$, DMF, 55°	I + II	159
		$\begin{array}{ll} & I \quad II \\ \end{array}$	
	Pd(OAc)$_2$, KOAc, NPr$_4$Br, 3 h	(81) (<1)	
	Pd$_2$(dba)$_3$, Ag$_2$O, 5 h	(5) (64)	
C$_{16-19}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°	I + II	
$\begin{array}{ll} R^1 & R^2 \\ \hline H & H \\ H & Ac \\ Cl & Ac \\ OMe & Ac \end{array}$		$\begin{array}{ll} I & II \\ \hline (8) & (69) \\ (56) & (19) \\ (36) & (16) \\ (50) & (22) \end{array}$	188, 330 188 188 188
C$_{16}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 4 h	(75)	310, 311
	1. Pd(OAc)$_2$, PPh$_3$ 2. H$_2$, Pd/C	(72)	331
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 24 h	(30) + (30) + (30)	245
	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 120°, 20 h	(92)	68
	Pd(OAc)$_2$, PPh$_3$, AgNO$_3$, Et$_4$NCl, Et$_3$N, CH$_3$CN, 80°	(94)	301

TABLE 1. EXO CYCLIZATIONS *(Continued)*
C. 6-EXO CYCLIZATIONS *(Continued)*

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	K₂CO₃, CH₃CN		267

	Temp	Time	I	II
Pd(OAc)₂, PPh₃ HBC	80°	60 h	(35)	(5)
	88°	96 h	(22)	(18)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, CH₃CN, THF, reflux, 24 h	(86)	76
	Pd(OAc)₂, PPh₃, Et₃N, tol, 110°, 48 h	(58) + (tr)	332
	Pd(OAc)₂, PPh₃, Et₃N, tol, 110°, 18 h	(51) + (13)	332

C₁₇₋₂₀

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 12 h		185

R¹	R²	Temp	I	II
H	H	80°	(58)	(0)
H	OMe	70°	(25)	(26)
OMe	OMe	80°	(56)	(0)

C₁₇

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN, 45°, 3.5 h	(52)	334
	1. Pd(OAc)₂, PPh₃, n-Bu₃SnH, THF, 0°, 1 h 2. Et₄NCl•H₂O, CH₃CN, reflux	(52)	233
			334

R			
Cl			
Cl			
I			

	Solv	Temp	Time	I	II	III
Pd(PPh₃)₄, NaHCO₃, Et₄NCl	CH₃CN	80°	3 h	(0)	(68)	(18)
Pd(OAc)₂, PPh₃, Et₃N	CH₃CN	50°	18 h	(0)	(0)	(80)
Pd(OAc)₂, PPh₃, K₂CO₃	CH₃CN	45°	3.5 h	(54)	(0)	(0)

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{17-23}$

R^1	R^3		I	II	III	
O	Me	PPh$_3$, 8 h	(54)	(4)	(8)	318
H$_2$	Me	PPh$_3$, KOAc	(61)	(7)	(10)	319
O	Et	PPh$_3$, 8 h	(57)	(4)	(7)	318
H$_2$	Et	PPh$_3$, KOAc	(62)	(1)	(7)	319
O	i-Pr	PPh$_3$, 8 h	(75)	(3)	(4)	318
H$_2$	i-Pr	PPh$_3$, KOAc	(72)	(1)	(2)	319
O	Bn	PPh$_3$, 8 h	(58)	(3)	(4)	318
O	Bn	P(tol-o)$_3$, 8 h	(11)	(3)	(41)	318
H$_2$	Bn	PPh$_3$, KOAc	(58)	(1)	(3)	319

C$_{17}$

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 48 h	(62)	245
Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 36 h	(52)	245
Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux, 18 h	(72)	60

C$_{13-24}$

R	Conditions	Temp	Time	I	II	III	IV	
H	PPh$_3$	120°	6 h	(24)	(<2)	(0)	(0)	
H	PPh$_3$, K$_2$CO$_3$	reflux	6 h	(14)	(14)	(0)	(0)	
i-Pr	(R)-BINAP, K$_2$CO$_3$	reflux	21 h	(33)	(1)	(0)	(0)	
Ph	P(tol-o)$_3$	120°	4 h	(45)	(15)	(18)	(15)	323, 324
2-O$_2$NC$_6$H$_4$	P(tol-o)$_3$, K$_2$CO$_3$	reflux	5 h	(31)	(10)	(0)	(0)	
4-O$_2$NC$_6$H$_4$	P(tol-o)$_3$	120°	5 h	(30)	(11)	(0)	(0)	
4-MeOC$_6$H$_4$	P(tol-o)$_3$	120°	3 h	(28)	(9)	(35)	(25)	
4-MeOC$_6$H$_4$	(R)-BINAP	120°	6.5 h	(40)	(13)	(24)	(0)	
n-C$_7$H$_{15}$	(R)-BINAP	120°	48 h	(20)	(20)	(5)	(0)	
n-C$_7$H$_{15}$	(R)-BINAP, K$_2$CO$_3$	reflux	48 h	(27)	(1)	(0)	(0)	

C$_{17-23}$

Conditions	R^1	R^2	R^3	R^4	Time		
Pd(OAc)$_2$, Ph$_3$P, K$_2$CO$_3$, CH$_3$CN, reflux	H	H	CO$_2$Et	H	18 h	(66)	
	OTBS	H	CO$_2$Et	H	—	(71)	335
	H	OTBS	CO$_2$Et	H	—	(86)	
	H	OTBS	H	CO$_2$Et	—	(90)	

C$_{18}$

Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, 80°, 10 h	(90)	336

TABLE 1. EXO-CYCLIZATIONS (Continued)
C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₈

Pd(OAc)₂, n-Bu₄NCl, K₂CO₃, DMF, 60°

(79)

337

HBC, n-Bu₄NOAc, H₂O, CH₃CN, DMF, 110-120°, 20 h

(75)

333

Pd(OAc)₂, P(PPh₃)₃, Et₃N, CH₃CN, 70°, 6 h

(71) + (24)

338

C₁₈-₂₈

Pd(OAc)₂, PPh₃, n-Bu₄NHSO₄, Et₃N, DMF, 80°, 48 h

I + II

52

R	I	II
H	(68)	(0)
OEt	(16)	(12)
OC₆H₄(Bu-t)-p	(47)	(0)

C₁₉-₂₀

Pd(PPh₃)₄, Et₃N, CH₃CN, reflux

I + II

272

R¹	R²		Conditions	R³	Time	I	II
Br	CH₂		—	CH	1 h	(23)	(2)
I	CH₂		—	CH	1 h	(62)	(21)
I	CH₂		AgNO₃	CH	3.5 h	(97)	(0)
I	(CH₂)₂		—	CHCH₃	1 h	(57)	(29)
I	(CH₂)₂		AgNO₃, 7 h	CHCH₂	7 h	(94)	(0)

C₁₉

Pd(OAc)₂, PPh₃, K₂CO₃, Proton Sponge®, PhMe, 110°, 18 h

(82)

339

Pd(OAc)₂, PPh₃, K₂CO₃, Et₄NCl, CH₃CN, 80°, 40 h

(52)

340

Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 80°, 7 d

(61)

65

Pd(OAc)₂, K₂CO₃, DMF, 45-60°

I + II

341

PPh₃, Et₃N
Bu₄NBr

I	II
(18)	(49)
(49)	(10)

TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd$_2$(dba)$_3$, Et$_3$N, C$_6$H$_6$ 60°, 8 h	(13)	61
	Pd/C (10%), Et$_3$N, CH$_3$CN, 85°, 22 h	(14)	61
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, 80°, 10 h	(91)	61
	Pd$_2$(dba)$_3$·CHCl$_3$, P(tol-o)$_3$, K$_2$CO$_3$, Et$_4$NCl, tol, 120°, 3 h	(32) *E:Z* 85:15 H^1 dr 3:4	323, 324
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, t-BuOMe, reflux	(46) + (21)	38

C$_{19}$

| | Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, 80° | | 279 |

	I	II	III	I+II+III
TFP, 19 h	(—)	(—)	(—)	(79)
AsPh$_3$, 38 h	(0)	(0)	(44)	(44)
(*R*)-BINAP, cyclohexene, 20 h	(0)	(49) <10%ee	(0)	(49)
PPh$_3$, TlOAc, 17 h	(52)	(0)	(0)	(52)

| | Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, reflux, 90 min | (—) | 64 |

C$_{19-25}$

| | Pd(OAc)$_2$, PPh$_3$, n-Bu$_4$NHSO$_4$, Et$_3$N, DMF, 80°, 48 h | | 52 |

R
———
H
OEt
OC$_6$H$_4$(Bu-t)-p

	I	II
	(70)	(0)
	(15)	(13)
	(40)	(0)

TABLE 1. EXO CYCLIZATIONS (Continued)
C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{19}$	Pd(OAc)$_2$, PPh$_3$, PhCN, 125°, 3 h	(47) 1.54:1 dr	251
C$_{20}$	Pd(OAc)$_2$, PPh$_3$, TlOAc CH$_3$CN, 80°, 10 min	(90)	242, 312
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 50°, 3 h	(45) + (5)	334
C$_{20-28}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, THF, reflux, 15 h	(—) R / dr OMe 1.8:1 OTs 2.5:1 OTIPS 1.9:1 OMEM 1.7:1 NHCO$_2$Me 1.4:1 NEt$_2$ 1.7:1 SPh 2.0:1	38
C$_{20-22}$ 4:1 E:Z	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl CH$_3$CN, 80°	 R H (99) OMe (91)	342
C$_{20}$	Pd(OAc)$_2$, 80° KOAc, n-Bu$_4$NCl PPh$_3$, Ag$_2$CO$_3$	 Solv / Time / I / II DMF 48 h (10) (53) CH$_3$CN 4 d (72) (4)	65
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	(82)	64

TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Ag₂CO₃, THF, reflux, 15 h	(63–70)	37
	Pd(PPh₃)₄, K₂CO₃, n-Bu₄NCl, xylene, 85°, 16 h	(92)	296
	Pd(OAc)₂, PPh₃, Et₄NCl, K₂CO₃, CH₃CN	see below	250, 263
	Pd(PPh₃)₄, K₂CO₃, n-Bu₄NCl, xylene, 80–85°, 24 h	(68)	296
	Pd(PPh₃)₄, Et₃N, CH₃CN, 56°, 23 h	(75)	296
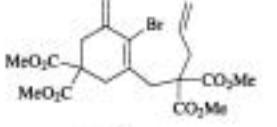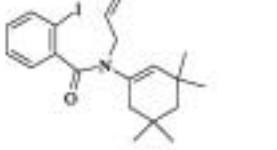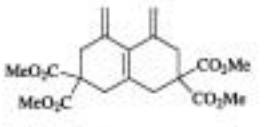
Temp	Time	I	II
50°	3 d	(18)	(32)
80°	36 h	(50)	(0)

C₂₁₋₂₈

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, P(tol-o)₃, Et₃N, CH₃CN	I + II + III	343, 344, 345

R¹	R²		Temp	Time	I	II	III
H	H	—	100°	18 h	(0)	(0)	(30)
MOM	MOM	—	100°	22 h	(83)	(0)	(0)
H	Me	n-Bu₄NCl	110°	26 h	(75)	(19)	(0)
H	TBDMS	—	100°	18 h	(64)	(0)	(4)
H	Bn	—	100°	26 h	(82)	(11)	(0)

C₃₁

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, Ph₃P, Et₃N, CH₃CN, reflux, 3 h	(35)	346
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, rt, 24 h	(81)	259
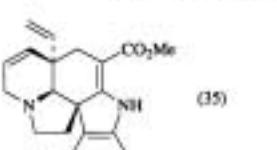
TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 2 h	(81)	347
C₂₂	Pd₂(dba)₃•CHCl₃, P(tol-*o*)₃, *i*-Pr₂NEt, BSA, DMF, 70°, 1 h	(67) + (10)	213
	Pd(OAc)₂, K₂CO₃, *n*-Bu₄NCl, CH₃CN, 80° — AgNO₃ or Ag₂CO₃	I + II Time I II; 3 h (50) (28); 24 h (36) (0)	231, 249
C₂₂₋₂₄	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux, 3 h	R¹ R² R³ R⁴; H H Br H (85); H Me I H (90); Me H I H (90); Me H I Me (89)	348
C₂₂	Pd(dppb), KOAc, DMA, 75°	(90)	349
C₂₂₋₂₃	HBC, *n*-Bu₄NOAc, DMF, CH₃CN, H₂O, 115°, 4.5 h	R; H (99); OMe (99)	72, 73
	Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN, reflux, 12 h	(90)	60
C₂₃	Pd(OAc)₂, PPh₃, TMEDA, 125°, 69 h	(27) + (8)	350
	Pd(dba)₂, P(tol-*o*)₃, K₂CO₃, MeCN, H₂O, 80°, 16 h	(65) + (3)	74
C₂₃₋₂₈	Pd(dppb), KOAc, DMA, 75°	R; Me (20); Ph (70)	351
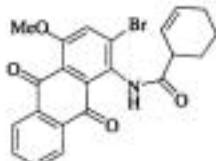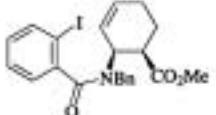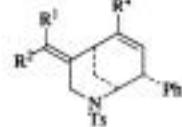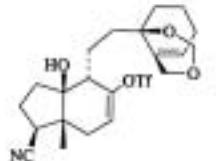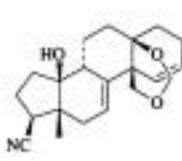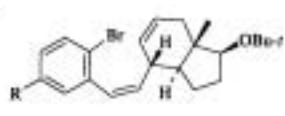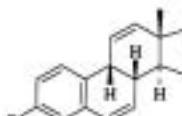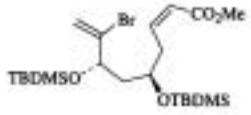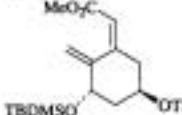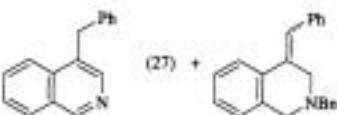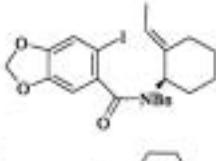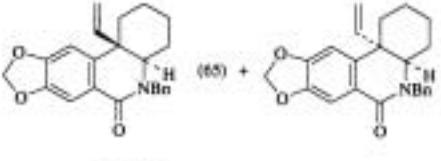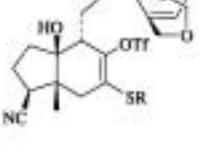
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TABLE 1. EXO CYCLIZATIONS (Continued)

C. 6-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{21}

| | Pd(OAc)$_2$, dppp or dppf, Ag$_2$CO$_3$, CH$_3$CN, 60° | (61) >98:<2 | 136 |

| | Pd(PPh$_3$)$_4$, K$_2$CO$_3$, CH$_3$CN, reflux | (92) | 58, 59, 60 |

| | Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux, 12 h | (72) | 60 |

C_{24}

| | Pd(OAc)$_2$, dppe, TlOAc, DMF, 68°, 36 h | (27) | 352 |

| | Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 23°, 15 h | (55) | 334 |

| | HBC, n-Bu$_4$NOAc, H$_2$O, CH$_3$CN, DMF, 115°, 15 h | (74) | 353 |

C_{25}

| | Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, 90°, 18 h | (93) | 161 |

C_{26-30}

| | Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux | R | 187 |

R	
CO$_2$Me	(80)
Ph	(92)

C_{28}

| | Et$_3$N, CH$_3$CN, reflux, 100°, 6 h | I + II + III + IV | 354 |

	I	II	III	IV
Pd(OAc)$_2$, P(tol-o)$_3$	(53)	(0)	(0)	(47)
Pd(PPh$_3$)$_4$	(1)	(50)	(46)	(0)
Pd(OAc)$_2$, dppp	(62)	(38)	(0)	(0)

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TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

Et₃N, CH₃CN, reflux, 100°, 6 h

354

R =

	I	II	III	IV
Pd(PPh₃)₄	(5)	(65)	(24)	(0)
Pd(OAc)₂, dppp	(87)	(1)	(0)	(7)

PdCl₂(dppp)₂, Ag₃PO₄, CaCO₃, DMF, 100°, 5 h — (77) — 355

C₂₇

Pd(OAc)₂, n-Bu₄NCl, K₂CO₃, DMF, 70°, 3 h — (74) — 93

C₂₈

Pd(OAc)₂, PPh₃, Et₃N, THF, reflux, 17 h — (6) + (56) — 307, 308, 309

Pd(OAc)₂, PPh₃, DMF, H₂O, HCO₂Na, 62° — (93) — 356

Pd(OAc)₂, DPPE, TlOAc, anisole, 135°, 7 h — (27) — 359, 360

C₂₉

α:β OH 5:1

Pd(OAc)₂, dppb, K₂CO₃, tol, 60°, 24 h — (56) + (6) — 357

Pd(dppb)₂, KOAc, DMAC, 120°, 30 h — (65) + (3) + (5-10) — 338

TABLE 1. EXO CYCLIZATIONS (*Continued*)
C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
OC$_6$H$_4$(Bu-t)-p	Pd(OAc)$_2$, PPh$_3$, Bu$_4$NHSO$_4$, Et$_3$N, DMF, 80°, 48 h	OC$_6$H$_4$(Bu-t)-p OTBDMS (55)	52
C$_{30}$	Pd(O$_2$CCF$_3$)$_2$(Ph$_3$P)$_2$, i-Pr$_2$NEt, xylene, 140°	(48)	358
	Pd(O$_2$CCF$_3$)$_2$(Ph$_3$P)$_2$, i-Pr$_2$NEt, xylene, 140°	R^1 R^2 / CH N (51) / N CH (51)	358
	Pd$_2$(dba)$_3$, dppb, KOAc, DMAC, 75°	(65–70)	361
C$_{34}$ OTf OTBDPS	Pd(OAc)$_2$, dppp, K$_2$CO$_3$, THF, 50°, 120 h	OTBDPS (42)	70, 71
OPMB OMOM NPMB OMOM	Pd(OAc)$_2$, DPPE, TlOAc, DMF, 140°, 7 h	OPMB OMOM OMOM NPMB (68)	46, 362, 363
C$_{36}$ TBDMSO TBDMSO NH MeO MeO	Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, H$_2$O	TBDMSO TBDMSO NH MeO MeO (32)	364
SEMO SEMO NH MeO MeO	Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, H$_2$O, 80°	SEMO SEMO MeO MeO (64)	365
C$_{38}$ MOMO OTf OTBDPS	Pd(OAc)$_2$	MOMO OTBDPS I + MOMO OTBDPS II	137

	Solv	Temp	Time	I	II
PPh$_3$, KOAc, TPAB	DMSO	85°	14 h	(35)	(23)
dppp, K$_2$CO$_3$	tol	100°	7 h	(5)	(85)

TABLE 1. EXO CYCLIZATIONS (*Continued*)

C. 6-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{39}	Pd(O$_2$CCF$_3$)$_2$(PPh$_3$)$_2$, PMP, tol, 120°	(60)	162

[a] A second product (12%) appeared to be a Diels-Alder dimer of unknown structure.

[b] An isomer of undetermined stereochemistry was also formed.

TABLE 1. EXO CYCLIZATIONS (*Continued*)

D. 7-EXO CYCLIZATIONS

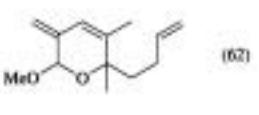| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 100°	R Time I 5 h (60) Br 4 h (60)	81, 82

C_{12-26}

Pd(OAc)$_2$, PPh$_3$, Et$_3$N

366

R^1	R^2	R^3	R^4	Solv	Temp	Time	I	II	III
H	H	H	CO$_2$Me	THF	reflux	60 h	(32)	(20)	(0)
H	H	H	CO$_2$Me	THF	reflux	4 h	(76)	(9)	(14)
Me	H	H	CO$_2$Me	THF	reflux	—	(89)	(0)	(0)
Bn	H	H	CO$_2$Me	THF	reflux	—	(95)	(0)	(0)
H	Bn	H	CO$_2$Me	THF	reflux	—	(96)	(0)	(0)
CH$_2$OBn	H	H	CO$_2$Me	THF	reflux	—	(89)	(0)	(0)
CH$_2$(2-indolyl)	H	H	CO$_2$Me	THF	reflux	—	(89)	(0)	(0)
(CH$_2$)$_4$NHCbz	H	H	CO$_2$Me	THF	reflux	—	(100)	(0)	(0)
2-(S)-N-methyl-pyrrolidinyl	H	H	CO$_2$Me	THF	reflux	—	(100)	(0)	(0)
CH$_2$(2-indolyl)	H	Me	CO$_2$Me	THF	reflux	—	(72)	(0)	(0)
H	Bn	Bn	CO$_2$Me	THF	reflux	—	(79)	(0)	(0)
H	Bn	H	Ph	DMF	100°	2 h	(64)	(0)	(0)

TABLE 1. EXO CYCLIZATIONS (*Continued*)

D. 7-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12}

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux — (96) — 75

C_{13}
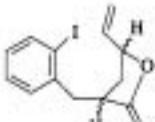
Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 82°, 18 h — (9) — 367
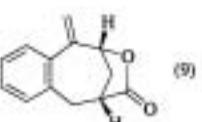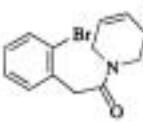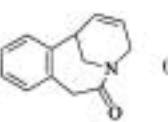
Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 36 h — (60) — 68
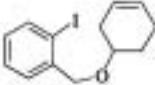
PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, CH$_3$CN, reflux, 9 h — (84) — 76
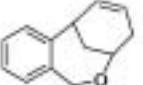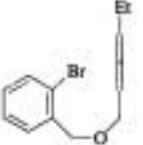
Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 100°, 4 h — (61) — 81, 82
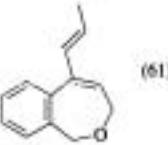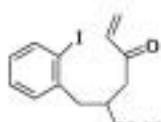
Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 82°, 30 min — (61) + (7) — 367
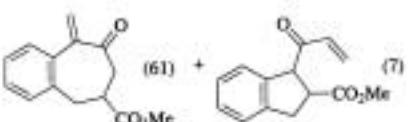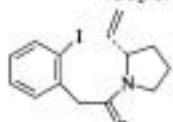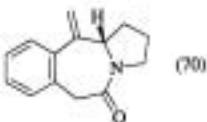
Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 1 h — (70) — 310, 311
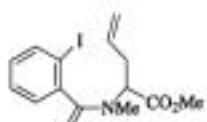
Pd(OAc)$_2$, PPh$_3$, n-Bu$_4$NCl, KOAc, DMF, 70°, 2 h — (55) — 178
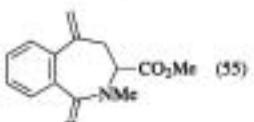
C_{14-18}
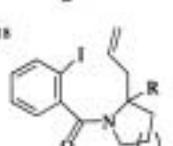
Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 2 h
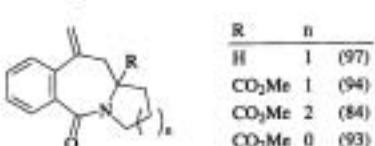
R	n	
H	1	(97)
CO$_2$Me	1	(94)
CO$_2$Me	2	(84)
CO$_2$Me	0	(93)

311

C_{15-17}

R^1	R^2
H	H
Me	H
Me	Me
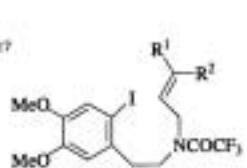
Pd(OAc)$_2$, PPh$_3$, n-Pr$_4$NBr, KOAc, DMF, 80°

I + II

368

Time	I		II
12 h	(92)		(0)
2 h	(43)	1.23:1 *E:Z*	(49)
2 h	(23)		(53)

296

297

TABLE 1. EXO CYCLIZATIONS (Continued)
D. 7-EXO CYCLIZATIONS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C15

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 82°, 4 h — (56) + (17) — 252

C16-29

Pd(PPh₃)₂Cl₂

Solv	Temp	Time	I	II	III	IV	
R¹ H, R² H	NaOAc	DMA	125°	30 min	(48)	(11)	(8)	(0)	190
R¹ H, R² H	NaOAc	DMF	85°	45 min	(58)	(13)	(2)	(0)	190
R¹ H, R² H	NaOAc	CH₃CN	90°	48 h	(75)	(6)	(0)	(0)	190, 369
R¹ OBn, R² H	NaOAc	CH₃CN	90°	68 h	(53)	(tr)	(0)	(13)	190, 369
R¹ OBn, R² CO₂Bn	NaOAc	CH₃CN	90°	144 h	(34)	(11)	(0)	(19)	190
R¹ OBn, R² CO₂Bn	NaOAc	CH₃CN	90°	79 h	(70)	(13)	(0)	(5)	190, 369
R¹ OBn, R² CO₂Bn	i-PrNEt₂	CH₃CN	90°	10 h	(44)	(20)	(0)	(0)	190

C16

Pd(OAc)₂, dppp, PBu₃, Ag₂CO₃, DMF, reflux, 3 h — (51) — 310

Pd(OAc)₂, PPh₃, K₂CO₃, n-Bu₄NCl, CH₃CN, 82°, 24 h — (28) + (20) + (10) + (1) — 252

C16

6:1 E:Z

	I	II	I:II
Pd(OAc)₂, PPh₃, KOAc, NPr₄Br, DMF	(—)	(—)	1:1
Pd₂(dba)₃, PPh₃, Ag₂O, DMF	(—)	(—)	1.4:1

— 159

Pd(PPh₃)₄, K₂CO₃, n-Bu₄NCl, xylene, 83°, 15 h — (57) — 296

C17

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux — (51) + (<20)ᵉ — 310, 311

TABLE 1. EXO CYCLIZATIONS (*Continued*)

D. 7-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{17-19}

HBC, *n*-Bu$_4$NOAc, H$_2$O, CH$_3$CN, DMF

R^1	R^2
—CH$_2$—	CH$_2$
—CH$_2$—	CH$_2$CH$_2$
CH$_3$, CH$_3$	CH$_2$CH$_2$

Temp	Time		
120°	7 h	(81)	77, 78, 79
110-120°	3-7 h	(84)	79
110-120°	3-7 h	(87)	79

C_{17}

HBC, *n*-Bu$_4$NOAc, H$_2$O, CH$_3$CN, DMF, 110-120°, 5 h

 (81) 370

1. Pd(OAc)$_2$, PPh$_3$, *n*-Bu$_3$SnH, THF, 0°, 1 h
2. Et$_4$NCl·H$_2$O, CH$_3$CN, reflux

 (50) 233

Pd(OAc)$_2$, PPh$_3$, TPAB, KOAc, DMF, 80°

 (46) + (8) 314

 (1)

Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 120°, 4 h

 (58) 81, 82

Pd$_2$(dba)$_3$·CHCl$_3$, dppb, KOAc, DMF, 90°, 16 h

 (33) + (28) 268

C_{18-22}

PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, DMF, 100°

 I + II 371

R^1	R^2	R^3
Ts	H	CO$_2$Me
H	CO$_2$Et	CO$_2$Me
Ts	H	CO$_2$Me

Time	I	II
7 h	(67)	(0)
7 h	(49)	(0)
—	(0)	(—)

C_{18}

Pd(PPh$_3$)$_2$(OAc)$_2$, Et$_3$N, THF, 70°

 (52) 80

Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 120°, 4 h

 (65) 81, 82

TABLE 1. EXO CYCLIZATIONS (*Continued*)
D. 7-EXO CYCLIZATIONS (*Continued*)

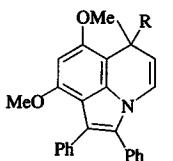| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{18}	HBC, *n*-Bu$_4$NOAc, H$_2$O, CH$_3$CN, DMF, 140°, 30 h	(55) dr 1.1:1	333
	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, EtOH, DMF, 120°, 3 h	(66)	82
C_{19}	PdCl$_2$(PPh$_3$)$_2$, K$_2$CO$_3$, EtOH, DMF, 120°, 22 h	(58)	81, 82
	PPh$_3$, DMF, 80°		159, 160

Time	I	II
Pd(OAc)$_2$, KOAc, NPr$_4$Br	6 h	(70) (4)
Pd$_2$(dba)$_3$, Ag$_2$O	24 h	(4) (72)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21}	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, *n*-Bu$_4$NCl, xylene, 85°, 11 h	(56)	296
C_{22}	Pd(OAc)$_2$, dppp, BnEt$_3$NCl, K$_2$CO$_3$, CH$_3$CN, reflux, 4 d	(17) + (66)	372, 373
	Pd(PPh$_3$)$_4$, Ag$_2$CO$_3$, *n*-Bu$_4$NCl, xylene, 85°, 5 h	(38)	296
C_{23}	Pd(OAc)$_2$, dppp, BnEt$_3$NCl, K$_2$CO$_3$, CH$_3$CN, reflux, 4 d	(70)	373
	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, 100°, 13 h	(44) + (23)	398
	Pd(OAc)$_2$, PPh$_3$, PhCN, 125°, 6 h	(38)	251

TABLE 1. EXO CYCLIZATIONS (*Continued*)
D. 7-EXO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₄	Pd(OAc)₂, PPh₃, Et₃N, DMF, 100°, 2 h	(55) + (29)	366
	Pd(OAc)₂(PPh₃)₂, Et₃N, THF, reflux, 96 h	(92)	164
C₂₆	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 120°, 28 h	(54) + (16)	374
C₂₇₋₂₉	Pd(PPh₃)₄, Et₃N, CH₃CN, 130°, 14 h	R: H (89), CO₂Me (90)	375
C₂₈₋₃₁	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 120°	I + II	82

R
CH=CH₂
CH₂CH=CH₂
CH₂C≡C—CH₃

Time	I	II
18 h	(31)	(16)
23 h	(66)	—
18 h	(69)	—

C₂₉₋₃₁	Pd(PPh₃)₄, Me₃NBnCl, Et₃N, CH₃CN, 48 h	R Temp: H 120° (74), Ac 110° (92)	376, 377
C₃₈	Pd(OAc)₂(PPh₃)₂, Et₃N, THF, reflux, 72 h	(85)	164

* A third product of undetermined structure was formed.

TABLE 1. EXO CYCLIZATIONS *(Continued)*

E. 8-EXO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12-14}	$PdCl_2(PPh_3)_2$, K_2CO_3, EtOH, DMF, 100°	 Time **I** **II** 2 h (52) (0) 3 h (35) 66%Z (41) 3 h (35) 100%E (41)	81, 82
C_{19}	$PdCl_2(PPh_3)_2$, K_2CO_3, EtOH, DMF, 120°, 22 h	(56)	81, 82
C_{21}	$Pd(PPh_3)_2Cl_2$, K_2CO_3, n-Bu$_4$NCl, DMF, 80–120°, 27 h	(23)	82
C_{22}	$Pd(OAc)_2$, K_2CO_3, 80°, 46 h	(80)	80
C_{26}	$Pd(PPh_3)_4$, K_2CO_3, CH_3CN, reflux, 36 h	(70)	378
C_{27}	$Pd(PPh_3)_4$, K_2CO_3, CH_3CN, reflux, 32 h	(78)	378
C_{36}	$Pd(PPh_3)_4$, K_2CO_3, 4 Å MS, CH_3CN, 90°, 16.5 h	(49)	165, 166
C_{38}	$Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 85°, 5 h	(50)	379

TABLE 1. EXO CYCLIZATIONS (Continued)

E. MACROCYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-14} 9-exo	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF		82

$\dfrac{R}{O}$

CH₂

I + II

Temp	Time	I	II
60°	41 h	(33)	(18)
120°	12 h	(55)	(0)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{15-20}	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 120°		82

R	ring size
C(CO₂Et)₂	9-exo
(CH₂)₂	10-exo
(CH₂)₃	11-exo

Time		
42 h	(62)	E:Z 100:0
16 h	(48)	E:Z 73:27
12 h	(40)	E:Z 100:0

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21-27}	1. Pd(OAc)₂, PPh₃, n-Bu₃SnH, THF, 0°, 1 h 2. Et₄NCl·H₂O, CH₃CN, reflux		233

n	ring size	
5	11	(40)
6	12	(44)
7	13	(43)
9	15	(46)
11	17	(46)

Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C_{26}	12-exo	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 80°, 29 h	(50)	82
	12-exo	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 120°, 60 h	(27)	82
C_{37}	20-exo	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 120°, 5 h	(86)	82
	20-exo	Pd(PPh₃)₂Cl₂, K₂CO₃, n-Bu₄NCl, DMF, 80°, 37 h	(47)	82

TABLE 2. ENDO CYCLIZATIONS
A. 5-ENDO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{3-13}

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 85°, 1-3 h

R^1	R^2	
CO$_2$Me	H	(24)
Ts	H	(39)
CO$_2$Me	Me	(41)
CO$_2$Me	n-C$_6$H$_{13}$	(68)
CO$_2$Me	CH$_2$OMe	(65)
CO$_2$Me	Ph	(69)

Ref. 380

C_{10-22}

Pd(OAc)$_2$, Et$_3$N

R^1	R^2	R^3	R^4	R^5	R^6	Conditions	Temp	Time		Refs.
H	H	H	Br	H	Me	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(95)	381
H	H	H	Br	H	OEt	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(96)	381
H	OMe	H	Br	H	Me	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(80)	381
H	OMe	H	Br	H	OEt	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(82)	381
H	H	CO$_2$Me	Br	H	Me	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(95)	381
H	H	CO$_2$Me	Br	H	OEt	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(93)	381
CO$_2$Me	H	H	Br	H	Me	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(84)	381
CO$_2$Me	H	H	Br	H	OEt	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(85)	381
H	CO$_2$Me	H	Br	H	Me	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(86)	381
H	CO$_2$Me	H	Br	H	OEt	P(tol-o)$_3$, CH$_3$CN	100°	20 h	(90)	381
H	H	H	I	H	Me	DMF	120°	12 h	(70)	382
H	H	H	I	H	OEt	DMF	120°	2 h	(78)	382
H	H	H	I	Me	Me	DMF	120°	6 h	(49)	382
H	H	H	Br	Me	Me	P(tol-o)$_3$, DMF	120°	6 h	(35)	382
H	H	H	I	Me	Ph	DMF	120°	4 h	(43)	382
H	H	H	Br	Me	Ph	P(tol-o)$_3$, DMF	120°	4 h	(36)	382
H	H	H	I	Me	OMe	DMF	120°	7 h	(65)	382
H	H	H	I	Me	OEt	DMF	120°	8 h	(73)	382
H	H	H	Br	Me	OEt	P(tol-o)$_3$	120°	8 h	(65)	382
H	H	H	I	CH$_2$CO$_2$Et	OEt	DMF	120°	4 h	(45)	382
H	H	H	Br	CH$_2$CO$_2$Et	OEt	P(tol-o)$_3$	120°	4 h	(35)	382
H	H	H	I	CO$_2$Me	OMe	DMF	120°	3 h	(82)	382
H	H	H	Br	CO$_2$Me	OMe	P(tol-o)$_3$	120°	3 h	(69)	382
H	H	H	I	CO$_2$Et	OEt	DMF	120°	3 h	(88)	382
H	H	H	I	Ph	Ph	DMF	120°	24 h	(78)	382
H	H	H	Br	Ph	Ph	P(tol-o)$_3$	120°	24 h	(71)	382
H	H	H	I	H	OMe	DMF	120°	2 h	(83)	382

C_{11}

Pd(OAc)$_2$, PPh$_3$, NaHCO$_3$, DMF, 110°, 16 h

 (36)

313

C_{13-16}

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 85°, 1-3 h

R^1	R^2	
CO$_2$Me	H	(68)
Ts	H	(35)
CO$_2$Me	CH$_2$OMe	(73)

380

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

A. 5-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C12-17

R¹	R²	R³	R⁴	R⁵		Time	
H	H	H	H	CO₂Et	PPh₃	25.5 h	(100)
H	Me	H	H	CO₂Et	PPh₃	9 h	(78)
H	OMe	OMe	H	CO₂Et	PPh₃	18 h	(63)
Me	H	H	H	CO₂Et	P(tol-o)₃	19.5 h	(81)
H	Me	H	Me	CO₂Et	P(tol-o)₃	45 h	(87)
OMe	H	H	H	CO₂Et	P(tol-o)₃	11 d	(55)
H	OMe	H	H	CO₂Et	P(tol-o)₃	20 h	(84)
H	H	H	H	COMe	P(tol-o)₃	4 d	(66)
H	H	H	H	COPh	P(tol-o)₃	4 d	(79)
H	H	H	H	CN	P(tol-o)₃	4 d	(55)
OH	H	H	H	CO₂Et	P(tol-o)₃	5 d	(50)

Conditions: Pd(OAc)₂, Et₃N, CH₃CN, reflux. Ref. 383

C12-14

Pd(OAc)₂, Et₃N, DMF, 120°, 1 h — Ref. 382

R¹	R²		
I	H	—	(82)
Br	H	P(tol-o)₃	(65)
I	Me	—	(82)

C12-20
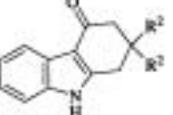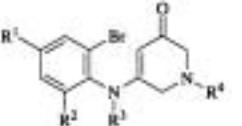
Conditions: Pd(PPh₃)₄, NaHCO₃ / Pd(OAc)₂, PPh₃, NaHCO₃

R¹	R²	R³	R⁴	Catalyst	Solv	Temp	Time		Refs.
H	H	H	Bn	Pd(PPh₃)₄, NaHCO₃	HMPA	140°	2 h	(72)	384
Me	H	H	Bn	"	HMPA	140°	2 h	(70)	384
Me	Me	H	Bn	"	HMPA	140°	2 h	(74)	384
H	H	H	CO₂Et	"	HMPA	140°	2 h	(73)	384
Me	H	H	CO₂Et	"	HMPA	140°	2 h	(75)	384
Me	Me	H	CO₂Et	"	HMPA	140°	2 h	(76)	384
H	H	H	Me	Pd(OAc)₂, PPh₃, NaHCO₃	DMF	—	—	(9)	385
H	H	Et	H	"	DMF	—	—	(15)	385
H	H	Et	Me	"	DMF	—	—	(32)	385
Me	H	Et	H	"	DMF	—	—	(14)	385
Me	H	Et	Me	"	DMF	—	—	(36)	385

C13
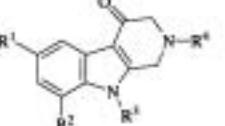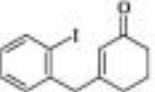
Pd(OAc)₂(PPh₃)₂, NaHCO₃, DMF, 80° — (68) — Ref. 64

C14

Pd(OAc)₂, PPh₃, Et₄NCl, K₂CO₃, LiCl, DMF, 100°, 5 h — I + II + III (25) — Ref. 258

I, II, III

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

A. 5-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	(65)	64
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 6 d	(48)	245
	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN	(63)	64
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 48 h	(52)	245
C$_{16}$	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, rt, 2 h	(97)	386
C$_{17}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 85°	(94)	380
C$_{18-20}$	Pd(OAc)$_2$, PPh$_3$, NaHCO$_3$, DMF	R^1 R^2 H Me (8) Et H (100) Et Me (35)	385
C$_{18-23}$	Pd(OAc)$_2$, DMF		84
R			
H	Et$_3$N, 110°	(30)	
Ac	Et$_3$N, 110°	(30)	
THP	NaHCO$_3$, n-Bu$_4$NCl, 25°	(46)	
C$_{23}$	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, rt, 12 h	(96)	85

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

B. 6-ENDO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₉₋₁₃

i-Pr₂NEt, CH₃CN — I + II + III — 261

	R¹	R²		Temp	Time	I	II	III
	I	Bn	PdCl₂, TPPTS, H₂O	65°	14 h	(59)	(2)	(0)
	Br	Bn	PdCl₂, TPPTS, H₂O	70°	24 h	(60)	(5)	(0)
	Br	Bn	Pd(OAc)₂, PPh₃, Ag₂CO₃	90°	20 h	(8)	(52)	(0)
	Br	Ts	PdCl₂, TPPTS, H₂O	reflux	24 h	(49)	(0)	(21)
	I	Ts	PdCl₂, TPPTS, H₂O	reflux	24 h	(44)	(0)	(15)
	Br	allyl	PdCl₂, TPPTS, H₂O	70°	14 h	(59)	(32)	(0)
	Br	allyl	Pd(OAc)₂, PPh₃, Ag₂CO₃	80°	20 h	(0)	(77)	(0)
	I	allyl	Pd(OAc)₂, TPPTS, H₂O	50°	10 h	(66)	(16)	(0)
	I	allyl	Pd(OAc)₂, TPPTS, H₂O	80°	10 h	(71)	(8)	(0)

C₁₀

PdCl₂, TPPTS, i-Pr₂NEt, H₂O, CH₃CN, reflux — (65) + (18) — 75

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 80°, 4 h — (46) + (46) — 245

C₁₁

PdCl₂, TPPTS, i-Pr₂NEt, CH₃CN, H₂O, 90°, 24 h — (30) — 261

C₁₁₋₁₇

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux

R¹	R²	Time	
H	H	10 h	(99)
Me	H	—	(95)
Ph	H	—	(94)
—CH₂NMe(CH₂)₂—		12 h	(99)
—(CH₂)₄—		—	(88)

86

C₁₂

Pd(OAc)₂, P(tol-o)₃, Et₃N, CH₃CN, 110°, 72 h — (49) — 230

C₁₂₋₂₉

1. Pd(OAc)₂, PPh₃, K₂CO₃, n-Bu₄NCl, DMF, 100°, 15 h
2. O₃, DCE, rt, 48 h

I

R¹	R²	R³	R⁴	I
CH₂O₂CC₆H₄OMe-p	O	Ts	n-Bu	(58)
CH₂O₂CC₆H₄OMe-p	O	COMe	n-Bu	(56)
CH₂O₂CC₆H₄OMe-p	O	CO-N-pyrrolidinyl	n-Bu	(30)
H	O	CO₂Me	Me	(52)
H	O	CO₂Me	Et	(74)

235

| CH₂O₂CC₆H₄OMe-p | H,H | CO₂Me | n-Bu | Pd(OAc)₂, PPh₃, K₂CO₃, n-Bu₄NCl, DMF, 100°, 15 h | I (86) | 235 |

C₁₅

Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, reflux — (57) + (15) + (11) — 86

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

B. 6-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PdCl$_2$, TPPTS, *i*-Pr$_2$NEt, H$_2$O, CH$_3$CN, reflux	(28) + (10) + (20) + (6)	75
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, rt, 9 h	(62)	254
C$_{14}$	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, H$_2$O, THF, 80°	(90)	387
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 80°	(42) + (58)	257
	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 100°, 12 h	(72) + (22)	388
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux	(35) + (50)	86
	Pd(PPh$_3$)$_4$, K$_2$CO$_3$, CH$_3$CN, 80°, 48 h	(20) + (23)	267
C$_{16}$	Pd(OAc)$_2$, NaHCO$_3$, *n*-Bu$_4$NCl	(15)	89
C$_{17}$	Pd(OAc)$_2$, KOAc, *n*-Bu$_4$NCl, DMF, 100°	(50)	389
	Pd(OAc)$_2$	I II	390
	Na$_2$CO$_3$, Et$_4$NCl, DMF	(54) (1)	
	PPh$_3$, CH$_3$CN	(24) (56)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{17-21}

R^1	R^2	R^3	R^4	R^5	R^6		Solv	Temp	Time	I	II	
H	CH	H	Br	H	OMe	Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, Et$_4$NCl	CH$_3$CN	reflux	—	(67)	(0)	249, 390
H	CH	H	I	H	OMe	Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, Et$_4$NCl	CH$_3$CN	reflux	—	(67)	(0)	249, 250, 390
H	N	H	Cl	H	OMe	Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, Et$_4$NCl	CH$_3$CN	reflux	—	(40)	(0)	249
H	CH	H	I	H	—OCH$_2$O—	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$	CH$_3$CN	80°	14 h	(44)	(0)	249
OMe	CH	OMe	I	H	—OCH$_2$O—	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl	DMF	100°	4.75 h	(55)	(0)	249, 250
OMe	CH	OMe	I	H	OMe	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl	CH$_3$CN	80°	24 h	(38)	(0)	249, 250
H	CH	H	I	H	H	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$	CH$_3$CN	80°	2 h	(57)	(0)	250
H	CH	H	I	Me	H	Pd, PPh$_3$, K$_2$CO$_3$	DMF	100°	1 h	(16)	(64)	249
H	CH	H	I	Me	H	Pd, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl	CH$_3$CN	80°	1 h	(8)	(83)	249

C_{18}

Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, 85°, 4 h

(89)

391

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°, 12 h

(62)

249

C_{18-21}

Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN

R	Temp	Time		
H	—	—	(50)	391
CO$_2$Et	100°	24 h	(64)	

C_{19}

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°, 24 h

(32)

249, 250

C_{21}

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 6 d

(63) + (37)

392

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, reflux, 6 d

(87)

393

C_{22}

Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$

Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, DMF, 90°, 5 h

(75)

191, 192

C_{22-34}

Pd(OAc)$_2$, KOAc, Bu$_4$NCl, DMF

R	Temp	Time		
H	100°	2 h	(71)	364, 394
OTBS	—	—	(64)	

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

B. 6-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{25}	Pd(OAc)$_2$, P(tol-*o*)$_3$, Et$_3$N, CH$_3$CN, 100°, 15 h	(96)	87
C_{26-27}	Pd(OAc)$_2$, P(tol-*o*)$_3$, Et$_3$N, CH$_3$CN, 100°, 15 h	$\begin{array}{ll} R & \\ \hline H & (92) \\ Me & (78) \end{array}$	87
n-Bu	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, THF, reflux, 1 h	(49) + (21)	65
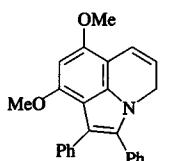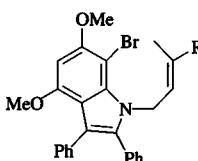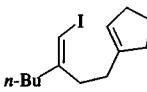
TABLE 2. ENDO CYCLIZATIONS (*Continued*)

C. 7-ENDO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}	PdCl$_2$, TPPTS, *i*-Pr$_2$NEt, H$_2$O, CH$_3$CN, reflux	(71) + (14)	75
C_{14}	HBC, *n*-Bu$_4$NOAc, H$_2$O, DMF, CH$_3$CN, reflux, 2 h	(70)	315
C_{14-17}	Pd(OAc)$_2$, NaHCO$_3$, *n*-Bu$_4$NCl, 3 Å MS	$\begin{array}{lllll} R & Solv & Temp & Time & \\ \hline Ac & CH_3CN & 95° & 16.5\,h & (54) \\ Boc & DMF & 110° & 16\,h & (55) \end{array}$	88, 89, 90
C_{15}	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, DMF, 100°, 12 h	(53)	388
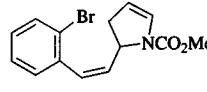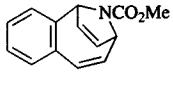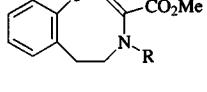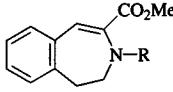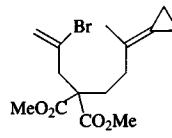
TABLE 2. ENDO CYCLIZATIONS (*Continued*).

C. 7-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{20-22}$	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, CH$_3$CN, 80°, 48 h		395

R		I:II
OBn	(70)	5:1
N-Phth	(74)	6:1
	(70)	1:1

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{25-36}$			364

R^1	R^2		I	II
H	4-MeOC$_6$H$_4$	Pd(OAc)$_2$, P(tol-*o*)$_3$, Et$_3$N, CH$_3$CN, H$_2$O, 80°	(26)	(46)
H	4-MeOC$_6$H$_4$	Pd(OAc)$_2$, *n*-Bu$_4$NCl, KOAc, DMF, 100°	(48)	(0)
OTBDMS	*c*-C$_6$H$_{11}$	Pd(OAc)$_2$, *n*-Bu$_4$NCl, KOAc, DMF	(58)	(0)

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

D. 8-ENDO CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	PdCl$_2$, TPPTS, *i*-Pr$_2$NEt, H$_2$O, CH$_3$CN, reflux	(55) + (22)	75
C$_{15-18}$	Pd(OAc)$_2$, NaHCO$_3$, *n*-Bu$_4$NCl, 3Å MS		88, 89, 90
C$_{18}$	Pd(OAc)$_2$, *n*-Bu$_4$NCl, KOAc, DMF	(68)	364
C$_{23}$	Pd(OAc)$_2$, P(tol-*o*)$_3$, Et$_3$N, CH$_3$CN, reflux, 6 h	(59) + (15) + (15)	396, 397

R	Solv	Temp	Time	
Ac	CH$_3$CN	95°	16.5 h	(60)
Boc	DMF	105°	16 h	(73)

TABLE 2. ENDO CYCLIZATIONS (*Continued*)
D. 8-ENDO CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{24}	Pd(OAc)$_2$, *n*-Bu$_4$NCl, KOAc, DMF	(30)	364
C_{25-28}	Pd(OAc)$_2$, *n*-Bu$_4$NCl, KOAc, DMF		398
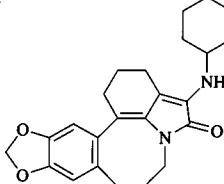
R^1	R^2
H	CO$_2$Et
Me	CO$_2$Et
H	SO$_2$Ph
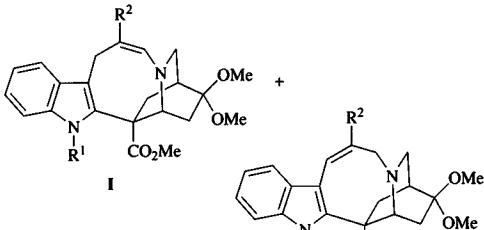
Temp	Time	I	II
40-80°	2 h	(18)	(12)
80°	6 h	(89)	(0)
—	—	(14)	(0)

TABLE 2. ENDO CYCLIZATIONS (*Continued*)
E. MACROCYCLIZATIONS

Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16-19}	9-endo	Pd(OAc)$_2$, NaHCO$_3$, *n*-Bu$_4$NCl, 3Å MS		88, 89, 90
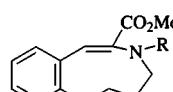
R	Solv	Temp	Time	
Ac	CH$_3$CN	95°	16.5	(58)
Boc	DMF	110°	16 h	(86)

C_{29}	13-endo	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, *n*-Bu$_4$NCl, DMF, 80°, 35 h	(18) + (37) + dimer (<5)	82
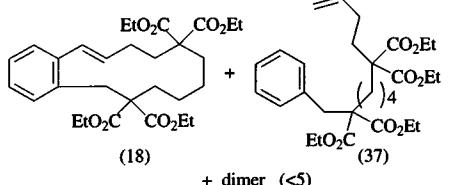
C_{37-38}	13-endo	Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, THF		
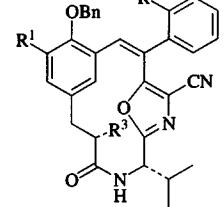
R^1	R^2	R^3	R^4		Temp	Time		Refs.
H	I	NHBoc	H	—	75°	—	(6)	167
H	I	NHBoc	OH	2-(di-*tert*-butylphosphanyl)-biphenyl	90°	—	(69)	167, 168
H	I	NHBoc	OMe	—	75°	—	(2)	167
Br	Br	NHBoc	OH	—	75°	12 h	(12)	167

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

E. MACROCYCLIZATIONS (*Continued*)

Substrate		Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}	16-endo	PdCl$_2$(CH$_3$CN)$_2$, CH$_3$CN, 25°, 11 h	(55)	399
C_{30-32}		Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, 85°	n 1 18-endo (24) 3 20-endo (16)	83
C_{54}	20-endo	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 37°	(—)	179
C_{37}	21-endo	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, n-Bu$_4$NCl, DMF, 120°, 12 h	(66) + (<5)	82
	21-endo	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, n-Bu$_4$NCl, DMF, 80-120°, 36 h	(15) + (30) (30)	82

TABLE 2. ENDO CYCLIZATIONS (*Continued*)

E. MACROCYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{35-38}$

Pd(OAc)$_2$, P(tol-o)$_3$,
Et$_3$N, CH$_3$CN, 85°

n		Time	
1	22-endo	2 h	(42)
2	23-endo	—	(29)
4	25-endo	—	(24)
6	27-endo	—	(38)

83

TABLE 3A. 5-AROMATIC CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{9-10}$

R^1	R^2	R^3	R^4
Br	OH	H	H
I	OH	H	H
Br	OH	H	OH
Br	H	Me	OH

HBC, Cs$_2$CO$_3$, DMA

I + II + III   400

Temp	Time	I	II	III
70°	3 d	(41)	(41)	(15)
70°	2 d	(17)	(37)	(—)
65°	3 d	(77)	(0)	(—)
70°	1.5 d	(61)	(0)	(—)

C$_{11}$

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, reflux, 12 h

(80)   249

C$_{11-13}$

Pd(OAc)$_2$

I + II + PhOPh III

R^1	R^2	R^3	R^4	R^5		Temp	Time	I	II	III	
H	H	H	Br	N	Na$_2$CO$_3$, DMAC	170°	48 h	(10)	(0)	(0)	94
H	H	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	0.75 h	(74)	(0)	(0)	401
H	H	H	I	CH	NMI	190°	8 h	(95)	(0)	(5)	94
H	H	NO$_2$	Br	CH	Na$_2$CO$_3$, DMAC	170°	2 h	(78)	(0)	(0)	401
H	NO$_2$	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	3 h	(68)	(0)	(0)	401
NO$_2$	H	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	2 h	(78)	(0)	(0)	401
CN	H	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	1.5 h	(80)	(0)	(0)	401
CH$_2$OH	H	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	24 h	(56)	(0)	(0)	401
H	Me	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	0.75 h	(66)	(7)	(0)	401
CO$_2$H	H	H	Br	CH	Na$_2$CO$_3$, DMAC	170°	7 h	(66)	(0)	(0)	401

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 14 h	(51)	401a
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 10 h	(70)	401a
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 67 h	(31)	401a
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 67 h	(61)	401a
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 67 h	(47)	401a
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 67 h	(51)	401a
	HBC, Cs$_2$CO$_3$, DMA, 1 d		400
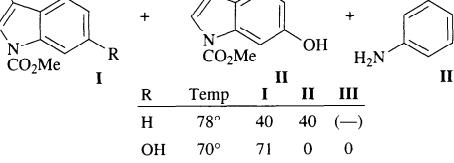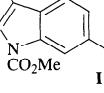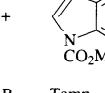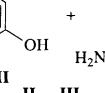
		R	Temp	I	II	III
		H	78°	40	40	(—)
		OH	70°	71	0	0

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 12 h	(62)	249

C$_{12}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMF, reflux, 15 h	(41)	401a

C$_{13}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Na$_2$CO$_3$, DMA, 170°, 22 h	+ PhOPh (—) I:II = 4:1	94
	Pd(OAc)$_2$, NMI, 190°, 4.5 h		94

		R	I	II
		Br	(99)	(1)
		I	(99)	(1)
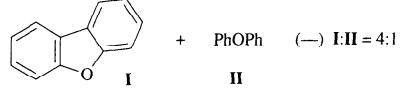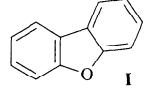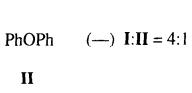
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, 150°, 7 h	(73)	94

C$_{14}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, ethyl acrylate, Et$_3$N, CH$_3$CN, 150°, 5 h		402

		R	
		O	(19)
		NH	(55)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{15}$

Pd(OAc)$_2$ or Pd(PPh$_3$)$_2$Cl$_2$, NaOAc, DMA, 130°

(92)

403

C$_{15-17}$

PdCl$_2$, Et$_3$N, reflux, 8 h

(75-95)

404

R^1	R^2	R^3
H	H	H
OMe	OMe	H
OMe	H	OMe

C$_{15-16}$

R^1	R^2	R^3	R^4	Conditions	Temp	Time		Refs.
Br	O	H	CH	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN	reflux	12 h	(80)	405
I	O	H	CH	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN	reflux	12 h	(80)	249
Br	O	CHO	CH	Pd(CH$_3$CN)$_2$(PPh$_3$)$_2$, TBAC, NaOCHO, DMF	90°	—	(48)	186
I	O	CHO	CH	Pd(CH$_3$CN)$_2$(PPh$_3$)$_2$, TBAC, NaOCHO, DMF	90°	—	(70)	186
Br	O	Me	CH	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN	reflux	4 h	(63)	249
I	O	Me	CH	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN	reflux	4 h	(63)	249
Br	H,H	H	CH	Pd(PPh$_3$)$_4$, KOAc, DMA	130°	10 h	(86)	405
Br	H,H	CHO	CH	Pd(PPh$_3$)$_4$, KOAc, DMF	110°	2.5 h	(87)	406
Br	H,H	CHO	N	Pd(PPh$_3$)$_4$, KOAc, DMF	110°	10 h	(25)	406
Br	H,H	CN	CH	Pd(PPh$_3$)$_4$, KOAc, DMF	110°	1.5 h	(87)	406

C$_{16}$

Pd(PPh$_3$)$_4$, KOAc, DMA, 130°, 8 h

(95)

405

Pd(CH$_3$CN)$_2$(PPh$_3$)$_2$, TBAC, NaOCHO, DMF, 90°

(60)

186

C$_{17}$

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 100°, 1 h

(59)

249

PdCl$_2$(PPh$_3$)$_2$, PPh$_3$, LiCl, DBU, DMF, 140°, 6 h

(90)

407

C$_{18}$

Pd(OAc)$_2$, K$_2$CO$_3$, DMA, 130°

(85)

403

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{19-21}$

Pd(PR$^3{}_3$)$_2$Cl$_2$, 140°

200

R^1	R^2	R^3		
Cl	OTf	Ph	DBU, LiCl, 6 h	(88)
Me	OTf	Ph	DBU, LiCl, 6 h	(92)
OMe	OTf	Ph	DBU, LiCl, 6 h	(94)
CO$_2$Me	OTf	Ph	DBU, LiCl, 6 h	(93)
Me	Br	Ph	NaOAc, DMA, 6 h	(85)
Me	Cl	Cy	DBU, DMA, 10 h	(72)
CO$_2$Me	Cl	Cy	NaOAc, DMA, 12 h	(79)

C$_{19}$

Pd(OAc)$_2$, *n*-Bu$_4$NBr, KOAc, CH$_3$CN, reflux, 3 h

(57) 408

C$_{20}$

Pd(OAc)$_2$, TBAC, NaHCO$_3$, DMF, rt, 30 h

(92) 409

Pd(OAc)$_2$, 90°

169, 170, 410, 411, 412

R		
Br	*n*-Bu$_4$NBr, KOAc, DMF, 3 h	(59)
I	K$_2$CO$_3$, *n*-Bu$_4$NBr, CH$_3$CN, 5 h	(47)

C$_{21}$

Pd(PPh$_3$)$_2$Cl$_2$, LiCl, DBU, DMF, 140°, 15 h

(52) 97

Pd(PPh$_3$)$_2$Cl$_2$, LiCl, DBU, DMF, 140°

(29) + (29) 97

C$_{21-22}$

Pd(PPh$_3$)$_2$Cl$_2$, LiCl, DBU, DMF, 140°

R^1	R^2	R^3		Time		Refs.
F	H	H	—	10 h	(55)	97
H	F	H	—	8 h	(72)	97, 407
H	H	F	—	15 h	(50)	97
H	H	H	—	6 h	(85)	97, 407
OMe	H	H	PPh$_3$, LiCl	14 h	(73)	97
H	OMe	H	PPh$_3$, LiCl	10 h	(62)	97, 407
H	H	OMe	PPh$_3$, LiCl	6 h	(42)	97

C$_{21}$

Pd(PPh$_3$)$_2$Cl$_2$, LiCl, DBU, DMF, 120°, 3 h

(64) 97

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(PPh₃)₂Cl₂, LiCl, DBU, DMF, 120°, 10 h	(93)	97
	Pd(PPh₃)₂Cl₂, LiCl, DBU, DMF, 120°, 10 h	(60) + (30)	97
	Pd(PPh₃)₂Cl₂, LiCl, DBU, DMF, 140°, 15 h	(84)	97, 407
C₂₂	Pd(PPh₃)₂Cl₂, NaOAc, DMA, 140°, microwave, 1 min	(53)	403
C₂₃	PdCl₂(PPh₃)₂, LiCl, DBU, DMF, 140°, 6 h	(91)	407
C₂₃₋₂₄	PdCl₂(PPh₃)₂, PPh₃, DBU, DMF, 155°		413
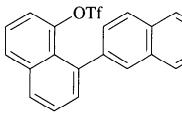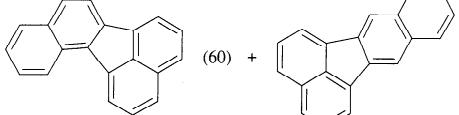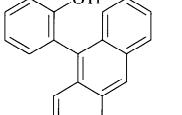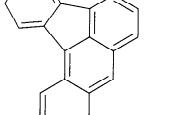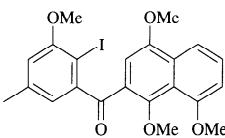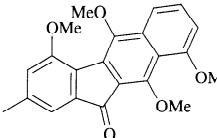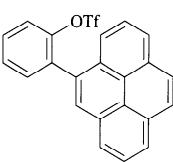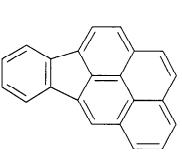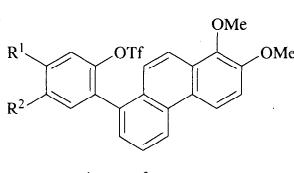
For C₂₃₋₂₄ substrate:

R¹	R²		Time	
H	H		8 h	(73)
H	OMe		8 h	(55)
OMe	H		7 h	(83)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₃	Pd(PPh₃)₄, KOAc, DMA, 160°, 6 h	(74)	405
C₂₅	PdCl₂(PPh₃)₂, PPh₃, LiCl, DBU, DMF, 140°, 6 h	(73)	407
C₂₈	Pd(PCy₃)₂Cl₂, DBU, DMA, 140°, 30 h		201
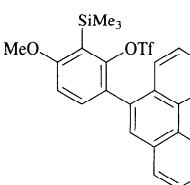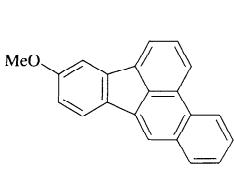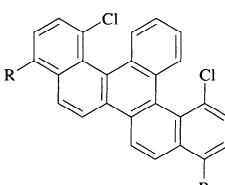
For C₂₈ substrate:

R	
Me	(91)
OMe	(70)

TABLE 3A. 5-AROMATIC CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux		171, 300

R		Time	
I		16 h	(65-72)
Br		12 h	(67-78)
Cl		19 h	(55)

TABLE 3B. 6-AROMATIC CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-13}

| | Pd(OAc)$_2$, Na$_2$CO$_3$, DMA, 170° | | 94 |

R^1	R^2	Time	
N	Cl	20 h	(42)
CH	Cl	36 h	(15)
CH	Br	2.5 h	(53)
CH	I	2 h	(44)

C_{13-15}

R^1	R^2	R^4	R^4	R^5
Br	O	H	H	H
Br	O	H	H	OH
I	O	H	H	OH
I	O	H	H	OMe
I	O	H	Me	OH
Br	CH$_2$	H	H	OH
I	NCO$_2$Me	H	H	OH
Br	O	OH	H	OH

Conditions	Temp	Time	I	II	Refs.
Pd(PPh$_3$)$_2$Cl$_2$, NaOAc, DMA	160°	2 h	(40)^a	(0)	94
Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DMA	95°	2 d	(88)	(<5)	99
HBC, Cs$_2$CO$_3$, DMA	80°	1 d	(97)	(0)	99
HBC, Cs$_2$CO$_3$, DMA	80°	1 d	(0)	(10)	99
IIBC, Cs$_2$CO$_3$, DMA	95°	1 d	(0)	(80)	99
HBC, Cs$_2$CO$_3$, DMA	115°	2 d	(75)	(0)	99
HBC, Cs$_2$CO$_3$, DMA	90°	60 h	(76)	(0)	99
HBC, Cs$_2$CO$_3$, DMA	95°	2 d	(84)	(0)	99

C_{13}

| | HBC, Cs$_2$CO$_3$, DMA, 70°, 2 d | (55) + (—) | 400 |

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13-16}

R^1	R^2	R^3		Temp	Time	
H	Br	O	Pd(OAc)$_2$, PPh$_3$, NaOAc, DMA	170°	2 h	(41)	94
H	I	NMe	Pd(OAc)$_2$, dppp, PBu$_3$, i-Pr$_2$NEt, DMF	reflux	1.5 h	(98)	95, 96
H	Br	NMe	Pd(OAc)$_2$, Ag$_2$CO$_3$, P(tol-o)$_3$, DMF	reflux	1.5 h	(99)	94, 95, 96
H	OTf	NMe	Pd(OAc)$_2$, dppp, PBu$_3$, Ag$_2$CO$_3$, DMF	reflux	5 h	(93)	96
OMe	OTf	NMe	Pd(OAc)$_2$, dppp, PBu$_3$, i-Pr$_2$NEt, DMF	reflux	30 min	(88)	96

C_{14-17}

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°

R^1	R^2	R^3	I+II	I:II		414
H	N	H	(82)	1:1		
CHO	CH	OMe	(82)	6:1		

C_{15}

Pd(OAc)$_2$, PPh$_3$, n-Bu$_4$NBr, K$_2$CO$_3$, DMF, 120°   (92)   415, 416
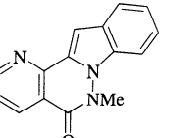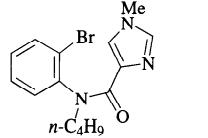
Pd(OAc)$_2$, NaHCO$_3$, n-Bu$_3$NCl, DMA, 150°, 24 h   (83)   418

Pd(OAc)$_2$, KOAc   (38)   417

C_{16-18}

Pd(PPh$_3$)$_4$, KOAc, DMF, 110°
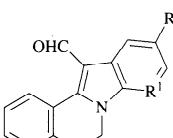
R^1	R^2	Time	
N	H	3 h	(90)
CH	H	3 h	(85)
CH	Br	4 h	(34)
CH	OMe	2 h	(76)

Refs.: 406

C_{17-33}

NaOAc, DMA

R^1	R^2	R^3		Temp	Time		
Et	Me	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(73)	421
i-Pr	Me	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(70)	421
OMe	Et	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(73)	421
Me	Et	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(62)	421
H	i-Pr	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(77)	421
OMe	i-Pr	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(84)	421
Me	i-Pr	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(76)	421
Et	i-Pr	H	Pd(OAc)$_2$, PPh$_3$	130°	18 h	(69)	421
t-Bu	H	t-Bu	HBC	160°	3 h	(81)	419, 420, 422
H	H	H	Pd(OAc)$_2$, PPh$_3$	120°	15 h	(70-91)	419, 420
OMe	H	OMe	Pd(OAc)$_2$, PPh$_3$	120°	15 h	(77-90)	419, 420
OC$_8$H$_{17}$-n	H	OC$_8$H$_{17}$-n	Pd(PPh$_3$)$_2$Cl$_2$	130°	.5-7 h	(81)	419
Me	H	Me	Pd(OAc)$_2$, PPh$_3$	120°	15 h	(72-90)	419, 420
Et	H	Et	Pd(PPh$_3$)$_2$Cl$_2$	130°	.5-7 h	(71-83)	419, 420
i-Pr	H	i-Pr	Pd(PPh$_3$)$_2$Cl$_2$	130°	.5-7 h	(72 82)	419, 420

TABLE 3B. 6-AROMATIC CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{17}$	HBC, Cs$_2$CO$_3$, DMA, 115°, 2 d	(32) + (64)	99
	Pd(PPh$_3$)$_4$, KOAc, DMF, 110°, 1 h	CHO (97)	406

C$_{17-18}$

Bu$_4$NBr, KOAc, DMF, 100°

423

R^1	R^2		
Me	Br	PdCl$_2$, 30 h	(60)
Me	I	Pd(OAc)$_2$, 3 h	(98)
H	I	Pd(OAc)$_2$, 4 h	(93)
NO$_2$	Br	Pd(OAc)$_2$, 3 h	(78)

C$_{17-19}$
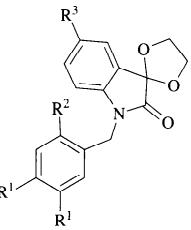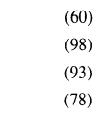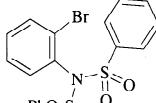
Pd(OAc)$_2$, Bu$_4$NBr, KOAc, DMF, 100°

R^1	R^2	R^3	Time		
H	Br	NO$_2$	1.5 h	(77)	423
H	I	NO$_2$	1.5 h	(90)	
—OCH$_2$O—	Br	H	24 h	(76)	
—OCH$_2$O—	I	H	5-6 h	(90-96)	
OMe	I	H	9-10 h	(81-87)	

C$_{18}$
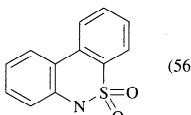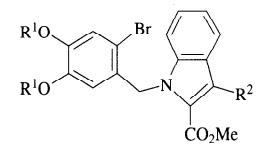
Pd(OAc)$_2$, Na$_2$CO$_3$, DMA, 160°, 24 h

(56)

94

C$_{18-21}$

Pd(PPh$_3$)$_2$, KOAc, dioxane

R^1	R^2		
—CH$_2$—	H	(91)	424
Me	H	(96)	
Me	CO$_2$Me	(76)	

C$_{19}$
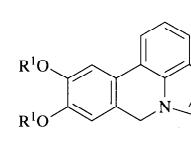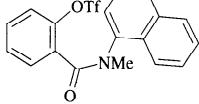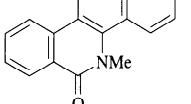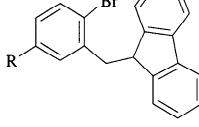
Pd(OAc)$_2$, dppp, PBu$_3$, Ag$_2$CO$_3$, DMF, reflux, 20 min

(97)

96

C$_{20-21}$

Pd(OAc)$_2$, K$_2$CO$_3$, DMF

425

		Temp	Time	
R				
F	BnMe$_3$NBr	130°	2 d	(65)
NO$_2$	*n*-Bu$_4$NBr	70°	48 h	(57)
H	*n*-Bu$_4$NBr	130°	2 d	(52)
OMe	LiI	130°	4 d	(50)

C$_{20}$
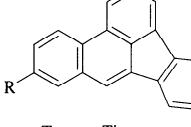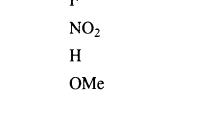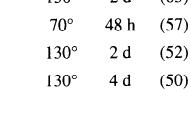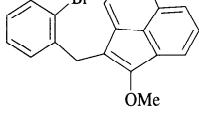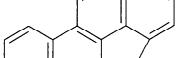
Pd(OAc)$_2$, K$_2$CO$_3$, BnMe$_3$NBr, DMF, 160°, 4 d

(39)

425

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{21\ 8}$

Pd(OAc)$_2$, PPh$_3$, NaOAc, DMA, 100°

R	I	II	I:II	
H	(—)	(—)	3:1	426
OBn	(76)	(0)	—	435

C$_{21}$

Pd(OAc)$_2$, K$_2$CO$_3$, BnMe$_3$NBr, DMF, 100°, 24 h

(41) + (21) 425

C$_{21-22}$

Pd(OAc)$_2$, DMF, reflux

R^1	R^2	R^3			
H	OMe	I	dppp, Ag$_2$CO$_3$, 15 min	(95)	95, 427
H	OMe	Br	P(tol-*o*)$_3$, Ag$_2$CO$_3$, 3 h	(96)	95, 427
H	OMe	OTf	dppp, *i*-Pr$_2$NEt, 30 min	(73)	427
OMe	H	OTf	dppp, *i*-Pr$_2$NEt, 30 min	(93)	427
OMe	H	I	dppp, *i*-Pr$_2$NEt, 30 min	(94)	427

C$_{21}$

4-MeOC$_6$H$_4$SO$_2$

Pd(OAc)$_2$, Na$_2$CO$_3$, DMA, 150°, 6 h

(25) 94

C$_{22}$

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°

(62) 414

C$_{23}$

Pd [II]

(89) 420

C$_{24-29}$

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°

I + II + III

R	I+II+III	I:II:III
NCO$_2$Me	(94)	5.7:1:0
NTs	(96)	5.7:1:8.3

414

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{25}$	Pd(OAc)$_2$, PPh$_3$, NaOAc, DMF, 135°, 6 h	(16)	428
	Pd(OAc)$_2$, PPh$_3$, NaOAc, DMF, 110° 19 h	(17) + (8.5)	428
	IIBC, NaOAc, DMF, 140°, 72 h	(13) + (39)	428
C$_{25-28}$	Pd(PPh$_3$)$_2$Cl$_2$, NaOAc, DMAC, 130°, 2-3 h	$\begin{array}{ccc} R^1 & R^2 & R^3 \\ \hline H & H & Br \ (40) \\ Me & OMe & I \ (76) \\ Et & OMe & I \ (79) \end{array}$	429
C$_{25-26}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, DMF, 100°, 24 h	$\begin{array}{cc} R & \\ \hline N & (72) \\ CH & (75) \end{array}$	430
C$_{25}$	1. Pd(OAc)$_2$, PPh$_3$, *t*-BuCO$_2$Na, DMA, 110°, 1.5 h 2. NaBH$_4$, THF, MeOH, −40°, 3 h	(86)	431
	Pd(PPh$_3$)$_2$Cl$_2$, NaOAc, DMA, 130°	(25) + (—)	432
	Pd(OAc)$_2$, PPh$_3$, NaOAc, DMA, 140°, 100 min	(32)	433
C$_{26}$ 2-naphthylSO$_2$	Pd(OAc)$_2$, Na$_2$CO$_3$, DMA, 150°, 6 h	(25)	94
	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°, 45 min	(85)	340
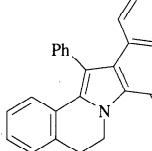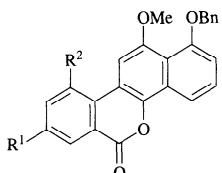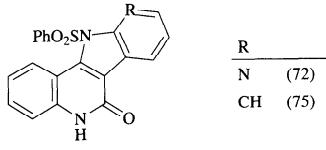
TABLE 3B. 6-AROMATIC CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, K₂CO₃, Et₄NCl, CH₃CN, 80°, 45 min	(85)	340

C₂₇₋₂₉

| | Pd(OAc)₂, K₂CO₃, DMF | | 425 |

R¹	R²	R³		Temp	Time	
H	H	H	*n*-Bu₄NBr	130°	24 h	(68)
OMe	OMe	H	LiI	135°	5 d	(30)
H	OMc	H	LiI	130°	4 d	(62)
H	NO₂	H	*n*-Bu₄NBr	95°	48 h	(53)
H	H	NO₂	BnMe₃NBr	70°	32 h	(53)

C₂₇₋₂₈

| | Pd(OAc)₂, K₂CO₃, BnMe₃NBr, DMF, 70° | | 425 |

R	Time	
H	48 h	(41)
OMe	24 h	(67)

C₂₈

| | Pd(OAc)₂, K₂CO₃, *n*-Bu₄NBr, DMF, 140°, 36 h | (80) | 425 |

I **II** **III**

	I	II	III	
HBC, DBU, DMF, 150°, 72 h	60ᵇ (57)	20ᵇ	20ᵇ	434
Pd₂(dba)₃, P(Bu-*t*)₃, Cs₂CO₃, DMF, 150°, 72 h	10ᵇ (8)	85ᵇ	5ᵇ	

C₃₁₋₃₂

	PdCl₂(PPh₃)₂, NaOAc, DMA, 130°		

R		
H	(75)	437, 438
OMe	(87)	436

TABLE 3B. 6-AROMATIC CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₃₁	Pd(OAc)₂, P(tol-*o*)₃, NaOAc, DMA, 140°, 22 h	(74)	439, 440
C₃₂	Pd(OAc)₂, PPh₃, NaOAc, DMA, 130°	(20) + (—)	435
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 150°, 5 h	(71)	441
	PdCl₂(PPh₃)₂, DMA, 95°	(67) + (15)	420, 438, 442
	Pd(PPh₃)₂Cl₂, NaOAc, DMA, 130°	(61)	443
C₃₃	Pd(OAc)₂, PPh₃, NaOAc, DMA, 130°	(37)	435
	Pd(PPh₃)₂Cl₂, NaOAc, DMA, 100°	(92)	444
C₃₃₋₄₄	Pd(PPh₃)₂Cl₂	R: Me (39); Ph–Ph (87)	331
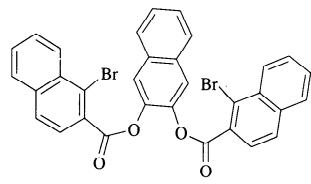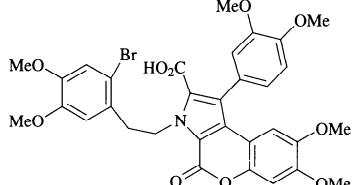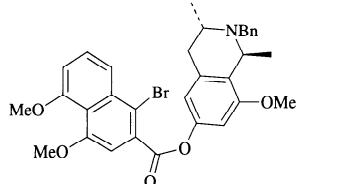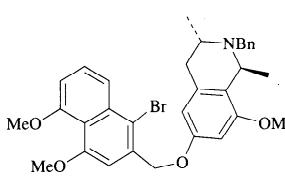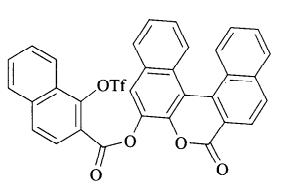
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₃₆

Pd(PPh₃)₂Cl₂, NaOAc, DMA, 100°

I + II (69); I:II = 2.5:1

445

C₄₈₋₆₃

R¹	R²	R³			
H	Br	α-H	Pd(OAc)₂, K₂CO₃, BnMe₃NBr, DMF, 130°, 24 h	(71-79)	174
H	Br	β-H	Pd(OAc)₂, DMF or DMA, 150-165°, 36 h	(—)	174
	Br	α-H	Pd(OAc)₂, K₂CO₃, BnMe₃NBr, DMA, 140°, 36 h	(42)	446
"	OTf	α-H	Pd(PPh₃)₂Cl₂, NaOPiv, DMA, 120°, 26 h	(11)	446

C₅₄

PdCl₂(PPh₃)₂, NaOAc, DMA, 125°, 6 h

(90)

172

PdCl₂(PPh₃)₂, NaOAc, DMA, 125°, 5 h

(90)

173

C₅₈

PdCl₂(PPh₃)₂, NaOPiv, DMA, 80°, 1 h

(65)

173

[a] PhOBn is also isolated in 35% yield.

[b] These yields were determined by HPLC. Isolated yields are in parentheses.

TABLE 3C. 7-AROMATIC CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{16}	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, n-Bu$_4$NBr, DMF, 110°, 2 h	(41)	416
C_{21}	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°, 48 h	R O (60) S (66)	395
C_{21-25}	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$		395
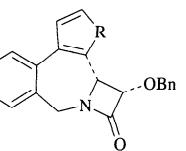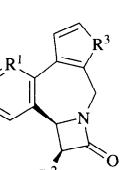
R^1	R^2	R^3		
CH	OBn	O	tol, 110°, 24 h	(52)
CH	OBn	S	tol, 110°, 24 h	(65)
CH		O	CH$_3$CN, 80°, 48 h	(73)
CH	"	S	CH$_3$CN, 80°, 48 h	(62)
CH	"	CH=CH	CH$_3$CN, 80°, 48 h	(68)
N	"	CH=CH	DMF, 140°	(—)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{25}	Pd(PPh$_3$)$_4$, KOAc, DMA, 160°, 6 h	(81)	405
C_{27}	Pd(OAc)$_2$, dppp, Et$_3$N, DMF, 110°, 18 h	(81)	98
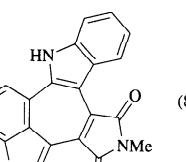
TABLE 4. TANDEM REACTIONS

A. 4-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	Pd$_2$(dba)$_3$, n-Bu$_4$NCl, DMSO, 100°, 16 h		447
	CH$_2$(CO$_2$Et)$_2$, K$_2$CO$_3$		
	morpholine, Na$_2$CO$_3$		

R	
CH(CO$_2$Et)$_2$	(70)
N-morpholinyl	(54)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{26}$	Pd(OAc)$_2$, PPh$_3$, $tert$-butyl acrylate, Et$_3$N, DMF, 80°, 12 h	(43)	63
	Pd(OAc)$_2$, PPh$_3$, $tert$-butylethyne, Et$_3$N, DMF, 80°, 12 h	(49)	63

TABLE 4. TANDEM REACTIONS (*Continued*)

B-1. 5-EXO; INTERMOLECULAR HECK REACTIONS; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{8-13}$	Pd(OAc)$_2$, PPh$_3$, methyl acrylate, K$_2$CO$_3$, AgNO$_3$, CH$_3$CN, 110°, 3 h		106

R	
C(CO$_2$Me)$_2$	(56)
O	(20)
NPh	(14)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{9-15}$	Pd(OAc)$_2$, PPh$_3$, allene, R^{2}H, K$_2$CO$_3$, tol, 70°, 20 h	I + II	449

R^1	R^2	I	II
O	N-piperidinyl	(61)	(0)
O	N-(S)-(+)-2-pyrrolidylmethanol	(67)	(0)
O	N-tetrahydroisoquinolinyl	(61)	(0)
NSO$_2$Ph	N-piperidinyl	(30)	(30)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{9-12}

R^1	R^2		
O	H	Et$_3$N, reflux	(45)
NCOMe	H	K$_2$CO$_3$, Et$_4$NCl, rt, 18 h	(40)
NCOMe	Me	Et$_3$N, reflux	(45)

Pd(OAc)$_2$, PPh$_3$, norbornene, CH$_3$CN — 107, 108

C_{10-17}

Pd(OAc)$_2$, PPh$_3$, allene, R^{3}H, Et$_4$NCl, K$_2$CO$_3$, tol, 20 h — 450

R^1	R^2	R^3	Temp	
O	H,H	*N*-pyrrolidinyl	110°	(60)
O	H,H	*N*-piperidinyl	110°	(60)
NMe	O	*N*-pyrrolidinyl	90°	(76)
NMe	O	*N*-piperidinyl	90°	(82)
NTs	H,H	*N*-pyrrolidinyl	110°	(72)
NTs	H,H	*N*-piperidinyl	110°	(60)

C_{11}

Pd(PPh$_3$)$_4$, methyl acrylate, Et$_3$N, CH$_3$CN, reflux, 12 h — MeO$_2$C (80) 451

C_{11-16}

Pd(OAc)$_2$, PPh$_3$, 1,1-dimethylallene, *N*-methylmaleimide, Ag$_2$CO$_3$, 120°, 48 h
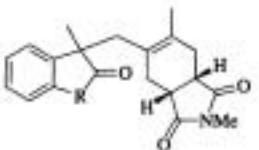
R		dr	
NMe	(72)	1.5:1	452
NSO$_2$Ph	(69)	1.7:1	

TABLE 4. TANDEM REACTIONS (*Continued*)

B-1. 5-EXO; INTERMOLECULAR HECK REACTIONS; MISCELLANEOUS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{13-19}$

R^2—$\equiv$—R^3

R^1	R^2	R^3	Conditions	Temp	Time	I	%D	II	III	%D	Refs.
H	Et	Et	Pd(PPh$_3$)$_4$, Et$_3$N, DMF	—	—	(28)	—	(0)	(0)	—	454
SiMe$_3$	Et	Et	Pd(PPh$_3$)$_4$, Et$_3$N, DMF	65°	12 h	(40)	—	(0)	(0)	—	454
H	H	n-C$_6$H$_{13}$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	12 h	(50)	—	(0)	(0)	—	455
Me	H	n-C$_6$H$_{13}$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	1 h	(89)	—	(0)	(0)	—	455
Me	n-C$_6$H$_{13}$	SiMe$_3$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	16 h	(62)	—	(0)	(0)	—	455
SiMe$_3$	H	n-C$_6$H$_{13}$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	4 h	(47)	—	(47)	(0)	—	455
SiMe$_3$	n-C$_6$H$_{13}$	SiMe$_3$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	12 h	(58)	—	(0)	(0)	—	455
Ph	H	n-C$_6$H$_{13}$	1. Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	-78° 100°	— 1 h	(67)	—	(0)	(0)	—	455
Ph	D	n-C$_6$H$_{13}$	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, Et$_3$N, DMF	125°	2 h	(65)	—	(0)	(0)	—	455
Ph	H	Ph	1. Pd(PPh$_3$)Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	-78° 100°	— 1 h	(73)	75-85%	(0)	(0)	—	455
Ph	n-C$_6$H$_{13}$	SiMe$_3$	1. Pd(PPh$_3$)Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	— 100°	— 3 h	(63)	—	(0)	(0)	—	455
Ph	Ph	SiMe$_3$	1. Pd(PPh$_3$)Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	— 100°	— 3 h	(62)	—	(0)	(0)	—	455
Ph	n-Pr	n-Pr	1. Pd(PPh$_3$)Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	— 100°	— 3 h	(83)	—	(0)	(0)	—	455
Ph	Ph	Ph	1. Pd(PPh$_3$)Cl$_2$, n-BuLi, THF, hexane 2. Et$_3$N	— 100°	— 3 h	(62)	—	(0)	(0)	—	455
Ph	D	n-C$_6$H$_{13}$	Pd(OAc)$_2$, PPh$_3$, CuI, Et$_3$N, DMF	100°	2 h	(48)	40-50%	(0)	(12)	40-50%	455

C$_{13}$

Pd(PPh$_3$)$_4$, allene, RH, K$_2$CO$_3$, CH$_3$CN, 75°, 15 h

R		
N-pyrrolidinyl	(60)	449
N-tetrahydroisoquinolinyl	(77)	

C$_{16-17}$

, Pd(OAc)$_2$, n-Bu$_4$NCl, DMF, 50°

R^1	R^2	R^3			Refs.
allyl	H	Et	Et$_3$N, 6 h	(44)	456
H	(CH$_2$)$_7$CO$_2$Et	n-C$_5$H$_{11}$	i-Pr$_2$NEt	(42)	105

C$_{19}$

Pd(OAc)$_2$, PPh$_3$, methyl acrylate, Ag$_2$CO$_3$, CH$_3$CN, 120°, 3 h

(56)   106

Pd(OAc)$_2$, PPh$_3$, ethyl vinyl ether, Ag$_2$CO$_3$, CH$_3$CN, 80°, 36 h

(43)   457

TABLE 4. TANDEM REACTIONS (Continued)

B-2. 5-EXO; 3-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13-15}

Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°

R^1	R^2		I	II
CH$_2$	Me		(70-73)	(0)
CH$_2$CH$_2$	Et		(70-73)	(0)
CH$_2$CH$_2$CH$_2$	Me		(50)	(20-23)

100, 127

C_{14}

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 82°

(90)

110

C_{14-15}

Pd(OAc)$_2$, CH$_3$CN, 85°, 5-6 h

271

R^1	R^2		I	II	III	IV	V	VI	
CH$_2$OAc	H	PPh$_3$, Et$_3$N	(30)	(3)	(0)	(0)	(0)	(0)	
CH$_2$OAc	H	PPh$_3$, NaO$_2$CH	(27)	(13)	(0)	(0)	(5)	(0)	
CH$_2$OAc	H	PPh$_3$, Et$_3$N	(28)	(2)	(2)	(7)	(0)	(0)	
CH$_2$OAc	H	dmphen, Et$_3$N	(2)	(31)	(4)	(0)	(0)	(0)	
CH$_2$OAc	H	PPh$_3$, Ag$_2$CO$_3$	(6)	(0)	(30)	(0)	(0)	(19)	(E/Z 1:3)
H	CH$_2$OAc	PPh$_3$, Et$_3$N	(14)	(5)	(4)	(0)	(0)	(0)	
H	CH$_2$OAc	PPh$_3$, Ag$_2$CO$_3$	(23)	(trace)	(7)	(0)	(0)	(0)	
H	CH$_2$OAc	dmphen, Et$_3$N	(0)	(31)	(0)	(0)	(0)	(20)	(E/Z 3:1)
CH$_2$OCO$_2$Et	H	PPh$_3$, Et$_3$N	(22)	(10)	(0)	(0)	(0)	(0)	
CH$_2$COCF$_3$	H	PPh$_3$, Et$_3$N	(34)	(4)	(2)	(0)	(0)	(0)	
CH$_2$COCF$_3$	H	dmphen, Et$_3$N	(trace)	(20)	(14)	(0)	(0)	(0)	

TABLE 4. TANDEM REACTIONS (*Continued*)

B-3. 5-EXO; 3-EXO: MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_8	PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, Et$_2$NH, DMF, 80°, 8 h	(69)	91
C_13	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 80°, 12 h	(56)	458
C_14	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 90°, 6 h	(33)	15
C_16	1. Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, rt, 24 h 2. Reflux, time		458

Time	I	II
30 min	(40)	(19)
1.5 h	(55)	(4)

	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN	+ 458
	80°, 1 h Et$_4$NCl, rt, 18 h TlOAc, rt, 56 h	

	I	II	III	IV
	(30)	(55)	(15)	(0)
	(28)	(46)	(26)	(0)
	(17)	(14)	(14)	(41)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_18	PdCl$_2$(PPh$_3$)$_2$, Et$_3$N, Et$_2$NH, DMF, 80°, 8 h	(94)	91
C_19	Pd$_2$(dba)$_3$·CHCl$_3$, PPh$_3$, Et$_3$N, CH$_3$CN, 80°, 1 h	(85) + (8)	459

TABLE 4. TANDEM REACTIONS (*Continued*)
B-4. 5-EXO; 5-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13}

PdL$_n$

  (41) + (41)

109

C_{14}

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN

I + **II**

Temp	Time	I	II	
reflux	6 h	(43)	(43)	254
rt	2-8 h	(58)	(38)	32

C_{14-16}

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, rt, 2-8 h

R^1	R^2	R^3	R^4		dr	
H	H	H	H	(86)	—	32, 110, 254
H	Me	H	H	(81)	13:1	32, 110
H	H	Me	H	(73)	6.5:1	32, 110
Me	H	Me	H	(80)	9:1	110
H	H	H	Me	(80)	1.1:1	110

C_{15}

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, rt, 2-8 h

 (43) + (25)

32

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 70°

 (72) + (trace)

236

C_{17}

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 23°

 (71) >21:1 dr

110

C_{18-25}

Pd(OAc)$_2$, PPh$_3$, Bu$_4$NHSO$_4$, Et$_3$N, H$_2$O, CH$_3$CN, 80°, 15-24 h

R		
O	(75)	
NTs	(80)	50, 460
C(CO$_2$Me)$_2$	(78)	

C_{19-20}

Pd(OAc)$_2$, PPh$_3$, Bu$_4$NHSO$_4$, Et$_3$N, H$_2$O, CH$_3$CN, 80°, 15-24 h

R		
H	(77)	50
Me	(78)	

TABLE 4. TANDEM REACTIONS (Continued)

B-4. 5-EXO; 5-EXO (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{19-25}

Pd catalyst, DMF, 80°

I + II

R		Time	I	dr	II
H	Pd(OAc)₂, PPh₃, AgOAc	6 h	(73)	—	(1)
H	Pd₂(dba)₃•CHCl₃, PPh₃, Ag₂O	3 h	(70)	—	(16)
H	Pd(OAc)₂, PPh₃, KOAc, NPr₄Br	2 h	(82)	—	(9)
H	Pd₂(dba)₃•CHCl₃, (R)-BINAP, Ag₃PO₄	48 h	(15)	0% ee	(65)
OH	Pd(OAc)₂, PPh₃, AgOAc	3 h	(64)	3:1	(1)
OH	Pd₂(dba)₃•CHCl₃, PPh₃, Ag₂O	3 h	(80)	2.2:1	(1)
OH	Pd(OAc)₂, PPh₃, KOAc, NPr₄Br	3 h	(84)	1.4:1	(4)
OTBDMS	Pd(OAc)₂, PPh₃, AgOAc	3 h	(48)	1.2:1	(1)
OTBDMS	Pd₂(dba)₃•CHCl₃, PPh₃, Ag₂O	5 h	(66)	1.9:1	(17)
=O	Pd₂(dba)₃•CHCl₃, (R)-BINAP, Ag₃PO₄	23 h	(.2)	—	(18)

C_{20-22}

Pd(OAc)₂, PPh₃,
CH₃CN, 80°, 8 h

R		
K₂CO₃	H	(70)	113
K₂CO₃	Me	(65)	113
Ag₂CO₃	CO₂Me	(—)	113
Ag₂CO₃	CO₂Me E:Z = 1.7:1	(76) dr = 1.7:1	104

C_{24}

Pd(OAc)₂, PPh₃, Bu₄NHSO₄,
Et₃N, H₂O, CH₃CN,
80°, 15–24 h

(79)

50

C_{29}

Pd(OAc)₂, PPh₃, K₂CO₃,
CH₃CN, 80°, 48 h

(39)

113

TABLE 4. TANDEM REACTIONS (*Continued*)

B-5. 5-EXO; 5-EXO: MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{18-24}

HBC, K_2CO_3,
CH_3CN, 80°, 48 h

R^1	R^2	
H	NTs	(55)
Br	NTs	(60)
H	O	(>80)

104

C_{14-19}

$Pd(OAc)_2$, PPh_3

I + II

R^1	Conditions	R^2	Temp	Time	I	II	Refs.
Me	HCO_2Na, Et_4NCl, DMF	H	80°	6 h	(70)	(0)	101, 139, 140
Ph	$NaOCHO$, Et_4NCl, DMF	H	80-100°	16 h	(70)	(0)	101, 140
Me	$NaBPh_4$, Et_4NCl anisole	Ph	90°	16 h	(30)	(0)	128, 139, 140
Me	R^2SnBu_3	2-(1-*N*-SEM-indolyl)	—	—	(62)	(12)	101
Me	Et_4NCl, R^2SnBu_3	2-furyl	—	—	(62)	(12)	101, 131
Ph	R^2SnBu_3	2-(1-*N*-SEM-indolyl)	—	—	(53)	(18)	101
Ph	Et_4NCl, R^2SnBu_3	2-furyl	—	—	(52)	(18)	101, 131
Me	Et_4NCl, R^2SnBu_3	3-(1-*N*-SEM-indolyl)	—	—	(55)	(11)	131
Ph	Et_4NCl, R^2SnBu_3	3-(1-*N*-SEM-indolyl)	—	—	(48)	(16)	131
Ph	Et_4NCl, R^2SnBu_3	$CH=CH_2$	—	—	(18)	(12)	131

C_{18}

$Pd(PPh_3)_4$, Et_3N,
CH_3CN, reflux, 12 h

 (54)

454

C_{18-26}

$Pd(OAc)_2$, PPh_3, Ag_2CO_3,
CH_3CN

R	Temp	Time	
Me	80°	9 h	(84)
Et	80°	6 h	(81)
i-Pr	60°	6 h	(95)
Ph	80°	12 h	(51)
p-C_6H_4OMe	10°	7 h	(25)

457

C_{19}

$Pd(OAc)_2$, PPh_3, Ag_2CO_3,
DME, CH_3CN, 60°, 2 d

 (35) + (30) + I^a (10)

457, 462

C_{19-25}

1. $Pd(OAc)_2$, PPh_3, *n*-Bu_3SnH,
   THF, 0°, 1 h
2. Et_4NCl•H_2O, CH_3CN, reflux

R	
O	(41)
NSO_2Ph	(51)

233

C_{20-22}

$Pd(OAc)_2$, PPh_3, Ag_2CO_3,
CH_3CN, 80°

R^1	R^2	Time	
Me	Me	3 h	(60)
Me	H	2 h	(63)
—$(CH_2)_3$—	Me	4 h	(87)

463

TABLE 4. TANDEM REACTIONS (*Continued*)

B-5. 5-EXO; 5-EXO; MISCELLANEOUS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₁	Pd(OAc)₂, PPh₃, CH₃CN Ag₂CO₃ K₂CO₃	 Temp I II 60° (55) (0) 120° (24) (51)	113
C₂₁	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 80°, 3 h	(60)	457
C₂₁₋₂₂ R / E:Z Me / — CO₂Me / 1.7:1 CO₂Me / 1.7:1	Pd(OAc)₂, PPh₃, CH₃CN K₂CO₃ Ag₂CO₃ K₂CO₃	 Temp Time I cis:trans II 80° 8 h (65) 2:1 (0) 80° 8 h (72) 1.2:1 (0) 130° 14 h (31) 100:0 (47)	457
C₂₂	Pd(OAc)₂, PPh₃, HCO₂H, piperidine, Et₄NCl, CH₃CN, 70°, 1 h	(26) + (6)	139, 464
	Pd(OAc)₂, PPh₃, Et₄NCl, PhZnCl, THF Et₂O, 25°, 0.5 h	(40) + (17)	139
E:Z = 1.7:1	Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN, 130°, 8 h	(47) + (31)	104, 113

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{22-23}$

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$,
CH$_3$CN, 80°

R	Time	
H	3 h	(80)
Me	4 h	(88)

457, 463

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$,
CH$_3$CN, 80°

R	Time	
H	3 h	(85)
Me	4 h	(48)

457

C$_{25}$

Pd(OAc)$_2$, PPh$_3$,
Bu$_3$SnCH=CH$_2$, Et$_4$NCl,
CH$_3$CN, 25°, 2 h
or
Pd(OAc)$_2$, PPh$_3$,
NaOCHO, Et$_4$NCl,
DMF, 70°, 1 h

(40-65)

139

C$_{24}$

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$,
CH$_3$CN, 80°, 4 h

(87)

457

Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$,
CH$_3$CN, 60°, 6 h

(58)   +   (23)

457

C$_{25-31}$

R
H
Ph

Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$,
CH$_3$CN

I   +   II

113, 457

Temp	Time	I	II
60°	3 d	(83)	(0)
80°	7 d	(27)	(38)

TABLE 4. TANDEM REACTIONS (*Continued*)

B-5. 5-EXO; 5-EXO; MISCELLANEOUS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{27-31}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, NaOHCO, CH$_3$CN, 80°		
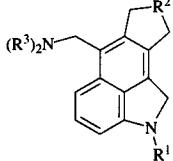
R^1	R^2	R^3	Time		
Ac	C(CO$_2$Et)$_2$	—(CH$_2$)$_5$—	1 h	(77)	464, 465
Ac	C(CO$_2$Et)$_2$	Et	2 h	(70)	464, 465
SO$_2$Ph	NSO$_2$Ph	—(CH$_2$)$_5$—	2 h	(60)	464
SO$_2$Ph	NSO$_2$Ph	Et	15 h	(65)	464
Ac	NSO$_2$Ph	—(CH$_2$)$_4$—	1-2 h	(65-77)	465
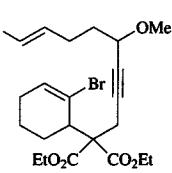
C$_{28}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 60°, 3 d	(30) + I^a (—)	457
C$_{29}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 60°, 72 h	(67) de >95%	113
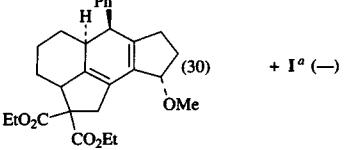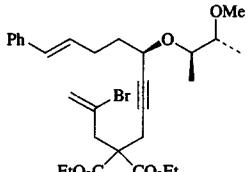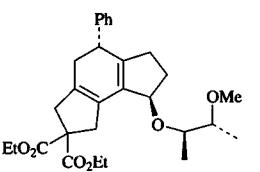
^{a} An unidentified product was formed in 10% yield.

TABLE 4. TANDEM REACTIONS (*Continued*)

B-6. 5-EXO; 6-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{14}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN, 80°, 3 h	(92)	111
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, THF, 65°	(70) 4:1 *cis:trans*	110
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 70°	(85)	32, 110
C$_{16}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 70°	(70)	236
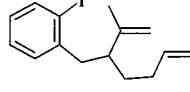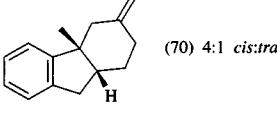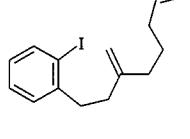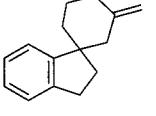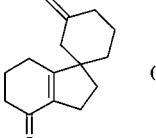
TABLE 4. TANDEM REACTIONS (*Continued*)

B-7. 5-EXO: 6-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 60°, 48 h	(67)	466
C$_{15}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, MeOH, 70°, 24 h	(59) + (19)	115
C$_{20-25}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 120°, 2-3 h	R: CO$_2$Me (61), H (42), C(OH)Et$_2$ (67), COCH$_3$ (75)	466
C$_{21}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, MeOH, 70°, 24 h	(71)	115
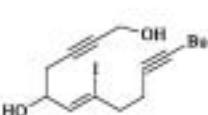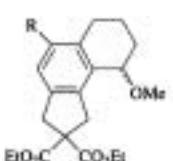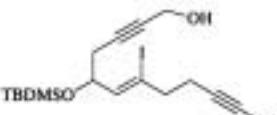
C$_{28}$

R	Temp	Time	I	II	
Pd(OAc)$_2$, PPh$_3$, NaOCHO, DMF	H	100°	4 h	(20)	(30)	139, 140
Pd(OAc)$_2$, PPh$_3$, NaOCHO, DMF, Tl$_2$CO$_3$	H	80°	48 h	(40)	(10)	140
Pd$_2$(dba)$_3$, TFP, Et$_4$NCl, RSnBu$_3$, tol	CH=CH$_2$	110°	—	(0)	(55)	131
PdCl$_2$(PPh$_3$)$_2$, CO, TlOAc, MeOH	CO$_2$Me	65°	—	(43)	(0)	101
Pd(0), 2-(Bu$_3$Sn)pyridine	2-pyridyl	—	—	(60)	(0)	101, 131
Pd$_2$(dba)$_3$, TFP, NaBPh$_4$, anisole	Ph	110°	24 h	(63)	(0)	101, 128, 139, 140

* An unstable compound of unproven structure was also isolated. Tentatively it has been assigned as the product resulting from aromatization of the central diene-containing ring.

TABLE 4. TANDEM REACTIONS (*Continued*)

B-8a. 5-EXO; CARBONYLATIVE; REDUCTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	Pd(OAc)$_2$, PPh$_3$, CO, Ph$_2$MeSiH, Et$_4$NCl, tol, 110°, 7 h	(45-60)	117
C$_{16}$	Pd(OAc)$_2$, PPh$_3$, CO, Ph$_2$MeSiH, Et$_4$NCl, tol, 110°, 7 h	(61)	117
C$_{17}$	Pd(OAc)$_2$, PPh$_3$, CO, Ph$_2$MeSiH, Et$_4$NCl, tol, 110°, 7 h	(45-60)	117
	Pd(OAc)$_2$, PPh$_3$, CO, Ph$_2$MeSiH, Et$_4$NCl, tol, 110°, 7 h	(45-60)	117

TABLE 4. TANDEM REACTIONS (*Continued*)

B-8b. 5-EXO; CARBONYLATIVE; ALCOHOL CAPTURE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{11}$	PdCl$_2$(PPh$_3$)$_2$, CO, TlOAc, MeOH, 65°, 21 h	(50)	114
	Pd(PPh$_3$)$_4$, CO, Et$_3$N, MeOH, CH$_3$CN, 100°	(42) + (28)	451
	PdCl$_2$(PPh$_3$)$_2$, COEt$_3$N, MeOH, DMF, 100°, 4 h	(63) + (<2) + (16)	327
C$_{13}$	Pd(PPh$_3$)$_4$, Et$_3$N, CO (4 bar), MeOH, CH$_3$CN, C$_6$H$_6$, 85°, 15 h	(50)	54
C$_{13-15}$	Pd(OAc)$_2$, PPh$_3$, CO, MeOH, reflux		127

R^1	R^2		
CH$_2$	Me	Et$_3$N	(56-69)
CH$_2$=CH$_2$	Et	Et$_3$N	(56-69)
CH$_2$CH$_2$=CH$_2$	Me	Ag$_2$CO$_3$	(56-69)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{14-19}

Pd(PPh₃)₄, Et₃N, CO (4 bar), MeOH, CH₃CN, C₆H₆, 80°, 12 h

R		de
Me	(73)	>98%
TBDMS	(72)	>98%

54

C_{15}

HO~R, PdCl₂(PPh₃)₂, K₂CO₃, CO, tol, 95°
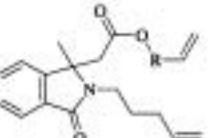
R	
—CH₂—	(61-64)
—(CH₂)₂—	(61-64)
—(CH₂)₃—	(61-64)

342

C_{16}
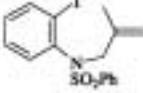
PdCl₂(PPh₃)₂, CO, TlOAc, MeOH, 65°, 21 h
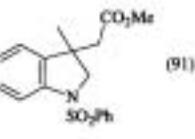
(91)

114

C_{17}
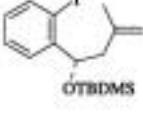
PdCl₂(PPh₃)₂, CO, Et₃N, DMF, MeOH, H₂O, O₂, 85°
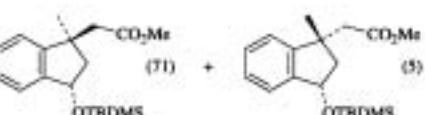
(71) + (5)

138

C_{21}
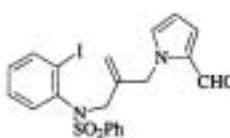
PdCl₂(PPh₃)₂, CO, TlOAc, MeOH, 65°

(44) + (22)

+ (22)

114
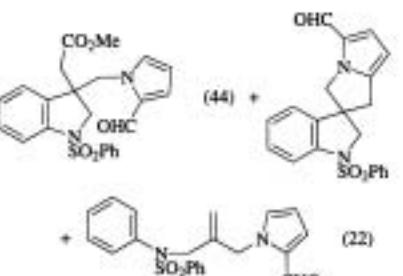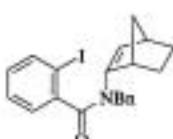
PdCl₂(PPh₃)₂, CO, TlOAc, MeOH, 65°, 21 h
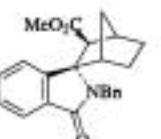
(86)

114

C_{23}
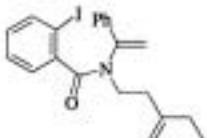
PdCl₂(PPh₃)₂, CO (280 psi), Et₃N, MeOH, 106°, 3 h

(65) + (32)

114

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₈₋₁₂

| | | Pd(OAc)₂, PPh₃, CO, NH₂OBn, K₂CO₃, tol, 110°, 16 h | | |

R	
O	(57)
NCO₂Me	(58)

467

C₂₀₋₁₇

Pd(OAc)₂, PPh₃, CO, R³NHOBn, K₂CO₃, tol, 110°, 16 h

467

R¹	R²	R³	I	II
O	H₂	H	(65)	(0)
O	H₂	Boc	(96)	(0)
NCO₂Me	H₂	H	(70)	(0)
NCO₂Me	H₂	Boc	(85)	(0)
NSO₂Ph	H₂	H	(21)	(—)
NSO₂Ph	H₂	Boc	(89)	(0)
NBn	O	Boc	(85)	(0)

C₁₀₋₁₇

342

R¹	R²	R³	
O	CH₂	CH₂	(60)
O	CH₂	(CH₂)₂	(52)
O	CH₂	(CH₂)₃	(59)
NTs	CH₂	CH₂	(82)
NTs	CH₂	(CH₂)₂	(61)
NTs	CH₂	(CH₂)₃	(76)
NMe	CO	CH₂	(69)
NBn	CO	(CH₂)₂	(63)
NBn	CO	(CH₂)₃	(57)

C₁₅

Pd(OAc)₂, P(tol-o)₃, CO, Proton Sponge®, CH₃CN, 60°, 18 h

Pd(0), CO

I	II
(55)	(—)
(0)	(—)

101, 102

Pd(0), CO

(—)   101

TABLE 4. TANDEM REACTIONS (*Continued*)
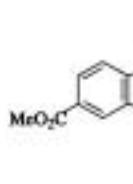
B-8d. 5-EXO; CARBONYLATIVE; INTRAMOLECULAR CAPTURE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, *i*-PrOH, 80-85°, 4 h	(30) + (13)	468
n-C$_6$H$_{13}$	Pd(OAc)$_2$, CO, CH$_3$CN, 100°, 24 h	*n*-C$_6$H$_{13}$ (36) + *n*-C$_6$H$_{13}$ (<2) + *n*-C$_6$H$_{13}$ (<2)	327
C$_{14}$ AcHN	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, CH$_3$CN, MeOH, 100°, 10 h	NHAc (20)	468
C$_{23}$ NHBn SO$_2$Ph	Pd(OAc)$_2$, PPh$_3$, CO, TlOAc, CH$_3$CN, 80°	(38) + (32) PhO$_2$S	116
C$_{23}$ EtO$_2$C CO$_2$Et SO$_2$Ph	Pd(OAc)$_2$, PPh$_3$, CO, TlOAc, CH$_3$CN, 80°, 24 h	CO$_2$Et CO$_2$Et (50) SO$_2$Ph	116
C$_{28}$ BnHN SO$_2$Ph	Pd(OAc)$_2$, PPh$_3$, CO, TlOAc, CH$_3$CN, 80°, 48 h	PhO$_2$SN NBn (45)	116

TABLE 4. TANDEM REACTIONS (*Continued*)

B-8e. 5-EXO; CARBONYLATIVE; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10-17}$ R^1 R^2	Pd(OAc)$_2$, PPh$_3$, CO, R^{3}SnBu$_3$, Et$_4$NCl, tol, 110°, 15 h	R^3 R^2 R^1	469

R^1	R^2	R^3	
O	H$_2$	2-furyl	(88)
O	H$_2$	2-pyridyl	(83)
O	H$_2$	*E*-CH=CHPh	(61)
O	H$_2$	2-(1-SEM-indolyl)	(52)
NSO$_2$Ph	H$_2$	2-pyridyl	(71)
NBn	O	2-furyl	(87)
NBn	O	*E*-CH=CHPh	(78)
NBn	O	2-(1-SEM-indolyl)	(61)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10-16}$ R	Pd(OAc)$_2$, TFP, CO, NaBPh$_4$, anisole, 110°, 15 h	Ph R O (80) NSO$_2$Ph (82)	469
C$_{11}$ Me O	1. Pd(OAc)$_2$, TFP, CO, RH, *i*-Pr$_2$NEt, tol, 50°, 18 h 2. HF, pyr, THF, 20 min 3. NaHCO$_3$, EtOAc	R OH O Me *N*-piperidinyl (60) 1-*N*-4-phenylpiperazinyl (50) CN (55) NO$_2$ (57)	453

TABLE 4. TANDEM REACTIONS (Continued)
B-8e. 5-EXO; CARBONYLATIVE; MISCELLANEOUS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁	Pd(0), allene, CO, piperidine	(56)	101
C₁₃	Pd(OAc)₂, TFP, CO, NaBPh₄, anisole, 120°	(84)	469
	1. MeO₂C CO₂Me, (PPh₃)₃RhCl, tol, reflux, 4 h 2. Pd(OAc)₂, PPh₃ RSnBu₃, 90°, 12-16 h NaBPh₄, Et₄NCl, 100°, 12-16 h	R 2-thienyl (45) Ph (56)	470
C₂₁	Pd(OAc)₂, PPh₃, CO, 2-furylSnBu₃, tol, 110°	(82)	469
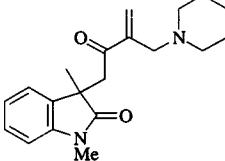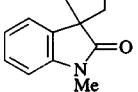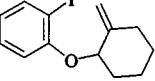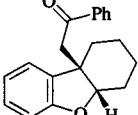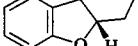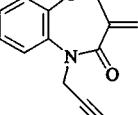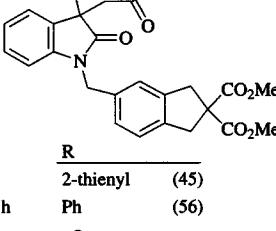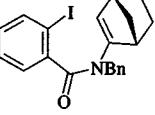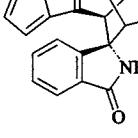
^{a} The polymer is a silane resin from Argonaut Technologies.

TABLE 4. TANDEM REACTIONS (Continued)
B-9a. 5-EXO; REDUCTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉	Pd(PPh₃)₄, HCO₂H, piperidine, CH₃CN, reflux, 17 h	(40)	231

C₁₀₋₂₈

R¹	R²	R³	R⁴	R⁵	R⁶	Conditions	Solv	Temp	Time	I	II	Refs.
H	H	H	H	H	H	Pd(OAc)₂(PPh₃)₂, Et₃N, HCO₂H	DMF	50°	1.5 h	(91)	(0)	471
H	H	H	H	Me	H	PdCl₂(CH₃CN)₂, Et₃N, HCO₂H	DMF	50°	3.5 h	(42)	(0)	471
Me	I	H	I	H	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(11)	(0)	472
OMe	H	OSO₂Ph	H	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(20)	(0)	472
OBn	H	OSO₂Ph	I	H	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(71)	(0)	472
OBn	H	OSO₂Ph	H	H	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(51)	(0)	471, 472
H	H	H	H	OMe	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(57)	(0)	189, 472
H	H	H	H	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(58)	(0)	189, 472
H	H	H	H	OC₅H₁₁-n	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(11)	(0)	472
OBn	H	OSO₂Ph	H	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, Bu₄NCl, NaOCHO	DMF	50-80°	—	(57)	(0)	189, 472
OBn	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, Bu₄NCl, dppe, NaOCHO	DMF	85°	4 h	(20)	(21)	472
OBn	H	OMe	I	O(CH₂)₂TMS	I	PdCl₂(CH₃CN)₂, Bu₄NCl, dppe, n-Bu₃SnH	C₆H₆	85°	23 h	(6)	(7)	472
OBn	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, dppe, n-Bu₃SnH	C₆H₆	81°	2 h	(31)	(34)	472
2-O₂NC₆H₄CH₂	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, dppp, LiOCHO	DMF	85°	3 h	(27)	(31)	472
OCON(CH₂)₅-c	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, dppe, n-Bu₃SnH	tol	110°	4 h	(27)	(40)	472
OCONPh₂	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, dppe, LiOCHO	DMF	120°	22 h	(0)	(15)	472
OCONMe₂	H	OMe	I	O(CH₂)₂TMS	I	PdCl₂(CH₃CN)₂, dppe, n-Bu₃SnH, ultrasound	C₆H₆	82°	3 h	(11)	(27)	472
OCONMe₂	H	OMe	I	O(CH₂)₂TMS	H	PdCl₂(CH₃CN)₂, dppe, LiOCHO	DMF	110°	12 h	(30)	(0)	472

TABLE 4. TANDEM REACTIONS (*Continued*)

B-9a. 5-EXO; REDUCTIVE (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₀₋₁ₜ · Pd(OAc)₂, PPh₃, NaOCHO, Et₄NCl, 80°

R	Solv	Time	I	II	III	
H	CH₃CN	24 h	(68)	(0)	(0)	140
H	DMF	16 h	(22)	(38)	(45)	122
Bn	CH₃CN	12 h	(80)	(0)	(0)	140

C₁₀ · Pd(OAc)₂, NaOCHO, Et₃N, n-Bu₄NBr, DMF, 80°, 24 h · (65) · 231

C₁₁₋₁ₜ · Pd(OAc)₂, PPh₃, HCO₂H, CH₃CN, 60°, 12 h · 473

R¹	R²		I	II
H	H	piperidine	(40-60)	(0)
CO₂Et	H	piperidine	(40-60)	(0)
H	Me	piperidine	(40-60)	(0)
H	CH₃-N-piperidinyl	—	(0)	(30)

C₁₁ · Pd(0), HCO₂Na, Et₄NCl, DMF, 110°, 3 h · (68) · 101

C₁₃₋₁ₜ · Pd(OAc)₂, PPh₃, CH₃CN · 464

R		Temp	Time	
Me	Ag₂CO₃, HCO₂H	rt	16 h	(60)
SiMe₃	Et₄NCl, HCO₂H, piperidine	60°	1 h	(50)
CH₂-N-piperidinyl	Ag₂CO₃, NaOCHO	60°	5 h	(54)
CH₂NEt₂	Ag₂CO₃, NaOCHO	60°	15 h	(56)

C₁₃ · Pd(CH₃CN)₂Cl₂, Et₃NH⁺HCO₂⁻, n-Bu₄NCl, DMF, 90°, 30 min · (97) · 189

· PdCl₂(CH₃CN)₂, HCO₂H, Et₃N, DMF, 50° · (64) + (8) · 474

C₁₃₋₁₅ · Pd(OAc)₂, PPh₃, NaOCHO, n-Pr₄NBr, DMF, 75-80°

R		
O	(58)	123
NCOCF₃	(22)	

C₁₃₋₁₈ · Pd(OAc)₂, PPh₃, HCO₂H, piperidine · 464

R	Solv	Temp	Time	I	II	III
H	DMF	60°	11 h	(0)	(38)	(0)
H	CH₃CN	80°	43 h	(0)	(32)	(8)
SiMe₃	C₆H₆	30°	9 h	(47)	(0)	(0)
SiMe₃	CH₃CN	80°	—	(30)	(20)	(0)
SiMe₃	CH₃CN	80°	—	(73)	(4)	(3)

TABLE 4. TANDEM REACTIONS (Continued)
B-9a. 5-EXO; REDUCTIVE (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{14-18}$

Pd(OAc)$_2$, PPh$_3$, NaOCHO, DMF, 85-90°, 24 h

R^1	R^2	R^3	R^4	I	II
H	H	Me	CO$_2$Me	(73)	(0)
H	OMe	Me	CO$_2$Me	(77)	(0)
OMe	H	Me	CO$_2$Me	(73)	(0)
H	H	Me	Me	(82)	(6)
H	OMe	Me	Me	(90)	(0)
OMe	H	Me	Me	(89)	(0)
H	H	H	H	(77)	(0)
H	OMe	Me	H	(82)	(0)

476

C$_{15}$

Pd(OAc)$_2$, PPh$_3$, n-Pr$_4$NBr, NaOCHO, DMF, 75-85°, 2-3 h

(22)

123

C$_{16}$

Pd(OAc)$_2$, PPh$_3$, NaOCHO, Et$_4$NCl, DMF, 120°, 16 h

(54)

140

Pd(OAc)$_2$, PPh$_3$, CO, NaOCHO, Et$_4$NCl, tol, 110°, 7 h

(61)

117

C$_{16-18}$

Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, DMF

R^1	R^2	R^3
H	H	CO$_2$Me
H	OMe	CO$_2$Me
OMe	H	CO$_2$Me
H	H	Me
H	OMe	Me
OMe	H	Me

(—)

477

C$_{17}$

Pd(OAc)$_2$, PPh$_3$, HCO$_2$Na, DMF, 80°, 24 h

(50) + (24)

122, 140

Pd(OAc)$_2$, P(tol-o)$_3$, Et$_3$N, CH$_3$CN, H$_2$O

(60)

364

TABLE 4. TANDEM REACTIONS (Continued)

B-9a. 5-EXO; REDUCTIVE (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, RCO₂Na, Et₄NCL CH₃CN, reflux	I + II R I II H (60) (2) D (—) (0)	390
	Pd(OAc)₂, PPh₃, HCO₂Na, Et₃N, n-Bu₄NHSO₄, H₂O, CH₃CN, 80°	(62)	49
C₁₈	Pd(PPh₃)₂(OAc)₂, HCO₂H, Et₃N, DMF, 80°	R Ph (79) c-C₆H₁₁ (75)	275
	Pd(OAc)₂, PPh₃, NaOCHO, Et₄NCl, DMF, 80°, 18 h	(74)	140
C₁₉	Pd(OAc)₂, PPh₃, HCO₂Na, Et₄NCl, CH₃CN, reflux	I + II R I II Br (56) (24) I (50) (34)	390
	Pd(OAc)₂, PPh₃, NaOCHO, Bu₄NHSO₄, Et₃N, H₂O, CH₃CN, 80°, 24 h	(56) + (10)	50
C₂₀₋₂₁ R¹ R² CH I N Cl	Pd(OAc)₂, PPh₃, DMF, 80-100° HCO₂H, piperidine, 2.5 h NaOCHO, Et₄NCl, 5 h	 (65) (66)	140
C₂₁	Pd(OAc)₂, PPh₃, HCO₂H, piperidine, CH₃CN, 80°, 1-2 h	(65)	122

TABLE 4. TANDEM REACTIONS (*Continued*)

B-9a. 5-EXO; REDUCTIVE (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₂	Pd(OAc)₂, PPh₃, HCO₂Na, Et₄NCl, DMF, 80°, 16 h	(55)	122
	Pd(OAc)₂, PPh₃, HCO₂H, piperidine, CH₃CN, 80°, 4.5 h	(68)	122, 140
	Pd(OAc)₂, PPh₃, K₂CO₃, TlOAc, HCO₂Na, CH₃CN, 110°, 3 h	(84)	192
	Pd(OAc)₂, HCO₂H, n-Bu₃N, CH₃CN, 60°	(39) + (21)	150

C₂₃₋₂₈

Pd(OAc)₂, n-Bu₃N, CH₃CN

R¹	R²	R³	R⁴	R⁵		Temp	Time	I	II	
H	CO₂Me	H	adamantyl	OMe	PPh₃	80°	7 d	(27)	(14)	150
H	CO₂Me	H	adamantyl	OMe	HCO₂H	60°	4 h	(72)	(0)	
H	CO₂Me	H	OMe	adamantyl	HCO₂H	60°	4 h	(91)	(0)	
H	CO₂Me	H	—C(Me)₂(CH₂)₂C(Me)—		HCO₂H	60°	4 h	(68)	(0)	
H	CO₂Me	Me	—C(Me)₂(CH₂)₂C(Me)₂—		HCO₂H	60°	4 h	(55)	(0)	
CO₂Me	H	H	adamantyl	OMe	HCO₂H	60°	4 h	(56)	(0)	
CO₂Me	H	H	—C(Me)₂(CH₂)₂CH₂—		HCO₂H	60°	4 h	(52)	(0)	
CO₂Me	H	H	—C(Me)₂(CH₂)₂C(Me)₂—		HCO₂H	60°	4 h	(70)	(0)	
CO₂Me	H	Me	—C(Me)₂(CH₂)₂C(Me)₂—		HCO₂H	60°	4 h	(42)	(0)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₄	Pd(OAc)₂, PPh₃, HCO₂Na, Et₄NCl, DMF, 120°, 12 h	(70)	470
	Pd(OAc)₂, PPh₃, NaOCHO, Et₄NCl, CH₃CN, 80°, 18 h	(45)	140

TABLE 4. TANDEM REACTIONS (*Continued*)
B-9a. 5-EXO; REDUCTIVE (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{26}$	Pd(OAc)$_2$, PPh$_3$, NaOCHO, Et$_4$NCl, CH$_3$CN, 80°, 20 h	(55)	140
C$_{27}$	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, NaOCHO, CH$_3$CN, 80°, 15 h	(60)	118
	Pd(OAc)$_2$, n-Bu$_3$N, HCO$_2$H, CH$_3$CN, 60°, 4 h	(85) 18% de	150

TABLE 4. TANDEM REACTIONS (*Continued*)
B-9b. 5-EXO DIENE; REDUCTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, pyrolidine, CH$_3$CN, reflux, 6 h	(34) + (33)	140
C$_{18}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, piperidine, CH$_3$CN, reflux, 3 h	(22) + (45)	140
C$_{21}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, piperidine, CH$_3$CN, reflux, 19 h	(45) + (45)	140
C$_{24}$	Pd(OAc)$_2$, PPh$_3$, NaOCHO, Et$_4$NCl, DMF, 80°, 24 h	(16) + (64)	140

TABLE 4. TANDEM REACTIONS (Continued)
B-10. 5-EXO; STILLE REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_9$

Bu$_3$Sn ———— OTBDMS ,
Pd(PPh$_3$)$_4$, THF, 40-45°

(32)

478

C$_{9-13}$

Bu$_3$Sn ———— OR^3

R^1	R^2	R^3			
I	H	TBDMS	Pd(PPh$_3$)$_4$, THF	(70-80)	478
I	MOM	TBDMS	Pd(PPh$_3$)$_4$, THF	(—)	478
I	TBDMS	TBDMS	Pd(PPh$_3$)$_4$, THF	(—)	478
Br	H	TBDMS	Pd(PPh$_3$)$_4$, THF	(—)	478
Br	Bn	THP	Pd(OAc)$_2$, PPh$_3$, tol, 60°, 5 h	(51)	479
Br	Bn	TBDMS	Pd(OAc)$_2$, PPh$_3$, tol, 60°, 5 h	(28)	479

C$_{10-11}$

R^{2}SnBu$_3$, LiCl,
DMF, 60°, 8 h

480

I   II

III   IV

R^1	R^2		I	II	III	IV
OTf	vinyl	Pd(OAc)$_2$, PPh$_3$, Et$_3$N	(63)	(0)	(0)	(0)
OTf	allyl	Pd(PPh$_3$)$_4$	(46)	(39)	(0)	(0)
OTf	allyl	Pd(dppf)Cl$_2$	(37)	(0)	(30)	(0)
OTf	———TMS	Pd(dppf)Cl$_2$	(44)	(0)	(0)	(9)
OTf	———TMS	Pd(OAc)$_2$, PPh$_3$, Et$_3$N	(45)	(0)	(0)	(0)
OTf	Me$_3$Si	Pd(PPh$_3$)$_4$	(37)	(0)	(0)	(0)
I	allyl	Pd(PPh$_3$)$_4$	(43)	(5)	(0)	(0)
I	Me$_3$Si	Pd(PPh$_3$)$_4$	(54)	(10)	(0)	(0)

C$_{18}$

Pd(OAc)$_2$, PPh$_3$, RSnBu$_3$,
Et$_4$NCl, tol, 90°, 8 h

R		
CH=CH$_2$	(45)^a	101, 131
trans-2-styryl	(90)	101, 131
2-furyl	(95)	101, 131
3-(1-SEM-indolyl)	(92)	100, 131
3-(1-phenylsulfonylindolyl)	(86)	131
2-pyridyl	(60)	131

C$_{10-16}$

1. R^{3}CH$_2$———— , Pd$_2$(dba)$_3$,
TFP, n-Bu$_3$SnH, tol, 0°
2. Substrate, 110°

481

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

R^1	R^2	R^3		dr	
NMe	O		(64)	1:1	
O	H, H		(66)	1:1	
NMe	O		(65)	1:1	
O	H, H	"	(63)	1:1	
NSO$_2$Ph	H, H		(59)[b]	1:1	
O	H, H		(59)	1:1	
NSO$_2$Ph	H, H		(60)	1:1	
O	H, H	"	(60)	1:1	
NMe	O		(67)	—	
O	H, H	"	(68)	—	
NSO$_2$Ph	H, H		(63)	—	
O	H, H	"	(66)	—	
NSO$_2$Ph	H, H		(72)	—	
O	H, H	"	(80)	—	
NMe	O		(64)	1:1	

C_{11-14}

R^1		R^2	Temp	Time		
H	THF	vinyl	rt	2-5 h	(42)	130, 131
Me	CH$_3$CN	vinyl	5-25°	2-6 h	(60)	130, 131
SiMe$_3$	CH$_3$CN	vinyl	5-25°	2-6 h	(50)	130, 131
H	Et$_4$NCl, THF	allyl	60°	0.5-3 h	(54)	130, 131
Me	Et$_4$NCl, THF	allyl	60°	0.5-3 h	(55)	130, 131
H	CH$_3$CN	—≡—Bu-n	5-25°	2-6 h	(40)	130

Pd(OAc)$_2$, PPh$_3$, R^{2}SnBu$_3$

404

405

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₁

n-Bu SnMe₃, Pd(PPh₃)₄, THF, HMPA, reflux

(69) + (<2) 482

C₁₃

1. MeO₂C, MeO₂C ═══ , (PPh₃)₃RhCl, tol, reflux, 4 h;
2. Pd(OAc)₂, PPh₃, 2-tributylstannylthiophene, 100°, 12-16 h

(41) 470

C₁₃₋₂₀

1. Pd(OAc)₂, PPh₃, n-Bu₃SnH, tol, 25°, 1h
2. 100°
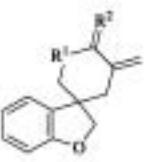
R¹	R²	
O	H, H	(70)
NSO₂Ph	H, H	(79)
NCOPh	H, H	(67)
NBn	O	(56)

483, 484

C₁₅

Pd(OAc)₂, TFP, Bu₃SnCH=CH₂, tol, 110°

(67) 342

C₁₇

Pd(OAc)₂, PPh₃, RSnBu₃, Et₄NCl, tol, 90°, 8 h

R		
2-furyl	(90)	131
trans-2-styryl	(89)	101, 131
2-(1-SEM-indolyl)	(82)	101, 131
3-(1-SEM-indolyl)	(92)	131
3-(1-PhSO₂-indolyl)	(80)	131

n-Bu₃Sn, C₅H₁₁-n, Pd(OAc)₂, n-Bu₄NCl, i-Pr₂NEt, DMF, 25°, 12 h

(15) + (15) 105

C₁₉

Pd(OAc)₂, TFP, Bu₃SnCH=CH₂, tol, 110°, 15 h

(77) 342

Me₃Sn ═══ C₆H₁₃-n, Pd(PPh₃)Cl₂, DMF, 100°, 3 h

(29) + (12) 455

C₂₀

Bu₃Sn ═══ OTBDMS, Pd(PPh₃)₄, tol, 70°, 5-6 h

(75) 129

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C[21]

Pd(OAc)$_2$, PPh$_3$, R^{1}Sn(R^2)$_3$

R^1	R^2	Solv	Temp	Time	I		II		
vinyl	n-Bu	CH$_3$CN	80°	1 h	(63)		(0)		130, 131
Me$_3$Sn	Me	CH$_3$CN	80°	1 h	(80)		(0)		130, 131
2-furyl	n-Bu	tol	110°	2 h	(32)		(0)		131
2-pyridyl	n-Bu	tol	110°	2 h	(40)		(0)		130, 131
2-thiazolyl	n-Bu	THF	60°	—	(40)		(0)		130, 131
≡—Ph	n-Bu	THF[b]	60°	4 h	(41)		(5)		130
≡—Ph	n-Bu	THF	60°	15 h	(19)		(19)		130

C[22]

Pd(OAc)$_2$, PPh$_3$, RSnBu$_3$, Et$_4$NCl
CH$_3$CN, 80°, 4.5 h

R	I	II	
vinyl	(47)	(8)	130
allyl	(23)	(12)	

C[23-29]

1. Pd$_2$dba$_3$, TFP, n-Bu$_3$SnH, tol, 0°
2. 100°, 12 h

n	ring size		
2	11	(38)	484
3	12	(53)	483, 484
4	13	(52)	483, 484
5	14	(52)	483, 484
6	15	(53)	483, 484
7	16	(50)	483, 484
8	17	(53)	483, 484

C[24-33]

		ring size	Temp	Time		
R	n					
O	3	1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_3$SnH, tol	12	25°	1 h	(59)	483, 484
		2. Heat		100°	—		
O	4	1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_3$SnH, tol	13	25°	1 h	(44)	483, 484
		2. Heat		100°	—		
O	5	1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_3$SnH, tol	14	25°	1 h	(59)	483, 484
		2. Heat		100°	—		
NSO$_2$Ph	6	1. Pd$_2$dba$_3$, TFP, n-Bu$_3$SnH, tol	15	0°	—	(23)	484
		2. Heat		110°	—		

C[25-29]

Pd$_2$dba$_3$, TFP, n-Bu$_3$SnH,
LiCl, tol, 100°

n	ring size		
6	13	(51)	483, 484
7	14	(30)	483, 484
8	15	(39)	483, 484
10	17	(37)	484

[a] The styrene Stille product from reaction of the aryl iodide with the vinyl stannane was also isolated in 28% yield.
[b] This was the yield after THP removal with 0.2 M HCl, THF, 1 d.
[c] This was the yield after THP and acetonide removal with 2 M HCl, THF, 1 d.

TABLE 4. TANDEM REACTIONS (*Continued*)
B-11. 5-EXO; SUZUKI REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{8-14}$

Pd(PPh$_3$)$_4$, R^{3}B(OH)$_2$,
Na$_2$CO$_3$, H$_2$O, THF, 80°

R^1	R^2	R^3	I	II	III
Ac	H	Ph	(18)	(0)	(0)
Bn	H	4-FC$_6$H$_4$	(30)	(0)	(0)
Ts	H	4-FC$_6$H$_4$	(92)	(0)	(0)
Ts	H	Ph	(75)	(0)	(0)
Ts	H	1-naphthyl	(88)	(0)	(0)
Ts	H	4-MeOC$_6$H$_4$	(69)	(0)	(0)
Ts	H	3-O$_2$NC$_6$H$_4$	(49)	(0)	(0)
Ts	H	2-furanyl	(0)	(20)	(6)
Ts	H	ferrocenyl	(0)	(46)	(15)
Ts	Me	Ph	(42)	(18)	(0)

387

C$_9$

Pd(OAc)$_2$, PPh$_3$, tol

R	I	II
Ph	(65)	(trace)
E-CH=CHPh	(60)	(trace)

128

NaBPh$_4$, 110°, 1 h
E-2-(2'-phenylethenyl)-
1,3,2-benzodioxaborole,
Na$_2$CO$_3$, H$_2$O, 90°, 1.5 h

C$_{10}$

1. Pd(OAc)$_2$, PPh$_3$, tol, rt,
10 min
2. Na$_2$CO$_3$, Et$_4$NCl, H$_2$O

128

Added in step 2	R	Temp (step 2)	Time (step 2)	
RBEt$_2$	3-pyridyl	110°	10 h	(72)
RB(OH)$_2$, EtOH	Ph	110°	8 h	(91)
RB(OH)$_2$, EtOH	3-O$_2$NC$_6$H$_4$	110°	2 h	(93)
RB(OH)$_2$, EtOH	4-BrC$_6$H$_4$	110°	4 h	(90)
RB(OH)$_2$, EtOH	E-CH=CHPh	90°	8 h	(67)
RB(OH)$_2$, EtOH	2-furyl	110°	8 h	(85)
RB(OH)$_2$, EtOH	3-1-(phenylsulfonyl)indole	90°	8 h	(60)

C$_{11}$

n-Bu benzodioxaborole-1,3,2
Pd(PPh$_3$)$_4$, C$_6$H$_6$, reflux

(41) + (<4) 482

C$_{12}$

Pd(OAc)$_2$, PPh$_3$

R	
Ph	(31)

111, 128

1. Anisole, rt, 15 min
2. NaBPh$_4$, 80°, 1 h

1. THF, rt, 10 min; 2. E-hex-1-enyl-
1,3,2-benzodioxaborole,
KOH, H$_2$O, 50°, 2.5 h

E-CH=CHBu-n (41)

C$_{13}$

1. MeO$_2$C ≡ , MeO$_2$C ≡ ,
(PPh$_3$)$_3$RhCl, tol, reflux, 4 h
2. Pd(OAc)$_2$, PPh$_3$

470

R	Temp	Time	
RBEt$_2$	3-pyridyl	110° 12-16 h	(49)
NaBPh$_4$	Ph	100° 12-16 h	(54)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{16}$ — Substrate

Conditions:
1. Pd(OAc)$_2$, PPh$_3$, R^{1}B(R^2)$_2$, tol, rt, 10 min
2. Na$_2$CO$_3$, Et$_4$NCl, H$_2$O, EtOH, 110°

Product:

R^1	R^2	Time		
Ph	OH	8 h	(60)	128
3-pyridyl	Et	8 h	(70)	
3-O$_2$NC$_6$H$_4$	OH	8 h	(63)	
4-BrC$_6$H$_4$	OH	12 h	(58)	

Substrate (OTf, CO$_2$Me)

Conditions: Pd(OAc)$_2$, PPh$_3$, Na$_2$CO$_3$, Et$_4$NCl

Product (R, CO$_2$Me)

Refs. 127, 128
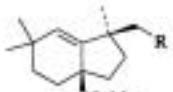
Conditions	R
Diethyl(3-pyridyl)borane, toluene, reflux (92)	3-pyridyl
3-Nitrophenylboronic acid, toluene, reflux (94)	3-O$_2$NC$_6$H$_4$
NaBPh$_4$, DMF, 100°, 8 h (90)	Ph

C$_{17}$ — Substrate

Conditions: Pd(OAc)$_2$, PPh$_3$

Product (R^1, Bn, O)

	R^1	R^2	Time		
1. R^{1}B(R^2)$_2$, tol, rt, 10 min	Ph	OH	10 h	(98)	128
2. Na$_2$CO$_3$, Et$_4$NCl, H$_2$O, EtOH, 110°					
"	3-O$_2$NC$_6$H$_4$	OH	8 h	(95)	128
"	4-BrC$_6$H$_4$	OH	8 h	(96)	128
"	E-CH=CHPh	OH	8 h	(72)	128
"	2-furyl	OH	8 h	(74)	128
"	3-1-(phenylsulfonyl)indole	OH	8 h	(65)	128
"	3-pyridyl	Et	9 h	(72)	128
1. R^{1}B(R^2)$_2$, C$_6$H$_6$, rt, 10 min	E-1-hexenyl	benzodioxaborole	5 h	(35)	111, 128
2. NaOEt, EtOH, reflux, 5 h					

C$_{21}$ — Substrate

Conditions: Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, NaBPh$_4$, CH$_3$CN, 80°, 19 h

Product (56), Refs. 128

Substrate (n-Bu, NBn, O)
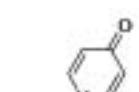
Conditions: Pd(OAc)$_2$, PPh$_3$, E-hex-1-enyl-1,3,2-benzodioxaborole, NaOEt, C$_6$H$_6$, 60°, 6 h

Product (48) + (48), Refs. 111, 128

C$_{24$}$ — Substrate
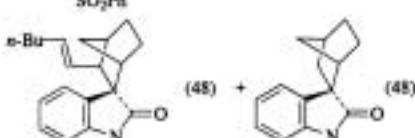
Conditions: Pd(OAc)$_2$, PPh$_3$, NaOEt, E-hex-1-enyl-1,3,2-benzodioxaborole, C$_6$H$_6$, 80°, 24 h

Product (10), Refs. 111

TABLE 4. TANDEM REACTIONS (*Continued*)
B-12. 5-EXO; ORGANOZINC

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_9$

Pd(OAc)$_2$, PPh$_3$, RZnCl, Et$_3$N, THF, rt, 2 h

R	
Ph	(62)
2-furyl	(44)
2-thienyl	(48)
2-*N*-methylpyrrolyl	(54)
2-pyridyl	(47)
3-pyridyl	(64)

485

C$_{10-13}$

Pd(PPh$_3$)$_4$, R^{2}ZnCl, THF, 8 h

Products I, II, III

R^1	R^2	Temp	I	II	III	
H	2-pyridyl	rt	(66)	(trace)	(0)	486
H	3-pyridyl	rt	(53)	(trace)	(0)	486
H	2-furyl	rt	(58)	(28)	(0)	486
H	2-thienyl	rt	(74)	(6)	(0)	486
H	2-*N*-methylpyrrolyl	rt	(52)	(33)	(0)	486
H	2-benzothiazolyl	rt	(70)	(21)	(0)	486
H	vinyl	60°	(53)	(0)	(0)	480
H	TMS—≡	60°	(69)	(0)	(0)	480
H	allyl	60°	(trace)	(0)	(46)	480
H	Me$_3$Si	60°	(8)	(0)	(23)	480
H	Ph	rt	(60)	(0)	(0)	487
Me	Ph	rt	(68)	(0)	(0)	487
Me	*E*-CH=CHPh	rt	(19)	(68)	(0)	482
SiMe$_3$	Ph	rt	(46)	(0)	(0)	487

C$_{10-12}$

Pd(OAc)$_2$, PPh$_3$

Products I, II

R^1		R^2	Temp	Time	I	II	
H	PhZnCl, Et$_2$O, THF	Ph	rt	4-5 h	(60)	(0)	111
Me	PhZnCl, Et$_2$O, THF	Ph	rt	4-5 h	(43)	(0)	
Me	EtO$_2$CCH$_2$ZnBr, Et$_2$O, HMPA	CH$_2$CO$_2$Et	35°	18 h	(36)	(26)	

C$_{18}$

Pd(OAc)$_2$, PPh$_3$, RZnCl, Et$_3$N, THF, rt, 2 h

R	
Ph	(76)
2-furyl	(72)
2-thienyl	(67)
2-pyridyl	(56)
n-Bu	(67)
2-styryl	(69)
n-Bu—≡	(61)
Me$_3$Si—≡	(53)

133

C$_{18}$ (cyclohexene substrate)

Pd(OAc)$_2$, PPh$_3$, PhZnCl, Et$_2$O, THF, 50°, 2.5 h

(66)

111

C$_{19}$

ClZr—≡—C$_6$H$_{13}$-*n*, Pd(PPh$_3$)Cl$_2$, *n*-BuLi, Et$_3$N, DMF, 100°, 2 h

(53)

455
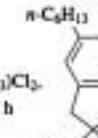
TABLE 4. TANDEM REACTIONS (*Continued*)

B-12. 5-EXO; ORGANOZINC (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{21}	Pd(OAc)$_2$, PPh$_3$, PhZnCl, Et$_2$O, THF, 25°, 3 h	(19) + (49) + (18)	111
C_{24}	Pd(OAc)$_2$, PPh$_3$, PhZnCl, THF, 50°, 7 h	(21) + (62)	219

TABLE 4. TANDEM REACTIONS (*Continued*)

B-13. 5-EXO; SONOGASHIRA REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)			Refs.
C_{11-13}	≡—R^2, Pd(OAc)$_2$, PPh$_3$, CuI, Et$_3$N, CH$_3$CN, reflux, 10-14 h		R^1 R^2		488
			H C(CH$_3$)$_2$OH	(77)	
			H 1-hydroxycyclohexyl	(92)	
			H CH$_2$OTHP	(76)	
			H n-C$_6$H$_{13}$	(70)	
			Et C(CH$_3$)$_2$OH	(79)	
			Et 1-hydroxycyclohexyl	(97)	
			Et CH$_2$OTHP	(84)	
			Et n-C$_6$H$_{13}$	(73)	
C_{12}	Pd(PPh$_3$)$_2$Cl$_2$, n-BuLi, 1-octyne, Et$_3$N, DMF, 125°, 1.5 h	(75)			455
C_{15}	≡—R, Pd(OAc)$_2$, PPh$_3$, CuI, Et$_3$N, CH$_3$CN, reflux, 10-14 h		R		488
			C(CH$_3$)$_2$OH	(81)	
			n-C$_6$H$_{13}$	(61)	
C_{21}	Pd(OAc)$_2$, PPh$_3$Ph—≡ , KOAc, C$_6$H$_6$, 80°, 8 h	(30)			489

TABLE 4. TANDEM REACTIONS (Continued)
B-14. 5-EXO; π-ALLYL

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_6	Pd(OAc)₂, P(tol-o)₃, piperidine, 100°, 4 h	(44) + (19)	298
$C_{6,7}$	Pd(OAc)₂, P(tol-o)₃, piperidine	I + II	490

$$\begin{array}{ccc} R & I & II \\ \hline H & (68) & (9) \\ H & (—) & (29) \quad C_6H_5 \\ Me & (30) & (0) \quad 100°, 60 \text{ h} \end{array}$$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
$C_{6,8}$	Pd(OAc)₂, P(tol-o)₃, piperidine, 100°	I + II	298

$$\begin{array}{ccc} R & I & II \\ \hline H & (15) & (4) \\ Me & (33) & (11) \\ Ac & (38) & (38) \end{array}$$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7	Pd(OAc)₂, P(tol-o)₃, piperidine, CH₃CN, 100°, 64 h	(60)	298
	Pd(OAc)₂, P(tol-o)₃, Et₃N, 100°, 5 h	(47)	298
$C_{7,8}$	Pd(OAc)₂, P(tol-o)₃, piperidine, 100°	R Time; H 44 h (71); Me 168 h (40)	490
C_7	Pd(OAc)₂, CH₂(CO₂Me)₂, NaH, n-Bu₄NCl, DMF, 90°, 26 h	I + II + III	491, 492

$$\begin{array}{ccc} I & II & III \\ \hline (50) & (18) & (12) \quad P(tol-o)_3 \\ (11) & (10) & (20) \quad dppp \end{array}$$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_9		I + II	

R		Solv	Temp	Time	I	II	
Pd(PPh₃)₄, NaR	N₃	DMF	rt	12 h	(71)	(0)	121
Pd(PPh₃)₄, NaR	SO₂Ph	DMF	rt	12 h	(64)	(0)	121
Pd(OAc)₂, PPh₃, K₂CO₃, RH	N-1,2,3,4-tetrahydroisoquinolinyl	CH₃CN	80°	6 h	(71)	(0)	120
Pd(OAc)₂, PPh₃, Ag₂CO₃, RH	N-1,2,3,4-tetrahydroisoquinolinyl	CH₃CN	60°	6 h	(0)	(83)	120

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, P(tol-o)₃, piperidine, 100°, 42 h	(41)	298
C_{10}	Pd(PPh₃)₂Cl₂, CH₂(CO₂Et)₂, K₂CO₃, EtOH, DMF, 120°, 2 h	(61)	82

TABLE 4. TANDEM REACTIONS (Continued)
B-14. 5-EXO: π-ALLYL (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₁

Pd(OAc)₂, DIPHOS, Bu₄NOAc, CH₃CN, 60°, 112 h — (52) — 154, 155
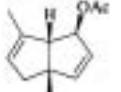
Pd(OAc)₂, DIPHOS, Bu₄NOAc, tol, 50° — (61) — 155

C₁₁₋₂₃

Pd₂(dba)₃, n-Bu₄NCl, DMSO, 100° — 447

R¹	R²		R³	Time	
H	H	CH₂(CO₂Et)₂, K₂CO₃	CH(CO₂Et)₂	22 h	(70)
H	H	PhNH₂, Na₂CO₃	PhNH	22 h	(62)
H	Me	CH₂(CO₂Et)₂, K₂CO₃	CH(CO₂Et)₂	22 h	(65)
H	Me	PhNH₂, Na₂CO₃	PhNH	18 h	(79)
Ph	Ph	CH₂(CO₂Et)₂, K₂CO₃	CH(CO₂Et)₂	23 h	(80)
Ph	Ph	morpholine, Na₂CO₃	N-morpholino	23 h	(78)
Ph	Ph	LiOAc•H₂O, LiCl	OAc	26 h	(50)

C₁₂

Pd₂(dba)₃, o-IC₆H₄OH, NaHCO₃, n-Bu₄NCl, DMSO, 100°, 23 h — (51) — 447
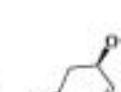
C₁₄

Pd₂(dba)₃, RH, n-Bu₄NCl, DMSO, 24 h — 447

R	Base	Temp	
CH(CO₂Et)₂	K₂CO₃	80°	(69)
PhNH	Na₂CO₃	100°	(100)

Pd(OAc)₂, P(tol-o)₃, NaH, n-Bu₄NCl, DMF, 50°, 24 h — (50) + (24) — 491, 492

C₁₅

Pd(0), 1,2,3,4-tetrahydroisoquinoline, CH₃CN, 80°, 18 h — (60) — 100

Pd₂(dba)₃, n-Bu₄NCl, DMSO — 447

R	Temp	Time	
CH(CO₂Et)₂	RH, K₂CO₃	80°	27 h	(80)
OAc	RLi•2H₂O, LiCl	100°	26 h	(67)

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, Bu₄NCl, DMF, 65°, 24 h — (49) — 493, 515

C₁₅₋₂₂

Pd(OAc)₂, PPh₃, CH₃CN, 80° —

R¹	R²		R³	Time		Z:E	
CO₂Et	H	R³Na	CH(CN)₂	1 h	(91)	8:1	489
CO₂Et	H	R³SnBu₃, LiCl	vinyl	48 h	(60)	0:100	131, 130
CO₂Et	Me	HCO₂H, pyrrolidine	H	1-2 h	(77)	1:1	122
CO₂Et	Me	R³Na	CH(CN)₂	1 h	(56)	3:1	489
SO₂Ph	Me	R³Na	CH(CN)₂	1 h	(83)	1:1	489
CO₂Et	Me	R³Na	CH(CO₂Et)₂	1 h	(83)	0:100	489

TABLE 4. TANDEM REACTIONS (*Continued*)

B-14. 5-EXO; π-ALLYL (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₆

PhO₂S ... Br

Pd(OAc)₂, P(tol-o)₃, NaH, n-Bu₄NCl, DMF, 50°, 24 h

PhO₂S ... (32) + PhO₂S ... (32) 491, 492

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, Bu₄NCl, DMF

I + II   493, 515

R	Temp	Time	I	II
Bn	—	—	(10)	(0)
Ts	65°	48 h	(62)	(16)

R–NH ... Br

Pd(OAc)₂, P(tol-o)₃

R	Temp	Time	
Bn	100°	28 h	(31)
Ts	75°	22 h	(67)

Et₃N, CH₃CN
Na₂CO₃, Bu₄NCl, DMF

C₁₇

TsHN ... Br

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, n-Bu₄NCl, DMF, 100°, 48 h

(52)   493, 515

TsHN ... I

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, n-Bu₄NCl, DMF, 70°, 48 h

(39)   493, 515

C₂₁

... Br

Pd(OAc)₂, PPh₃, CH₃CN, 80°

HCO₂H, pyrrolidine, 1–2 h
RSnBu₃, LiCl, 24 h

R		
H	(90) 1.3:1 *E:Z*	122
CH=CH₂	(60) 100% *E*	130, 131

C₂₂

... OAc

Pd(OAc)₂, PPh₃, 18 h

CH(CO₂Me)₂ ... NBn / NBn

I + II   489

(MeO₂C)₂CHNa, DMF, 100°
1,2,3,4-tetrahydroisoquinoline, tol, 110°

	I	II
	(40)	(10)
	(0)	(60)

C₂₄₋₂₅

R¹	
Bn	
Bn	
Bn	
Bn	
Bn	
Bn	
Bn	
Bn	

Pd(OAc)₂, PPh₃, 80°

I + II + III

	R²	Solv	Time	I	II + III	
HCO₂Na	H	DMF	24 h	(0)	(80)	122
R²SnBu₃, Et₄NCl	vinyl	CH₃CN	—	(60)	(0)	131, 130
R²SnBu₃, Bu₄NCl	2-thiazolyl	CH₃CN	—	(10)	(—)	130
R³SnBu₃, Et₄NCl	Me₃Sn	CH₃CN	—	(10)	(—)	130
R²Na, CH₃CN	CH(CN)₂	CH₃CN	1 h	(60)	(0)	489
R²H, CH₃CN	morpholino	CH₃CN	1 h	(40–60)	(0)	489
R³H, CH₃CN	1,2,3,4-tetrahydroisoquinolinyl	CH₃CN	1 h	(40–60)	(0)	489
R²Li, Et₄NCl, K₂CO₃	OAc	DMF	4 h	(50)	(0)	489

TABLE 4. TANDEM REACTIONS (*Continued*)
B-15. 5-EXO; CAPTURE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{17}$	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, C$_6$H$_6$, 80°, 8 h	(62)	125
C$_{18}$	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, C$_6$H$_6$, 80°, 12 h	(68)	125
C$_{21}$	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, C$_6$H$_6$, 80°, 8 h	(50)	125

TABLE 4. TANDEM REACTIONS (*Continued*)
B-16a. 5-EXO; 5-AROMATIC CYCLIZATION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{20-21}$	Pd(OAc)$_2$, PPh$_3$, KOAc, anisole, 130°	 R Time H 64 h (59) CHO 24 h (81)	118
C$_{21}$	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 3.5 h	(80)	118
	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 3 h	(75)	118
C$_{24-25}$ R H CHO Me	Pd(OAc)$_2$, PPh$_3$ K$_2$CO$_3$, Et$_4$NCl, CH$_3$CN KOAc, anisole KOAc, anisole	 Temp Time 60° 15 h (74) 130° 24 h (91) 130° 24 h (77)	118

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{16-18}

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$

	R^1	R^2	R^3		Temp	Time	
	CH	I	O	tol	110°	18 h	(72)
	CH	I	S	tol	110°	18 h	(72)
	N	Cl	O	Et$_4$NI, DMF	130°	16 h	(70-72)
	N	Cl	S	Et$_4$NI, DMF	130°	16 h	(70-72)

475

C_{16-18}

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°, 16 h

R^1	R^2	R^3	
CH	I	H	(70-71)
CH	I	Me	(70-71)
N	Cl	H	(70-71)

475

C_{19-24}

R

O

C(CO$_2$Me)$_2$

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°

	I:II	
(73)	6:1	
(78)	6:1	

414

C_{22}

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 3.5 h

(68)

118

C_{23}

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, K$_2$CO$_3$, CH$_3$CN, 80°, 3.5 h

(68)

118

C_{26}

Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, anisole, 130°, 24 h

(50)

475

C_{27}

Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, TlOAc

R	Solv	Temp	Time	
O	CH$_3$CN	80°	15 h	(64)
S	DMF	100°	9 h	(41)

118

TABLE 4. TANDEM REACTIONS (*Continued*)

B-17. 5-EXO; DIELS-ALDER REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C[7-13]

R[1]		R[2]	R[3]	R[4]		dr
H		CO$_2$Me	H	H	(87)	1:2
COMe		CO$_2$Me	H	H	(87)	1:2
TBDMS		CO$_2$H	H	H	(77)	1:2
TBDMS		CO$_2$Bu-*t*	H	H	(73)	1:2
TBDMS		CO$_2$Me	H	CO$_2$Et	(80)	1:4
THP		CO$_2$Me	H	H	(77)	4 diastereomers
THP		CO$_2$Me	Me	H	(86)	(—)

R[1]	R[2]	R[3]	R[4]			Refs.
Me	O	H$_2$	CO$_2$Me	dppe	(55)[a]	15, 104
H	NCHO	H$_2$	CO$_2$Me	dppe	(62)	15, 104
H	NBn	H$_2$	CO$_2$Me	dppe	(46)	15, 104
H	NAc	H$_2$	CO$_2$Bu-*t*	dppe	(63)	15, 104
H	NSO$_2$C$_6$H$_4$NO$_2$-*p*	H$_2$	CO$_2$Bu-*t*	dppe	(72)	15, 104
Me	NBn	O	CO$_2$Me	dppe	(51)[b]	15, 104
H	CHOH	H$_2$	CO$_2$Me	PPh$_3$	(87)	104

C[11]

1. Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 90°, 90 min	2. diethyl diazodicarboxylate	(78)	134
1. Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 90°, 90 min	2. DMAD	(94)	134
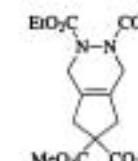
C[12]

Pd(OAc)$_2$, PPh$_3$, methyl acrylate, Ag$_2$CO$_3$, CH$_3$CN, 90°, 45 min	I + II (67)	134
Pd(OAc)$_2$, PPh$_3$, methyl acrylate, K$_2$CO$_3$, CH$_3$CN, 90°, 90 min	(48) + (24)	134
Pd(OAc)$_2$, PPh$_3$, methyl acrylate, Ag$_2$CO$_3$, CH$_3$CN, 90°, 90 min	(35) 1:2 dr + (36-59)	134

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, diethyl fumarate, Ag$_2$CO$_3$, CH$_3$CN, 90°, 90 min	(24) + (36-59) 1:1.8 dr	134
C$_{13}$	Pd(OAc)$_2$, PPh$_3$, ethyl acrylate, Ag$_2$CO$_3$, CH$_3$CN, 90°, 45 min	(86)	11
	Pd(OAc)$_2$, PPh$_3$, CH$_3$CN, 90°		134

Temp	Time		R
tert-Butyl acrylate, Ag$_2$CO$_3$	90°	90 min	(68) OBu-*t*
K$_2$CO$_3$, *N*-acryloylcamphorsultam	—	180 min	(57) camphorsultam

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, methyl acrylate, K$_2$CO$_3$, CH$_3$CN, 90°, 180 min	(24) + (44)	134
	1. Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 90°, 45 min 2. DMAD, 50°, 1 h	(94)	255
	R^1, R^2, R^3, R^4, Pd(OAc)$_2$, Ag$_2$CO$_3$, CH$_3$CN, 90°, 45 min	I + II	

R^1	R^2	R^3	R^4		I	de	II	
CN	H	H	H	PPh$_3$	(83)	—	(0)	134, 255
COMe	H	H	H	PPh$_3$	(81)	—	(0)	134, 255
CO$_2$Me	H	H	H	PPh$_3$	(93)	—	(0)	134, 255
CN	Cl	H	H	PPh$_3$	(74)	—	(0)	134
CO$_2$Me	H	CO$_2$Me	H	PPh$_3$	(93)	—	(0)	134
CO$_2$Et	H	CO$_2$Et	H	dmphen	(88)	—	(12)	134
CO$_2$Et	H	CO$_2$Et	H	PPh$_3$	(94)	—	(0)	134
CO$_2$Me	H	H	CO$_2$Me	PPh$_3$	(93)	—	(0)	134, 255
CO$_2$Et	CO$_2$Et	CO$_2$Et	CO$_2$Et	PPh$_3$	(78)	—	(0)	134, 255
—CH$_2$CH$_2$—		CO$_2$Me	H	PPh$_3$	(83)	—	(0)	134
—CH$_2$CH$_2$—		CO$_2$Me	Cl	PPh$_3$	(83)	—	(0)	134, 255
(*R*)-myrtenylO$_2$C	H	H	H	PPh$_3$	(55)	82%	(0)	134
CO-camphorsultam	H	H	H	PPh$_3$	(52)	>95%	(0)	134
CN	CN	CN	CN	PPh$_3$	(79)	—	(0)	134, 255
H	—CH$_2$CH$_2$CO—		H	PPh$_3$, AlCl$_3$	(30)	—	(0)	134
CN	—CH$_2$CH$_2$—		CN	PPh$_3$, 10 kbar, 25°, 3 d	(71)	—	(0)	134
H	—C(CH$_3$)$_2$—		CO$_2$Me	PPh$_3$, 10 kbar, 25°, 3 d	(60)	—	(0)	134

430

431

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 90°, 45 min 2. *p*-Benzoquinone, 65°, 24 h	(43)	134, 255
	Pd(OAc)₂, PPh₃, Ag₂CO₃, 1,4-napthoquinone, CH₃CN, 90°, 45 min	(78)	134
	1. Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 90°, 45 min 2. *p*-benzoquinone, 65°, 24 h	(71) + (<3)	134, 255
C₁₆	R, Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 90°, 45 min	R: COMe (86); CO₂Me (86)	134
	Pd(OAc)₂, PPh₃, methyl acrylate, K₂CO₃, CH₃CN, 90°, 45-180 min	(18) + (32) + (15)	134
C₁₅	Pd(OAc)₂, PPh₃, Ag₂CO₃, diethyl fumarate, CH₃CN, 90°, 90 min	(30)	134
C₁₆	1. Pd(OAc)₂, PPh₃, Tl₂CO₃, NaOCHO, CH₃CN, rt, 3 h 2. *N*-methylmaleimide, reflux	R: NEt₂ (1 h) (56); *N*-pyrrolidinyl (2 h) (60)	464
	Pd(OAc)₂, PPh₃, methyl acrylate, K₂CO₃, CH₃CN, 90°, 45-180 min	(43) + (45)	134

a The product was a mixture of regioisomers and diastereomers with the *cis*-2,3-(quasiortho) isomer predominating (67%).
b The product was a mixture of regioisomers and diastereomers with the *cis*-2,3-isomer predominating (71%).
c This example is a 5-exo reductive Diels-Alder tandem reaction.

432
433

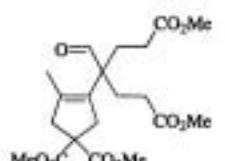TABLE 4. TANDEM REACTIONS (Continued)

B-18. 5-EXO, MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C9	Pd(PPh3)4, NaN3, norbornadiene, DMF, 80-120°, 8 h	(56)	121
	1. EtO2C—CL DMAP, Et3N, THF, rt, 1 h 2. Pd(OAc)2, PPh3, 40°, 72 h	(27)	264
	1. EtO2C—Br, K2CO3, DMF, rt, 48 h 2. Pd(OAc)2, PPh3, 60-65°, 5 h	(66)	264
	1. EtO2C—Br, K2CO3, DMF, rt, 2.5 h 2. Pd(OAc)2, PPh3, 60-65°, 24 h	(72)	264
	1. EtO2C—Br, K2CO3, DMF, rt, 48 h 2. Pd(OAc)2, PPh3, 60-65°, 5 h	(66)	264
	1. EtO2C—Br, K2CO3, DMF, rt, 3 h 2. Pd(OAc)2, PPh3, 60-65°, 24 h	(59)	264

C10-15

Pd(OAc)2, P(tol-o)3, Et3N, CH3CN, 100°

R	Time	
Me	15.5 h	(43)
Ph	19.5 h	(36)

262

C11

Pd(OAc)2, TFP, In, allene (1 bar), 4-methoxybenzaldehyde, DMF, 84°, 8-16 h

 (43)

494

Pd(PPh3)4, PhR

 I +   II

R	Solv	Temp	I	II
AlPh2	C6H6	reflux	(93)	(<2)
AlMe3	THF	reflux	(40)	(5)

482

n-Bu——R , Pd(PPh3)4, THF

 I +   II

R	Temp	I	II
ZrCp2Cl	reflux	(84)	(<3)
Al(Bu-i)2	reflux	(57)	(32)

482

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{11-12}$

R-iodoaniline NHBoc substrate

1. EtO$_2$C–CH=CH–CH$_2$Br, K$_2$CO$_3$, DMF, rt
2. Pd(OAc)$_2$, PPh$_3$, 60–65°

Product: indole with CH$_2$CO$_2$Et, N-Boc
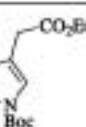
R	1. Time	2. Time	
NO$_2$	3 h	19 h	(68)
OMe	94 h	5 h	(67)
Br	30 h	24 h	(67)

Ref. 264

C$_{12}$

Substrate (allylic OH, vinyl bromide, MeO$_2$C, CO$_2$Me)
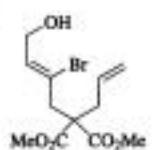
Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, methyl acrylate, Et$_4$NBr, CH$_3$CN, 85°, 9 h

Product (30)

Ref. 271

C$_{14}$

Substrate (2-bromophenyl, allyl ether, lactam)

Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, reflux, 6 h

Product (53)

Ref. 495

Substrate (OAc, vinyl bromide, MeO$_2$C, CO$_2$Me)
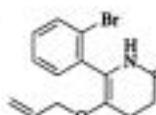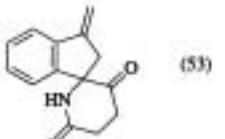
Pd(OAc)$_2$, dmphen, Et$_3$N, CH$_3$CN, 85°, 8 h

Product (39)

Ref. 271

C$_{17-18}$

Substrate (R^1, R^2, aryl bromide, methylenecyclohexane, CO$_2$Me)

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, THF

Product (CO$_2$Me)

R^1	R^2	
H	H	(—)
H	OMe	(—)
OMe	H	(—)

Ref. 477

Substrate (R, aryl bromide, methylenecyclohexane, CO$_2$Me)

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, THF, reflux, 10 h

Product (CO$_2$Me)

R	
H	(74)
OMe	(67)

Ref. 476

C$_{17}$

Substrate (allyl bromide, R^1, R^2, OTBDMS)

Pd(OAc)$_2$, PPh$_3$, Et$_3$N, n-Bu$_4$NHSO$_4$, H$_2$O, CH$_3$CN, 80°

Product (OEt, OH, OTBDMS)

R^1	R^2	
OEt	H	(57)
H	OEt	(67)

Ref. 49

C$_{20}$

Substrate (bis-iodoaryl, SO$_2$Ph, alkyne, SO$_2$Ph)

Pd(OAc)$_2$, PPh$_3$, (Me$_3$Sn)$_2$, K$_2$CO$_3$, anisole, 100°, 16 h

Product (SO$_2$Ph) (48)

Ref. 496

Substrate (bis-iodoaryl, PhO$_2$SN, SO$_2$Ph)

Pd(OAc)$_2$, PPh$_3$, (Me$_3$Sn)$_2$, K$_2$CO$_3$, anisole, 124°, 17 h

Product (PhO$_2$SN, SO$_2$Ph) (70)

Ref. 496

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{11}

Pd(OAc)₂, PPh₃, Et₃N, norbornene, CH₃CN, reflux

 (40)

107, 108

C_{11-12}
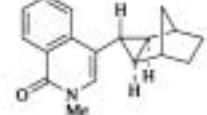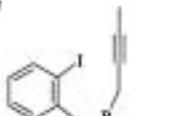
Pd(PPh₃)₄, methyl acrylate, Et₃N, CH₃CN, reflux, 12 h
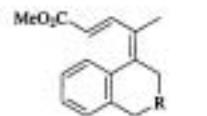
R	
O	(71)
CH₂	(72)

451

C_{11-18}

Pd(OAc)₂, PPh₃, allene, R³H, Et₄NCl, K₂CO₃, 24 h

450

R¹	R²		R³		Solv	Temp	
H, H	O		N-pyrrolidinyl		xylene	140°	(50)
H, H	O		N-piperidinyl		xylene	140°	(50)
O	NBn		N-piperidinyl		tol	120°	(50)

C_{14-17}

Pd(OAc)₂, PPh₃, TlOAc, CH₃CN, reflux, 2 d

108

R¹	R²	R³			R⁴	
H, H	O	S	norbornene		CH₂CH₂	(64)
H, H	O	CH=CH	norbornene		CH₂CH₂	(67)
O	NMe	CH=CH	norbornene		CH₂CH₃	(67)
H, H	O	CH=CH	norbornadiene		CH=CH	(75)

C_{15}
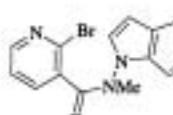
Pd(OAc)₂, PPh₃, ethyl acrylate, n-Bu₄NBr, K₂CO₃, DMF, 120°, 24 h

 (63)

416
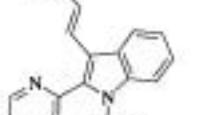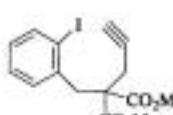
Pd(OAc)₂, PPh₃, allene, piperidine, K₂CO₃, tol, 70°, 20 h

 (73)

449

C_{16}
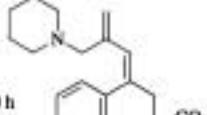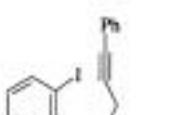
, Pd(OAc)₂, PPh₃, TlOAc, CH₃CN, reflux, 2 d

 (40) + (30)

108

C_{20}
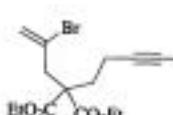
Pd(PPh₃)₂Cl₂, n-BuLi, 1-octyne, Et₃N, DMF, 125°, 2 h

 (53)

455

TABLE 4. TANDEM REACTIONS (*Continued*)

C-2. 6-EXO; 3-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C9	Pd(PPh3)4, Et3N or PdCl2(PPh3)2, Et2NH, Et3N	(72)	91
C10	PdCl2(PPh3)2, Et3N, Et2NH, DMF, 80°, 8 h	(68)	91
C15-16 R $\frac{}{}$ NSO2Ph C(CO2Me)2	Pd(OAc)2, PPh3, 80° KOAc, anisole K2CO3, Bu4NCl, CH3CN	Time 12 h (78) 9 h (67)	497
C15-21	Pd(PPh3)4, Et3N or PdCl2(PPh3)2, Et2NH, Et3N	R $\frac{}{}$ Me (75) (CH2)2CH=CMe2 (73) (CH2)2-*trans*-CH=CHCO2Et (90)	91 91, 109 91, 109
C16	PdCl2(PPh3)2, Et3N, CH3CN, reflux, 48 h	(71)	327
C20	Pd(OAc)2, n-Bu4NCl, K2CO3, DMF, 60°	(84)	93
C25	Pd(OAc)2, PPh3, KOAc, anisole, 140°	(—)	497

TABLE 4. TANDEM REACTIONS *(Continued)*

C-3. 6-EXO; 5-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux		462

	I	II	III
—	(60)	(0)	(5)
AgNO$_3$	(0)	(52)	(10)

C$_{14}$	Pd(OAc)$_2$, K$_2$CO$_3$		498

Conditions	Temp	Time	I	II	III	IV	V	VI	VII	VIII
CH$_3$CN	80°	48 h	(23)	(0)	(0)	(3)	(0)	(17)	(0)	(32)
PPh$_3$, n-Bu$_4$NBr, CH$_3$CN	80°	24 h	(18)	(0)	(0)	(trace)	(trace)	(25)	(0)	(14)
PPh$_3$, n-Bu$_4$NBr, EtOH, H$_2$O	60°	24 h	(0)	(15)	(0)	(0)	(0)	(66)	(0)	(0)
Na$^+$[3-(Ph$_2$P)C$_6$H$_4$SO$_3$]$^-$, EtOH, H$_2$O	60°	24 h	(0)	(trace)	(0)	(trace)	(trace)	(68)	(0)	(0)
dppp, n-Bu$_4$NBr, EtOH, H$_2$O	60°	24 h	(9)	(0)	(0)	(13)	(10)	(7)	(13)	(0)
n-Bu$_4$NBr, EtOH, H$_2$O	60°	24 h	(33)	(0)	(trace)	(17)	(15)	(3)	(0)	(trace)
EtOH, H$_2$O	60°	24 h	(31)	(0)	(trace)	(9)	(12)	(3)	(trace)	(trace)
n-Bu$_4$NBr, CH$_3$CN, H$_2$O	60°	48 h	(14)	(0)	(0)	(25)	(14)	(7)	(0)	(13)
1,10-phenanthroline, n-Bu$_4$NBr, EtOH, H$_2$O	60°	48 h	(0)	(0)	(8)	(28)	(16)	(0)	(15)	(0)
1,10-phenanthroline, n-Bu$_4$NBr, 1,2-dinitrobenzene, EtOH, H$_2$O	60°	48 h	(0)	(0)	(9)	(26)	(10)	(0)	(12)	(0)
2,9-dimethyl-1,10-phenanthroline, n-Bu$_4$NBr, EtOH, H$_2$O	60°	48 h	(13)	(0)	(0)	(5)	(2)	(32)	(0)	(0)
1,10-phenanthroline, n-Bu$_4$NBr, CH$_3$CN	60°	240 h	(0)	(0)	(trace)	(0)	(0)	(4)	(0)	(0)

	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, THF, 65°, 18 h	(—)	175
C$_{15}$	Pd(PPh$_3$)$_4$, Et$_3$N, CH$_3$CN, reflux, 16 h	(63)	451

TABLE 4. TANDEM REACTIONS (Continued)
C-3. 6-EXO; 5-EXO (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 70°, 9 h	(29) + (38)	32
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 80°	(86)	110
	Pd(OAc)₂, PPh₃, TlNO₃, NaOCHO, CH₃CN, reflux, 6 h	I II I:II 4.6:1 (—)ᵃ	499
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 83°, 10 h	(52) + (40)	32
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 70°	(53) + (10) + (5)	236
	Pd(OAc)₂, PPh₃, CH₃CN, 80°	I + II + III I:III 1.2-1.5:1 I+II+III (80-85)	500
	PdLₙ	(95)	109
	1. Pd(OAc)₂, PPh₃, Ag₂CO₃, THF, 65°, 18 h 2. TBAF, THF, rt	(90)	175
	1. Pd(OAc)₂, PPh₃, Ag₂CO₃, THF, 65°, 18 h 2. TBAF, THF, rt	(90)	175, 501
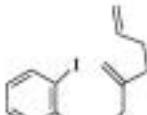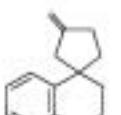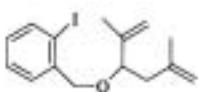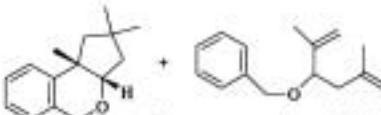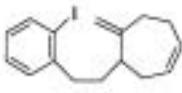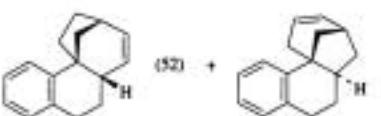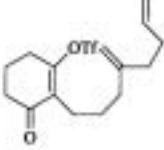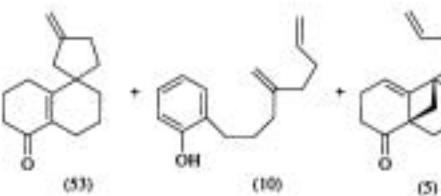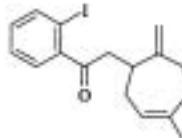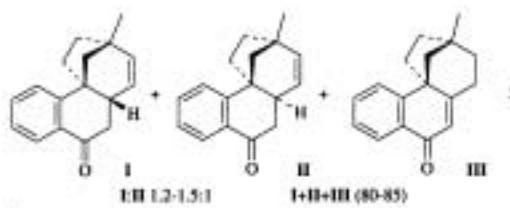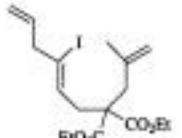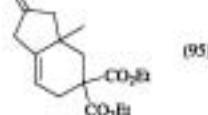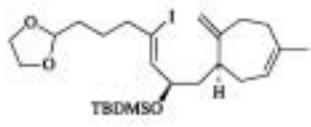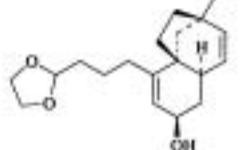
Cₙ
C₁₇
C₂₅
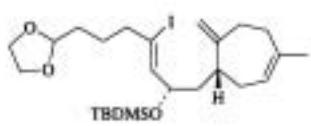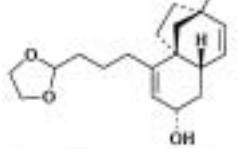
ᵃ An additional minor product of unknown structure was also isolated.

TABLE 4. TANDEM REACTIONS (*Continued*)

C-4. 6-EXO; 5-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-18}

R^1	R^2							
			Temp	Time	I	II	III	
Me	H	Pd(PPh₃)₄, AgNO₃, CH₃CN	reflux	3 d	(62)	(0)	(0)	104, 462
CO₂Me	CO₂Me	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN	130°	3 h	(71)	(0)	(0)	
H	H	Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN	—	—	(5)	(60)	(0)	
H	H	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN	—	—	(10)	(0)	(52)	
Me	H	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN	—	—	(62)	(0)	(0)	

C_{15-23}

Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 14 h

R^1	R^2	R^3	Temp		
H	H	Me	80°	(62)	466
OBn	Me	CO₂Me	60°	(47)	

C_{15}

Pd(OAc)₂, PPh₃,

NaOCHO, Et₄NCl, DMF
NaBPh₄, anisole

R	Temp	Time	I	II	
H	80°	6 h	(70)	(0)	128, 139
Ph	90°	16 h	(47)	(23)	

C_{19}

Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 12 h

(56)[g]   451

C_{20}

Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 7 h

(90)   112

TABLE 4. TANDEM REACTIONS (*Continued*)

C-4. 6-EXO; 5-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{21}$	Pd(PPh$_3$)$_4$, allene, K$_2$CO$_3$, 70-75°, 15 h		503
	NaSO$_2$Ph, DMF 1,2,3,4-tetrahydroisoquinoline, CH$_3$CN		
C$_{22}$	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°, 15 h	(46)	475
C$_{24}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 70°	(82) 1:1 dr	110
C$_{25}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, CH$_3$CN, 70°	(95) 1:1 dr	110
C$_{32}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, NaO$_2$CH, CH$_3$CN, 80°, 15 h	(60)	464, 465
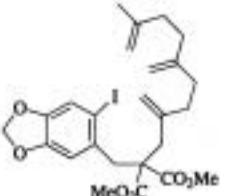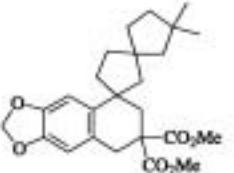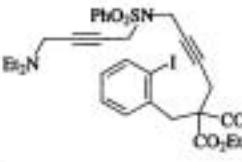
For the C$_{21}$ product:

R	
SO$_2$Ph	(66)
1,2,3,4-tetrahydroisoquinolinyl	(76)
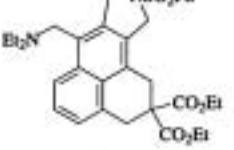
[a] An unidentified mixture of isomers was also formed in 14% yield.

TABLE 4. TANDEM REACTIONS (Continued)

C-5. 6-EXO; 6-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₄	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 110°	(33) + (16)	243
	Pd(OAc)₂, n-Bu₄NCl, Et₃N, DMF, 75°	(60)	243
C₁₆	Pd(OAc)₂, PPh₃, Ag₂CO₃, THF, 65°	(60) 4:1 cis:trans	110
C₁₇ 1.2:1 mixture of diastereomers 2:1 mixture of diastereomers	Pd(OAc)₂, PPh₃, anisole KOAc TlOAc	I + II	68

	Temp	Time	I	II
	130–140°	42 h	(26)ᵃ	(42)ᵃ
	100°	24 h	(45)ᵃ	(22.5)ᵃ

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, Et₃N, CH₃CN, 70°	(50)	236
C₁₈	PdLₙ	(50) + (35)	109
	Pd(OAc)₂, PPh₃, Ag₂CO₃, DMF, 90°	(47) + (23) + (<3–5)	138
C₂₀	Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 6 h	(76)	451
C₂₂	PdLₙ	(75)	109
C₂₉	PdCl₂(PPh₃)₂, K₂CO₃	(—)	14

ᵃ The yield was based on the first diastereomer.

TABLE 4. TANDEM REACTIONS (*Continued*)

C-6. 6-EXO; 6-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₇	PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 24 h	(72)	115
C₁₈	Pd(OAc)₂, n-Bu₄NCl, Et₃N, DMF, 75°	(8)	243
	Pd(PPh₃)₄, Et₃N or PdCl₂(PPh₃)₂, Et₂NH, Et₃N	(50) + (35)	91
C₂₀	Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 4 h	(95)	112
	HBC, K₂CO₃, n-Bu₄NBr, LiCl, DMF, 110°, 48 h	(48)	502
	Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN, 80°, 72 h	(74)	502
C₂₁	Pd(PPh₃)₄, allene, K₂CO₃, DMF, 70-75°, 15 h piperidine NaSO₂Ph	$\begin{array}{ll} R & \\ \hline \text{piperidinyl} & (40) \\ \text{SO}_2\text{Ph} & (65) \end{array}$	503

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₂₁₋₂₆

Pd(OAc)₂, PPh₃, Ag₂CO₃, CH₃CN

R¹	R²	R³	
CO₂Et	CO₂Et	Me	—
OTBDMS	H	TBMDS 1:1 dr	(*i*-Pr)₂NH

Temp	Time		
80°	48 h	(63)	*dr* = 1.2:1.0
120°	18 h	(76)	*dr* = 1.2:1.0:1.7:2.0

104, 502

C₂₂
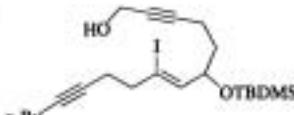
PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 24 h

(62)

115

C₂₃
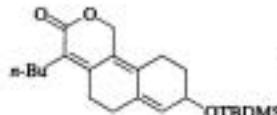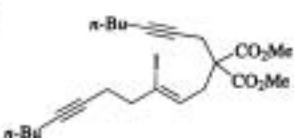
PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 24 h

(86)

115

C₂₅
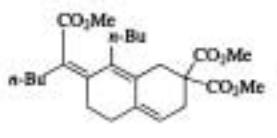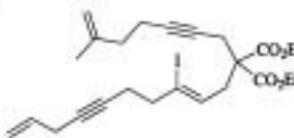
Pd(PPh₃)₄, Et₃N, CH₃CN, reflux, 12 h

(76)

112

C₂₆
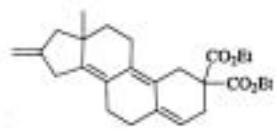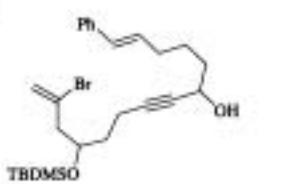
Pd(OAc)₂, PPh₃, K₂CO₃, CH₃CN, 80°, 1 d

(35)

104

C₂₈
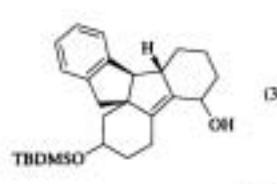
PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 24 h

(66)

115

C₂₈
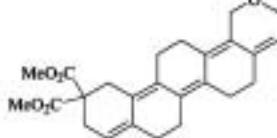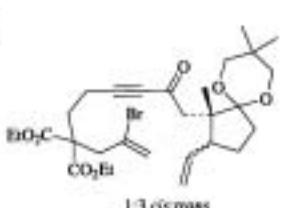
1:3 *cis:trans*

Pd(OAc)₂, PPh₃, Ag₂CO₃, (*i*-Pr)₂NH, CH₃CN, 120°, 48 h

(35) 1:2.5 *cis:trans*

502

454

455

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, (*i*-Pr)$_2$NH, CH$_3$CN, 120°, 48 h	(40)	502
C$_{29-35}$ R = H, TBDMS	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, (*i*-Pr)$_2$NH, CH$_3$CN, 120°, 48 h	(—) + (—) + (—) + (—)	104

TABLE 4. TANDEM REACTIONS (*Continued*)

C-7. 6-EXO; 6-ENDO
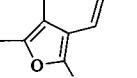
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{22}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N, H$_2$O, tol, 110°, 12 h	(50) + (12)	504
C$_{22-28}$	Pd(PPh$_3$)$_4$, Et$_3$N	I + II + III	

R^1	R^2		Temp	Time	I	II	III	
H	TBDMS	H$_2$O, tol	100°	12 h	(49)	(25)	(0)	504, 505
OMe	TBDMS	tol	110°	12 h	(50)	(25)	(0)	505
OMe	TBDMS	NMP or Pd$_2$(dba)$_3$	reflux	—	(59)	(0)	(23)	505
OMe	H	NMP	reflux	—	(87)	(0)	(0)	505

C$_{23}$	Pd$_2$(dba)$_3$, PPh$_3$, PMP, toluene, 110°, 4 d	(57)	137

TABLE 4. TANDEM REACTIONS (*Continued*)

C-8. 6-EXO; REDUCTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10-13}$	Pd(OAc)$_2$, PPh$_3$, NH$_4$OCHO, CH$_3$CN, reflux	R n Me 1 (61) Me 2 (54) H 1 (48)[a]	506
C$_{11-18}$		I II	
R^1 / R^2:		Time I II	
H / Me	Et$_4$NCl, HCO$_2$H, piperidine	2 h (60) (0)	464, 473
Me / Bn	Et$_4$NCl, HCO$_2$H, piperidine	8 h (50) (0)	464, 473
CH$_2$-N-piperidinyl / Me	TlNO$_3$, NaOCHO	12 h (53) (0)	464, 499
CH$_2$-N-piperidinyl / Me	Et$_4$NCl, HCO$_2$H	12 h (0) (32)	464, 473, 499
C$_{11-17}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, piperidine, Et$_4$NCl, CH$_3$CN, 80°	R H (57) SPh (40) SiMe$_3$ (35)	301
C$_{12}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$H, piperidine, Et$_4$NCl, CH$_3$CN, 80°	(65)	301
C$_{13-28}$	Pd(OAc)$_2$, PPh$_3$, Et$_3$N	I II	
R^1 / R^2:		Solv Temp I II	
H / H		THF-d$_8$ 80° (92) (8)	307, 308
H / OBn		THF-d$_8$ 80° (52) (12)	307
—OCH$_2$O— / OBn		THF reflux (56) (11)	307, 308, 309
C$_{14-18}$	Pd(PPh$_3$)$_2$(OAc)$_2$, HCO$_2$H, n-Bu$_4$NCl, DMF, 70°	R H (46) n-Bu (72)	275
C$_{14}$	Pd(PPh$_3$)$_2$(OAc)$_2$, HCO$_2$H, Et$_3$N, DMF, 80°	(11) + (45) + (16)	275
	Pd(OAc)$_2$, Et$_3$N, CH$_3$CN, 110°, 120 h	(35) + (31) + (22)	88

458

459

TABLE 4. TANDEM REACTIONS (Continued)
C-8. 6-EXO; REDUCTIVE (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(OAc)₂, PPh₃, HCO₂H, piperidine, CH₃CN, 80°, 43 h	(10)	473
C₁₆	Pd(OAc)₂, PPh₃, NaOCHO, TPAB, DMF, 75–80°	(72)	123
C₁₇₋₁₈	Pd(OAc)₂, PPh₃, HCO₂Na, DMF, 95–100°, 36 h	+ (507)	507
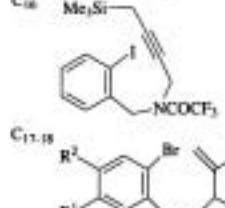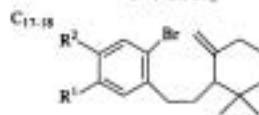
R¹	R²	I	II	III
H	H	(18)	(52)	(18)
OMe	H	(17)	(58)	(19)
H	OMe	(17)	(56)	(18)

C₁₆₋₂₄   At = 2-O₂NC₆H₄

R	Conditions	Temp	Time	
H	Pd(PPh₃)₄, LiCN	—	—	(26)	508
OTBDMS	Pd(OAc)₂, PPh₃, Et₃N	90°	30 min	(56)	509, 510

C₁₈	Pd(OAc)₂, PPh₃, HCO₂Na, DMF, 95–100°, 36 h	(50) + (22)	507
		+ (24)	
C₃₀	Pd(OAc)₂, PPh₃, Et₃N, THF, reflux	(38) + (—)	309
C₂₁	Pd(OAc)₂, Ph₃P, HCO₂Na, Et₃N, CH₃CN, reflux, 12 h	(43)	346
C₂₃	Pd₂(dba)₃, (R)-BINAP, PMP, toluene, 110°, 3 d	(85) + (6)	137
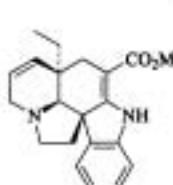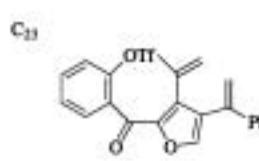
460

461

TABLE 4. TANDEM REACTIONS (*Continued*)

C-8. 6-EXO; REDUCTIVE (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{25}$	Pd(OAc)$_2$, PPh$_3$, HCO$_2$Na, Et$_4$NCl, DMF, 120°, 12 h	(62)	470
	1. TBAF, THF, 0° 2. Pd(O$_2$CCF$_3$)$_2$·(PPh$_3$)$_2$, Et$_3$N, tol, 110°	(48)	119
C$_{26}$	Pd(OAc)$_2$, HCO$_2$K, *n*-Bu$_4$NBr	(75)	511

a An additional unidentified product was also isolated.

TABLE 4. TANDEM REACTIONS (*Continued*)

C-9. 6-EXO; CARBONYLATIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{11}$	Pd(OAc)$_2$, PPh$_3$, CO, TlOAc, CH$_3$CN, 80°, 24 h	(60)	116
	Pd(OAc)$_2$, PPh$_3$, CO, tol, 110°		

		R		
	Ph$_2$MeSiH, Et$_4$NCl, 7 h	H	(61)	117
	RH, K$_2$CO$_3$, 16 h	NHOBn	(51)	467
	RH, K$_2$CO$_3$, 16 h	NBocOBn	(92)	467
	RH, K$_2$CO$_3$, 16 h		(68)	467

| | Pd(PPh$_3$)$_4$, CO, Et$_3$N, MeOH, CH$_3$CN, 100° | (18) + (42) | 451 |
| C$_{12}$ | PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, MeOH, 70°, 24 h | (80) | 115 |

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₄

1. MeO₂C, MeO₂C (alkyne substrate), (PPh₃)₃RhCl, tol, reflux, 4 h
2. Pd(OAc)₂, PPh₃, CO, 12-16 h

2-Tributylstannylthiophene, 80°
NaBPh₄, Et₄NCl, 100°

R	
2-thienyl	(58)
Ph	(41)

470

C₁₆₋₁₈

PdCl₂(PPh₃)₂, CO, Et₃N, DMF, MeOH, H₂O, O₂, 85°

I + II

R	I	II
MOM	(47)	(47)
TBDMS	(92)	(2)

138

C₁₄

Pd(PPh₃)₄, CO, Et₃N, DMF, 70°, 6 h

(80)

109

Pd(PPh₃)₄, CO, CH₃OH, 60°

(78)

512

C₁₄₋₂₀

PdCl₂(PPh₃)₂, CO, Et₃N, DMF, MeOH, H₂O, O₂, 85°

I + II + III

R	I	de	II	III
H	(91)	94	(<2)	(<3)
n-Bu	(84)	95	(<2)	(5)
—(CH₂)₂CH=CH₂	(65)	85	(<2)	(<2)
—(CH₂)₂CH=CMe₂	(80)	93	(<2)	(<2)

138

C₁₅

PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 24 h

(73)

115

C₁₆

PdCl₂(PPh₃)₂, CO, Et₃N

I + II + III

MeOH
EtOH
i-PrOH
MeOH, H₂O, DMF
MeOH, DMF

R	Temp	Time	I	II	III
Me	reflux	30 h	(52)	(23)	(22)
Et	reflux	24 h	(26)	(2)	(45)
i-Pr	reflux	24 h	(55)	(10)	(6)
Me	85°	1 h	(74)	(3)	(<3)
Me	85°	1 h	(63)	(8)	(<3)

327

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₈₋₂₃

PdCl₂(PPh₃)₂, CO, Et₃N, alcohol

R¹	R²	R³	Alcohol	Temp	Time	I	II	III
H	H	i-Pr	i-PrOH	75°	7 h	(48)	(<5)	(22)
Ac	H	Me	MeOH	65°	24 h	(78)	(11)	(0)
Ts	Ts	Me	MeOH	65°	12 h	(75)	(9)	(0)

C₁₈

Pd(OAc)₂, CO, 110°

PPh₃, Ph₂MeSiH, Et₄NCl

TFP, NaBPh₄

R	Solv	Time		
H	tol	7 h	(54)	117
Ph	anisole	15 h	(60)	469

PdCl₂(PPh₃)₂, CO, Et₃N, i-PrOH, 85°, 20 h

  (54) + (20)   468, 513

C₂₀

PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 70°, 36 h

 + (17)   (65)   468, 513

+ (<2)

PdCl₂(PPh₃)₂, CO, Et₃N, MeOH, 65°, 36 h

 (72) + (29)   468, 513

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{22}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, MeOH, 65°, 24 h	(64) + (<3) + (7)	468, 513
C$_{23}$	Pd(OAc)$_2$, P(tol-*o*)$_3$, CO, TlOAc, MeOH, reflux, 12 h	(72)	101
C$_{25}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, *i*-PrOH, 85°, 12 h	(43)	468, 513

468

469

TABLE 4. TANDEM REACTIONS (*Continued*)
C-10. 6-EXO; STILLE REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{11-18}$	Pd(OAc)$_2$, PPh$_3$, R^{3}SnBu$_3$, CH$_3$CN, 60°	I II	

R^1	R^2		R^3	I	II	
Me	H	LiCl, 2 h	vinyl	(16)	(4)	130, 131
Me	H	Et$_4$NCl, 1.5 h	allyl	(50)	(0)	130, 131
Bn	Me	Et$_4$NCl	vinyl	(25)	(5)	131
Bn	Me	Et$_4$NCl	allyl	(29)	(0)	131

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd(0), 2-pyridylSnBu$_3$, Et$_4$NCl, tol, 110°	(60)	100, 131
C$_{12}$	RSnBu$_3$, LiCl, DMF, 60°, 8 h	I + II	480

	R	I	II
Pd(dppf)Cl$_2$	vinyl	(51)	(0)
Pd(PPh$_3$)$_4$	allyl	(51)	(0)
Pd(PPh$_3$)$_4$	Me$_3$Si—≡	(54)	(0)
Pd(dppf)Cl$_2$	Me$_3$Si—≡	(24)	(25)

Substrate	Conditions	Product(s) and Yield(s) (%)	R		Refs.
C$_{13}$	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, RSnBu$_3$, tol, 110°, 16-24 h		≡—Ph (66) vinyl (60) 2-thienyl (88) 2-furyl (30)		131

TABLE 4. TANDEM REACTIONS (*Continued*)

C-10. 6-EXO; STILLE REACTIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₄	1. (PPh₃)₃RhCl, tol, reflux, 4 h 2. 2-Tributylstannylthiophene, Pd(OAc)₂, PPh₃, 110°, 12-16 h	(39)	470
	Bu₃Sn , Pd(PPh₃)₄, THF, 60°	(6) + (66)	512
C₁₅	Pd(PPh₃)₄, allylSn(Bu-*n*)₃ THF, HMPA, reflux	(89)	482
C₁₇₋₁₈	Pd(PPh₃)₄, R²M, THF, reflux		482
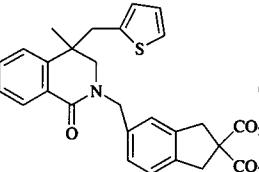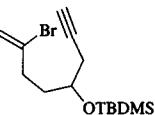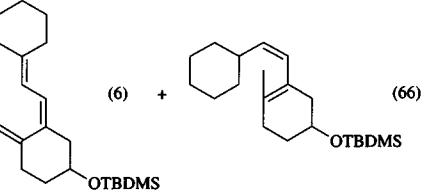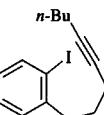
R¹	R²M	Solv	R²	
n-Bu	*n*-Bu——≡——SnMe₃	HMPA	*n*-Bu—≡	(73)
n-Pr	[(*E*)-1-hexenyl]ZrCp₂Cl	—	(*E*)-1-hexenyl	(85)

TABLE 4. TANDEM REACTIONS (*Continued*)

C-11. 6-EXO; SUZUKI REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₀₋₁₇	BEt₃Li, THF, 60°, 30 min	I + II	514

R¹	R²		I	II
H	Ac	Pd(OAc)₂	(39)	(23)
Me	Ac	PdCl₂(PPh₃)₂	(53)	(—)
H	CO₂Bn	Pd(OAc)₂	(38)	(20)
Me	CO₂Bn	PdCl₂(PPh₃)₂	(55)	(—)
H	Boc	Pd(OAc)₂	(40)	(22)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁	1. Pd(OAc)₂, PPh₃, C₆H₆, rt, 10 min 2. *E*-Hex-1-enyl-1,3,2-benzo- dioxaborole, NaOEt, EtOH, reflux, 2 h	(45)	111, 128
	Pd(OAc)₂, PPh₃, tol, H₂O, reflux	I + II + III	128
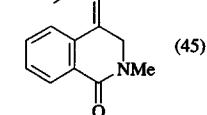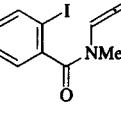
R	Time	I	II	III
NaBPh₄	Ph	3.5 h	(71)	(trace)	(0)
NaBPh₄, Na₂CO₃	Ph	1 h	(34)	(34)	(0)
2-thienylboronic acid, Na₂CO₃	2-thienyl	1 h	(60)	(trace)	(0)
E-styr-1-enyl-1,3,2-benzo- dioxaborole, Na₂CO₃	*E*-CH=CHPh	1 h	(54)	(21)	(8)

TABLE 4. TANDEM REACTIONS (*Continued*)

C-11. 6-EXO; SUZUKI REACTION (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	Pd$_2$(dba)$_3$, P(furyl)$_3$, NaBPh$_4$, Et$_4$NCl, DMF, 110°, 24 h	(60)	128
	Pd(OAc)$_2$, PPh$_3$, NaBPh$_4$, Et$_4$NCl, anisole, 100°, 24 h	(43)	128
C$_{14}$	1. (PPh$_3$)$_3$RhCl, tol, reflux, 4 h 2. Pd(OAc)$_2$, PPh$_3$, NaBPh$_4$, reflux, 12-16 h	(58)	470
	Pd(OAc)$_2$, PPh$_3$, NaBPh$_4$, AgNO$_3$, Et$_4$NCl, anisole, 120°	(15)	301
C$_{18}$	Pd(PPh$_3$)$_4$, n-Bu—≡—B(Bu-n)$_2$, THF, 25°	(45)	482
C$_{25}$	Pd(OAc)$_2$, PPh$_3$, NaBPh$_4$, anisole, 80°, 12 h	(50)	497

TABLE 4. TANDEM REACTIONS (*Continued*)

C-12. 6-EXO; ORGANOZINC

Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.
C$_{17-20}$	Pd(PPh$_3$)$_4$, PhZnCl, THF, rt, 8 h	R		487
		H	(51)	
		Me	(55)	
		SiMe$_3$	(43)	

TABLE 4. TANDEM REACTIONS (*Continued*)
C-13. 6-EXO: π-ALLYL

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₈

Pd(OAc)₂, P(tol-o)₃, CH₂(CO₂Me)₂, NaH, n-Bu₄NCl, DMF, 100°, 43 h
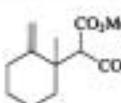
(63) 491, 492

Pd(OAc)₂, P(tol-o)₃, piperidine, 100°, 68 h

I + II + III + IV 490

	I	II	III	IV
—	(10)	(8)	(72)	(6)
CH₃CN	I+II (48)	(28)	(5)	

Pd(OAc)₂, P(tol-o)₃, piperidine, 100°, 36 h

(33) 298

Pd(OAc)₂, P(tol-o)₃, piperidine, 100°, 96 h

(1) (1) (57) (4) 490

C₁₀₋₁₈

R¹	R²	R³		Solv	Temp	Time	I	cis:trans	II	
H	NTs	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	reflux	4 h	(12)	—	(47)	120
H	NTs	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, K₂CO₃	CH₃CN	reflux	4 h	(0)	—	(91)	120
Me	NTs	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, K₂CO₃	CH₃CN	reflux	4 h	(0)	—	(96)	120
Me	NTs	piperidinyl	Pd(OAc)₂, PPh₃, R³H, K₂CO₃	CH₃CN	reflux	4 h	(0)	—	(93)	120
Me	NTs	Et₂N	Pd(OAc)₂, PPh₃, R³H, K₂CO₃	CH₃CN	reflux	4 h	(0)	—	(88)	120
H	O	N₃	Pd(PPh₃)₄, NaR³	DMF	reflux	12 h	(0)	—	(58)	121
H	O	SO₂Ph	Pd(PPh₃)₄, NaR³	DMF	reflux	12 h	(0)	—	(55)	121
H	O	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	reflux	4 h	(88)	—	(0)	120
H	O	piperidinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	reflux	4 h	(70)	—	(0)	120
Me	O	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	reflux	2 h	(78)	3:1	(0)	120
Me	O	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	rt	2 h	(87)	8:1	(0)	120
Me	O	1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, R³H, Ag₂CO₃	CH₃CN	0°	4 h	(—)	11:1	(0)	120

C₁₁
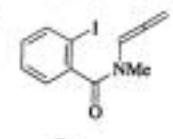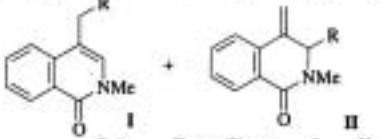
R		Solv	Temp	Time	I	II	
N₃	Pd(PPh₃)₄, NaR	DMF	rt	12 h	(70)	(0)	121
SO₂Ph	Pd(PPh₃)₄, NaR	DMF	rt	12 h	(62)	(0)	121
N-1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, RH, K₂CO₃	CH₃CN	80°	—	(91)	(0)	120
N-1,2,3,4-tetrahydroisoquinolinyl	Pd(OAc)₂, PPh₃, Ag₂CO₃, RH	CH₃CN	80°	6 h	(0)	(77)	120
N-β-carbolinyl	Pd(OAc)₂, PPh₃, β-carboline, K₂CO₃	CH₃CN	80°	12 h	(60)	(0)	120
CH=CH₂	Pd₂(dba)₃, TFP, RSnBu₃	tol	110°	—	(38)	(38)	131
2-furyl	Pd₂(dba)₃, TFP, RSnBu₃	tol	110°	—	(45)	(30)	131
2-furyl	Pd₂(dba)₃, TFP, RSnBu₃, Ag₂CO₃	tol	110°	—	(61)	(10)	131

474

475

TABLE 4. TANDEM REACTIONS (*Continued*)

C-13. 6-EXO; π-ALLYL (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

Pd(PPh₃)₂Cl₂, CH₂(CO₂Et)₂, K₂CO₃, EtOH, DMF, 120°, 5 h

(47) + (8) 82

C₁₃

Pd₂(dba)₃   447

I + II

R		Solv	Temp	Time	I	dr	II
CH(CO₂Et)₂	RH, K₂CO₃, n-Bu₄NCl	DMSO	80°	4 h	(72)		(0)
2-(2-methyl-1,3-cyclohexanedione)	RH, NaHCO₃, n-Bu₄NCl	DMSO	100°	20 h	(55)		(0)
N-morpholino	RH, Na₂CO₃, n-Bu₄NCl	DMSO	100°	36 h	(91)		(0)
N₃	RLi, LiCl	DMSO	100°	18 h	(51)	80:10:5:5	(0)
phthalimide	RK, LiCl	DMSO	100°	18 h	(31)		(0)
NTsBn	RH, Na₂CO₃, n-Bu₄NCl	DMF	100°	42 h	(60)		(0)
N(CO₂Bu-t)₂	RH, Na₂CO₃, n-Bu₄NCl	DMSO	100°	16 h	(52)		(0)
NHPh	PhNH₂, Na₂CO₃, n-Bu₄NCl	DMSO	100°	16 h	(90)		(0)
OAc	LiR·2H₂O, LiCl, n-Bu₄NCl	DMSO	100°	24 h	(73)		(7)

Pd₂(dba)₃, n-Bu₄NCl, DMSO, 100°   447

R		
SO₂Ph	PhSO₂Na, LiCl, 24 h	(62)
OPh	PhOH, NaHCO₃, 15 h	(62)
o-BrC₆H₄O	o-BrC₆H₄OH, NaHCO₃, 16 h	(59)

C₁₃₋₂₀

Pd₂(dba)₃, n-Bu₄NCl, 24 h   447

I + II

R¹		R²	Solv	Temp	I	II
H	CH₂(CO₂Et)₂, K₂CO₃	CH(CO₂Et)₂	DMSO	80°	(19)	(0)
H	TsBnNH, Na₂CO₃	TsBnN	DMF	100°	(39)	(0)
Bn	CH₂(CO₂Et)₂, K₂CO₃	CH(CO₂Et)₂	DMSO	100°	(48)	(16)
Bn	PhNH₂, Na₂CO₃	PhNH	DMSO	100°	(59)	(0)

C₁₃

Pd₂(dba)₃, PhNH₂, Na₂CO₃, n-Bu₄NCl, DMSO, 100°, 17 h   (62)   447

C₁₆

Pd(OAc)₂, P(tol-o)₃, n-Bu₄NCl, DMF, 90°, 24 h   (42)   492

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, n-Bu₄NCl, DMF, 60°, 48 h   (58)   493, 515

C₁₇

Pd(OAc)₂, P(tol-o)₃, Na₂CO₃, Bu₄NCl, DMF

I + II

	Temp	Time	I	II	
	60°	46 h	(18)	(66)	493, 515
	75°	24 h	(84)	(0)	

TABLE 4. TANDEM REACTIONS (*Continued*)

C-13. 6-EXO; π-ALLYL (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(C structure, Br, TsNH)	Pd(OAc)$_2$, P(tol-o)$_3$, Na$_2$CO$_3$, n-Bu$_4$NCl, DMF, 75°, 24 h	(23)	515

C$_{18}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(TsHN structure, R)	Pd(OAc)$_2$, P(tol-o)$_3$, Na$_2$CO$_3$, n-Bu$_4$NCl, DMF		515

R	Temp	Time	
Br	100°	24 h	(67)
I	80°	12 h	(51)

C$_{19}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(structure, I, NTs)	Pd$_2$(dba)$_3$, n-Bu$_4$NCl, DMSO, 22 h	**I** + **II**	447

R	Conditions	I	II
CH(CO$_2$Et)$_2$	CH$_2$(CO$_2$Et)$_2$, K$_2$CO$_3$, 80°	(37)	(24)
PhNH	PhNH$_2$, Na$_2$CO$_3$, 100°	(44)	(27)

C$_{20}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(MeO, OH, I, NCO$_2$Me structure)	Pd(O$_2$CCF$_3$)$_2$(PPh$_3$)$_2$, PMP, tol, 120°, 10 h	(56)	119, 162

TABLE 4. TANDEM REACTIONS (*Continued*)

C-14. 6-EXO; CAPTURE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{11}$ (I, O structure)	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, tol, 110°, 18 h	(62)	125
(I, O structure)	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, tol, 110°, 18 h	(58)	125
C$_{18}$ (I, NBn, O structure)	Pd(OAc)$_2$, PPh$_3$, 18-crown-6, KCN, C$_6$H$_6$, 80°, 12 h	(45)	125

C$_{25-31}$

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
(OH, I, R^1, R^2, MeO, OMe structure)	Pd$_2$(dba)$_3$•CHCl$_3$, K$_2$CO$_3$, CH$_3$CN, rt, 24 h		

R^1	R^2	Conditions	Yield	Refs.
H	OCH$_2$CH$_2$CH$_2$O	CH$_3$CN, rt, 24 h	(36)	70, 71
TIPS	O	DMF, rt, 8 h	(72)	70, 71, 126

TABLE 4. TANDEM REACTIONS (*Continued*)

C-15. 6-EXO; AROMATIC CYCLIZATION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{15}$	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°, 16 h	R: O (70–85), S (70–85)	475
	Pd(PPh$_3$)$_4$, piperidine, 80°, 40 h	(41)	516
C$_{16-17}$	Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, tol, 110°, 16 h	R: CH (80), N (70)	475
C$_{25}$	Pd(OAc)$_2$, PPh$_3$, KOAc, anisole, 140–150°, 18 h	(50)	497

TABLE 4. TANDEM REACTIONS (*Continued*)

C-16. 6-EXO; DIELS-ALDER REACTION

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{16}$	, Pd(OAc)$_2$, Ag$_2$CO$_3$, CH$_3$CN, 90°, 45 min	I + II R: Me dppe (67); Et PPh$_3$ (78)	11, 104
	Pd(OAc)$_2$, PPh$_3$, methyl acrylate, Ag$_2$CO$_3$, CH$_3$CN, 90°, 90 min	I, R = Me + II, R = Me; I + II (56)	134
C$_{16-17}$	1. Pd(OAc)$_2$, PPh$_3$, Tl$_2$CO$_3$, NaOCHO, CH$_3$CN, 80°, 3 h 2. *N*-methylmaleimide, reflux	 R	Time *N*-piperidinyl 12 h (70) *N*-pyrrolidinyl 6 h (62) NEt$_2$ 3 h (64)	464 464, 499 464
C$_{17}$	1. Pd(OAc)$_2$, PPh$_3$, NaOCHO, CH$_3$CN, 80° 2. *N*-methylmaleimide, reflux, 1 h	(80)[a]	464

[a] This reaction is a 6-exo; reductive; Diels-Alder tandem reaction.

TABLE 4. TANDEM REACTIONS (*Continued*)

C-17. 6-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{7-8}$ 	Pd(OAc)$_2$, P(tol-o)$_3$, piperidine, CH$_3$CN, 100°, 42 h	 n Time 1 42 h (71) 2 55 h (45)	298
C$_{10}$ 	Pd(PPh$_3$)$_4$, NaN$_3$, norbornadiene, DMF, 80-120°, 8 h	(54)	121
	Pd(PPh$_3$)$_4$, In[0], RCHO, DMF, 90°, 14 h	 R dr CH=CMe$_2$ (50) 1.2:1 n-C$_5$H$_{11}$ (51) 6:1	517
	Pd(OAc)$_2$, TFP, In(0), allene (1 bar), RCHO, DMF, 84°, 8-16 h	 R Ph (52) 2-thienyl (51) 2-furyl (50) cyclohexyl (46)	494
C$_{11}$ 	Pd(PPh$_3$)$_4$, NaN$_3$, norbornadiene, DMF, 80-120°, 8 h	(52)	121
	Pd(OAc)$_2$, TFP, In, allene (1 bar), PhCHO, DMF, 84°, 8-16 h	(43)	494
C$_{12}$ 	PS bound Pd catalyst, Tl$_2$CO$_3$, tol, rt-110°, 16 h, (Cy$_3$P)$_2$Ru(=CHPh)Cl$_2$	(71)	218
C$_{14-15}$ R SO$_2$	 (Cy$_3$P)$_2$Ru(=CHPh)Cl$_2$; PS bound Pd catalyst, Tl$_2$CO$_3$, tol, rt-110°, 16 h	 (58)	218
CO	"	(80)	
SO$_2$	(Cy$_3$P)$_2$Ru(=CHPh)Cl$_2$; Pd(OAc)$_2$, Tl$_2$CO$_3$, perfluorous solvent system, 110°, 16 h	(37)	
CO	"	(57)	
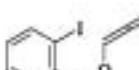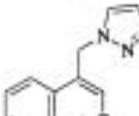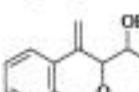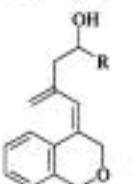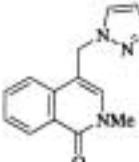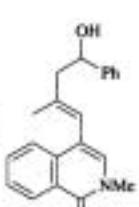
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{14}	$(Cy_3P)_2Ru(=CHPh)Cl_2$; PS bound Pd catalyst, Tl_2CO_3, tol, rt-110°, 16 h	(73)	218
	$(Cy_3P)_2Ru(=CHPh)Cl_2$; $Pd(OAc)_2$, Tl_2CO_3, perfluorous solvent system, 110°, 16 h	I (67)	218
C_{15}	$Pd(OAc)_2$, TFP, In, allene (1 bar), 4-methoxybenzaldehyde, DMF, 84, 8-16 h	(54)	494
C_{16}	$Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, reflux	(89)	310
C_{20}	Pd/C (10%) , Et_3N, CH_3CN, 80°, 18 h	(50)	61
C_{23} $R = \beta\text{-H and } \alpha\text{-H}^a$	1. 1-Bromo-3,4-dihydro-naphthalene-2-carboxaldehyde, *N*-methylmaleimide, *N*-allylethylglycinate, anisole, 110°, 20 h 2. $Pd(OAc)_2$, PPh_3, KOAc, Bu_4NCl, CH_3CN, 125°, 4 h	(68) + (7)	340
C_{26}	$Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, reflux	(45)	187

[a] This mixture of two diastereomers was generated as indicated in step 1. The intramolecular Heck reaction was then conducted in the same pot by adding the reagents, and utilizing the conditions delineated in step 2.

TABLE 4. TANDEM REACTIONS (*Continued*)
D-1. 7-EXO; REDUCTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{12}	Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, HCO$_2$H, piperidine, CH$_3$CN, 80°, 16 h	(62)	464
C_{15}	Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, 82°, 65 h	(2) + (8) + (2)	367, 518
C_{18}	Pd(OAc)$_2$, P(tol-*o*)$_3$, HCO$_2$H, piperidine, CH$_3$CN, reflux, 18 h	(53)	124
C_{19-26}	Pd(OAc)$_2$, PPh$_3$, *n*-Pr$_4$NBr, NaOCHO, DMF, 75-85°, 2-3 h	R: SO$_2$-mesityl (90), COCF$_3$ (78)	123
C_{20}	Pd(OAc)$_2$, PPh$_3$, *n*-Bu$_4$NCl, HCO$_2$Na, DMF, 70°	(34-40) + (0-65)	178
C_{21}	Pd(OAc)$_2$, P(tol-*o*)$_3$, HCO$_2$H, piperidine, CH$_3$CN	(60)	124
	Pd(OAc)$_2$, P(tol-*o*)$_3$, HCO$_2$H, piperidine, CH$_3$CN, reflux, 18 h	(56)	124
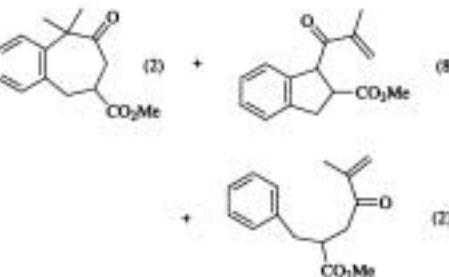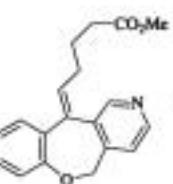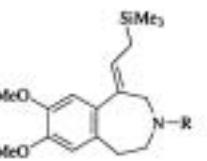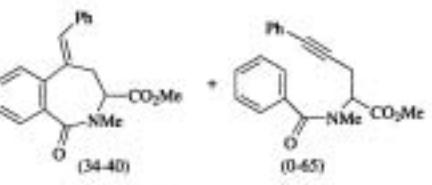
TABLE 4. TANDEM REACTIONS (Continued)

D-2. 7-EXO; π-ALLYL

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C9	Pd(OAc)2, P(tol-o)3, piperidine, CH3CN, 125°, 12 h	(8) + (4)	490
C11	Pd(OAc)2, P(tol-o)3, piperidine, 100°, 27 h	(14) + (29)	298
C12	Pd(PPh3)2Cl2, CH2(CO2Et)2, K2CO3, EtOH, DMF, 120°, 5 h	(73)	82
C14	Pd2(dba)3, morpholine, Na2CO3, n-Bu4NCl, DMSO, 100°, 24 h	(52)	447
C14	Pd2(dba)3, CH2(CO2Et)2, K2CO3, n-Bu4NCl, DMSO, 100°, 24 h	(40) + (8) + (8) + (4)	447
C18	Pd(PPh3)2Cl2, CH2(CO2Et)2, K2CO3, EtOH, DMF, 120°, 4 h	(87)	82
	Pd(PPh3)2Cl2, K2CO3, EtOH, DMF, 110-120°, 22 h	(20)	82

TABLE 4. TANDEM REACTIONS (*Continued*)

D-2. 7-EXO; π-ALLYL (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{18}$	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, DMF, 120°	I + II	82

R	Time	I	II
	CH$_2$(CO$_2$Et)$_2$, EtOH	H	3 h	(73)	(0)
	CHMe(CO$_2$Et)$_2$, n-Bu$_4$NCl	Me	4 h	(50)	(4)

| C$_{26}$ | Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, n-Bu$_3$NCl, DMF, 110-120°, 24 h | (40) | 82 |
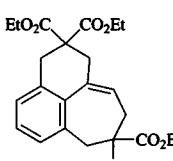
TABLE 4. TANDEM REACTIONS (*Continued*)

D-3. 7-EXO; CARBONYLATIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{17}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, i-PrOH, 75°, 50 h	(66) + (11)	468
C$_{19}$	PdCl$_2$(PPh$_3$)$_2$, CO, Et$_3$N, i-PrOH, 75°, 30 h	(43)	468
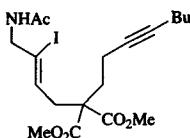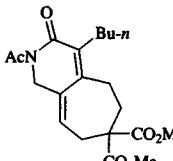
TABLE 4. TANDEM REACTIONS (*Continued*)
D-4. 7-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C11	Pd(OAc)2, TFP, In, allene (1 bar), RCHO, DMF, 84°, 8-16 h	<table><tr><td>R</td><td></td></tr><tr><td>Ph</td><td>(46)</td></tr><tr><td>2-thienyl</td><td>(53)</td></tr><tr><td>2-furyl</td><td>(53)</td></tr></table>	494
	Pd(OAc)2, PPh3, allene, K2CO3, tol, 70°, 20 h	<table><tr><td>R</td><td></td></tr><tr><td>N-piperidinyl</td><td>(68)</td></tr><tr><td>N-(S)-(+)-2-pyrrolidinylmethanol</td><td>(71)</td></tr></table>	449
	Piperidine (S)-(+)-2-pyrrolidinemethanol		
C13	(Cy3P)2Ru(=CHPh)Cl2; PS bound Pd catalyst, Tl2CO3, tol, rt-110°, 16 h	I (73)	218
	(Cy3P)2Ru(=CHPh)Cl2; Pd(OAc)2, Tl2CO3, P(C6H4-C6F13)3 perfluorous solvent system, 110°, 16 h	I (43)	218
C16	Pd(PPh3)4, Et3N, CH3CN, reflux, 5 h	(78)	451
C17	Pd(OAc)2, PPh3, K2CO3, Bu4NCl, DMF, 110°	(15)	367
C19	1. Pd(PPh3)4, THF 2. K2CO3, reflux, 16 h	(72)	519
C21	Pd(OAc)2, PPh3, Ag2CO3, CH3CN, 80°, 72 h	(76)	502
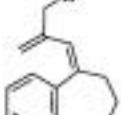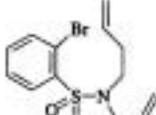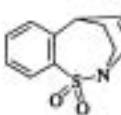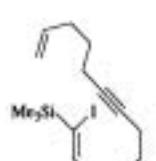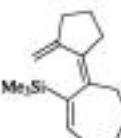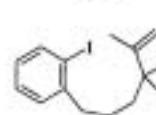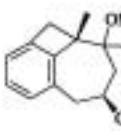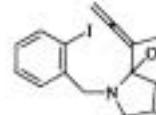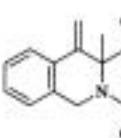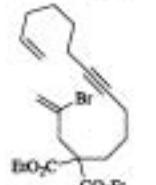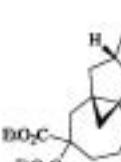
TABLE 4. TANDEM REACTIONS (*Continued*)

E-1. 8-EXO; π-ALLYL; MISCELLANEOUS TANDEM REACTIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Pd(PPh$_3$)$_4$, Ag$_2$CO$_3$, tol, 80°, 16 h	(63)	520
C$_{12}$	Pd(PPh$_3$)$_4$, Ag$_2$CO$_3$, tol, 80°, 16 h	(67)	520
C$_{19}$	Pd(PPh$_3$)$_2$Cl$_2$, CH$_2$(CO$_2$Et)$_2$, K$_2$CO$_3$, EtOH, DMF, 120°, 3 h	(84)	82
C$_{21}$	Pd(PPh$_3$)$_2$Cl$_2$, K$_2$CO$_3$, DMF		82

	R	Temp	Time	
CH$_2$(CO$_2$Et)$_2$, EtOH	CH(CO$_2$Et)$_2$	120°	23 h	(51)
PhSn(*n*-Bu)$_3$, *n*-Bu$_4$NCl	Ph	120°	11 h	(64)
PhOH, *n*-Bu$_4$NCl	OPh	80–120°	31 h	(54)
piperidine, *n*-Bu$_4$NCl	*N*-piperidinyl	80°	9 h	(56)

TABLE 4. TANDEM REACTIONS (*Continued*)

E-2. 8-EXO; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	Pd(OAc)$_2$, PPh$_3$, allene, piperidine, K$_2$CO$_3$, tol, 70°, 20 h	(18) + (25)	449
C$_{22}$	Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, CH$_3$CN, 80°, 72 h	(30)	502

TABLE 4. TANDEM REACTIONS (Continued)

F. MACROCYCLIZATION; MISCELLANEOUS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₃

Pd compound, tol, heat, 12 h

520

R		Temp	I	II	III	IV
α-OH	Pd(PPh₃)₄, Ag₂CO₃	reflux	(33)	(0)	(0)	(20)
α-OH	Pd(PPh₃)₄, Ag₂CO₃, 4 Å mol sieves	80°	(15)	(38)	(5)	(2)
β-OH	Pd(OAc)₂, dppe, 4 Å mol sieves	80°	(39)	(18)	(18)	(6)
β-OH	Pd(PPh₃)₄, Ag₂CO₃	80°	(0)	(0)	(24)	(0)
β-OH	Pd(PPh₃)₄, Ag₂CO₃	reflux	(34)	(0)	(0)	(0)

Pd(OAc)₂, P(tol-o)₃, piperidine,   I + II (15)ᵃ
CH₃CN, 100°, 43 h

63

ᵃ Two unidentified cyclic products were formed under these conditions.

TABLE 5. ASYMMETRIC CYCLIZATIONS

A. 5-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₈	Pd₂(dba)₃•CHCl₃, (R, S)-BPPFOH, silver-exchanged zeolite, DMF, DMSO, 0°, 5 d	(39) 86% ee + (55) 86% ee	227, 521
C₁₂	Pd₂(dba)₃, (R)-BINAP, Ag₃PO₄, DMA, 60-80°	(88) 63% ee	148
	Pd₂(dba)₃, (R)-BINAP, PMP, DMA, 100°, 1.3 h	(91) 25% ee	147, 148, 522
	Pd(R)-BINAP, PMP, DMA, 100°	(89) 84% ee	522, 523
	Pd₂(dba)₃, (R)-BINAP, Ag₃PO₄, DMA, 80°, 27 h	(88) 59% ee	147, 523
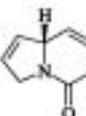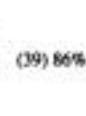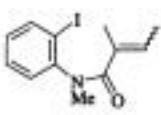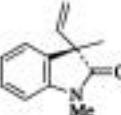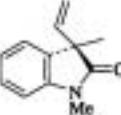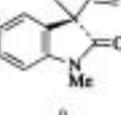
497

TABLE 5. ASYMMETRIC CYCLIZATIONS (Continued)

A. 5-EXO (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-28}

1. $Pd_2(dba)_3 \cdot CHCl_3$, (R)-BINAP, PMP, DMA, 100°
2. HCl (3 N), 23°

I

R^1	R^2
Me	OMe
Me	OTBDMS
Me	OTIPS
t-Bu	OTIPS
$CH_2CH(OMe)_2$	OTIPS
Ph	OTIPS

I	% ee	config
(76)	89	R
(73)	97	R
(87)	90	R
(76)	0	(—)
(93)	91	S
(—)	19	(—)

523

1. $Pd_2(dba)_3 \cdot CHCl_3$, (R)-BINAP, Ag_3PO_4, DMA, 100° **I**
2. HCl (3 N), 23°

R^1	R^2
Me	OMe
Me	OTBDMS
Me	OTIPS
t-Bu	OTIPS
Ph	OTIPS

I	% ee	config
(72)	80	R
(53)	78	R
(73)	80	R
(55)	33	S
(86)	65	(—)

523

C_{13}

$Pd_2(dba)_3$, (R)-BINAP, Ag_3PO_4, DMA, 60°, 23 h

(81) 7% ee

147

$Pd_2(dba)_3$, (R)-BINAP, PMP, DMA, 100°, 1.3 h

(96) 56% ee

147

C_{13-28}

1. Pd(R)-BINAP, PMP, DMA, 100°
2. HCl (3 N), 23°

  I

R^1	R^2			% ee	
Me	OMe	Z	(76)	88	R
Me	OTBDMS	E	(85)	45	R
Me	OTBDMS	Z	(81)	92	R
Me	OTIPS	Z	(87)	90	R

	522
	147, 522
	522
	522

1. $Pd_2(dba)_3$, (R)-BINAP, DMA **I**
2. HCl (3 N), 23°

R^1	R^2		Additional (1.)	1. Temp	1. Time	**I**	% ee		
Me	OTBDMS	E	Ag_3PO_4	80°	2 h	(80)	45	S	147, 522
t-Bu	OTIPS	E	Ag_3PO_4	120°	4 h	(41)	72	R	147
t-Bu	OTIPS	E	PMP	120°	2 h	(90)	27	R	147
Ph	OTIPS	E	Ag_3PO_4	80°	2.5 h	(93)	73	(—)	147
Ph	OTIPS	E	PMP	100°	14 h	(74)	35	(—)	147

C_{14-22}

$Pd_2(dba)_3$, Ag_3PO_4

  I +   **II**

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

A. 5-EXO (*Continued*)

Substrate			Conditions	Product(s) and Yield(s) (%)					Refs.
R^1	R^2	R^3		Temp	Time	I	% ee	II	
H	Me	O	(R)-BINAP, NMP	60°	25 h	(70)	80	(14)	147, 148
H	Me	O	(S)-7,7'-dimethoxy-2,2'-bis(diphenylphosphino)-1-1'-binaphthalene, DMA	80°	26 h	(93)	89	(0)	524
Me	Me	O	(R)-BINAP, DMA	60°	3.5 h	(99)	72	(0)	147, 148
—OCH₂CH₂O—	Me	O	(R)-BINAP, DMA	60°	26 h	(81)	71	(0)	147, 148
—OCH₂CH₂O—	CO₂Me	H, H	(R)-BINAP, NMP	80°	24 h	(90)	64	(0)	147, 148
—OCH₂CH₂O—	Boc	O	(R)-BINAP, DMA	80°	72 h	(65)	42	(0)	147
—OCH₂CH₂O—	SEM	O	(R)-BINAP, NMP	80°	29 h	(78)	58	(0)	147, 148
—OCH₂CH₂O—	Bn	O	(R)-BINAP, NMP	80°	52 h	(76)	65	(0)	147
—OCH₂CH₂O—	Bn	O	(R)-BINAP, NMP	80°	13 h	(91)	50	(0)	147, 148

C_{14-32}

Pd₂(dba)₃, (R)-BINAP, PMP, DMA

R^1	R^2	R^3	R^4	Temp	Time	I	% ee	II	% ee	
H	Me	O	Br	120°	9 h	(51)	32	(36)	(—)	147, 148
H	Me	O	I	100°	1 h	(45)	89-95	(44)	31	
Me	Me	O	I	100°	1 h	(89)	71	(0)	0	
—OCH₂CH₂O—	Me	O	I	80°	140 h	(77)	66	(0)	0	
—OCH₂CH₂O—	CO₂Me	H,H	I	100°	7 h	(68)	8	(0)	0	
—OCH₂CH₂O—	SEM	O	I	100°	6.5 h	(74)	75	(0)	0	
—OCH₂CH₂O—	Bn	O	I	100°	4.5 h	(66)	66	(0)	0	

C_{15}

Pd₂(dba)₃, (R)-BINAP, Ag₃PO₄, NMP, 60°, 24 h

(91) 49-55% ee

147, 148

Pd₂(dba)₃, (R)-BINAP, PMP, DMA, 100°, 6 h

(66) 0-7% ee

147, 148

Pd₂(dba)₃, (R)-BINAP, Ag₃PO₄, DMA, 80°, 24 h

(62) + (13) + (17)

147

Pd₂(dba)₃, (R)-BINAP, PMP, DMA, 100°, 1.5 h

(50) 88% ee + (40) + (4)

147

C_{16}

Pd₂(dba)₃, (S)-BINAP, Ag₃PO₄, DMA, 50°

(—) 45-50% ee

270

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

A. 5-EXO (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{19}$	1. Pd$_2$(dba)$_3$•CHCl$_3$, (*R*)-BINAP, *n*-Bu$_4$NI, PMP, DMA 2. HCl (3 N), 23° 3. NaBH$_4$	(89) 93% ee	523
C$_{20}$	Pd(OAc)$_2$, (*R*)-BINAP, Et$_3$N		525
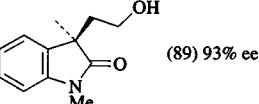
R^1	R^2	Solv		% ee^a
CH	N	CH$_3$CN	(41)	10
CH	N	THF	(—)	41
N	CH	CH$_3$CN	(—)	(—)
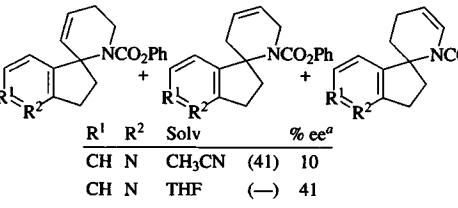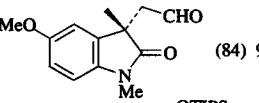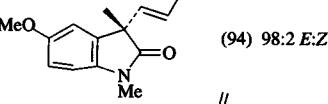
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{22}$	1. Pd$_2$(dba)$_3$•CHCl$_3$, (*S*)-BINAP, PMP, DMA, 100° 2. HCl (3 N), 23°	(84) 95% ee	522, 526
	Pd$_2$(dba)$_3$•CHCl$_3$, (*S*)-BINAP, PMP, DMA, 100°	(94) 98:2 *E:Z*	522, 526
C$_{47}$	Pd$_2$(dba)$_2$•CHCl$_3$, Ag$_3$PO$_4$, DMA, 100°		527

	Time		% ee
(*R*)-BINAP	22 h	(74)	14
(*R*)-Tol-BINAP	21 h	(67)	19
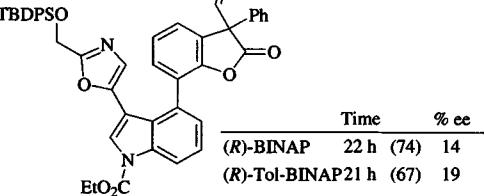
^{a} The %ee was determined after alkene hydrogenation of the mixture of all three regioisomers.

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

B. 6-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{15-16}$	Pd(OAc)$_2$	I + II + III	260
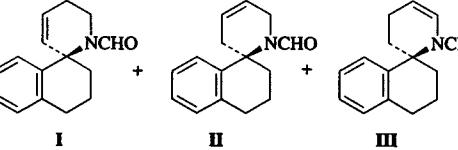
R	Conditions	Solv	Temp	Temp	I		% ee		II	% ee	III	% ee
I	(*R*)-BINAP, Et$_3$N, AgNO$_3$	CH$_3$CN	80°	144 h	(6)		8	(*S*)	(14)	35	(39)	38
I	(*R*)-BINAP, CaCO$_3$, Ag$_3$PO$_4$, Et$_3$N	DMA	80°	23 h	(21)		27	(*R*)	(8)	30	(28)	54
I	(*R*)-BINAP, Ag$_3$PO$_4$	DMA	80°	74 h	(56)		38	(*R*)	(3)	15	(15)	18
OTf	(*R*)-BINAP, Et$_3$N	THF	60°	48 h	(10)		13	(*S*)	(19)	68	(30)	71
OTf	(*R*)-BINAP, Et$_3$N	THF	40°	144 h	(9)		21	(*S*)	(19)	73	(31)	69
OTf	(*R*)-BINAP, Et$_3$N	tol	60°	168 h	(11)		8	(*R*)	(22)	89	(8)	90
OTf	(*i*-Pr)$_2$NEt, [oxazoline-PPh$_2$, *t*-Bu]	tol	110°	48 h	(64)		87	(*R*)	(7)	>99	(0)	—
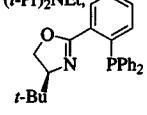
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{16}$	Pd$_2$(dba)$_3$•CHCl$_3$, (*S*)-BINAP, K$_2$CO$_3$, pinacol, DCE, 70°, 69 h	(81) 45% ee	153
	Pd$_2$(dba)$_3$•CHCl$_3$, (*R*)-BINAP, K$_2$CO$_3$, THF, 70°, 87 h	(70) 39% ee + (19) 32% ee	146
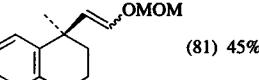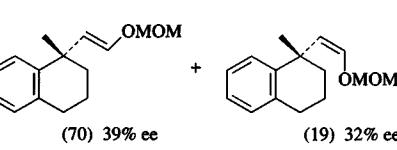
TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

B. 6-EXO (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{17-18} — Pd(OAc)₂, (*R*)-BINAP, K₂CO₃, tol

R	Temp	Time	I	% ee	II	% ee	
H	80°	72 h	(24)	95	(47)	95	528, 529
OMe	50°	96 h	(47)	95	(15)	95	528

C_{19} — Pd(OAc)₂, (*R*)-BINAP, Et₃N, AgNO₃, cyclohexene, CH₃CN

(—) 68% ee   I 0% ee   + 279

II <15% ee   I:II = 2:1

C_{20} — Pd₂(dba)₃·CHCl₃, (*R*)-BINAP, K₂CO₃, THF, 70°, 48 h

(95) 51% ee; E:Z = 84:11   146

C_{20-21} — (*R*)-BINAP, K₂CO₃, THF   146

R		
H	Pd₂(dba)₃·CHCl₃, 50°, 50 h	(79) 91% ee; E:Z = 98:2
OMe	Pd(OAc)₂, 60°, 48 h	(87) 93% ee; E:Z = 21:3

C_{34}

Conditions	Solv	Temp	Time		% ee	Refs.
Pd(OAc)₂, (*R*)-BINAP, K₂CO₃	THF	50°	32 h	(68)	92	70, 71, 208
Pd₂(dba)₃, (*R*)-BINAP, K₂CO₃	tol	40°	46 h	(74)	89	71, 208
Pd₂(dba)₃, (*R*)-BINAPAs, K₂CO₃	tol	40°	46 h	(91)	88	208
Pd₂(dba)₃, (*R*)-BINAPAs, K₂CO₃	DCE	40°	48 h	(95)	81	208

C_{36} — Pd(OAc)₂, (*S*)-BINAP, K₂CO₃, THF, 60°, 22 h

(78) 87% ee   70, 71, 126

C_{38} — Pd(OAc)₂, (*R*)-Tol-BINAP, K₂CO₃, tol, 100°, 2 h

(18) 96% ee   137

+ (2)

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

C. 5-EXO GROUP SELECTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-27}

R^1	R^2		Temp	Time		% ee	
I	CO_2Me	PdCl$_2$[(*R*)-BINAP], cyclohexene, Ag$_3$PO$_4$, CaCO$_3$, NMP	40°	138 h	(72)	86	
I	$CH_2OTBDMS$	PdCl$_2$[(*R*)-BINAP], cyclohexene, Ag$_3$PO$_4$, CaCO$_3$, NMP	40°	142 h	(55)	86	
I	CH_2OAc	PdCl$_2$[(*R*)-BINAP], cyclohexene, Ag$_3$PO$_4$, CaCO$_3$, NMP	40°	92 h	(70)	85	
I	$CH_2OTBDPS$	PdCl$_2$[(*R*)-BINAP], Ag$_3$PO$_4$, CaCO$_3$, NMP	60°	38 h	(53)	76	
I	CH_2OPiv	PdCl$_2$[(*R*)-BINAP], Ag$_3$PO$_4$, CaCO$_3$, NMP	60°	23 h	(74)	80	
OTf	$CH_2OTBDMS$	Pd(OAc)$_2$, (*R*)-BINAP, K$_2$CO$_3$, C$_6$H$_6$	60°	64 h	(63)	73	

151

C_{16}

PdCl$_2$[(*R*)-BINAP], Ag$_3$PO$_4$, CaCO$_3$, NMP, 60°, 68 h

(63) 3% ee

151

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

D. 6-EXO GROUP SELECTIVE

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12-18}

R^1	R^2		Temp	Time		% ee	
I	CO_2Me	PdCl$_2$[(R)-BINAP], Ag$_3$PO$_4$, NMP	60°	188 h	(48)	69	153, 305, 521
I	$CH_2OTBDMS$	PdCl$_2$[(R)-BINAP], Ag$_3$PO$_4$, CaCO$_3$, NMP	60°	84 h	(67)	80	153, 305, 521, 530
I	$CH_2OTBDMS$	Pd$_2$(dba)$_3$, (R)-BINAs, Ag$_3$PO$_4$, CaCO$_3$, NMP	60°	24 h	(90)	82	209
I	CH_2OAc	Pd(OAc)$_2$, cyclohexene, (R)-BINAP, Ag$_2$CO$_3$, NMP	40°	88 h	(66)	36	153, 305, 521
OTf	CO_2Me	Pd(OAc)$_2$, (R)-BINAP, K$_2$CO$_3$, DCE	60°	84 h	(51)	92	153, 530
OTf	CH_2OPiv	Pd(OAc)$_2$, (R)-BINAP, K$_2$CO$_3$, DCE	60°	47 h	(78)	95	153, 530
OTf	$CH_2OTBDMS$	Pd(OAc)$_2$, (R)-BINAP, K$_2$CO$_3$, tol	60°	74 h	(35)	92	153, 209, 530
OTf	CH_2OAc	Pd(OAc)$_2$, (R)-BINAP, K$_2$CO$_3$, tol	60°	45 h	(44)	89	153, 530

C_{17}

Pd$_2$(dba)$_3$•CHCl$_3$, (*R*)-BINAP, DCE, K$_2$CO$_3$, 40°, 167 h

(66) 83% ee

357

TABLE 5. ASYMMETRIC CYCLIZATIONS (*Continued*)

D. 6-EXO GROUP SELECTIVE (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pd$_2$(dba)$_3$•CHCl$_3$, (*R*)-BINAP, *t*-BuOH, K$_2$CO$_3$, DCE, 60°, 42 h	(76) 86% ee	152, 153

C$_{18-24}$
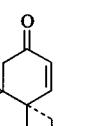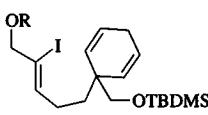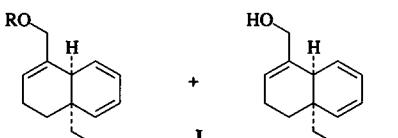
| | PdCl$_2$[(*R*)-BINAP], Ag$_3$PO$_4$, CaCO$_3$, NMP, 60° | | 521, 530 |
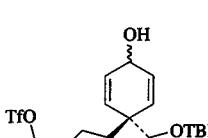
R
H
Ac
TBDMS

Time	I		% ee	II		% ee
—	(—)		71	—		—
100 h	(67)		87	(0)		—
41 h	(63)		83	(35)		92

C$_{29}$

| | Pd(OAc)$_2$, (*S, S*)-BCPM, K$_2$CO$_3$, tol, 60°, 15 h | (17) 30% ee | 357 |
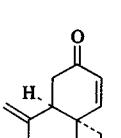
TABLE 5E. ALLYL SILANE TERMINATED ASYMMETRIC CYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{16}$

| | Pd$_2$(dba)$_3$, (*S*)-BINAP, Ag$_3$PO$_4$, DMF | | 159 |

R^1	R^2
H	NCOCF$_3$
OMe	CH$_2$

Temp	Time	I	% ee	II
75°	5 h	(63)	72	(7)
80°	24 h	(76)	90	(16)

C$_{16-18}$

| | Pd$_2$(dba)$_3$, Ag$_3$PO$_4$, DMF | | 160 |

R^1	R^2	R^3		Temp	Time	I	% ee		II	% ee	
H	H	CH$_2$SiMe$_3$	(+)-TMBTP	80°	65 h	(80)	84	*S*	(0)	(—)	—
H	H	CH$_2$SiMe$_3$	(+)-TMBTP	90°	63 h	(61)	86	*S*	(0)	(—)	—
H	CH$_2$SiMe$_3$	H	(*R*)-BINAP	80°	20 h	(32)	67	*R*	(40)	2	*R*
H	CH$_2$SiMe$_3$	H	(*R*)-BITIANP	70°	14 h	(51)	50	*R*	(14)	0	—
H	CH$_2$SiMe$_3$	H	(+)-TMBTP	80°	46 h	(35)	<5	*S*	(38)	<5	*R*
OMe	H	CH$_2$SiMe$_3$	(*R*)-BITIANP	80°	20 h	(80)	16	*S*	(6)	<10	*R*
OMe	H	CH$_2$SiMe$_3$	(+)-TMBTP	80°	64 h	(73)	84	*S*	(0)	(—)	—
OMe	CH$_2$SiMe$_3$	H	(*R*)-BITIANP	80°	48 h	(24)	34	*R*	(42)	30	*R*
OMe	CH$_2$SiMe$_3$	H	(+)-TMBTP	80°	48 h	(56)	56	*R*	(9)	76	*R*

TABLE 5E. ALLYL SILANE TERMINATED ASYMMETRIC CYCLIZATIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)									Refs.

C_{17-19}

R^1	R^2	R^3		Temp	Time	I	% ee		II	% ee		
H	H	CH₂SiMe₃	(R)-BINAP	90°	27 h	(73)	48	R	(4)	—	—	160
H	H	CH₂SiMe₃	(+)-TMBTP	90°	27 h	(71)	70	S	(6)	—	—	160
H	CH₂SiMe₃	H	(R)-BITIANP	80°	26 h	(41)	22	S	(42)	86	S	160
H	CH₂SiMe₃	H	(+)-TMBTP	80°	16 h	(43)	64	R	(25)	12	R	160
OMe	H	CH₂SiMe₃	(R)-MeO-BIPHEP	80°	65 h	(42)	<25	R	(15)	<5	S	160
OMe	H	CH₂SiMe₃	(S)-BINAP	80°	40 h	(72)	64	S	(7)	<18	R	159, 160
OMe	H	CH₂SiMe₃	(+)-TMBTP	80°	68 h	(71)	92	S	(0)	—	—	160
OMe	CH₂SiMe₃	H	(R)-BITIANP	80°	24 h	(21)	60	S	(66)	91	S	160
OMe	CH₂SiMe₃	H	(+)-TMBTP	80°	45 h	(33)	45	S	(57)	8	R	160

C_{17}

Pd₂(dba)₃•CHCl₃, (R)-BINAP, Ag₃PO₄, DMF, 80°, 48 h	(91) 92% ee	531, 532

TABLE 5F. ASYMMETRIC TANDEM CYCLIZATIC

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{10}

[Pd(allyl)Cl]₂, (R,R)-CHIRAPHOS, Bu₄NOAc, tol, 60°, 144 h	(61) 20% ee	154, 155

C_{11}

(S)-BINAP, DMSO

	R	Temp	Time		% ee	
Pd(OAc)₂, RNa	(ClCH₂CO)(CO₂Me)CH	rt	—	(67)	80	156
[Pd(allyl)Cl]₂, RNa, NaBr	(CO₂Me)₂CH	rt	1 h	(92)	83	156
[Pd(allyl)Cl]₂, RNa, NaBr	(TBDPSO(CH₂)₂)(CO₂Et)₂C	rt	1 h	(77)	87	156
[Pd(allyl)Cl]₂, RNa, NaBr	(SO₂Ph)₂CH	rt	1 h	(83)	94	156
[Pd(allyl)Cl]₂, RNa, NaBr	(MeCO)(CO₂Me)CH	rt	1 h	(74)	83	156
[Pd(allyl)Cl]₂, RNa, NaBr	(CO₂MeCH₂CO)(CO₂Me)CH	rt	1 h	(81)	82	156
[Pd(allyl)Cl]₂, RNa, NaBr	(TBDPSOCH₂CO)(CO₂Me)CH		1 h	(72)	82	156
[Pd(allyl)Cl]₂, RNa, NaBr	(PhCO)₂CH	rt	1 h	(90)	80	156
Pd(OAc)₂, Bu₄NOAc	OAc	20°	2.5 h	(89)	80	154, 55, 156
Pd(OAc)₂, BnNH₂	NHBn	20°	2 h	(76)	81	155, 156

C_{15}

Pd(OAc)₂, C₆H₆		236
(R,R)-DIOP	(>90) 45% ee	
(S,S)-DIOP	(>90) 45% ee (enantiomer of above)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₇₋₂₃

Pd₂(dba)₃, PMP, tol, 110°

137

R¹	R²			% ee	
H	H	(S)-BINAP, 2 d	(88)	71	S
H	H	(R)-BINAP, 2 d	(83)	71	R
H	Me	(R)-BINAP, 2 d	(83)	90	R
H	Me	(R)-BINAP, 3 d	(61)	24	S
Me	H	(R)-BINAP, 3 d	(71)	96	R
Me	Me	(R)-BINAP, 3 d	(68)	71	R
H	Ph	(R,R)-CHIRAPHOS, 4 d	(66)	77	S

C₂₂₋₂₃

R			% ee	
Br	Pd₂(dba)₃, (R)-BINAP, PMP	(—)	13	R	505
Br	Pd₂(dba)₃·CHCl₃, (S)-BINAP, Ag exchanged zeolite, CaCO₃, NMP, 80°, 4 d	(39)	63	S	533
OTf	Pd₂(dba)₃, (R)-BINAP, PMP, tol, 22 h	(78)	68	R	505
OTf	Pd₂(dba)₃, (S)-BINAP, PMP, tol, 22 h	(82)	68	S	505

C₂₅

Pd(OAc)₂, HCO₂Na, CaCO₃, Ag-zeolites, CH₃CN, 60°, 8 h

150

R¹	R²			% ee
H	CO₂Me	(R)-BINAP	(42)	81
H	CO₂Me	(S)-BINAP	(35)	80
CO₂Me	H	(R)-BINAP	(56)	69
CO₂Me	H	(S)-BINAP	(40)	59

C₂₆

Pd(OAc)₂, BINAP, t-Bu acrylate, Et₃N, DMF, 80°, 12 h

(37) 28% ee

63

C₂₇

HCO₂Na, Ag-zeolites, CH₃CN, 60°, 8 h

150

		% de
Pd(OAc)₂, (S)-BINAP, CaCO₃	(35)	80
Pd(OAc)₂, (R)-BINAP, CaCO₃	(33)	72
Pd(OAc)₂, (R)-BINAP, NBu₃	(40)	32
Pd(OAc)₂ (prereduced), (R)-BINAP, CaCO₃	(50)	44
PdCl₂[(R)-BINAP], CaCO₃	(46)	50

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS

A. 5-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	1. Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 80°, 6-8 h 2. TFA	 R H (83) Cl (81)	177
	1. Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 80°, 24 h 2. TFA	(<60)	177
C$_{12}$	1. Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 80°, 6-8 h 2. TFA	(79)	177
C$_{13-25}$	1. Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, DMF, 100°, 16 h 2. TFA		534
C$_{17}$	1. Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 80°, 6-8 h 2. TFA	(76)	177
C$_{17-20}$	1. Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, n-Bu$_4$NCl, DMF, H$_2$O, 80° 2. TFA		177

For C$_{13-25}$:

R^1	R^2		E:Z	HPLC purity %
cyclohexyl	Me	(81)	—	70
H	Me	(91)	3:1	65
H	Ph	(92)	5.5:1	76
H	H	(65)	—	10
CH$_2$C$_6$H$_{11}$	Me	(92)	2.7:1	70
CH$_2$C$_6$H$_{11}$	Ph	(90)	5.8:1	71
CH$_2$C$_6$H$_{11}$	H	(70)	(—)	17
Bu-i	Me	(90)	3:1	82
Bu-i	Ph	(90)	5.9:1	70
Bu-i	H	(75)	(—)	16

For C$_{17-20}$:

R^1	R^2	R^3	R^4	Time	
H	H	H	H	24 h	(80)
H	H	H	F	6-8 h	(85)
H	H	H	CF$_3$	6-8 h	(74)
H	H	H	Me	6-8 h	(78)
H	OMe	H	F	6-8 h	(74)
H	OMe	Cl	H	6-8 h	(72)
H	OMe	H	OCF$_3$	6-8 h	(67)
H	OMe	H	Me	6-8 h	(69)
CO$_2$Me	H	H	H	6-8 h	(88)
CO$_2$Me	H	H	F	6-8 h	(81)
CO$_2$Me	H	H	CF$_3$	6-8 h	(70)

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS (*Continued*)

A. 5-EXO (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{22-33}$

R^1	R^2	I	HPLC Purity %	II
Et	H	(90)	88	(0)
Et	Ph	(94)	93	(0)
i-Pr	Me	(92)	91	(0)
Ph	H	(70)	48	(0)
Ph	Ph	(65)	55	(0)
Ph	Me	(45)	25	(55)
3-MeOC$_6$H$_4$	H	(90)	89	(0)
3-MeOC$_6$H$_4$	Ph	(83)	75	(0)

Conditions: 1. Pd(PPh$_3$)$_4$, PPh$_3$, Et$_3$N, DMA, 85°, 6 h 2. TFA

Ref. 535

C$_{24}$

Conditions: 1. Pd(OAc)$_3$, PPh$_3$, K$_2$CO$_3$, n-Bu$_4$NCl, DMA, 100°, 27 h 2. TFA, CH$_2$Cl$_2$

R	
OMe	(80)
Me	(70)

Ref. 536

C$_{32}$

Conditions: 1. Pd(OAc)$_3$, PPh$_3$, K$_2$CO$_3$, n-Bu$_4$NCl, DMA, 100°, 27 h 2. NaOMe, MeOH, dioxane, rt, 24 h

(30-40)

Ref. 536

^{a} The polymer support is a Rink amide AM or Rink amide resin.

^{b} The polymer support is a Rink amide resin.

^{c} The polymer support is a Tentagel S-NH2 resin.

^{d} The polymer support is a Rink resin.

^{e} The polymer support is a polystyrene resin.

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS (*Continued*)

B. 6-ENDO AND 6-EXO

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{14-25}

1. Pd(PPh₃)₄, PPh₃, Et₃N, DMA, temp, time
2. TFA

537

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Temp	Time	I	HPLC Purity %	II
H	H	H	H	C	H	i-Bu	85°	6 h	(69)	83	(0)
H	H	H	H	C	H	CH₂CH₂Ph	85°	6 h	(65)	80	(0)
H	H	H	H	C	H	Ph	85°	6 h	(85)	>70	(0)
H	H	H	Me	C	H	i-Bu	85°	6 h	(22)	94	(70)
F	H	H	H	C	H	i-Bu	85°	6 h	(80)	90	(0)
H	OMe	OMe	H	C	H	i-Bu	85°	6 h	(77)	95	(0)
H	Cl	H	H	C	H	i-Bu	85°	6 h	(79)	90	(0)
H	H	H	OMe	C	H	i-Bu	85°	6 h	(43)	93	(26)
H	H	H	H	C	H	i-Bu	60°	18 h	2.3:1 I:II	(—)	
H	H	H	H	C	H	-CH₂-tetrahydrofuran	60°	18 h	(—)	(—)	(0)
H	H	H	H	C	H	4-(N-benzylpiperidine)	60°	18 h	(—)	(—)	(0)
H	H	H	H	C	H	-CH₂-cyclopropyl	60°	18 h	(—)	(—)	(0)
H	H	H	H	C	H	-CH₂-benzodioxole	60°	18 h	(—)	(—)	(0)
H	H	H	H	C	H	-CH₂-naphthyl	60°	18 h	(—)	—	(0)
H	H	H	H	C	H	4-biphenyl	60°	18 h	(—)	—	(0)
H	H	H	H	C	H	2,2-diphenylethyl	60°	18 h	(—)	—	(0)
H	H	H	H	C	Me	2-phenylethyl	85°	6 h	(0)	—	(—)
—	H	H	H	N	H	1-(2-methylpropyl)	85°	6 h	(0)	—	(—)

1. Pd(PPh₃)₄, PPh₃, Et₃N, DMA, 85°, 6 h
2. TFA

(—)

537

C_{35-41}

1. Pd(OAc)₂, PPh₃, K₂CO₃, n-Bu₄NCl, DMA, 100°, 24 h
2. NaOMe, MeOH, dioxane, rt, 24 h

R	
H	(90)
Ph	(78)

536

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS (*Continued*)

B. 6-ENDO AND 6-EXO (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{36-41}	1. Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, n-Bu$_4$NCl, DMA, 100°, 24 h 2. NaOMe, MeOH, dioxane, rt, 24 h	R CO$_2$Me (—) SO$_2$tol (—) COMe (—)	536
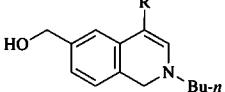
a The polymer support is a Rink amide polystyrene resin.

b The type of polymer support was not mentioned.

c The polymer support is a polystyrene resin.

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS (*Continued*)

C. 7-EXO

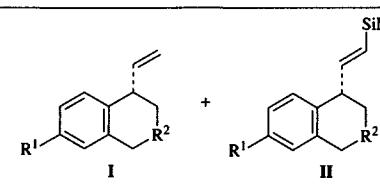| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{13-18}	1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_4$NCl, KOAc, DMF, 70° 2. TFA, CH$_2$Cl$_2$ 3. CH$_2$N$_2$	R Time Me 5 h (67) Ph — (60)	178
C_{19-30}	1. Pd(OAc)$_2$, PPh$_3$, n-Bu$_4$NCl, HCO$_2$Na, DMF, 70° 2. TFA, CH$_2$Cl$_2$ 3. CH$_2$N$_2$		178
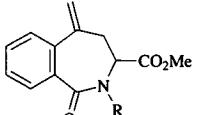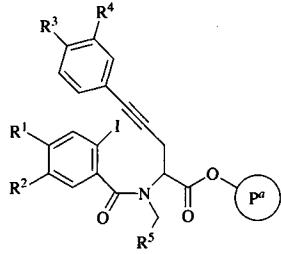
R^1	R^2	R^3	R^4	R^5		HPLC purity %
H	H	H	H	H	(63)	—
H	H	H	H	Ph	(68)	—
H	H	CONHBu	H	Ph	(55)	—
H	H	H	CF$_3$	Ph	(50)	93
Cl	H	H	H	Ph	(69)	71
OMe	OMe	H	H	Ph	(47)	—
H	H	H	H	CH$_2$CH$_2$Ph	(73)	77
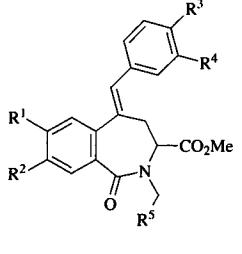
a The polymer support is a Wang resin.

TABLE 6. CYCLIZATIONS ON POLYMER SUPPORTS (*Continued*)

D. MACROCYCLIZATIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₄₋₃₅	1. Pd(OAc)₂, PPh₃, Et₃N, *n*-Bu₄NCl, H₂O, DMF, rt, overnight 2. TFA, CH₂Cl₂, anisole, rt, 30 min	(75-85)	538
C₃₄	1. Pd(OAc)₂, PPh₃, Et₃N, *n*-Bu₄NCl, DMF, H₂O, 37°, 4 h 2. AcOH, TFE, CH₂Cl₂, rt, 40 min	(30)	179

R¹ R² R¹ R² (cont.)

R¹	R²	R¹	R² (cont.)
Gly	Gly	Phe	β-Ala
Ala	Gly	Pro	β-Ala
Leu	Gly	Gly	ε-aminocaproic acid
Phe	Gly	Ala	ε-aminocaproic acid
Pro	Gly	Leu	ε-aminocaproic acid
Gly	β-Ala	Phe	ε-aminocaproic acid
Ala	β-Ala	Pro	ε-aminocaproic acid
Leu	β-Ala		

^a The polymer support is Tentagel PHB resin.

^b The polymer support is 2-chlorotrityl resin.

9. Acknowledgments

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