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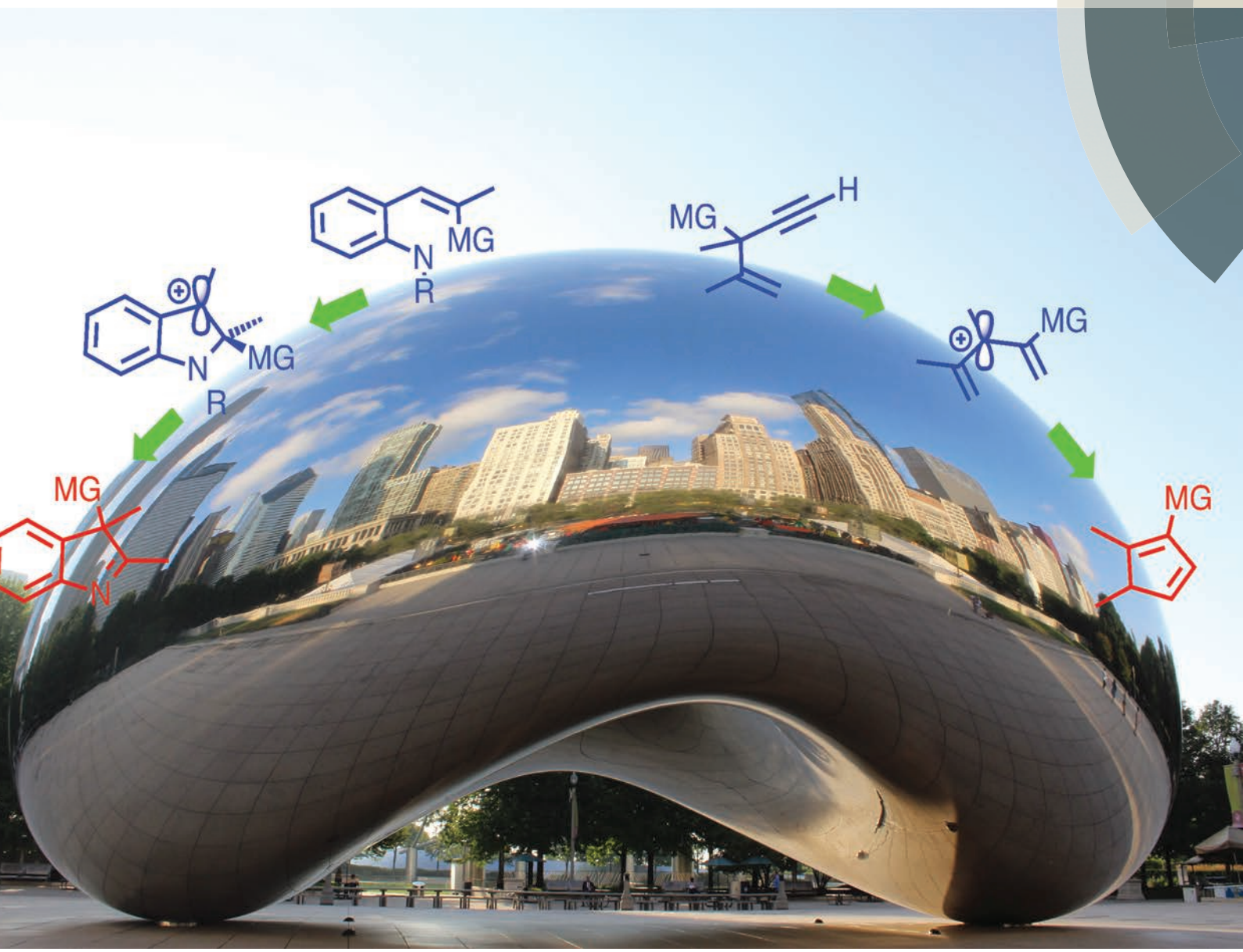

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REVIEW ARTICLE

Navendu Jana and Tom G. Driver

Assembly of functionalized carbocycles or N-heterocycles through a domino electrocyclization–[1,2] migration reaction sequence

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REVIEW

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Assembly of functionalized carbocycles or N-heterocycles through a domino electrocyclization–[1,2] migration reaction sequence

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The development of processes that streamline the synthesis of complex, functionalized carbocycles and heterocycles remains a hotly pursued topic because their scaffolds are present in a range of bioactive molecules and electronic materials. Although the Nazarov reaction has emerged to be useful in the synthesis of carbocycles and heterocycles, using an electrocyclization to trigger a migration remains underdeveloped. By constructing several bonds in one operation, domino reaction sequences are particularly effective at improving the efficiency of synthesis. The use of transition metal catalysts has the potential to render these processes stereoselective. This review examines the use of electrocyclization–[1,2] migrations to construct molecules and is organized by the type of ring constructed and the order of the two steps in this process.

Introduction

The development of a methodology to streamline the synthesis of complex, functionalized carbocycles and N-heterocycles continues to motivate synthetic chemists because of the prevalence of these scaffolds in molecules that exhibit exciting biological or electronic activity. Electrocyclization reactions are

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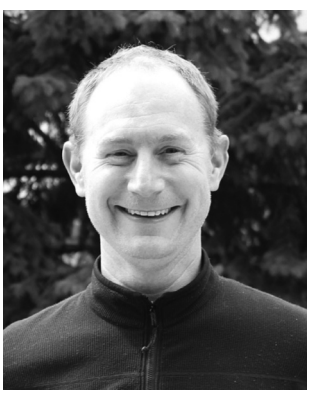
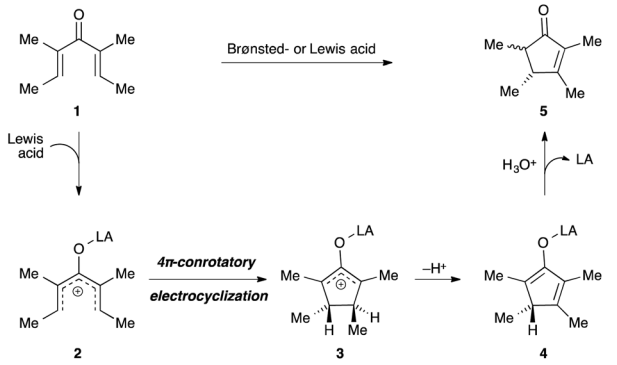


Tom G. Driver

Tom G. Driver is an Associate Professor of Chemistry at the University of Illinois at Chicago. He received his Bachelor's degree from Indiana University in 1999 where he was introduced to research in the laboratory of L. K. Montgomery, and his Doctoral degree with K. A. Woerpel (University of California, Irvine, 2004). After a Ruth L. Kirschstein NIH-funded postdoctoral fellowship with John E. Bercaw and Jay A. Labinger (California Institute of Technology), he started his independent academic career at UIC in 2006. The Driver group is focused on the development of new transition metal-catalyzed methods that harness the reactivity of metal divalent intermediates, and their application in the synthesis of bioactive or electronic organic molecules.

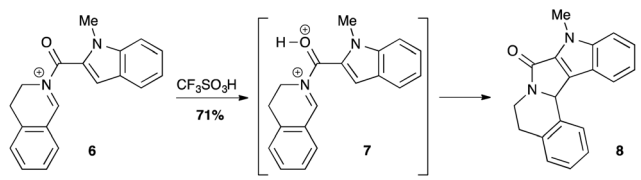


Scheme 1 The Nazarov reaction.

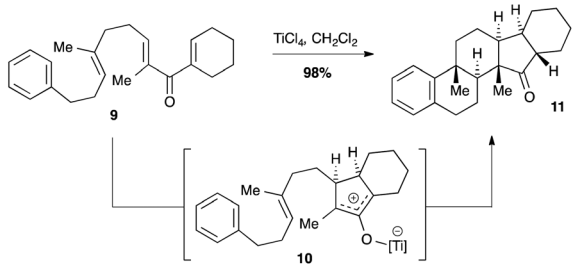
powerful transformations in organic synthesis that have been exploited to construct new C–C and new C–N bonds in a stereospecific manner. In particular, the Nazarov reaction—a 4π-electron-5-atom electrocyclization—has garnered much attention in the stereoselective synthesis of substituted cyclopentenones from simple divinyl ketones (Scheme 1).[1–9] The Nazarov reaction is often catalyzed by a Brønsted- or Lewis acid, coordination of which generates the requisite oxyallyl cation **2**, which undergoes a stereospecific 4π-electron-5-atom electrocyclization to generate the C–C bond. Elimination of a proton produces the cyclopentadiene **4**, which furnishes the cyclopentenone product **5** upon hydrolysis. Because of its ability to efficiently generate complex substituted five-membered rings, the Nazarov reaction has been employed to construct many natural products.[10–21]

In contrast to the legion of reports surrounding the development of the Nazarov cyclization, replacing one of the carbon-atoms in the pentadienyl cation with a nitrogen-atom has received less attention because of the challenges associated with generating and controlling the azapentadienyl cationic reactive intermediate. Illustrating the difficulties in overcoming these challenges, one of the first aza-Nazarov reactions was reported by Klumpp and co-workers in 2007—64 years after Nazarov's seminal report.[22] They reported that upon exposure to super acidic F_3CSO_3H, *N*-acyliminium ions, such as **6**, were transformed into pyrrolidinones *via* super electrophile **7** (Scheme 2). Since their report, processes have emerged that unlock the required electrophilic nitrogen from azide-,[23–26] imino-,[27–31] and azirine groups.[32,33]

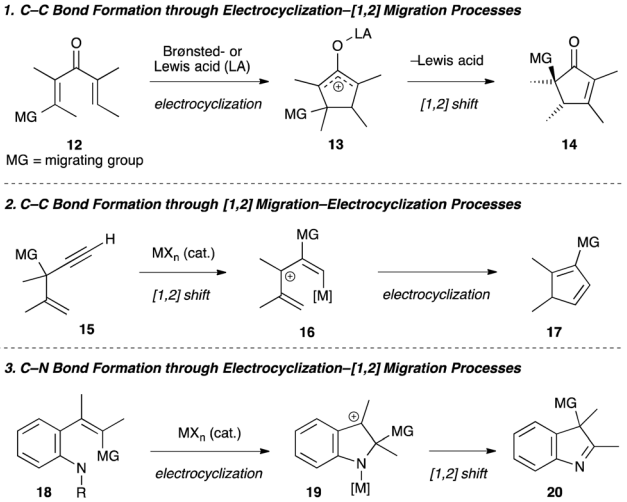
The cationic Nazarov electrocyclization intermediate has been exploited to trigger cascade processes.[34–40] The most



Scheme 2 The aza-Nazarov reaction.



Scheme 3 Triggering cascade processes from the electrocyclization of oxyallyl cation.



Scheme 4 Domino electrocyclization–[1,2] shift reactions to form carbocycles or heterocycles.

common approach is to intercept this intermediate with a nucleophile before deprotonation or elimination occurs. For example, West and co-workers reported an interrupted Nazarov reaction in 1999.[35] They reported that exposure of divinyl ketone **9** to $TiCl_4$ produced **11** through the cationic olefin polycyclization of the oxyallyl cation **10** (Scheme 3). Because these cascade processes have been recently reviewed,[40–46] we have chosen to focus the current review on intercepting the oxyallyl cation with a [1,2] migration. While the majority of these domino reactions have been initiated with a 4π-electron-5-atom electrocyclization, we do discuss the use of 6π-electron-6-atom electrocyclizations to trigger these sequences.

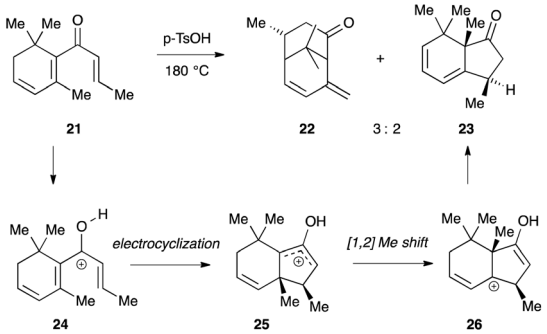
We have divided this review on electrocyclization–[1,2] migration domino reactions into three parts (Scheme 4). The first part focuses on domino reactions where a 4π-electron-5-atom- or 6π-electron-6-atom electrocyclization generates an intermediate that engages in a [1,2] migration to create densely functionalized cycloalkenones. In the second part, we describe the related processes in which the [1,2] migration triggers an electrocyclization. The final section focuses on electrocyclization–[1,2] migration sequences that form a C–N bond in the electrocyclization step. Altogether, these domino reactions

efficiently construct densely functionalized carbocyclic and heterocyclic scaffolds. Our goal in this review is to connect these apparent disparate reactions by their common mechanistic elementary steps.

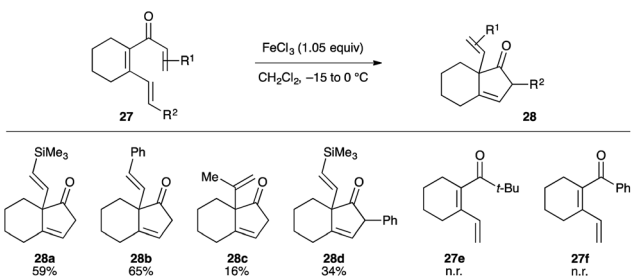
Domino electrocyclization–[1,2] shift reactions

While [1,2] migrations were observed as byproducts in the photolysis of divinyl ketones,[47–52] one of the earliest examples of products arising from an acid-catalyzed thermal domino electrocyclization–[1,2] migration reaction sequence was reported in 1971 (Scheme 5).[53] Ohloff and co-workers observed that acid-catalyzed thermolysis of β-damascone produced a 3 : 2 mixture of bicycles **22** and **23**. The formation of bicycle **23** was rationalized to occur through an electrocyclization–[1,2] methyl shift domino reaction. Protonation of vinyl dienyl ketone **21** produces a pentadienyl cation **24**, which undergoes a 4π-electron-5-atom-electrocyclization. The resulting oxyallyl cation **25** triggers a [1,2] methyl shift to produce the more stable allylic cation **26**. Deprotonation then produces **23**.

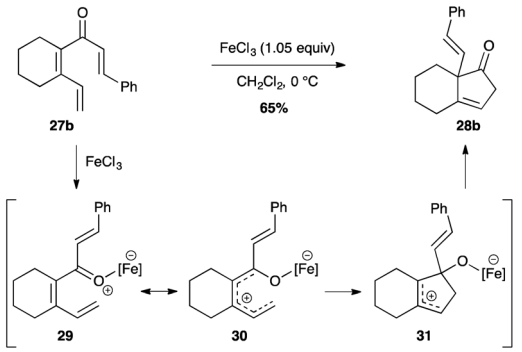
Denmark and Hite were the first to systematically study a Nazarov cyclization–[1,2] migration sequence in vinyl dienyl ketones (Scheme 6).[54] They reported that exposure of vinyl dienyl ketone **27** to stoichiometric amounts of ferric chloride produces the unusual α-vinyl cyclopentenone **28** instead of the expected cyclopentenone, which was observed by Peel and Johnson with tin-substituted vinyl dienyl ketones.[10] Denmark



Scheme 5 Byproduct formation from the electrocyclization–[1,2] Me shift reaction.



Scheme 6 $FeCl_3$-promoted electrocyclization–[1,2]-migration to form α-vinyl cyclopentenones.

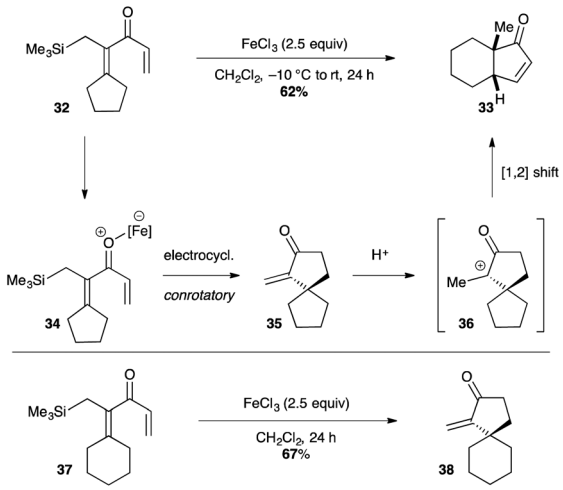


Scheme 7 Proposed mechanism for α-vinyl cyclopentenone formation from vinyl dienyl ketones.

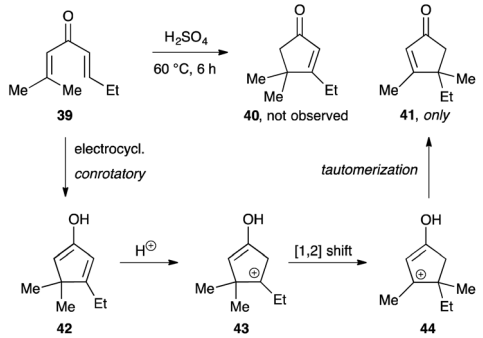
and Hite's domino reaction proved to be general with a variety of cyclohexenyl dienyl ketones transformed into cyclopentenones **28** irrespective of the substituent or substitution pattern on the dienyl- or vinyl component. Alkyl dienyl ketones or phenyl dienyl ketones (*e.g.* **27e** and **27f**), however, were inert to reaction conditions.

On the basis of these reactivity trends and ^{13}C-labeling experiments, the mechanism for α-vinyl cyclopentenone formation was proposed by Denmark and Hite to occur through an electrocyclization–[1,2] migration reaction (Scheme 7). Coordination of the ketone to the Lewis acid $FeCl_3$ triggers an electrocyclization of the pentadienyl cation **30**. This conrotatory closure appears to be favored because it occurs *via* the linearly conjugated dienyl moiety instead of the cross-conjugated divinyl ketone. The resulting allylic cation then undergoes a [1,2] vinyl migration to yield the α-vinyl cyclopentenone after dissociation of the Lewis acid. This mechanism, however, does not account for the lack of reactivity of phenyl dienyl ketone **27f**. Its inertness was speculated to originate either from an inability to access the dienyl cation or the availability of competitive decomposition pathways.

Building on reports from the Denmark group that employed the trimethylsilyl group to accelerate Nazarov electrocyclizations,[55–57] Kuroda and co-workers reported a domino electrocyclization–ring expansion sequence of β,β-disubstituted divinyl ketones (Scheme 8).[58] They showed that exposure of α-(trimethylsilylmethyl) divinyl ketone **32** to an excess amount of ferric chloride produced cyclopentenone **33**.[59] The authors proposed that the cyclopentenone product was formed through a conrotatory Nazarov cyclization of **34** that produces spirocycle **35**, which undergoes a ring expansion to form the observed product. In support of their proposed mechanism, the authors reported that the electrocyclization product spiro-[4,4]-nonane **35** could be isolated at −30 °C if the reaction time was shortened to 2 hours. Ring expansion of **35** occurred upon warming the reaction mixture to room temperature. This domino reaction was limited to divinyl ketones such as **32**. Increasing the size of the β,β-cycloalkane substituent in **37** resulted in the formation of spiro-[4,5]-decane **38** even if the reaction temperature was increased.



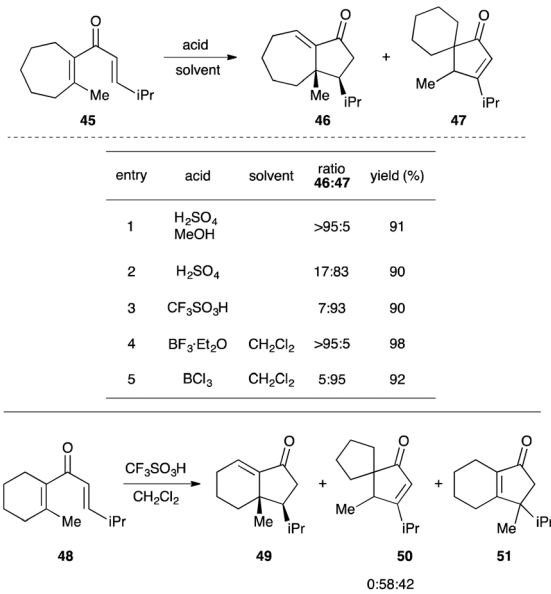
Scheme 8 $FeCl_3$-promoted electrocyclization–ring expansion to form bicycle-[4,3,0]-nonanes.



Scheme 9 Sulfuric acid-mediated electrocyclization–[1,2] migration domino reaction.

When ferric chloride was substituted with a stronger Brønsted acid,[60] a relief of ring strain was no longer required to trigger the [1,2] alkyl shift. Hayashi and co-workers reported that exposure of divinyl ketone **39** to concentrated sulfuric acid produced cyclopentenone **41** instead of the expected **40** (Scheme 9).[61] The authors proposed that **43** was formed from protonation of the Nazarov cyclization product **42**. The resulting cation triggers a [1,2] methyl shift to produce the thermodynamically more stable allylic cation **44**. Tautomerization then produces the observed cyclopentenone product.

Brønsted- and Lewis acid-catalyzed electrocyclization–ring contraction domino reactions were reported by Chiu and Li in their investigations toward building the hydroazulene core embedded in the natural product guanacastepene A.[62] When divinyl ketone **45** was exposed to methanolic sulfuric acid, the desired Nazarov cyclization product **46** was obtained. Changing the identity of the acid promoter affected the outcome of the reaction. When sulfuric acid or triflic acid was employed, ring-contraction to afford **47** became competitive with elimination to generate **46**. Boron Lewis acids also were able to

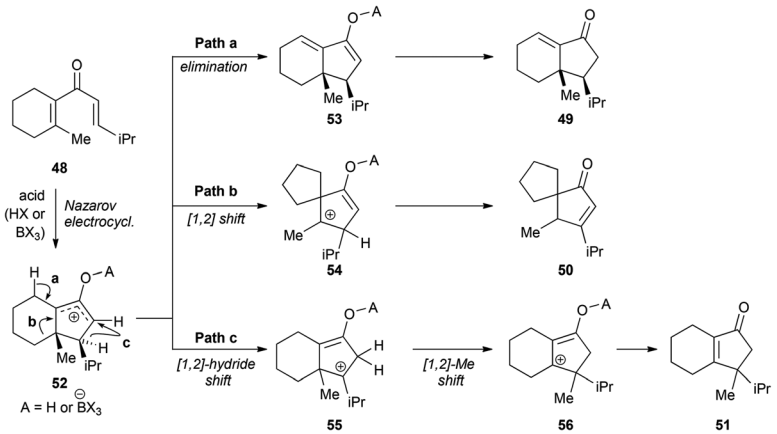


entry	acid	solvent	ratio 46:47	yield (%)
1	H_2SO_4 MeOH		>95:5	91
2	H_2SO_4		17:83	90
3	CF_3SO_3H		7:93	90
4	$BF_3{\cdot}Et_2O$	CH_2Cl_2	>95:5	98
5	BCl_3	CH_2Cl_2	5:95	92

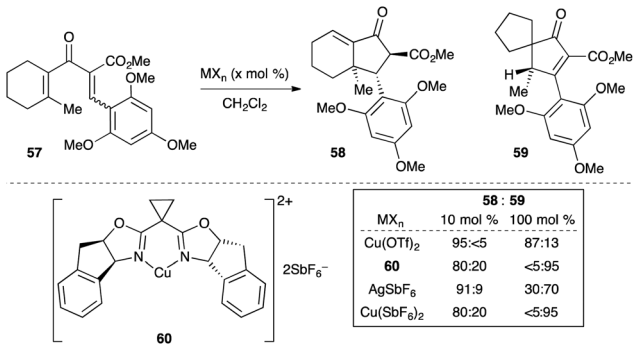
Scheme 10 Acid-mediated electrocyclization–ring contraction processes.

control the outcome of the process: exposure of divinyl ketone **45** to $BF_3{\cdot}OEt_2$ produced **46** as the only product in quantitative yield. Substituting BCl_3 as the Lewis acid induced a subsequent ring contraction to produce spirocycle **47** as the major product. Chiu and Li reported that the domino electrocyclization–[1,2] ring contraction is not limited to cycloheptenyl dienone **45**. Cyclohexenyl dienone reacts similarly—albeit less selectively—to produce the mixture of three different products (**49**, **50** and **51**). The best yield of the spirocyclic product was obtained using trifluoromethanesulfonic acid along with the [1,2] methyl shift product **51**. The overall reactivity trend indicates that the combination of a Lewis- or Brønsted acid and a non-coordinating solvent prefers a ring contraction product, whereas in the presence of a Lewis basic solvent, elimination circumvents the migration to produce the expected Nazarov product (Scheme 10).

Based on these reactivity trends, the authors proposed a mechanism to rationalize the reaction outcome (Scheme 11). Irrespective of the identity of the acid promoter, they posited that the reaction occurs through a common oxyallyl cation intermediate **52**, which is formed by acid-mediated Nazarov electrocyclization. When a Lewis base (*e.g.* MeOH or Et_2O) is present, elimination occurs to produce the expected Nazarov product **49** after tautomerization (path a). When the Lewis base is absent, the rate of elimination is reduced to enable a [1,2]-migration to form the more stabilized oxyallyl cation intermediate **54** (path b). Subsequent deprotonation and tautomerization affords the product **50**. When the smaller cyclohexenyl substituted divinyl ketone was examined, the increase in strain during the ring contraction from six- to five-membered rings induces path c to occur. The process involves a [1,2]-hydride shift followed by a second [1,2] methyl shift to



Scheme 11 Potential mechanism for electrocyclization–ring contraction process.



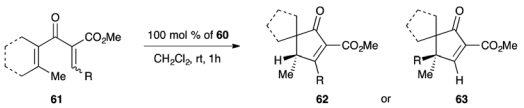
	58 : 59	
MX_n	10 mol %	100 mol %
$Cu(OTf)_2$	95:<5	87:13
60	80:20	<5:95
$AgSbF_6$	91:9	30:70
$Cu(SbF_6)_2$	80:20	<5:95

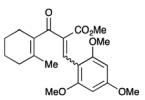
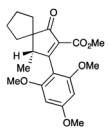
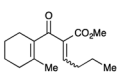
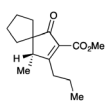
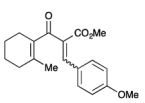
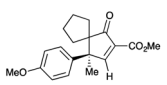
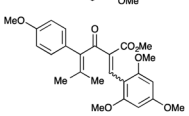
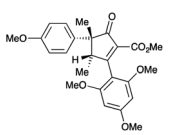
Scheme 12 Effect of catalyst identity and loading on the reaction outcome.

give intermediate **56**. Tautomerization of **56** followed by dissociation of acid affords **51**.

Recently, the Frontier group reported a Cu-catalyzed Nazarov cyclization-[1,2] migration reaction that results in the formation of unusual spirocycles.[63] They found that the reaction outcome could be controlled by the identity of the Cu(II) complex (Scheme 12). Employing 10 mol% of $Cu(OTf)_2$ produced expected bicyclic ketone **58** as a single diastereomer.[64] In an attempt to achieve an asymmetric version of this reaction, copper bisoxazoline **60** was examined as a catalyst. In addition to forming **58**, the authors observed the formation of spirocycle **59** as a by-product in 40% ee. As the catalyst loading of **60** was increased, the amount of spirocycle increased to become the only product observed once a stoichiometric amount of **60** was added. In contrast, simply increasing the amount of $Cu(OTf)_2$ did not change the identity of the major product. The authors posited that spirocycle **59** might be formed as a consequence of the SbF_6 counterion, and they found that when either stoichiometric amounts of $AgSbF_6$ or $Cu(SbF_6)_2$ were added spirocycle **59** was the major (or only) product formed. Exposure of dienyl ketone **57** to either

Table 1 Scope of the spirocyclization reaction



Entry	#	Dienone	Product	%, Yield	% ee
1	a			69	39
2	b			84	20
3	c			76	45
4	d			80	95

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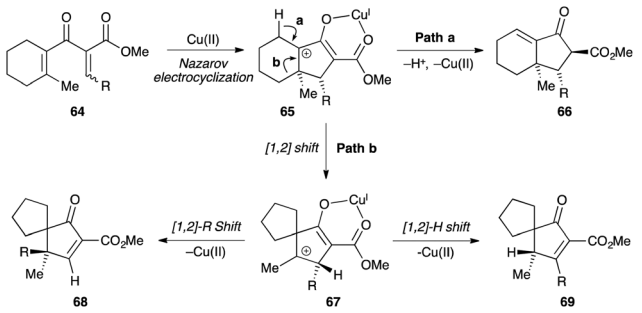
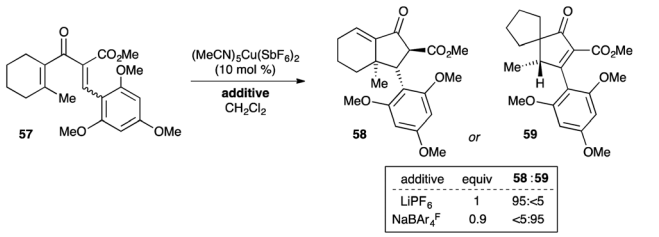
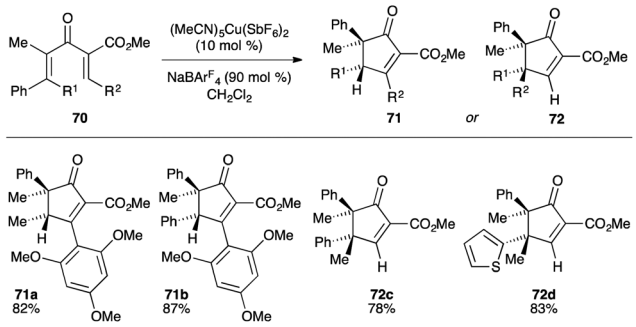
To explore the scope of spirocycle formation, the Frontier group examined the copper bisoxazoline-promoted cyclization of a variety of dienyl ketones (Table 1). The authors found that only the *Z*-isomer of the starting dienone reacts under reaction conditions.[65,66] They noticed that the identity of the spirocycle product was dependent on the nature of the β-substituent: while dienyl ketones with β-alkyl or sterically congested arenes produce spirocycle **62** (entries 1 and 2), an additional [1,2] migration occurred with a β-4-methoxyphenyl group to



Scheme 13 Proposed mechanism of spirocycle formation.



Scheme 14 Examination of additives to reduce the Cu(II)-catalyst loading.



Scheme 15 Copper(II)-catalyzed cyclization-migration domino reactions.

produce spirocycle **63c** (entry 3). In addition to ring contractions, Frontier and co-workers reported that acyclic dienyl ketones were competent substrates in their domino reaction to produce cyclopentenone **62d** with good yield and excellent enantioselectivity (entry 4).

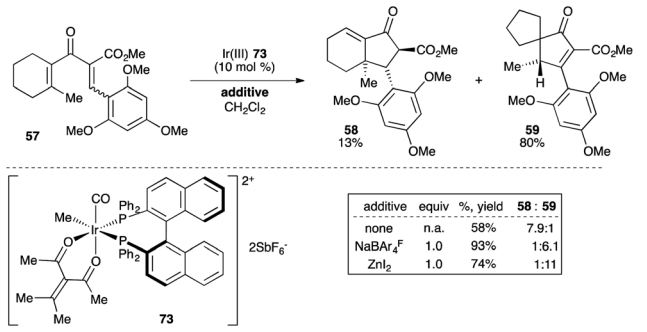
The authors proposed that their transformation proceeded through the Lewis acid-promoted electrocyclization–[1,2] domino reaction outlined in Scheme 13. Coordination of the copper(II) salt to dienyl ketone **64** triggers a conrotatory 4π-electron-5-atom electrocyclization to form the oxyallyl cation **65**. When substoichiometric amounts of the Lewis acid was employed, elimination through path a is favored to afford ketone **66**. When stoichiometric amounts of the Lewis acid is present, a [1,2] shift (path b) occurs instead to afford spirocycle **67**, which undergoes a second [1,2] shift to afford either **68** or **69**. The migratory aptitude of the second shift depends upon the steric- and electronic nature of the migrating group. While the sterically congested trimethoxybenzene favors a hydride shift, the smaller 4-methoxybenzene preferentially migrates over a hydride shift presumably because the requisite phenonium ion can be formed. The authors rationalize that the [1,2] hydride shift occurs in the propyl-substituted dienone because the propyl group does not suitably stabilize the carbocation intermediate.

Control of the reaction outcome by catalyst loading was explained by the authors to result from binding of the transition metal complex to the keto- and ester functionality. When substoichiometric quantities of the catalyst are used, the unbound substrate and the product will exist, and these free carbonyl oxygens will accelerate the elimination step. Instead, when the concentration of Lewis acid is increased, both carbonyl oxygens are bound to enable the [1,2] shift to occur. The author's assertion was grounded in their observations: (1) using a Lewis basic solvent such as THF favored the elimination pathway; and (2) using Brønsted acids such as HBF_4, $HNTf_2$, or $HSbF_6$ afforded cyclopentanones **66**.[65]

In order to reduce the copper catalyst loading in their domino cyclization–migration reaction, Frontier and co-workers examined the effect of additives on their domino cyclization–migration reaction (Scheme 14).[67] They anticipated that metal salts with non-coordinating anions might attenuate the Lewis basicity of the carbonyl group towards the copper catalyst and could be easily exchangeable with the catalyst. In line with their hypothesis, they found that the amount of the copper catalyst, $(MeCN)_5Cu(SbF_6)_2$, could be reduced to 10 mol% if 0.90 equiv. of $NaBAr_4^F$ was added to enable the formation of cyclopentenone **59** from dienyl ketone **57**. In contrast, the expected Nazarov product **58** was obtained when $LiPF_6$ (1 equiv.) was added to the reaction mixture. Other additives, such as $LiClO_4$, $Mg(OTf)_2$, $NaBPh_4$, and $NaPF_6$, led to a mixture of products. The success of $NaBAr_4^F$ was attributed to the non-coordinating nature of its counterion and its solubility in dichloromethane solvent relative to the other salts examined. The authors note that the unique ability of $NaBAr_4^F$ to suppress the elimination pathway suggests that only one of the two carbonyl's Lewis basicity must be quashed.

The scope of the author's reaction mirrored that of the stoichiometric copper results (Scheme 15). By examining a series of dienyl ketones **70**, they found that the identity of the cyclopentenone product was controlled by the steric- and electronic nature of the R^2-substituent: a [1,2] hydride shift was observed with the bulky trimethoxyphenyl group to afford **71a** or **71b**, whereas smaller electron-donating groups such as the phenyl group or a thiophene migrates selectively over the hydride shift (**72c** and **72d**). In every substrate examined by the authors, the reaction outcome was comparable to that of stoichiometric copper catalyst conditions.

In the search for different metal catalysts to promote their electrocyclization–migration domino reaction process, Eisenberg, Frontier and co-workers reported that the copper(II)

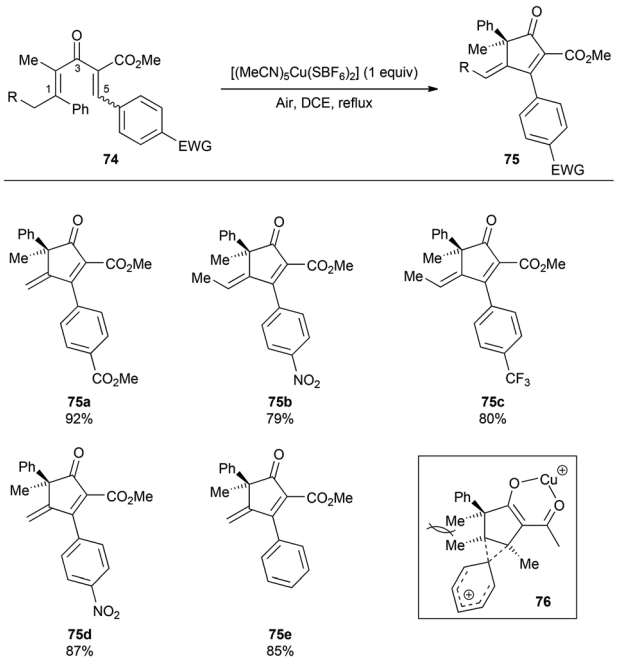


Scheme 16 Development of Ir(III)-catalyzed domino cyclization–migration reaction.

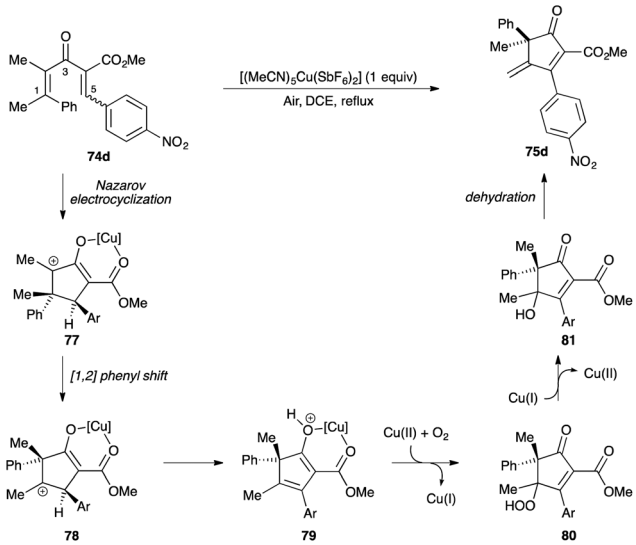
salt could be replaced with a chiral iridium(III) complex (Scheme 16).[68] The complex that worked best in the author's reaction was iridium(III) bishexafluoroantimonate catalyst **73** bearing a chiral (*R*)-(+)-BINAP ligand and an exchangeable diethylisopropylidine malonate (DIM) unit. While Nazarov cyclizations could be triggered by as little as 2 mol% of Ir(III)-**73**,[69–71] catalysis of the analogous electrocyclization–[1,2] shift reaction required 10 mol% of iridium. In contrast to the previous results using copper, the addition of 1 equivalent of $NaBAr_4^F$ as an additive a mixture of **58** and spirocycle **59** was obtained. The ratio of spirocycle could be improved to 1 : 11 by adding 1 equivalent of ZnI_2 instead, but the improved selectivity was accompanied by a drop in yield. The authors ascribe a similar mechanism for this transformation as with the copper catalyst.

Frontier and co-workers found that changing the electronic nature of the β-substituent on the divinyl ketone substrate changes the outcome of the reaction (Scheme 17).[72] The authors reported that replacing the electron-rich C5-substituent in **74** with an electron-poor group produces a 4-alkylidene cyclopentenone **75**—where the second [1,2] shift was circumvented by deprotonation. The optimal conditions for formation of **75** were found to be a stoichiometric amount of $(MeCN)_5Cu(SbF_6)_2$ and an atmosphere of oxygen. In comparison with the author's other reported domino electrocyclization–migration reactions, higher temperatures were also required. The scope of the author's transformation proved to be broad tolerating electron-deficient arenes bearing ester-, nitro- and trifluoromethyl groups. These results indicate that the second [1,2] migration is disfavored because the electron-withdrawing C5 group could not provide stabilization of the intermediate. The reactivity of the electron-neutral **74e**, however, suggests that obviating destabilizing steric interactions also play an important role. The formation of alkylidene **75e** was rationalized in that the second [1,2]-shift could not occur because the suprafacial phenyl migration from C5 to C1 would create destabilizing steric interactions in **76**.

Based on their experimental data, a mechanism for the transformation involving a Cu-mediated oxidation was proposed to account for alkylidene formation (Scheme 18). Coordination of the copper Lewis acid to dienone **74d** triggers

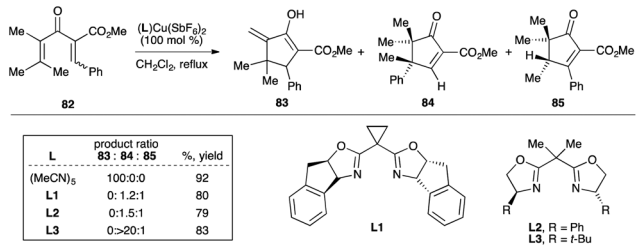


Scheme 17 Formation of alkylidene cyclopropentenones from divinyl ketones.



Scheme 18 Fenton-type mechanism to account for elimination product formation.

a Nazarov cyclization to form the oxyallyl cation **77**, which undergoes a [1,2]-phenyl shift to generate intermediate **78**. Because the C5-aryl substituent is electron-poor, the second [1,2]-aryl shift is aborted and an elimination of proton occurs instead to produce diene **79**. This diene undergoes a copper(II)-mediated $1e^-$ oxidation process to generate hydroperoxide **80** upon capture of the radical cation with molecular dioxygen. A Cu(I)-promoted Fenton-type fragmentation of **80** produces



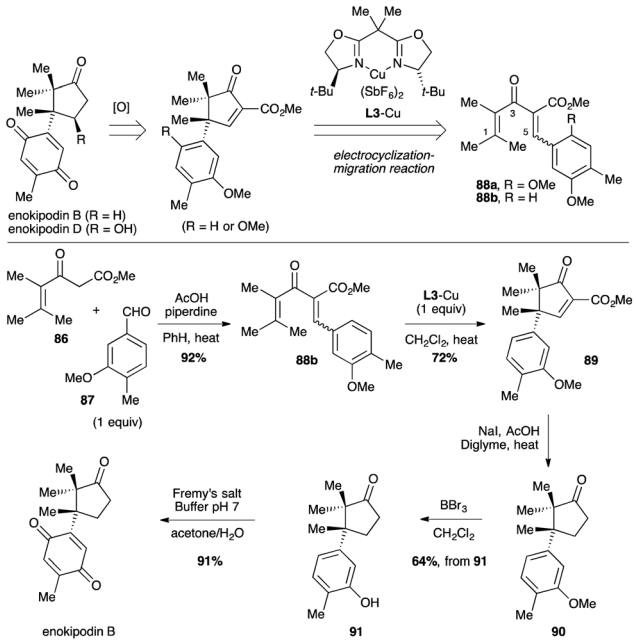
L	product ratio 83 : 84 : 85	%, yield
$(MeCN)_5$	100:0:0	92
L1	0: 1.2:1	80
L2	0:1.5:1	79
L3	0:>20:1	83

Scheme 19 Control of the chemoselectivity of alkylidene cyclopentenone formation.

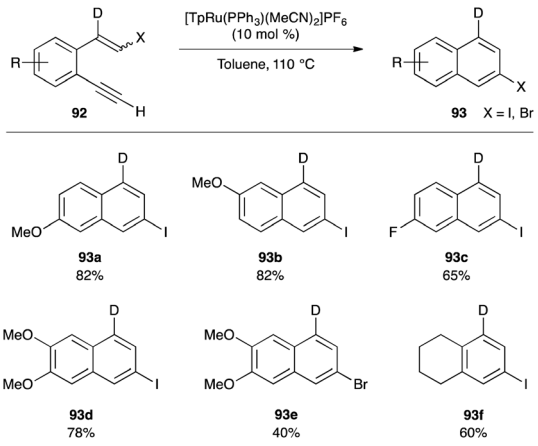
alcohol **81**,[73] which the authors reported could be isolated from incomplete reactions. Dehydration then produces alkylidene cyclopentenone 75**d**.

In addition to the steric- and electronic nature of the migrating group and the counterion affecting the chemoselectivity, Frontier and co-workers reported that the outcome of their domino electrocyclization–migration reaction was also affected by the copper(II) ligand (Scheme 19).[74] A systematic study of common ligands for copper(II) revealed the dependency of the [1,2] aryl migration step on the Cu(II) ligand. When an acetonitrile Cu(II) complex was employed, dienone **82** was converted to the Nazarov product **83** without any observed [1,2] migration events. Switching the ligand from acetonitrile to a chiral bisoxazoline ligand inhibits the elimination pathway; instead a cyclization-rearrangement pathway was exclusively favored. While bisoxazoline **L1** or **L2** provides a mixture of **84** and **85**, exclusive formation of **84** was achieved by using the *tert*-butyl-bisoxazoline Cu-**L3** complex. The authors attribute this product selectivity to the ability of **L1**-Cu and **L2**-Cu complexes to disrupt the second [1,2]-C5-aryl group migration. This disruption enables a hydride shift to occur to produce cyclopentenone **85**. In contrast, the overlap of the C5-aryl group with the C1 cation is not disrupted with the **L3**-Cu complex so the second [1,2] aryl shift occurs smoothly to form cyclopentenone **84** as the major product.

Frontier and co-workers applied this ligand-controlled chemoselectivity in the synthesis of the enokipodines (Scheme 20).[74] The enokipodines are natural products isolated from the mushroom *Flammulina velutipes*, and they possess antibacterial activity toward Gram-positive bacteria. Frontier and co-workers envisioned that the scaffold embedded in these sesquiterpenes could be synthesized from their domino electrocyclization–migration reaction sequence after oxidation of the migrating C5-aryl ring. Initial attempts toward this scaffold using 2,5-dimethoxy-substituted dienone **88a**, however, were not successful because of the steric bulk of the C5 substituent, which led to a mixture of products. The authors were able to synthesize enokipodine B starting from dienone **88b**, which was easily prepared by condensing β-keto-ester **86** with aryl aldehyde **87**. Exposure of dienone **88b** to 1 equivalent of *tert*-butyl-bisoxazoline **L3**-Cu produced cyclopentenone **89** in 72% as a single diastereomer. Both the methylcarboxylate and the enone functionality were excised by



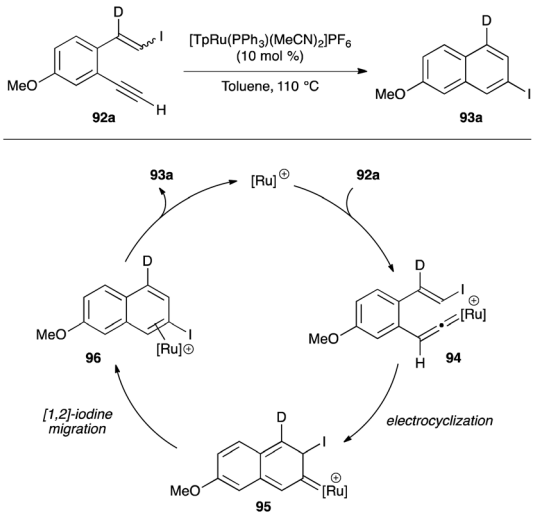
Scheme 20 Total synthesis of enokipodin B.



Scheme 21 Ru-catalyzed domino 6π-electron-electrocyclization–[1,2]-migration reactions.

exposing **89** to conditions developed by Agosta and co-workers.[75] Demethylation followed by oxidation with Fremy's salt furnished enokipodin B. The power of the author's method is revealed in the efficiency of this total synthesis: this natural product was assembled in only six-steps from the starting enone in 34% overall yield.

Domino 6π-electron-electrocyclization–migration processes. In contrast to domino reaction sequences where a Nazarov reaction initiated a migration, triggering this shift with a 6π-electron-electrocyclization is significantly rare. Liu and co-workers reported that these domino reactions could be promoted from terminal aryl acetylenes using a ruthenium catalyst to isomerize the alkynyl group to a metal alkylidene (Scheme 21).[76] In 2004, they reported that an *E*- and *Z*-mixture



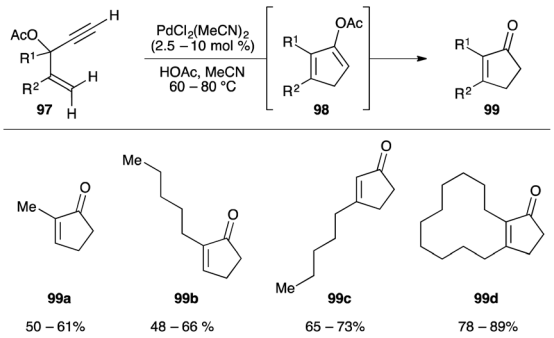
Scheme 22 Potential catalytic cycle for Ru-catalyzed naphthalene formation.

of *o*-ethynyl styrenes **92** could be converted to naphthalenes **93** by using 10 mol% of a Tp-Ru complex. Using isotopically labeled substrates in order to identify the substitution pattern of the naphthalene, the authors were able to confirm that a [1,2] halogen shift occurred after the electrocyclization step. While both bromine- and iodine migration could be triggered, reduced yields were obtained for [1,2] bromine migration. They reported that while their reaction tolerates methoxy groups without adversely affecting the yield, the presence of fluorine slightly attenuates the yield of the naphthalene (compare **93a** and **93b** with **93c**). The authors also reported that this electrocyclization–migration reaction is not limited to aromatic substrates: cyclohexenyl enyne **92f** was smoothly converted to tetrasubstituted benzene **93f**.

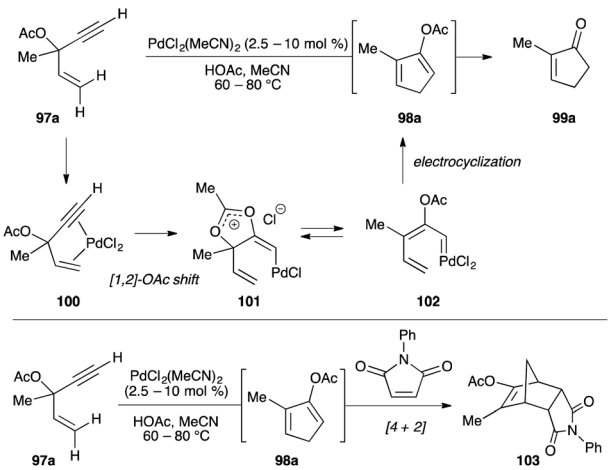
Liu and co-workers proposed a catalytic cycle to account for naphthalene formation from *o*-ethynyl styrenes (Scheme 22).[76] Coordination of the terminal acetylene to the cationic ruthenium complex triggers a [1,2] hydride migration to form vinylidene **94**. Although this species could directly insert into the *Z*-C–I bond to form the product, the authors proposed that a 6π-electron-electrocyclization of the vinylidene occurs. The resulting Ru-carbene **95** undergoes a [1,2] iodine shift to produce the η^2-ruthenium arene complex **96**. Dissociation of the catalyst regenerates the catalyst and forms the observed naphthalene product.

[1,2]-Migration followed by electrocyclization: Rautenstrauch rearrangement

Inverting the order of the electrocyclization and migration steps of the domino reaction has emerged as a great strategy to assemble complex, functionalized cyclopentenes or five-membered heteroaromatic compounds from acetylenes. These transformations are generally triggered by a π-Lewis acid



Scheme 23 Rautenstrauch rearrangement of propargyl acetate.



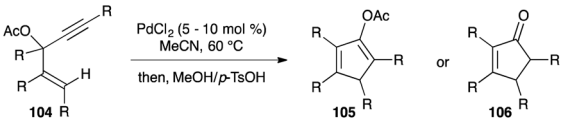
Scheme 24 Proposed mechanism for Rautenstrauch rearrangement.

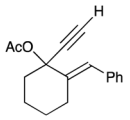
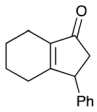
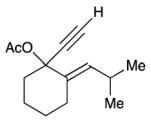
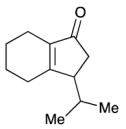
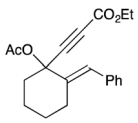
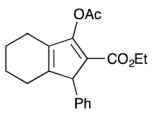
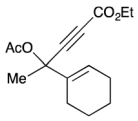
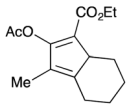
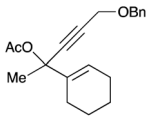
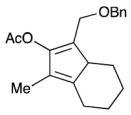
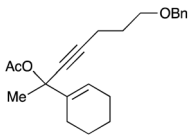
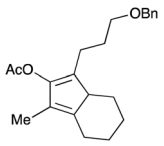
catalyst. Over the next few sections, we detail the similarities and differences between these reaction sequences.

In 1984, Rautenstrauch developed a Pd(II)-catalyzed rearrangement of propargyl acetate to efficiently access cyclopentenones (Scheme 23).[77] When exposed to a $PdCl_2(MeCN)_2$ catalyst, 1-ethynyl-2-propenyl acetates **97** rearranged to form 1,4-cyclopentadienyl acetates **98**, which hydrolyzed to produce **99**. The reaction tolerated different alkyl substituents including large cycloalkanes. A limitation of the domino reaction sequence was revealed in the poor reactivity of propargyl acetates that contained substituents on the terminus of either the acetylene or alkene moieties.

To account for the transformation of propargyl acetates into cyclopentenones, the mechanism outlined in Scheme 24 was proposed. Coordination of the enyne to the palladium(II) catalyst initiates a [1,2] acetoxy shift to generate the oxocarbenium ion **101**, which is in equilibration with palladium carbene **102**. This divalent species then undergoes a 4π-electron-5-atom electrocyclization to produce cyclopentadiene **98a**, which upon hydrolysis generates cyclopentenone **99a**. In support of their proposed mechanism, the authors reported that when *N*-phenyl phthalimide was added to the reaction mixture,

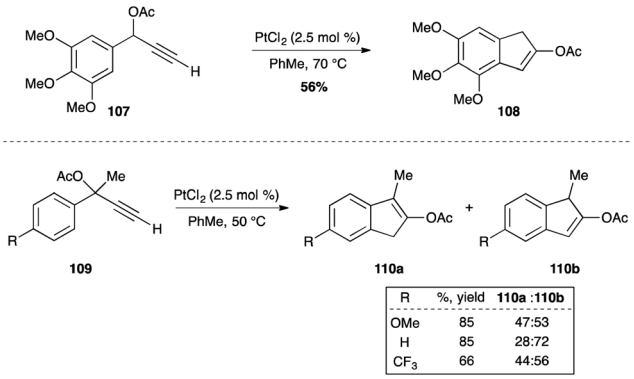
Table 2 Accessing functionalized cyclopentadienes and cyclopentenones



Entry	#	Enyne	Product	%, Yield
1	a			92
2	b			57
3	c			97
4	d			88
5	e			64
6	f			0

cyclopentadiene **98a** could be intercepted in a [4 + 2] cycloaddition reaction to afford the [2.2.1] bicycle **103**.

The Frontier group reported an advancement to the Rautenstrauch rearrangement by developing a method that enabled the incorporation of substituents on both the acetylene- and vinyl moieties (Table 2).[78] They reported that functionalized propargyl acetates **104** could be transformed into cyclopentenones upon exposure to only 2.5 mol% of $PdCl_2$ in acetonitrile. This transformation could be catalyzed using $HgCl_2$ as well, but diminished yields were obtained. Using $PdCl_2$, the scope of the reaction was explored. The effect of changing the identity of the vinyl substituent is illustrated in entries 1 and 2: switching from a phenyl- to an isopropyl substituent attenuated the yield of the cyclopentenone. Adding a carboxylate substituent to the terminus of the acetylene changed the identity of the product to a pentasubstituted cyclopentadiene (entries 3 and 4). When the acetylenic substituent was changed to an alkyl group the yield of the cyclopentadiene diminished (entry 5). The authors reported that the reaction was dependent on the number of methylenes between the benzyl ether and the acetylene: increasing from one- to three methylene units resulted in no reaction. Although Pd(II)–ether complexes are rare, the authors interpreted this result to indicate the importance of chelation to the oxygen of the benzyl ether to trigger the domino reaction.



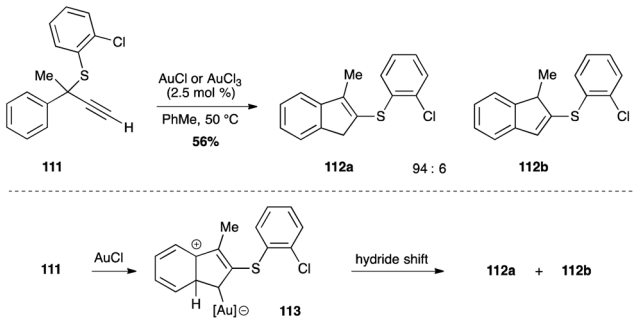
R	%, yield	110a :110b
OMe	85	47:53
H	85	28:72
CF_3	66	44:56

Scheme 25 Formation of substituted indenes using the Rautenstrauch rearrangement.

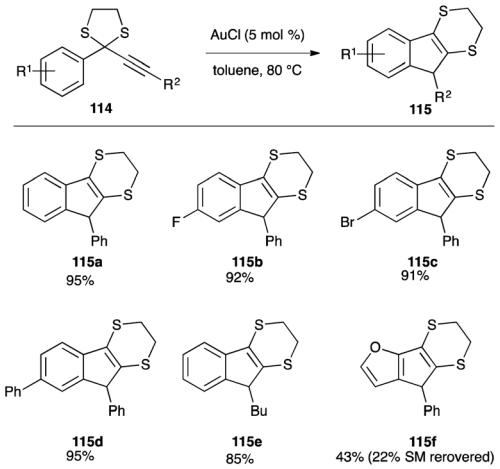
Several research groups recognized that the Rautenstrauch rearrangement could be used to generate complex, substituted indenes if the vinyl moiety was replaced with an aryl substituent (Scheme 25).[79–84] Ohe and co-workers reported that indenes **108** could be accessed from terminal propargyl acetates such as **107** through a Pt-catalyzed [1,2] acetoxy-electrocyclization.[80] Higher yields of indenes were observed from electron-rich secondary propargyl acetates such as **107**. While catalysis of tertiary progargyl acetates occurred at lower reaction temperatures, the reaction was not selective leading to a mixture of indenes **110a** and **110b** in every substrate investigated. The regioselectivity of indene formation was dependent on the electronic nature of the aryl substituent with electron-rich or electron-poor groups leading to an erosion of selectivity.

Using a gold catalyst, the Wang group reported that sulfur migration was also possible.[81] They showed that gold(I) or gold(III)-chloride triggered the transformation of propargyl sulfides into indenes **112a** and **112b** (Scheme 26). In contrast to the Ohe report, this domino reaction sequence preferred the formation of the more substituted indene. Wang and co-workers proposed that the mixture of indenes resulted from a non-selective hydride migration of **113** that terminated the reaction sequence.

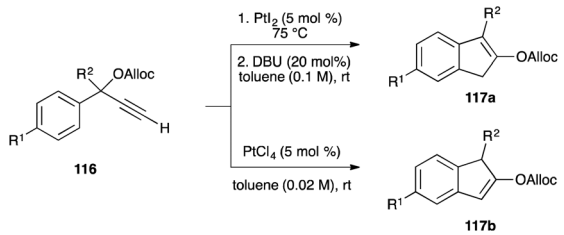
In the same study, Wang and co-workers reported that replacing the aryl sulfide with a dithioacetal improved the selectivity of indene formation (Scheme 27).[81] Exposure of phenyl-substituted propargyl dithiolane **114** to 5 mol% of AuCl catalyzed a ring expansion of the dithiolane to afford 1,2-dithioindene **115**. Their reaction tolerated both halogen- and phenyl substituents on the aryl moiety. Further, the acetylene could be substituted with either aryl- or alkyl groups without



Scheme 26 Triggering an electrocyclization with a [1,2] sulfide shift.



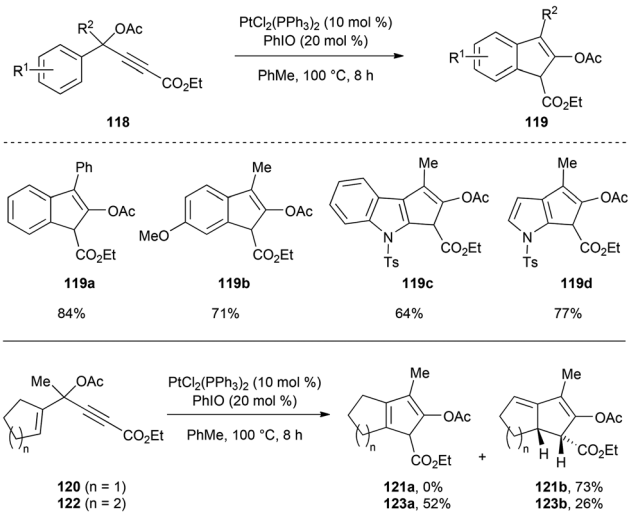
Scheme 27 [1,2] Sulfide migration to afford functionalized indenes.



Scheme 28 Control of the regioselectivity of indene formation.

attenuation of the yield of the reaction. Changing the identity of the aryl moiety to a furan, however, reduced the efficiency of their process to produce **115f** in only 43% with a significant amount of the starting material recovered.

In 2012, a solution to regioselectivity was published by Clark and Zhao (Scheme 28).[82] They reported a platinum-catalyzed reaction of propargyl allyl carbonates that generated either indene **117a** or **117b** depending on the reaction conditions. In the presence of PtI_2, the more substituted indene was formed when DBU was employed as a base. When DBU

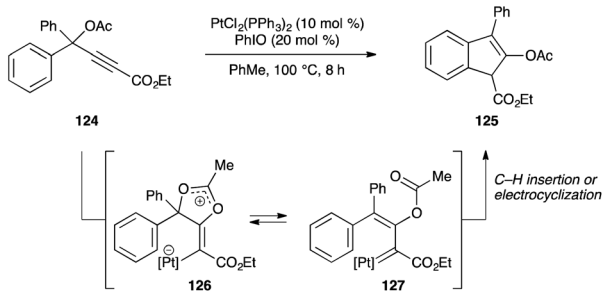


Scheme 29 Control of the regioselectivity of indene formation.

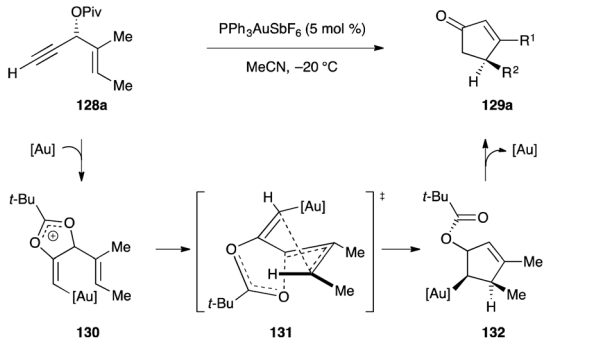
was excluded and platinum tetrachlorinate was used as the catalyst, the less substituted indene product was formed exclusively at room temperature.

A further advancement to generate highly functionalized indenes and *N*-heteroaromatic compounds from propargyl acetates was reported by Sarpong and co-workers (Scheme 29).[83] The authors reported that the combination of 10 mol% of $PtCl_2(PPh_3)_2$ and 20 mol% of iodosobenzene was able to trigger the formation of a broad range of functionalized carbocycles and heterocycles **119** from readily accessible propargyl acetates. The scope of their transformation is illustrated in that not only are indenes accessible from aryl propargyl acetates (*e.g.* **119a** and **119b**), but also the arene moiety can be replaced with an *N*-tosyl-protected indole or pyrrole to afford functionalized N-heterocycles **119c** or **119d** without diminishment of the yield of the domino reaction sequence. In comparison with indene or heteroarene formation, the construction of cyclopentadienes was more limited. In order for the domino reaction sequence to be high yielding, an acetylenic carboxylate group was required. Substitution of this group with a more electron rich group, such as an alkyl-, phenyl- or silyl group had a deleterious effect on the reaction outcome. Further, while exposure of enyne **120** to reaction conditions led to the formation of bicycle **121b** as the only product, increasing the size of the cycloalkenyl substituent from cyclopentene to cyclohexene led to a mixture of **123a** and **123b**.

A mechanism was proposed by the authors to explain the reaction outcome (Scheme 30).[83] They posited that the Pt(II)-catalyst initiates a [1,2] acetoxy migration *via* acetoxonium **126** to form platinum carbene **127**. The authors propose that this metal divalent species could insert into the aryl C–H bond to afford the product. Alternatively, this C–H bond functionalization could occur stepwise through a 4π-electron-5-atom electrocyclization followed by a [1,5] hydride shift, which would also afford the indene product. While the exact role of iodosobenzene in this transformation remains unclear, the

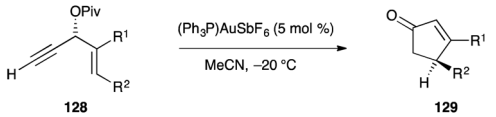


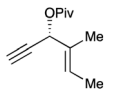
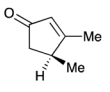
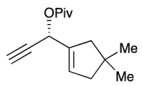
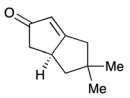
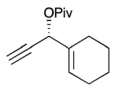
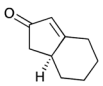
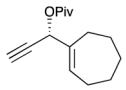
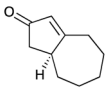
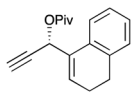
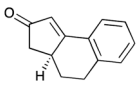
Scheme 30 Potential mechanism to account for product formation.

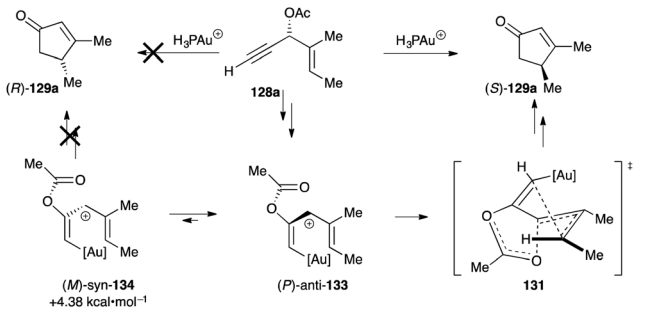


Scheme 31 Mechanism to explain the origin of chirality transfer.

Table 3 Development of the chiral, non-racemic variant of the Rautenstrauch rearrangement



Entry	#	Substrate	% ee	Product	%, Yield (% ee)
1	a		88		84 (82)
2	b		79		80 (77)
3	c		93		86 (91)
4	d		92		82 (83)
5	e		98		88 (96)



Scheme 32 Computational study that supports synchronous C–O bond scission and C–C bond formation.

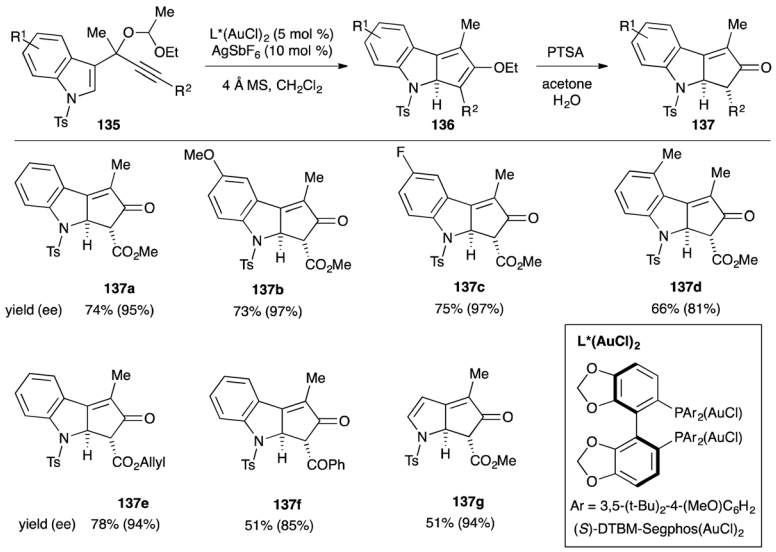
authors hypothesized that the oxidation of either platinum or phosphine helps in generating active metal catalysts.

A major limitation of this domino reaction was its inability to form chiral, non-racemic products. In 2006, Toste and co-workers reported that this limitation could be overcome by using enantioenriched propargyl pivolates (Table 3).[85] Subjecting chiral, non-racemic **128** to 5 mol% of $(Ph_3P)AuSbF_6$ at −20 °C resulted in formation of cyclopentenones **129** with good transfer of chirality. The non-coordinating SbF_6 counterion was critical to the success of this transformation. Switching to triflate resulted in a loss of enantioselectivity. Their reaction conditions could be used to access a range of substituted cyclopentenones from a variety of acyclic and cyclic substrates. Changing the ring size of the cycloalkenyl moiety did not affect the efficiency or selectivity of this transformation.

To account for the chirality transfer, the authors proposed a mechanism with a helical catalytic intermediate (Scheme 31).[85] The authors posited that the formation of enantioenriched cyclopentenones indicated that a metal carbene was not being formed since its formation would destroy the chiral information embedded in the molecule by breaking the C–O bond. Accordingly, Toste and co-workers proposed that coordination of the Au(I) catalyst to the terminal acetylene triggered a [1,2] pivaloate migration that proceeded *via* helical **131** to afford cyclopentene **129a**. The helical intermediate **131** enables efficient transfer of the chiral information because the new C–C bond forms concomitantly with the breaking of the C–O bond.

The formation of the C–C bond *via* a helical transition state was supported by a computational study on this reaction (Scheme 32).[86] de Lera and co-workers identified helical transition state **131** where C–O bond scission occurred slightly before C–C bond formation. Their study revealed a significant difference in stability between pentadienyl cations **133** and **134**: the (*P*)-anti **133** was found to be 4.38 kcal mol^{-1} which is more stable than the (*M*)-*syn* **134** to favor the formation of (*S*)-**129a** through the anti-helical transition state **131**.

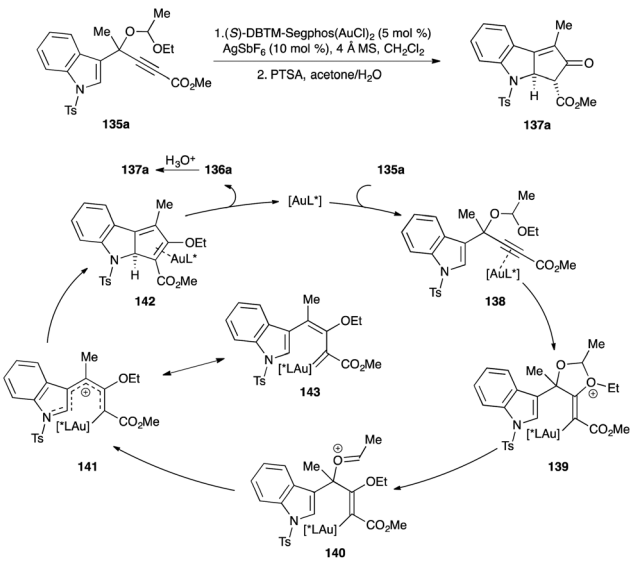
In 2015, the first enantioselective catalysis of the Rautenstrauch rearrangement was reported by Toste and co-workers (Scheme 33).[87] In order to achieve this transformation, the



Scheme 33 Development of asymmetric, nitrogen-assisted Au-catalyzed Rautenstrauch rearrangement.

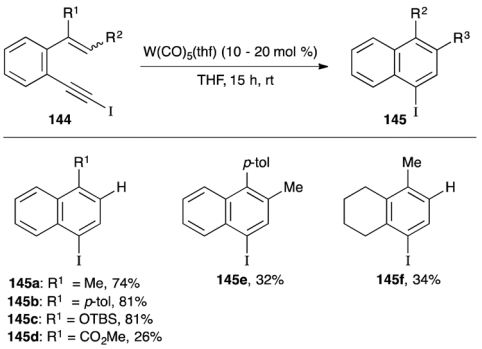
Toste group developed conditions where a nitrogen-atom-assisted Nazarov cyclization was able to dominate over the chiral transfer process. They were able to achieve this by changing the aryl moiety to an indole and substituting the pivaloate group with an acetal. Upon exposure to chiral gold(I) complexes, heterocyclic propargyl acetals such as **135** could be transformed into enantioenriched cyclopenta[*b*]indoles **137**. Their transformation tolerates a range of functionality on the indole moiety, but the enantioselectivity was slightly diminished when 4-substituted indoles were employed (*e.g.* **137d**). This loss in enantioselectivity was attributed by the authors to result from steric repulsion between the methyl substituents. The authors reported that their transformation could even be extended to other electron-rich heterocycles such as pyrrole to provide N-heterocycles such as **137g**.

In order to account for the ability of the chiral gold(I) catalyst to override the chiral information embedded in the indole starting material, the authors proposed the catalytic cycle illustrated in Scheme 34.[87] Coordination of the cationic gold species with the alkyne increases its electrophilicity to initiate attack by the proximal acetal. The C–O bond in the resulting oxonium ion **139** fragments to produce the oxocarbenium ion **140**. The stereocenter in **140** is ablated when the electron-rich indole expels acetaldehyde to produce the pentadienyl cation **141**, which undergoes an enantioselective Nazarov cyclization to form **142**, where the stereoselectivity of C–C bond formation is controlled by the chiral, non-racemic phosphine ligand. Dissociation of the cationic gold complex from **142** produces the N-heterocycle **136a**, which is hydrolyzed to produce the cyclopenta[*b*]indole **137a**.

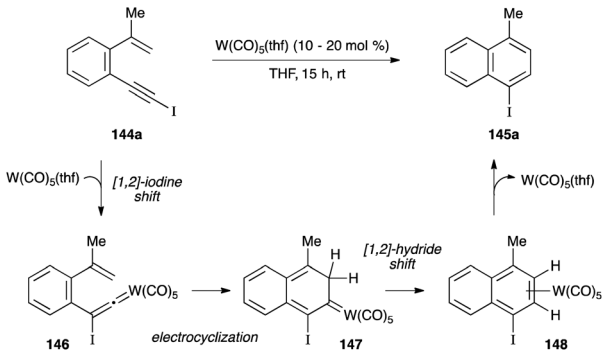


Scheme 34 Potential catalytic cycle involving enantioselective electrocyclization.

Domino 6π-electron-Rautenstrauch processes. While generation of a metal vinylidene intermediate by a [1,2] acetate or a [1,2] sulfide migration has emerged as a common tactic to construct new C–C bonds, initiating the electrocyclization with a [1,2] halogen migration is less common. The resulting products would contain an activated sp^2-C–I bond that could be further functionalized by using cross-coupling reactions. In 2002,[88] Iwasawa and co-workers addressed this gap in their report of a tungsten-catalyzed reaction of *ortho*-alkynylstyrenes to produce functionalized α-iodonaphthalenes **145** (Scheme 35). While the use of stoichiometric amounts of tungsten led to higher yields, the authors reported that their transformation could be catalyzed with as little as 10–20 mol% of the tungsten catalyst to access a range of trisubstituted naphthalenes. Their reaction tolerates a broad range of R^1-substituents including alkyl-, aryl- and silyl ethers without diminishing the yield of the naphthalene. The yield of their transformation was attenuated when either an R^1-carboxylate-



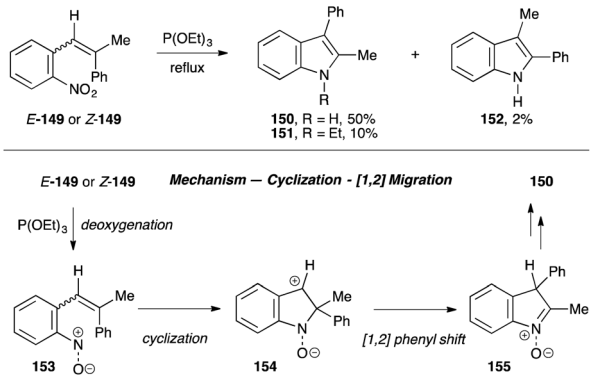
Scheme 35 [1,2] Iodide migration to initiate an electrocyclization.



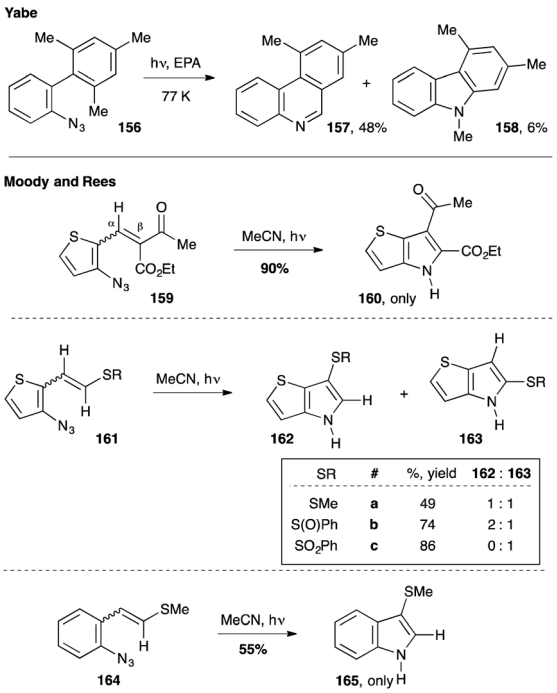
Scheme 36 Potential mechanism for naphthalene formation.

or α,β-disubstituted *o*-alkenyl substituted substrates was employed. The presence of the central arene appears to be critical, exposure of dienyne to reaction conditions led to only 34% of tetrasubstituted benzene **145f**.

Based on the reactivity patterns of their substrates, the authors proposed a potential mechanism to account for the regioselectivity of their transformation (Scheme 36).[88] Coordination of tungsten pentacarbonyl with the iodoacetylene triggers a [1,2] iodide shift to produce tungsten vinylidene **146**. 6π-Electrocyclization of **146** produces tungsten carbene **147**, which undergoes a [1,2] hydride shift to form **148**. Dissociation of the catalyst generates α-iodonaphthalene **145a**.



Scheme 37 Phosphite-mediated reductive cyclization–[1,2]-phenyl migration to form 2,3-disubstituted indoles.

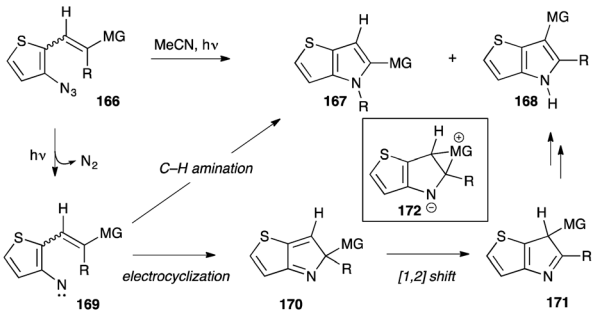


Scheme 38 Photolysis of thiophene azides to produce pyrrolothiophenes.

Domino electrocyclization–migration processes involving C–N bond formation

In comparison with Nazarov–[1,2] migration processes, domino reactions in which the electrocyclization forms a C–N bond are very rare. In our opinion, this sequence was first reported in a 1969 report by Sundberg and co-workers,[89,90] who observed the conversion of β-phenyl-β-methyl-*ortho*-nitrostyrene to 2-methyl-3-phenyl indole (Scheme 37). Their reaction exhibits excellent migratorial selectivity in favor of a [1,2] phenyl shift to produce **150**. Indole formation was not dependent on the nitrostyrene isomer: both *E*- and *Z*-isomers were converted to the product with nearly equal yield. Building on work by Cadogan and co-workers,[91] Sundberg and Kotchmar proposed that indole formation occurred through a phosphite-mediated deoxygenation of the nitroarene to afford nitroso- or nitrene **153**, which underwent a cyclization to afford **154**. Formation of this cation triggers a [1,2] phenyl shift to afford 3*H*-indole **155**, which tautomerizes (with an additional deoxygenation if necessary) to afford 2-methyl-3-phenyl indole.

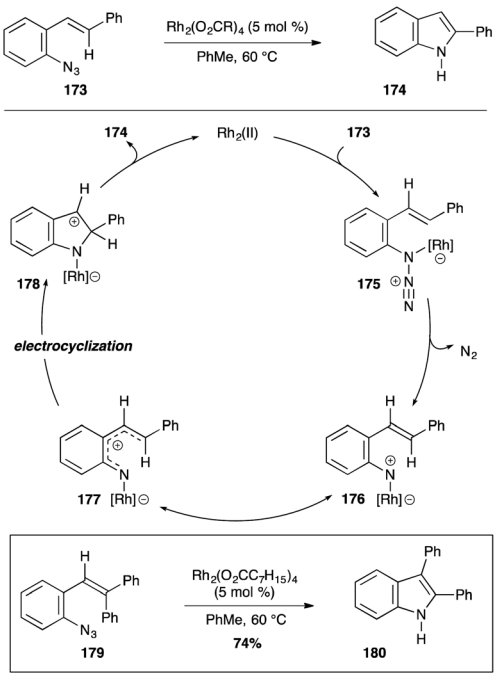
In 1981, Moody, Rees and co-workers reported the first systematic study of electrocyclization–[1,2] migration domino reaction involving an azide (Scheme 38).[92–96] Their study built on an observation of Yabe in 1980,[97] who reported that low temperature photolysis of *ortho*-substituted biarylazides such



Scheme 39 Proposed domino electrocyclization–[1,2] shift mechanism.

as **156** produced an *N*-methylcarbazole **158** byproduct arising from methyl migration in addition to azine formation. The results of Moody, Rees and co-workers revealed that these migrations were a general phenomenon: irradiation of β,β-disubstituted 3-azido-2-alkenylthiophene azide **159** produced thienopyrrole **160** where C–N bond formation was accompanied by a [1,2] migration of one of the β-substituents. In addition to the selective acyl migration pictured in Scheme 38, the authors reported that sulfur groups—including sulfides and sulfoxides—also migrated in preference to the ethyl carboxylate group. The authors also found that sulfide and sulfoxide migration was competitive with C–H bond amination:[94] photolysis of thiophene azide **161** produced a mixture of thienopyrroles **162** and **163** in favor of sulfide or sulfoxide migration. In contrast to the preference of sulfides and sulfoxides, which engage in [1,2] shift reactions, the analogous sulfone produced only the C–H bond amination product, **163c**. When the thiophene azide moiety was replaced with an aryl azide (**164**) exclusive migration of the methyl sulfide was observed to afford indole **165** as the only product.[96]

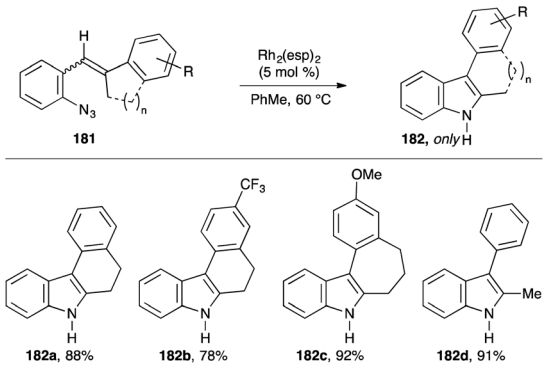
The mechanism for this transformation was postulated by the authors to occur through an electrocyclization–[1,2] migration sequence (Scheme 39). Photolysis of thiophene azide **166** produces nitrene **169**, which participates in a 4π-electron-5-atom electrocyclization to produce thiophene-fused 2*H*-pyrrole **170**. A [1,2] shift of the migrating group (MG) produces 3*H*-pyrrole **171**. The thieno[3,2-*b*]pyrrole product **168** is formed through either a photochemically allowed [1,3] hydrogen shift or two successive "dark" [1,5] shifts. When R = H, thienopyrrole **167** could be generated by a C–H bond amination: insertion of the nitrene into the sp^2-C–H bond or a two-step H-atom abstraction-radical recombination. On the basis of established reactivity trends in 2*H*-indenes,[98–101] the authors proposed that the C–H bond amination products are formed through an electrocyclization–[1,5] hydrogen migration mechanism. The difference in migration ability of sulfide and sulfoxide *versus* the inertness of sulfone was rationalized through the use of the lone pair of electrons on sulfur to form an episulfonium ion **172**, which could fragment to afford the [1,2] shift product.



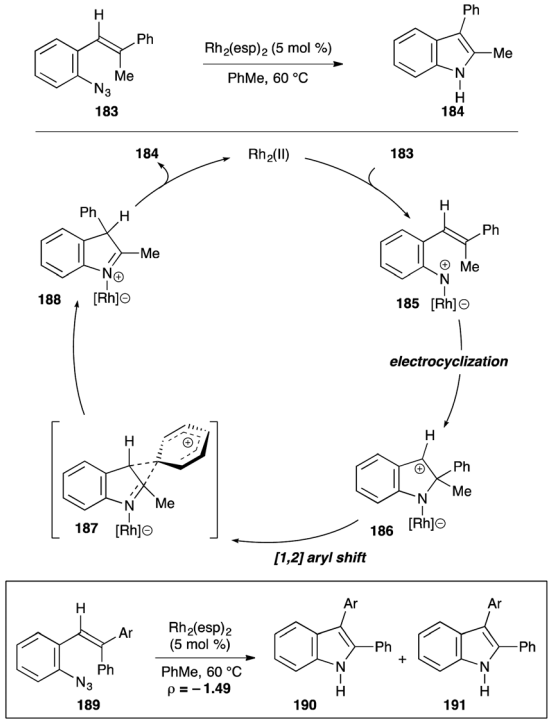
Scheme 40 Rh_2(II)-catalyzed N-heterocycle formation from aryl azides.

In 2006, the Driver group reported that Rh_2(II)-carboxylates catalyze the formation of indoles from vinyl- or aryl azides (Scheme 40).[23,24] Their mechanistic experiments indicated that C–H bond amination occurred in a step-wise fashion with C–N bond formation preceding C–H bond scission.[25] After coordination of the azide to the rhodium catalyst, extrusion of N_2 occurs to form rhodium nitrene **176**. Because dinitrogen loss is accelerated by electron rich *ortho*-substituents, the authors suggested that significant delocalization of the positive charge occurs in the adjacent π-system. This delocalization facilitates C–N bond formation through a 4π-electron-5-atom electrocyclization, which forms **178**. A [1,5] hydride shift then affords the product N-heterocycle after dissociation of the rhodium catalyst. In support of this step-wise mechanism, exposure of β,β-diphenylstyryl azide **179** to reaction conditions afforded 2,3-diphenylindole **180**.[24]

The migratorial aptitude of β-substituents was investigated by the Driver group by examining the reactivity of styryl azides towards Rh_2(II)-carboxylate catalysts. The first set of intramolecular competition experiments compared the reactivity of aryl- and alkyl groups to participate in the [1,2] shift (Scheme 41).[102] Exposure of a series of β,β-disubstituted styryl azides **181** to $Rh_2(O_2CC_7H_{15})_2$ triggered the formation of 2,3-disubstituted indole **182**. In every substrate examined, a [1,2] aryl shift occurred exclusively to afford the product irrespective of the electronic nature of the migrating aryl group or the stereochemistry of the starting styryl azide. The reaction was not affected by the size of the ring expansion, and even acetophenone-derived substrates could be converted to 2-methyl-3-aryl indole **182d**.

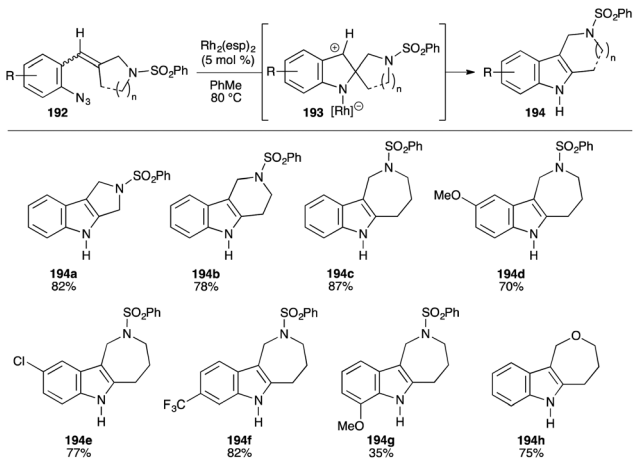


Scheme 41 Rh_2(II)-catalyzed formation of 2-alkyl-3-aryl indoles from β,β-disubstituted styryl azides.



Scheme 42 Rh_2(II)-catalyzed formation of 2-alkyl-3-aryl indoles from β,β-disubstituted styryl azides.

To account for the selectivity of 2-alkyl-3-arylindole formation, the authors proposed the catalytic cycle outlined in Scheme 42. Coordination of the rhodium catalyst to the azide promotes the extrusion of N_2 to form rhodium *N*-aryl nitrene **185**, which undergoes a 4π-electron-5-atom electrocyclization to produce **186**. The selective [1,2] aryl migration is rationalized through the formation of phenonium ion **187**. This shift forms 3*H*-indole **188**, which tautomerizes to form the observed indole product. In support of this catalytic cycle, the authors obtained and examined a series of β,β-diaryl substituted styryl azides. The ratio of indoles was analyzed using the Hammett

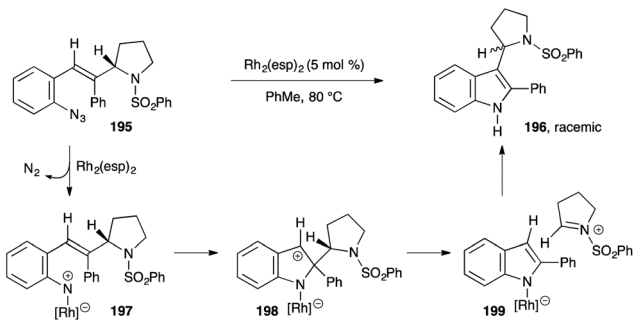


Scheme 43 Rh_2(II)-catalyzed selective aminomethylene migration.

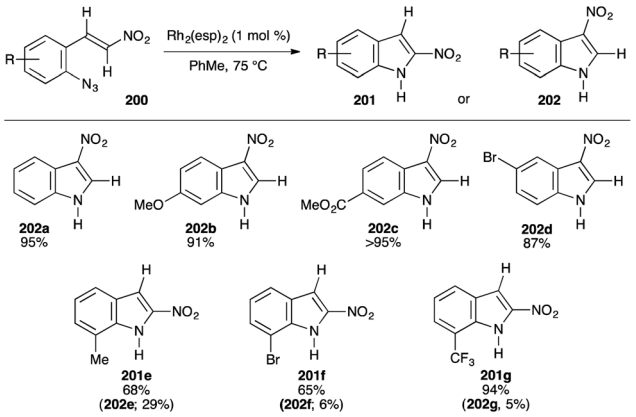
equation and the resulting ρ-value of −1.49 (*versus* σ_{para} values) supports the formation of the phenonium ion.

The Driver group next investigated the effect of distal substitution in styryl azides on controlling the migratorial preference of the β-substituent (Scheme 43).[103] The authors proposed that a γ-heteroatom might control the selectivity of the [1,2] shift reaction by using its lone pair of electrons to trigger C–C bond heterolysis and stabilize the build up of positive charge in the migration. In line with their assertion, exposure of styryl azides such as **192** to reaction conditions produced only tetrahydrocarbolines **194**—the product of exclusive aminomethylene migration. The scope of this reaction appeared broad: ring expansion to 5-, 6- and 7-membered heterocycles was tolerated and the reaction was unaffected by the electronic nature of the styryl azide. Their reaction, however, was sensitive to the steric environment around the azide. Introduction of an additional *ortho*-substituent dramatically reduced the yield of the transformation to afford indole **194g** in only 34%. This reactivity was not confined to aminomethylene shifts: ethereal [1,2] shifts also occurred exclusively over alkyl groups to afford indole **194h**.

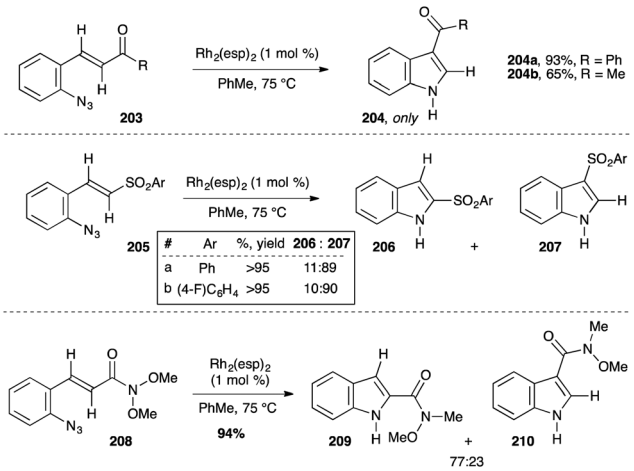
Insight into the mechanism of the [1,2] aminomethylene shift came from the reactivity of proline-derived styryl azide **195** (Scheme 44).[103] Subjecting chiral, non-racemic **195** to reac-



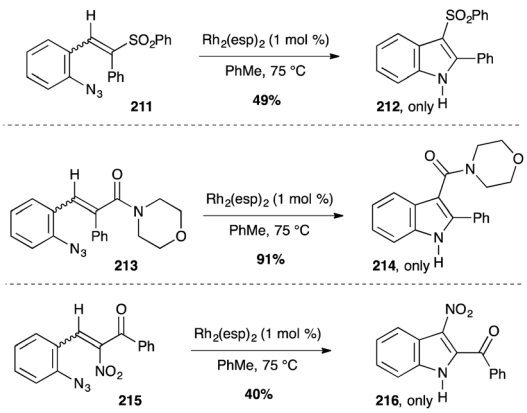
Scheme 44 Mechanism of [1,2] aminomethylene shift.



Scheme 45 Migratorial aptitude of nitro groups.



Scheme 46 Preference for electron-poor groups to migrate over hydrogen.



Scheme 47 Intramolecular competition experiments between β-substituents.

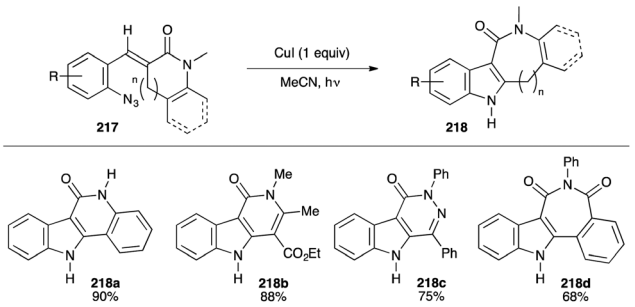
tion conditions produced the expected aminomethine shift product as a mixture of racemates. To account for the loss of optical activity, the authors proposed that the shift occurs *via* the iminium ion **199**. Double crossover experiments revealed that this iminium ion does not escape the solvent sheath. Further, the reactivity of this substrate established that aminomethine migration was preferred over the alternative [1,2] phenyl migration.

The Driver group reported the electrocyclization–[1,2] nitro shift domino reaction of styryl azides (Scheme 45).[104] In contrast to the thermolysis of β-nitro-substituted styryl azides,[105] which afforded 2-nitroindoles **201**, the presence of $Rh_2(esp)_2$ changed the reaction outcome to produce only 3-nitroindoles **202**. While this reaction was insensitive to the electronic environment of the aryl azide moiety, an additional *ortho*-substituent led to formation of 2-substituted nitroindoles **201** as the major product. The ratio of 2-nitroindole increased as the *ortho*-substituent became more electron-withdrawing. The additional *ortho*-substituent could lead to dissociation of the Rh_2(II)-carboxylate catalyst to result in *N*-aryl nitrene formation to mirror the results reported by Gribble and Pelkey in the thermolysis of β-nitrostyryl azides.[105]

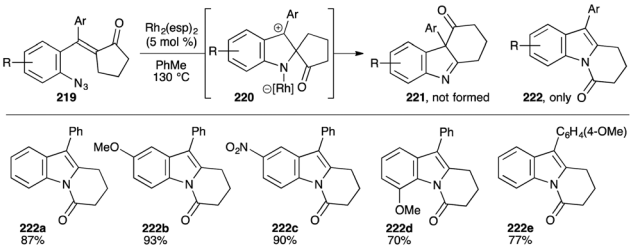
In addition to nitro-group migration, the authors also examined the migratorial aptitude of other electron withdrawing groups.[104] Acyl- and benzoyl groups were found to migrate preferentially to afford only 3-substituted indoles. The authors also reported that the [1,2] sulfone shift was competitive with a [1,5]-hydride shift. For the sulfones, a mixture of 2- and 3-substituted products was observed. In contrast to their expectations, the ratio of indoles was not dependent on the electronic nature of the migrating aryl sulfone—in each example a 90 : 10 ratio of 3- to 2-substituted indole was observed. Exposure of a β-amide-substituted styryl azide **208** to reaction conditions also afforded a mixture of 2- and 3-substituted indoles (77 : 23). Esters did not migrate affording only the 2-carboxylate-substituted indole (Scheme 46).

To place their results in context with other potential migrating groups, the authors performed several intramolecular competition experiments using β,β-disubstituted styryl azides (Scheme 47).[104] Subjecting β-sulfonyl-β-phenyl substituted styryl azide to reaction conditions produced only the 3-sulfonyl substituted indole **212**. Exposure of a β-amide-β-phenyl styryl azide resulted in exclusive amide migration to afford indole **214**. To compare the migratorial aptitude of nitro- and benzoyl groups, styryl azide **215** was tested. Only nitro-group migration occurred to produce indole **216**.

Electrocyclization–[1,2]-amide shift domino reactions of β,β-disubstituted styryl azides can also be promoted using CuI (Scheme 48).[106] Zhang and co-workers reported that photolysis of styryl azide **217** in the presence of a stoichiometric amount of CuI triggered ring expansion through the exclusive migration of the amide to form 2,3-disubstituted indole **218**. The authors reported that reducing the amount of CuI reduced the yield of indole formation. The reaction tolerated a broad range of functionality including esters and NH-amides without attenuation of indole yield. Similar to the results of Driver and



Scheme 48 Migratorial trends of trisubstituted styryl azides.

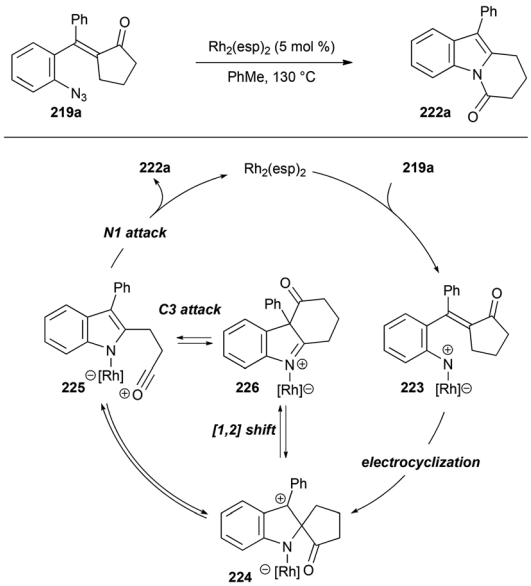


Scheme 49 Migratorial trends of trisubstituted styryl azides.

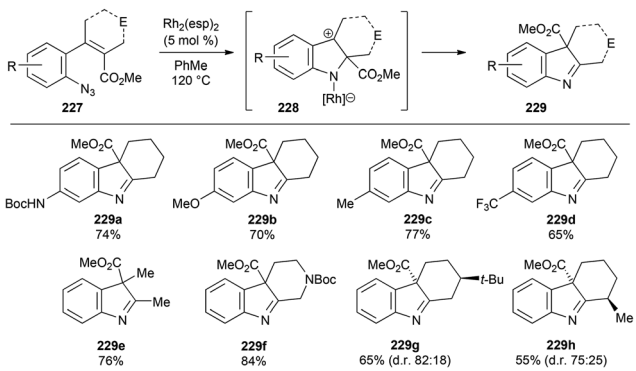
co-workers a variety of ring expansions could be triggered. In every case examined, the 2,3-disubstituted indole resulted from exclusive migration of the amide group.

Trisubstituted styryl azides were also investigated by the Driver group as potential substrates for domino electrocyclization–[1,2] migration reactions[107] (Scheme 49). Their goal was to induce migration of one of the β-substituents to the C3 cation **220** to form 3*H*-indole **221**. β-Acyl substituted styryl azides were first investigated because their previous investigations of disubstituted styryl azides had established migration of the acyl group to the C3 position as a facile process. Exposure of styryl azides **219** to reaction conditions, however, formed 1,2,3-trisubstituted indoles **222** as the only product. This transformation tolerates a range of substituents on both the aryl azide moiety and the α-substituent without attenuation of the yield of indole formation.

The authors asserted that these indoles were formed from the catalytic cycle pictured in Scheme 50. Rhodium-catalyzed decomposition of styryl azide **219a** generates the *N*-aryl metal nitrene **223**. A 4π-electron-5-atom electrocyclization of **223** forms the spirocyclic cation **224**, which fragments to form the acylium ion **225**. This electrophile could be attacked by the indole at the C3 position to form 3*H*-indole **226**. 3*H*-Indoles, which contain a 3-acyl group, were reported by Ban and co-workers to be unstable,[108,109] who reported that isolation or purification of these N-heterocycles triggered fragmentation. On the basis of this precedent, Driver and co-workers proposed that if C3 attack occurs it is reversible under reaction conditions. Acylation of the N1, however, appears to be irreversible



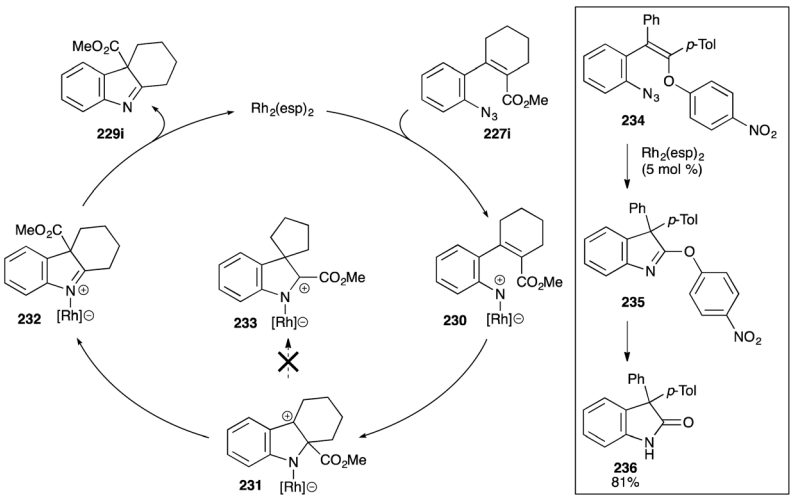
Scheme 50 Proposed mechanism to account for 1,2,3-trisubstituted indoles from styryl azides.



Scheme 51 Synthesis of 3*H*-indoles from trisubstituted styryl azides.

to form the isolated indole product **222a** after dissociation of the Rh_2(II)-carboxylate catalyst.

3*H*-Indoles could be accessed from trisubstituted styryl azides by changing the identity of the beta-substituent (Scheme 51).[110] Chen and Driver reported that exposure of β-carboxylate substituted styryl azides to 5 mol% of $Rh_2(esp)_2$ afforded 3*H*-indole **229**. This result was surprising because during the author's studies into the reactivity of disubstituted styryl azides, carboxylate migration was never observed. This transformation proved to be general tolerating a broad range of substitution on the aryl azide enabling access to 3*H*-indoles (**229a–229d**) that cannot be formed as single isomers using Fischer-indole-type reactions. While the migration of a chiral, non-racemic menthol-derived carboxylate was not selective, the authors reported that allylic- and homoallylic substituted substrates could be transformed in 3*H*-indoles with moderate selectivity (**229g** and **229h**).

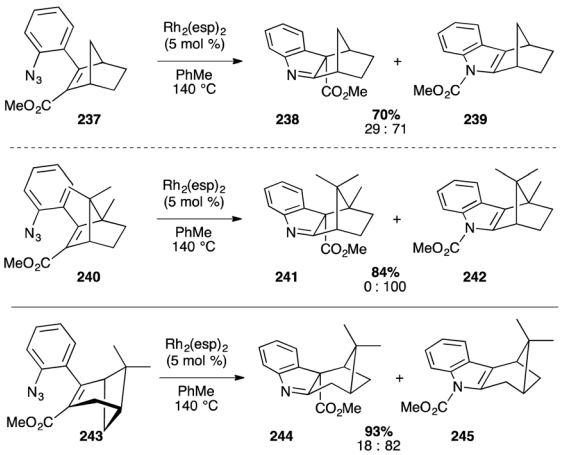


Scheme 52 Potential catalytic cycle to produce 3*H*-indoles from trisubstituted styryl azides.

The authors reported a domino reaction mechanism to account for the formation of 3*H*-indoles (Scheme 52). Coordination of the Rh_2(II) carboxylate catalyst to the azide triggers extrusion of N_2 to form rhodium *N*-aryl nitrene **230**, which undergoes electrocyclization to form **231**. From the cation **231**, two [1,2] shifts are possible. As predicted from the author's earlier results, an alkyl shift would go through a transition state in which a partial positive charge is generated next to the carboxylate substituent **233**. In contrast, if the carboxylate group migrated, a more stable iminium ion (**232**) would be generated. Dissociation of the rhodium catalyst would then generate the product.

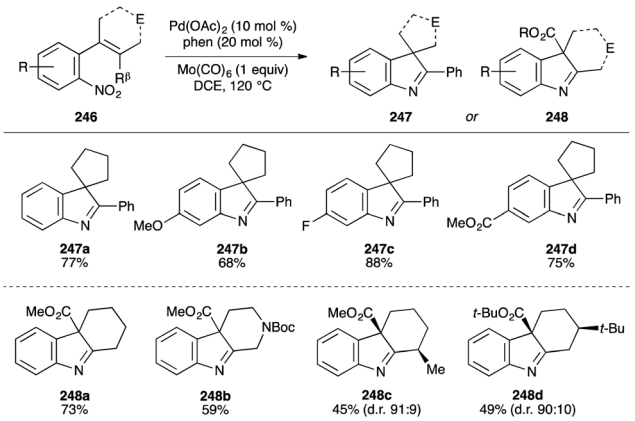
If stability of the iminium ion controlled the selectivity of the [1,2] migration step, it was anticipated that changing the identity of the β-substituent to an electron-donating substituent should change the outcome of the reaction. In line with their hypothesis, exposure of β-alkoxy styryl azide **234** to reaction conditions triggered aryl migration to produce oxindole **236** after acid-mediated hydrolysis of 3*H*-indole **235** (Scheme 52).

Next, the authors reported that increasing the steric environment around the *o*-alkenyl substituent could override the innate reactivity preference of the substrate (Scheme 53).[111] When aryl azides containing an *ortho*-[2.2.1] substituent were exposed to reaction conditions, carboxylate migration to the nitrogen-atom was observed as the major product instead of the carbon atom to result in the formation of indole **239**. Adding methyl substituents to the bridgehead eliminated the formation of 3*H*-indole **241** to result in only **242**. While this preference did not depend on the electronic nature of the aryl azide, simply moving one of the allylic substituents to the homoallylic position resulted in observation of 3*H*-indole **244** as the minor product. The authors proposed that the [1,2] migration selectivity resulted from minimizing the destabilizing steric interactions between the bridgehead methyl groups and the aryl moiety.

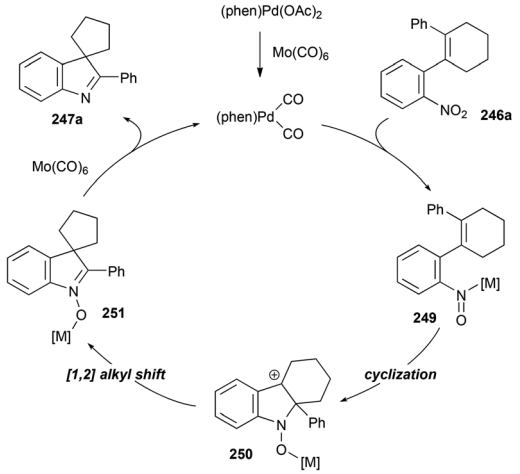


Scheme 53 Effect of increasing the steric environment on the reaction outcome.

Driver and co-workers have recently reported that domino cyclization–migration reactions can be achieved from the Pd(II)-catalyzed reduction of *ortho*-substituted nitrostyrenes (Scheme 54).[112] The authors turned their attention from aryl azides to nitrostyrenes because the latter require fewer steps to synthesize and the nitro-functional group is not as dangerous to introduce as an azide. The authors reported that β-phenyl trisubstituted nitrostyrenes—available in one step from cross-coupling commercially available 2-nitrophenylboronic acid with the vinyl triflate derived from 2-phenylcyclohexanone—could be transformed into spirocycle **247** through exposure to 10 mol% of (phen)$Pd(OAc)_2$ and $Mo(CO)_6$ as the source of CO. Their transformation tolerated a range of electron-releasing and electron-withdrawing functionality on the nitroarene without attenuation of the yield of **247**. Only when an additional *ortho*-substituent was introduced did the efficiency



Scheme 54 Pd(II)-catalyzed transformation of nitrostyrenes into 3*H*-indoles.



Scheme 55 Potential catalytic cycle for Pd(II)-catalyzed formation of 3*H*-indoles from nitrostyrenes.

of N-heterocycle formation plummet. Similar to their results with *ortho*-substituted aryl azides, the authors reported that when the identity of the β-substituent was changed to carboxylate that 3*H*-indoles **248** were produced. This transformation also tolerated heteroatoms in the *ortho*-alkenyl group and exhibited slightly higher stereoselectivity than the analogous aryl azide substrate. For example, substrates with either an allylic- or homoallylic substituent were transformed into the 3*H*-indole with 90 : 10 ratio of diastereomers.

The authors proposed a catalytic cycle to account for 3*H*-indole formation that involved the cyclization of a metal nitrosoarene as the key step (Scheme 55). Thermolysis of $Mo(CO)_6$ produced carbon monoxide required for $(phen)Pd(OAc)_2$ to reduce the nitro group to a nitrosoarene. Cyclization of the resulting metal nitrosoarene **249** could occur by nucleophilic attack of the *ortho*-alkenyl unit or a 6-electron-electrocyclization. The formation of the C–N bond by the latter pericyclic step was implicated by Houk and co-workers in their computation study of Pd(II)-catalyzed carbazole formation from biphenyl nitroarenes.[113,114] The resulting cation **250** triggers a [1,2] shift to form 3*H*-indole *N*-oxide **251**. Metal-mediated reduction of the N–O bond produces the N-heterocycle product and regenerates the catalyst. The authors concluded from a series of mechanistic experiments that the palladium catalyst functions to reduce the nitrostyrene to the nitrosoarene. Molybdenum carbonyl is competent to mediate the remaining steps of the transformation.

Summary and outlook

Significant progress has been made in the development of domino reactions that assemble functionalized cycloalkanes or N-heterocycles through an electrocyclization–[1,2] migration sequence. Despite this progress, we believe that domino reaction sequences involving electrocyclization and [1,2] migration steps are still at a nascent stage and with significant challenges remaining. Although many methods assemble five-membered rings, sequences that construct six membered rings through 6π-electron-6-atom electrocyclizations remain rare. Even though tremendous progress has been made by the Frontier and Toste groups to achieve the synthesis of chiral, non-racemic cycloalkanes, stereoselective formation of C–N bonds has lagged. These gaps in the synthetic literature will be plugged as our mechanistic understanding of the underpinning principles that govern each of the elementary steps increases. We eagerly anticipate these future reports that address these challenges to increase the accessibility of functionalized N-heterocycles and carbocycles.

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