Enolate-Directed Catalytic C–H Functionalization of 2-Aryl-1,3-dicarbonyl Compounds



Thesis Submitted in Accordance with the Requirement of the University of Nottingham for the Degree of Doctor of Philosophy

By

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August, 2015

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in April 2012, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Imtiaz Khan

Acknowledgements

First, I would like to thank Professor Hon Wai Lam for giving me the opportunity to undertake research within his group and for teaching me essential skills that will be exceedingly useful for my life as a chemist. I am very thankful for the time and effort he gave to help me during my studies and without him this work wouldn't have been possible.

I would also like to thank Dr. Suresh Reddy Chidipudi who provided support and guided me for the study of the described projects. Without him, I would not have been able to have such a productive spell of research. Thank you to everyone in the Lam group past and present for cooperation and assistance during my PhD stay at The University of Edinburgh as well as The University of Nottingham. I am also very thankful to Dr. David J. Burns for providing advice during my thesis writing (your input definitely helped), and proof reading of my thesis. I am also indebted to Dr. Ben Partridge and Joshua Smith for proof reading the final draft.

I am eternally grateful to the group Post-Docs: Alan, Dan, Suresh, Yunfei, David, Ben, Celia, Lucia, Jose, and Gabe for being so approachable and the occasions you took time out to share knowledge, skills or generally helped me during my time in the lab.

I would also like to take this opportunity to show my gratitude to The University of Edinburgh, and The University of Nottingham, particularly the School of Chemistry. The high quality of service provided by NMR, mass spectroscopy, X-ray crystallography, stores and maintenance teams were integral to the success of my projects.

Many thanks to The University of Edinburgh for the award of Tercentenary PhD Scholarship, and The University of Nottingham for funding my PhD studies.

Finally, I would like to thank my parents for everything you have done for me, my brothers especially Ijaz Ahmed for financial support during my study and outside the chemistry world, and my sisters for their love, prayers, encouragement and support throughout my life which has allowed me to be where and who I am today.

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Abbreviations

Ac_2O	acetic anhydride
AcOH	acetic acid
$AgSbF_6$	silver hexafluoroantimonate
AgOAc	silver acetate
app	apparent
Ar	aryl
ATR	attenuated total reflectance
BQ	benzoquinone
br	broad
Bz	benzoyl
Cat	catalyst
Cp*	pentamethylcyclopentadiene
cod	cyclooctadiene
$CHCl_3$	chloroform
CF_3COOH	trifluoroacetic acid
coe	cyclooctene
Conc	concentrated
Cu	copper
d	doublet
ddd	doublet of doublet of doublet
DABCO	diazabicyclooctane
DCE	dichloroethane
DEPT	Distortionless Enhancement by Polarization Transfer

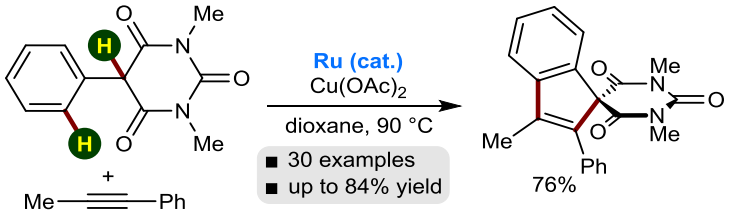
DIBAL	diisobutylaluminium hydride
DMA	dimethylacetamide
DMC	dimethyl carbonate
DMF	dimethylforamide
DMSO	dimethylsulfoxide
DME	dimethoxyethane
DNA	deoxyribonucleic acid
EI	electron impact
ESI	electron spray ionization
Equiv	equivalent
Eq	equation
GABA	γ-aminobutyric acid
g	gram(s)
h	hour(s)
HRMS	High Resolution Mass Spectroscopy
IR	infra-red
J	coupling constant
m	multiplet
M	metal
min	minute
Mn	manganese
NBS	*N*-bromosuccinimide
Ni	nickel
NMP	*N*-Methylpyrrolidone
NMR	Nuclear Magnetic Resonance

Pd	palladium
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
PEG	polyethylene glycol
ppm	parts per million
Ph	phenyl
q	quartet
quin	quintet
R_f	retention factor
RT	room temperature
Ru	ruthenium
s	singlet
SERMs	Selective Estrogen Receptors Modulators
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
THF	tetrahydofuran
TNF	tumor necrosis factor
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
μ	micro

ABSTRACT

I) Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds

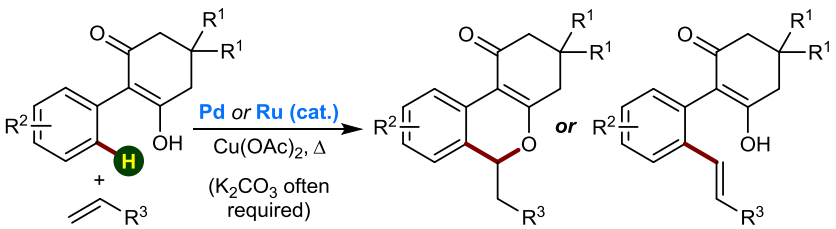
The synthesis of carbocycles by the ruthenium-catalyzed oxidative annulation of alkynes with 2-aryl cyclic 1,3-dicarbonyl substrates is described. Proceeding by the functionalization of C(sp^3)–H and C(sp^2)–H bonds, and the formation of all-carbon quaternary centers, the reactions provide a diverse range of spiroindenes in good yields and high levels of regioselectivity.



Angew. Chem. Int. Ed. **2012**, *51*, 12115–12119

II) Synthesis of Benzopyrans by Pd(II)- or Ru(II)-Catalyzed C–H Alkenylation of 2-Aryl-3-hydroxy-2-cyclohexenones

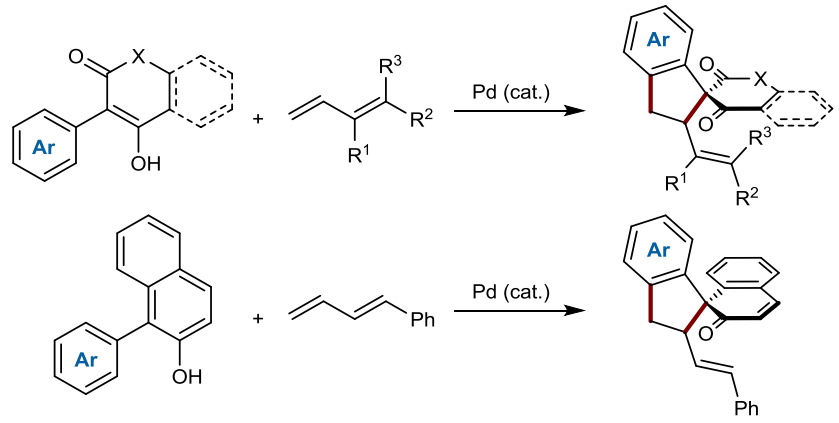
We have explored the 2-aryl-3-hydroxy-2-cyclohexenones as competent substrates for palladium- and ruthenium-catalyzed C–H alkenylation reactions with terminal alkenes. This process affords benzopyrans, in most cases, with good functional group tolerance.



Org. Lett. **2013**, *15*, 570–573

III) Synthesis of Spiroindanes by Palladium-Catalyzed Oxidative Annulations of 1,3-Dienes Involving C–H Functionalization

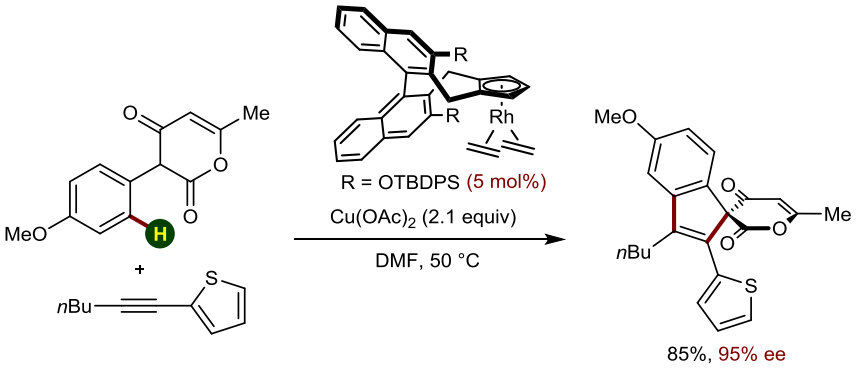
1,3-Dienes have been an underexplored class of substrates in catalytic oxidative annulation reactions involving C–H functionalization. The synthesis of spiroindanes by the palladium-catalyzed oxidative annulation of 1,3-dienes with 2-aryl cyclic 1,3-dicarbonyl compounds is described. Several examples of the dearomatizing oxidative annulation of 1,3-dienes with 1-aryl-2-naphthols are also presented.



Chem. Commun. **2015**, *51*, 2613–2616

IV) Enantioselective Spiroindene Formation *via* C–H Functionalization Using Chiral Cyclopentadienyl Rhodium Catalysts

A chiral cyclopentadienyl rhodium ligand with an atropchiral biaryl backbone enables an asymmetric synthesis of spiroindenes from 2-aryl-1,3-dicarbonyl compounds and alkynes. The process affords a range of products with all-carbon quaternary center in high yields and excellent enantiselectivities. The good functional group tolerance and broad substrate generality are the advantages of this reaction.



Chapter 1: Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds

1. Introduction

1.1. The Significance of Indenes

Indene ring frameworks are diverse and significant scaffolds occupying a considerable place in the realm of carbocyclic chemistry because these structural motifs have been found in numerous natural products **1**,**2** and bioactive compounds **3**-**5**.[1,2] These derivatives also find wide applications in metal complexes, pharmaceuticals, catalysis, polymer chemistry and for the synthesis of natural products.[3] In addition, indene derivatives are also of wide interest in the field of material chemistry.[4] Moreover, these structures have also been used as estrogen receptor ligands,[5] and H_1 antihistamines **6**.[6] Some indene derivatives such as **7** also possess photochromic properties[7] (Figure 1.1).

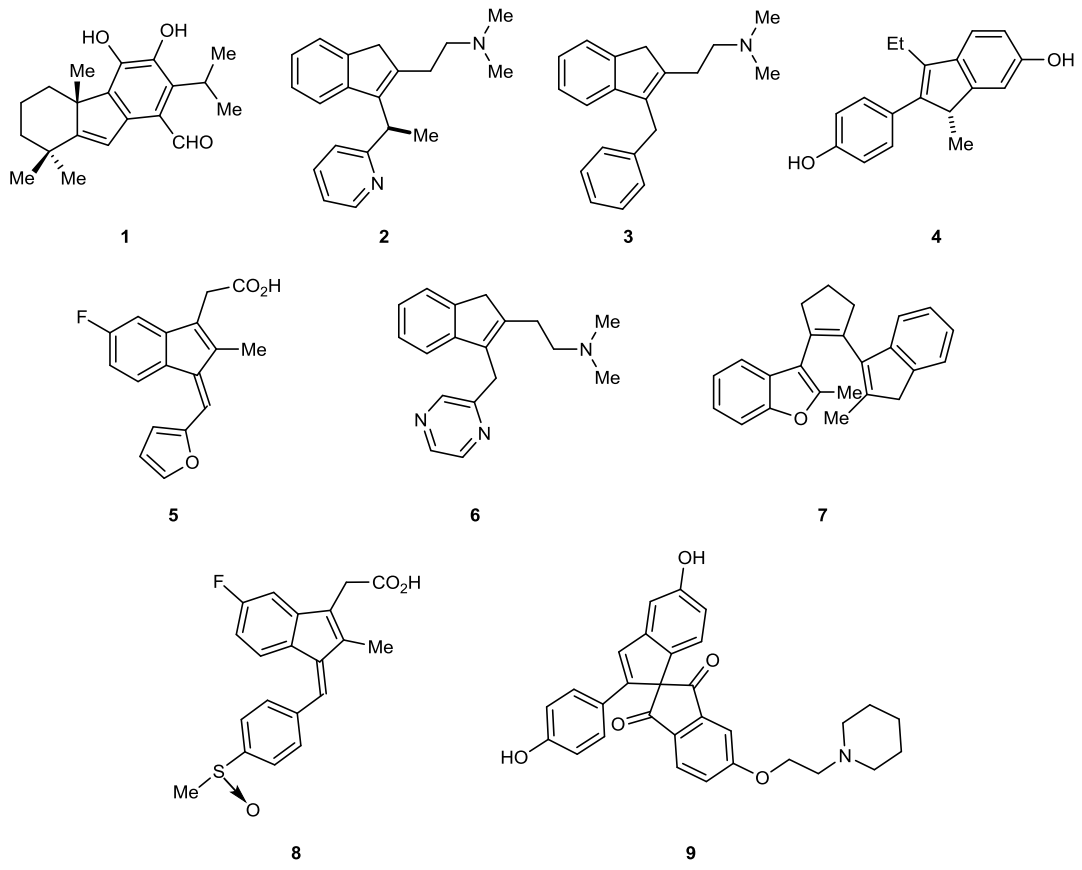


Figure 1.1. Representative examples of some pharmacologically active indenes.

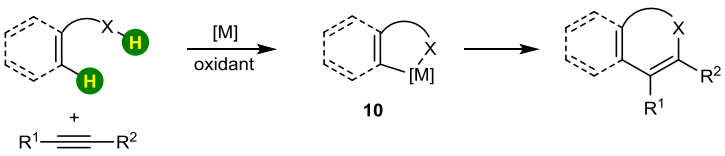
Several reduced benz[*e*]indene derivatives are structurally related to steroids and some analogues played an essential role in enhancing the actions of inhibitory neurotransmitter γ-aminobutyric acid (GABA) at $GABA_A$ receptors.[8] Due to this pharmacological action, indene compounds are of high interest as lead molecules for the identification of new drug candidates showing a broad spectrum of biological activities including analgesic, anticonvulsant and anti-inflammatory agents.[9] Sulindac, possessing an indene framework, is a non-steroid with remarkable anti-inflammatory activity **8**.[10] Indene derivatives also possess a mild growth inhibitory activity to L1210 and CCRF-CEM leukemia cells,[11] and showed interaction with DNAs.[12] Some indene derivatives also find wide practical applications in light-emitting diode devices.[13] Several spiroindene derivatives such as **9** have also been identified as novel and selective estrogen receptors modulators (SERMs).[14]

1.2. C–H Activation

Carbon-hydrogen bonds are ubiquitous in organic molecules with a tremendous potential for transformation into a diversity of other functional groups. In this context, C–H functionalization has emerged as a significant tool for the development of carbon-carbon and carbon-heteroatom bonds and has brought a revolution in synthetic methodologies to access a wide range of pharmaceuticals, natural products and medicinally relevant and attractive scaffolds, and also opened new routes to material and polymer chemistry.[15] The important features of C–H bond functionalization includes the shortening of reaction pathways, thus improving the step-economy by avoiding the use of functional group interconversions, as well as time and solvent consumption for the preparation of starting materials. This process leads to more efficient methods for the production of desired frameworks, and in some cases, to achieve unique regioselectivity patterns that are often unattainable by classical methods.[16] A remarkable diversity of structures is accessed through transition-metal-catalyzed C–H functionalizations involving several metals including rhodium, palladium, ruthenium, iridium, copper, nickel, etc. for the development of carbon-carbon bond from relatively inexpensive and easily available starting materials.[17-21]

1.2.1. Metal-Catalyzed Oxidative Annulation of Alkynes

Construction of carbon-carbon, carbon-nitrogen and carbon-oxygen bonds under oxidative conditions is of vital significance from a fundamental research point of view as well as from an industrial stand point. Inspired by the literature findings, during the past decade, remarkable progress has been witnessed in organometallic chemistry and several research groups have succeeded in constructing these bonds using viable metal catalysts for C–H bond activation reactions, and many privileged synthetic methodologies have been developed starting from substrates with or without chelation assistance in which the coupling partners are alkenes, alkynes, arenes and hetero-arenes.[22] Among these, the metal-catalyzed oxidative annulation of alkynes has proven to be a versatile, efficient, and atom-economic strategy to access a range of useful heterocyclic products.[23] These processes generally rely upon coordination of the metal center to the heteroatom-containing functional group which directs site selective C(sp^2)–H bond cleavage to form a metallacycle **10** (Scheme 1.1).[24] Migratory insertion of the alkyne followed by C–X (X = heteroatom) reductive elimination then forms the heterocyclic product.



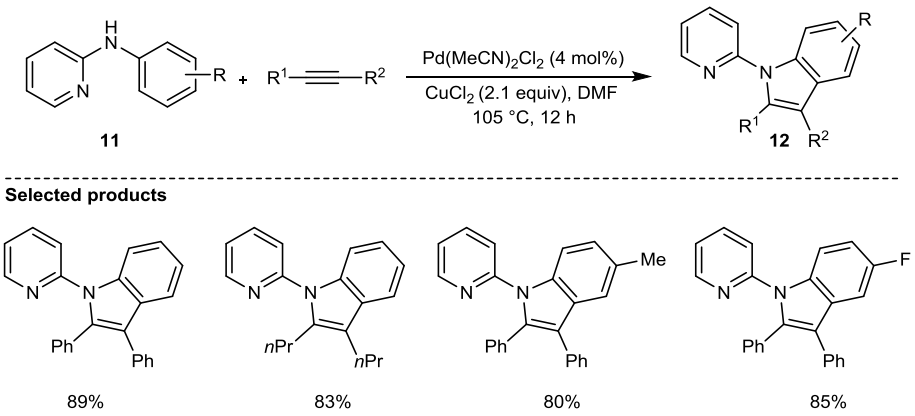
Scheme 1.1. Alkyne oxidative annulations by X–H/C(sp^2)–H bond cleavage.

There is a high volume of publications reporting the use of alkynes as coupling partners in oxidative processes directed by a variety of functional groups using different metal precatalysts. However, in the subsequent discussion, we will highlight some of the representative examples for the construction of C–C and C–X bonds involving metal-catalyzed C–H functionalization methods.

1.2.1.1. Palladium-Catalyzed Oxidative Annulation of Alkynes

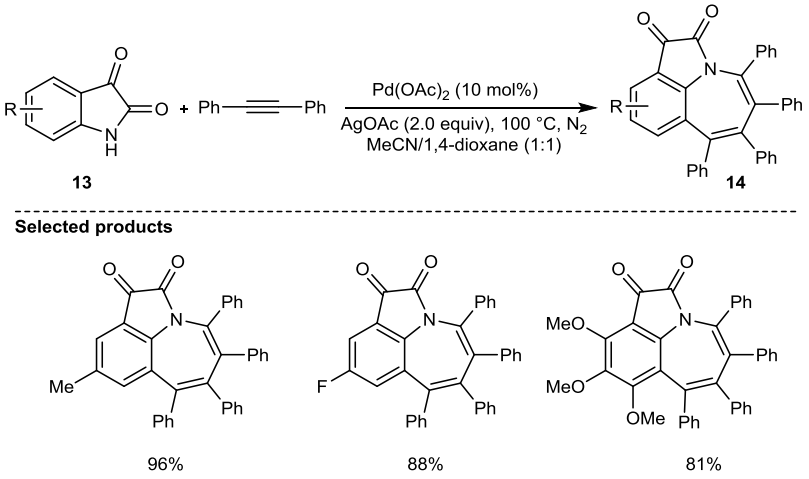
Chen *et al*. demonstrated the synthesis of pyridine substituted indoles **12** by the oxidative coupling of *N*-2-aryl-2-aminopyridines **11** and internal alkynes *via ortho*-C–H activation under palladium catalysis. $CuCl_2$ was employed as an oxidant in this process (Scheme 1.2).[25] A diverse range of products were obtained from the coupling

reactions of symmetrical as well as unsymmetrical alkynes and a variety of substrates. Heteroaryl-substituted alkynes were also good under these reaction conditions affording indoles in high yields. It is noteworthy that in case of *meta*-substituted substrates, indole products were obtained exclusively at the less hindered site.



Scheme 1.2. Synthesis of indole derivatives.

In the same time period, Jiang, Wang and co-workers demonstrated the synthesis of benzazepine heterocycles **14** through simple and readily available isatins **13** and internal alkynes. The strategy involves the oxidative cycloaddition through activation of C–H/N–H bonds under palladium catalysis (Scheme 1.3).[26] Having optimized conditions in hand, they evaluated the reaction scope with electron-donating, neutral and electron-withdrawing substituents at the C-5 position of isatins providing access to well-decorated benzazepine products in high yields. The substituents on the C-4 or C-7 position of isatin were also tolerated. In addition, a range of alkynes that could be the potential coupling partners, were also investigated. Electron-rich tolanes were found to be more reactive as compared to the electron-deficient alkynes. Heteroaryl, ester-containing and aliphatic alkynes were also examined in these coupling reactions. In case of unsymmetrical alkynes, two regioisomers were obtained.



Scheme 1.3. Synthesis of benzazepine derivatives.

On the basis of well-known metal-catalyzed oxidative processes, a proposed catalytic cycle is illustrated in Figure 1.2. The annulation into benzazepine starts with the palladation of isatin **13** to give palladium intermediate **15**. Next, intermolecular insertion of alkyne to **15** produces vinyl-palladium intermediate **16** which on another addition of alkyne generates intermediate **17**. Finally, intramolecular palladation of **17** leads to the formation of palladabenzocycloheptatriene **18**, which can subsequently undergo reductive elimination to yield benzazepine **14**.

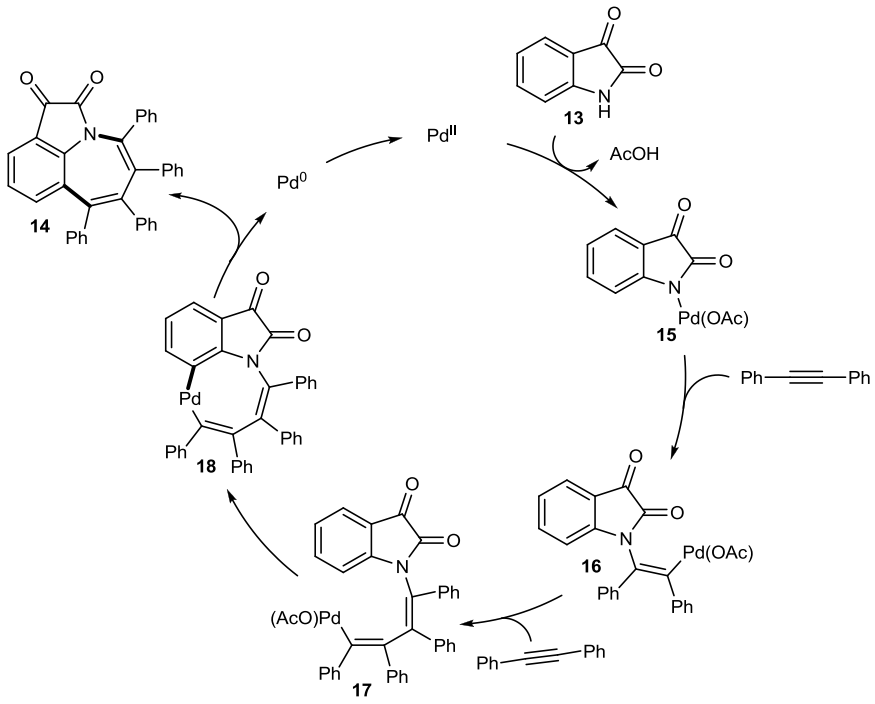
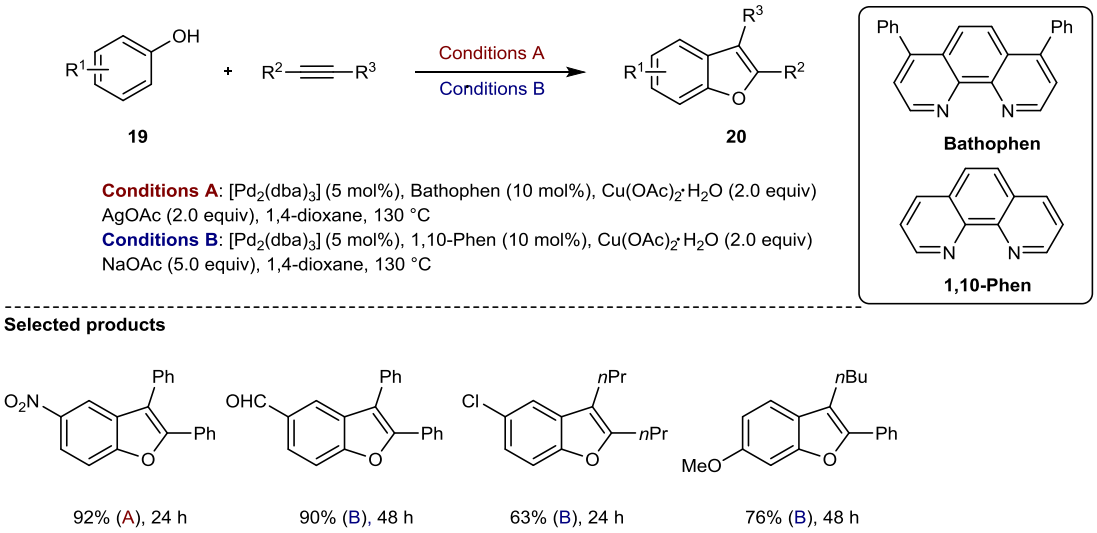


Figure 1.2. Proposed catalytic cycle for benzazepine formation.

Sahoo and co-workers have developed a novel one-step synthesis of 2,3-disubstituted benzofurans **20** involving Pd-catalyzed oxidative annulations of commercially available phenols **19** with unactivated internal alkynes (Scheme 1.4).[27] A range of substituents were tolerated in this process. The substituents included halo, nitro, cyano, ketone, aldehyde and ester functionalities on the phenol ring. The products were obtained in good yields. The reaction also proceeds well with phenols bearing electron-donating groups providing access to benzofurans in ample yields.



Scheme 1.4. Synthesis of benzofurans.

The plausible mechanistic cycle (Figure 1.3) suggests that Pd(0) is readily oxidized to Pd(II) in the presence of $Cu(OAc)_2$ to generate **21**. At this stage, attack of phenol onto the electrophilic Pd(II) species may occur in two different ways. Mechanistic cycle A involves the attack of phenol **19** to produce Pd(II)–phenoxide species **22** and liberate AcOH. Subsequently, the coordination of the alkyne to **22** would induce its phenoxypalladation to afford **23**. Base-assisted intramolecular *ortho*-C–H insertion by the Pd catalyst then leads to **24**,[28] which on reductive elimination delivers the benzofuran **20** and regenerates the Pd(0) species for the next catalytic cycle. On the other hand, mechanistic cycle B involves the *ortho*-palladation of phenol **19** by electrophilic Pd(II) species **21**, giving the quinone-type intermediate **25**. Alkyne coordination followed by carbopalladation then affords **26**, which on base induced rearomatization yields **27**. Finally, reductive elimination delivers product **20** along with the Pd(0) species.

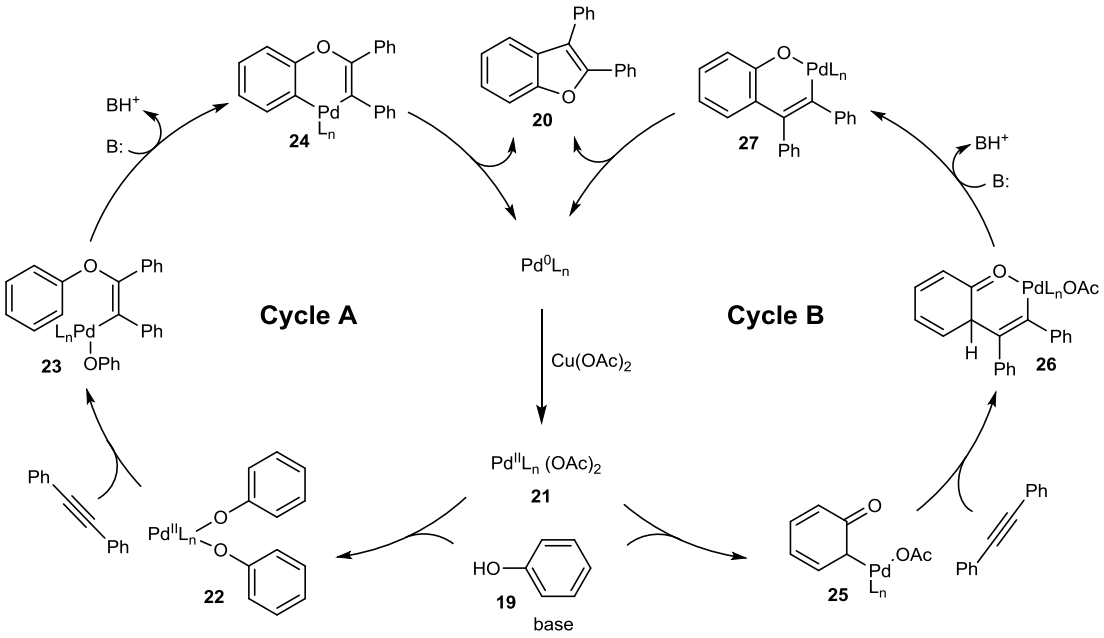
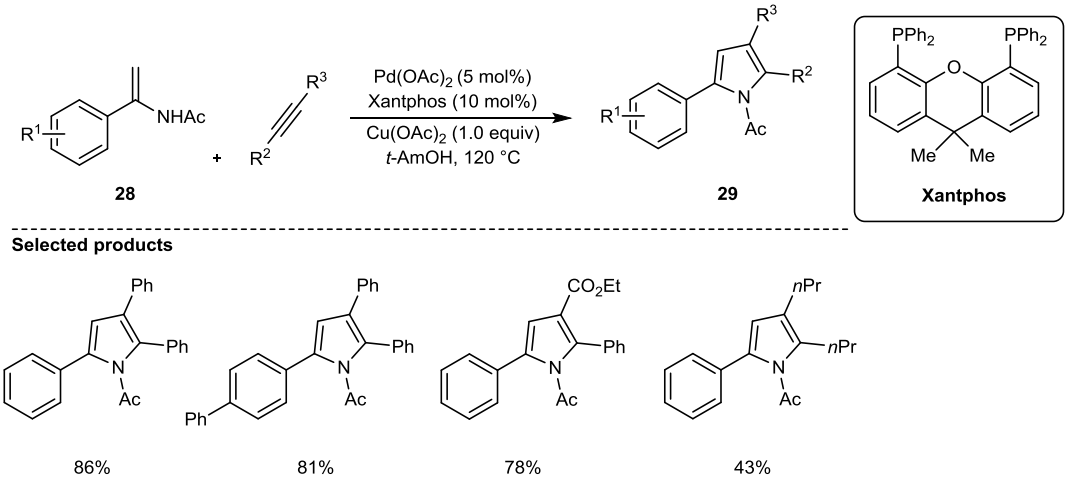


Figure 1.3. Possible mechanistic pathways for benzofuran formation.

Guan and co-workers reported a novel and efficient oxidative annulation procedure involving C–H functionalization of enamides **28** with internal alkynes as coupling partners under palladium catalysis. The process afforded an array of substituted pyrroles **29** in good yield with a diverse range of functional group compatibility (Scheme 1.5).[29] After an extensive screening of palladium source, and phosphine ligands in various solvents, they identified that $Pd(OAc)_2$ works best with catalytic amount of xantphos and $Cu(OAc)_2$ as an oxidant in *t*-AmOH as solvent.

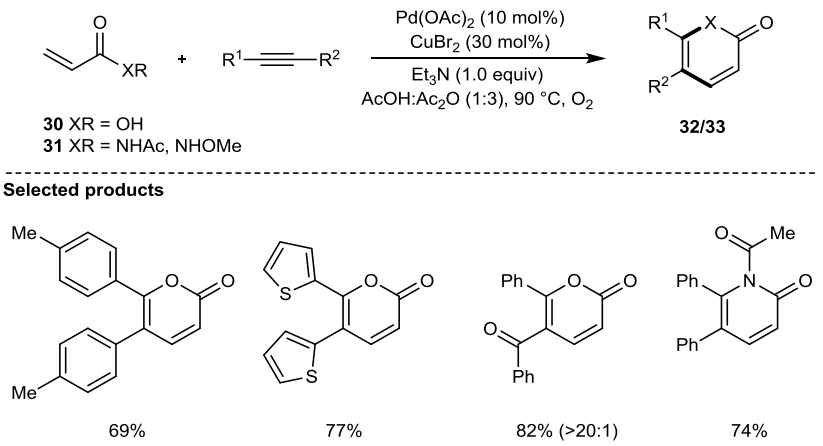
Having optimized reaction conditions, the process was extended to a range of enamide substrates to investigate the reaction scope. The results demonstrated that this transformation is quite general with high functional group tolerance affording triaryl-substituted pyrrole skeleton. The structural variations include electron-donating, electron-withdrawing and electron-neutral groups on aryl ring in addition to the phenyl, methoxyl, [1,3]dioxolyl, and amino groups. All these substrates were found as efficient starting materials for the preparation of *N*-acetyl-substituted pyrroles. *Ortho*-substituted enamides were also well transformed into the corresponding products. Sterically demanding substrates were insensitive to the reaction conditions and gave corresponding pyrroles in moderate yields. However, the aliphatic enamides as well as electron-deficient enamides were found to be unreactive substrates. On the other hand, this transformation showed broad tolerance among

internal alkynes. Symmetrical diaryl-substituted alkynes, dialkyl-substituted alkynes as well as unsymmetrical alkynes were all identified as efficient coupling partners leading to the desired products in moderate to good yields.



Scheme 1.5. Synthesis of pyrrole derivatives.

Jiang and co-workers developed an efficient palladium-catalyzed oxidative annulation of acrylic acid **30** and amide **31** with a range of internal alkynes to produce *α*-pyrones **32** and pyridones **33** using oxygen as a stoichiometric oxidant (Scheme 1.6).[30] The process affords good yields of products with high levels of regioselectivity with the liberation of H_2O as the only by-product. Using the optimized reaction conditions, the scope of this process in terms of alkynes and acrylates or amides was investigated. Initially, a range of *para*-substituted diphenylethynes, including electron-withdrawing and electron-donating groups, were tested affording the corresponding *α*-pyrones in good yields. The unsymmetrical diarylethynes were also converted to the *α*-pyrone products with high levels of regioselectivity in addition to the diheteroarylethynes which afforded desired product in 77% yield. Furthermore, the scope of this oxidative annulation was further extended to acrylic amide with internal alkynes affording pyridone products.



Scheme 1.6. Synthesis of pyrone and pyridone derivatives.

The plausible catalytic cycle for Pd-catalyzed oxidative annulation is illustrated in Figure 1.4. Initially, the coordination and ligand exchange of the acrylic derivative **30** or **31** with Pd(II) provided intermediate **34**.[31,32] followed by the coordination and insertion of the alkyne afforded the vinyl-palladium complex **35**. Subsequently, the intramolecular Heck-type process gave the alkyl-palladium intermediate **36**,[33] which on β-hydride elimination released the product **32** or **33** and Pd(0) species which was reoxidized to generate the active catalytic species.

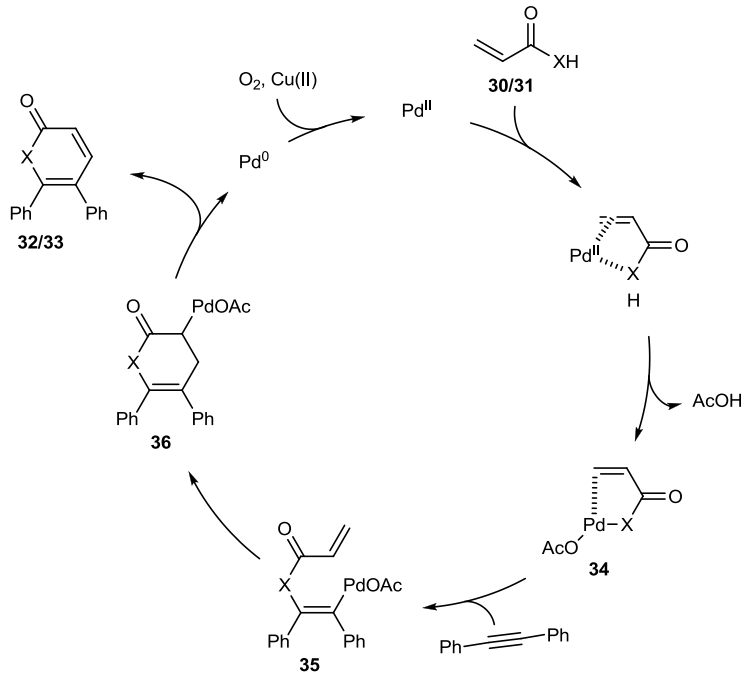
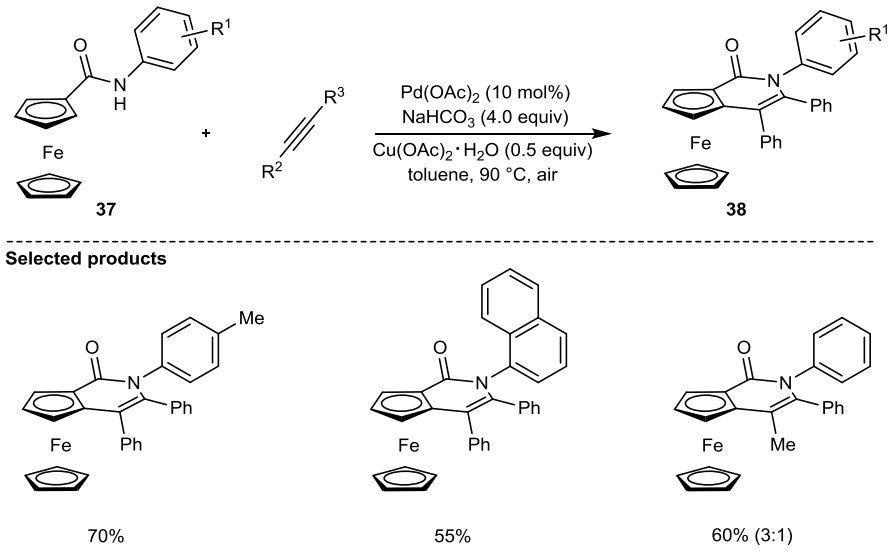


Figure 1.4. Proposed catalytic cycle for pyrone and pyridone formation.

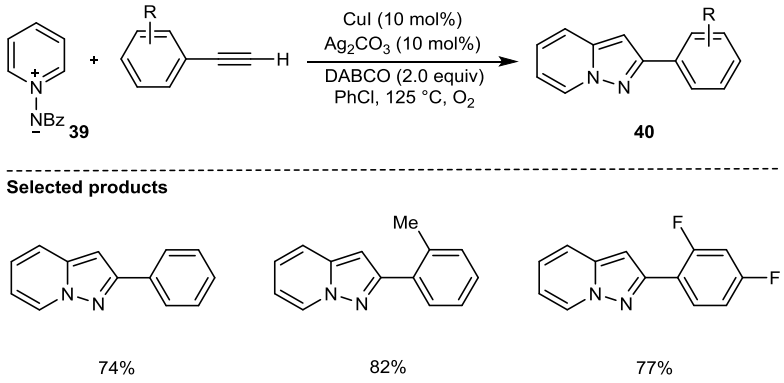
Wang and co-workers developed a novel palladium-catalyzed annulation procedure using ferrocenecarboxamides **37** with internal alkynes and air as an oxidant delivering racemic ferrocene[1,2-*c*]pyridine-3(4*H*)-ones **38** in good yields (Scheme 1.7).[34] Having established the optimal reaction conditions, various substituted ferrocenecarboxamides were tolerated with diphenylacetylene producing the corresponding ferrocene[1,2-*c*]pyridone derivatives in good yields. Various halogen-substituted analogues such as 4-fluoro-, 4-chloro-, and 4-bromoanilines were well tolerated affording the desired annulation products in good yields (52−65%). Also, amides with different electron-donating or electron-withdrawing groups at the *N*-phenyl ring, gave products in good yields. In addition, a range of alkynes were also employed and identified as effective coupling partners.



Scheme 1.7. Synthesis of pyrone and pyridone derivatives.

1.2.1.2. Copper-Catalyzed Oxidative Annulation of Alkynes

In 2012, Jiao and co-workers demonstrated a copper-catalyzed aerobic direct dehydrogenative annulation of *N*-iminopyridinium ylides **39** with alkynes using oxygen as an oxidant to access a diverse range of pyrazole[1,5-*a*]pyridines **40** (Scheme 1.8).[35] Under the optimized reaction conditions, a wide substrate scope was observed with respect to terminal alkynes. A variety of substrates bearing either electron-rich or electron poor substrates were tolerated leading to the desired products in good yield.



Scheme 1.8. Synthesis of pyrazole-pyridine derivatives.

On the basis of observed results, a possible mechanism is suggested for this reaction and is depicted in Figure 1.5. Initially, copper acetylide **41** is generated from alkyne with Cu(I) catalyst assisted by Ag_2CO_3. Then, the oxidative insertion of copper acetylide **41** into the pyridinium ylide **39** gives Cu(III) intermediate **42** *via* C–H bond activation. Subsequently, intermediate **42** undergoes reductive elimination to afford the direct alkynylation intermediate **43**, in which the alkyne can be activated by copper catalyst. Then, 5-endo cyclization of **43** *via* the *anti*-aminocupration of the alkyne attacked by the amido nitrogen generates **44**, which can be converted into **45** *via* a protonation process. Finally, product **40** is obtained *via* the rearomatization of **45**.

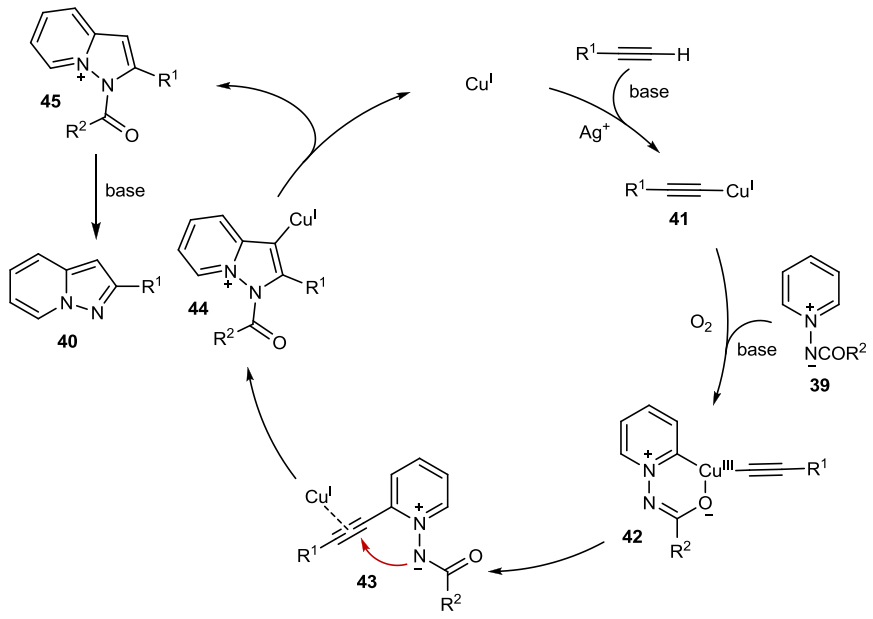
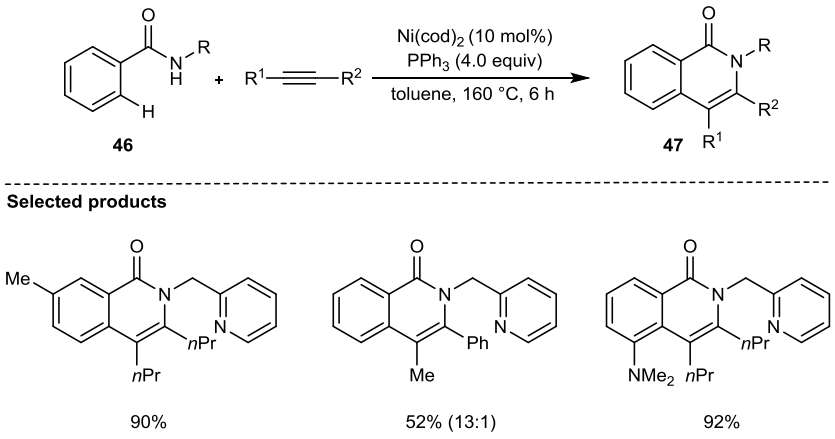


Figure 1.5. Proposed catalytic cycle for pyrazole[1,5-*a*]pyridine formation.

1.2.1.3. Nickel-Catalyzed Oxidative Annulation of Alkynes

In 2011, the research group of Chatani achieved the first example of nickel-catalyzed transformation of *ortho*-C–H bond that takes the advantage of chelation assistance. As a result, a wide range of isoquinolone derivatives **47** by cycloaddition of aromatic amides **46** to alkynes, is accessed (Scheme 1.9).[36] A diverse range of functional groups, such as methoxy, trifluoromethyl, amino, cyano, acetyl, and acetal groups, were tolerated under the reaction conditions. Substrates with electron-withdrawing groups were found to be more reactive as compared to substrates with electron-donating groups. The reaction produces highly regioselective products with unsymmetrical alkynes.



Scheme 1.9. Synthesis of isoquinolone derivatives.

Mechanistic approach adopted to establish the reaction pathway is depicted in Figure 1.6. Initially, coordination of amide **46** to the nickel center as an *N*,*N*-donor followed by activation of the N–H bond gives nickel hydride complex **48**. Then, the insertion of the alkyne into the H–Ni bond of **48** generates vinylnickel complex **49** which on cleavage of an *ortho* C–H bond generates another complex **50**. Finally, insertion of alkyne into complex **50**, and subsequently, reductive elimination gave isoquinolone **47**.

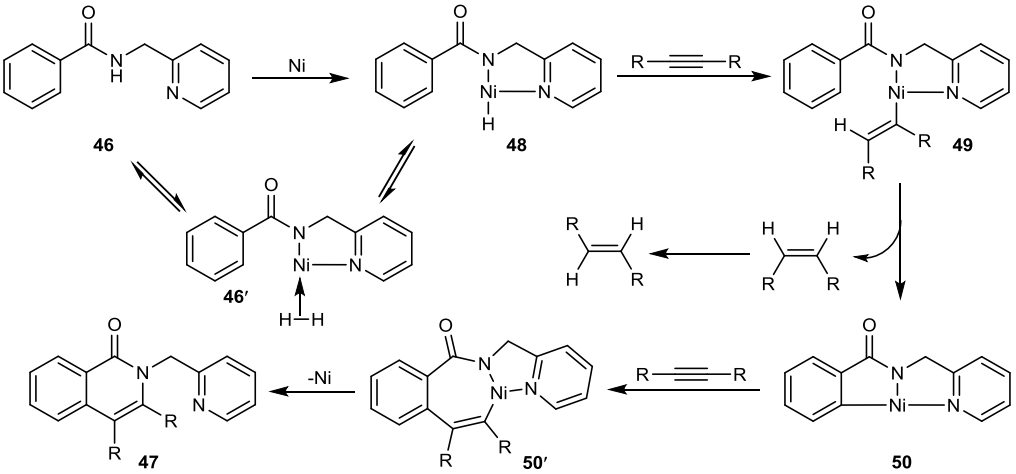
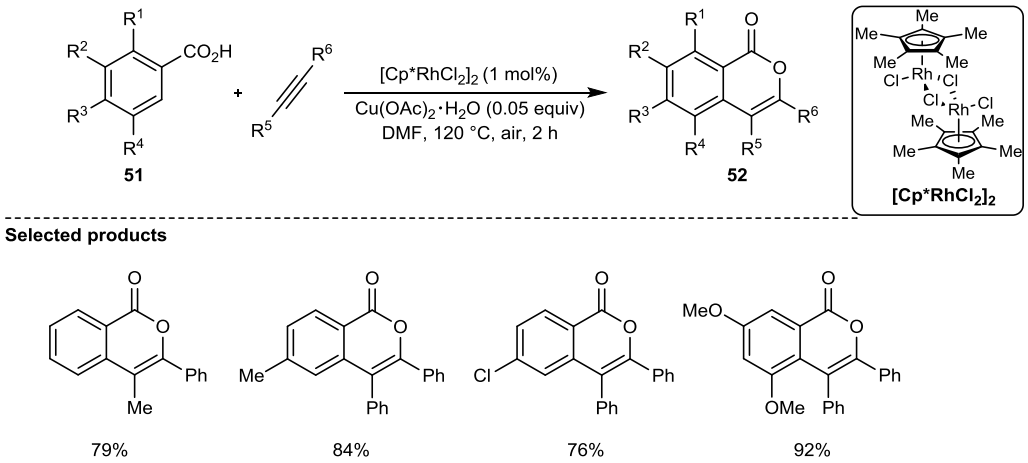


Figure 1.6. Proposed catalytic cycle for isoquinolone formation.

1.2.1.4. Rhodium-Catalyzed Oxidative Annulation of Alkynes

In 2007, the research group of Miura and Satoh carried out an efficient waste-free direct oxidative coupling of benzoic acids **51** with internal alkynes. The reaction proceeds best in the presence of rhodium/copper catalyst system under air affording the corresponding isocoumarin derivatives **52** (Scheme 1.10).[37] The process also tolerates a wide variety of benzoic acids and internal alkynes incorporating symmetrical as well as unsymmetrical substituents producing the isocoumarin products with high regioselectivity.



Scheme 1.10. Synthesis of isocoumarin derivatives.

A possible catalytic cycle for this oxidative coupling is illustrated in Figure 1.7. Coordination of the carboxylate oxygen to $[Cp^*Rh(OAc)_2]$ affords a rhodium(III) benzoate intermediate **53** which undergoes *ortho*-rhodation to give a five-membered rhodacycle **54**. Subsequently, alkyne insertion generates another seven-membered rhodacycle **55** which on reductive elimination produces iocoumarin **52**. The resulting Rh(I) species is oxidized by the $Cu(OAc)_2$ under air to regenerate the Rh(III) active catalyst.

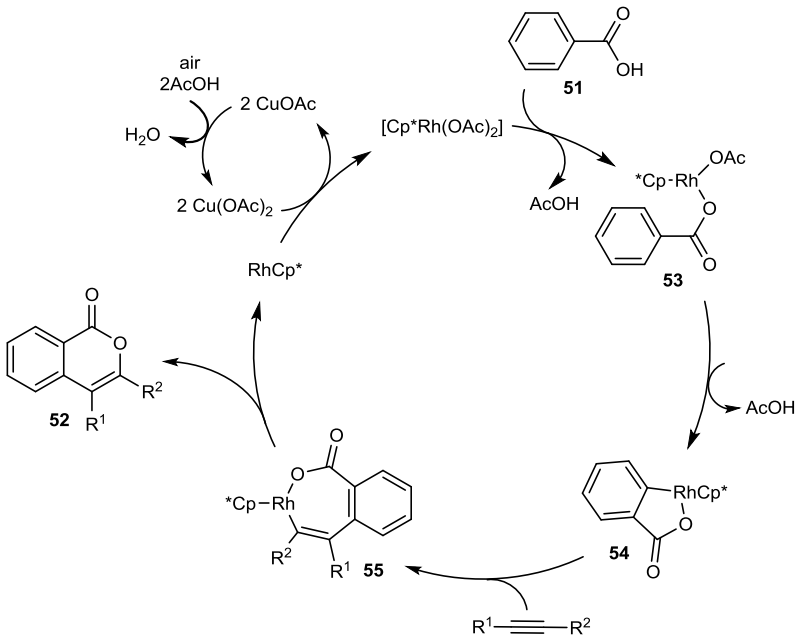
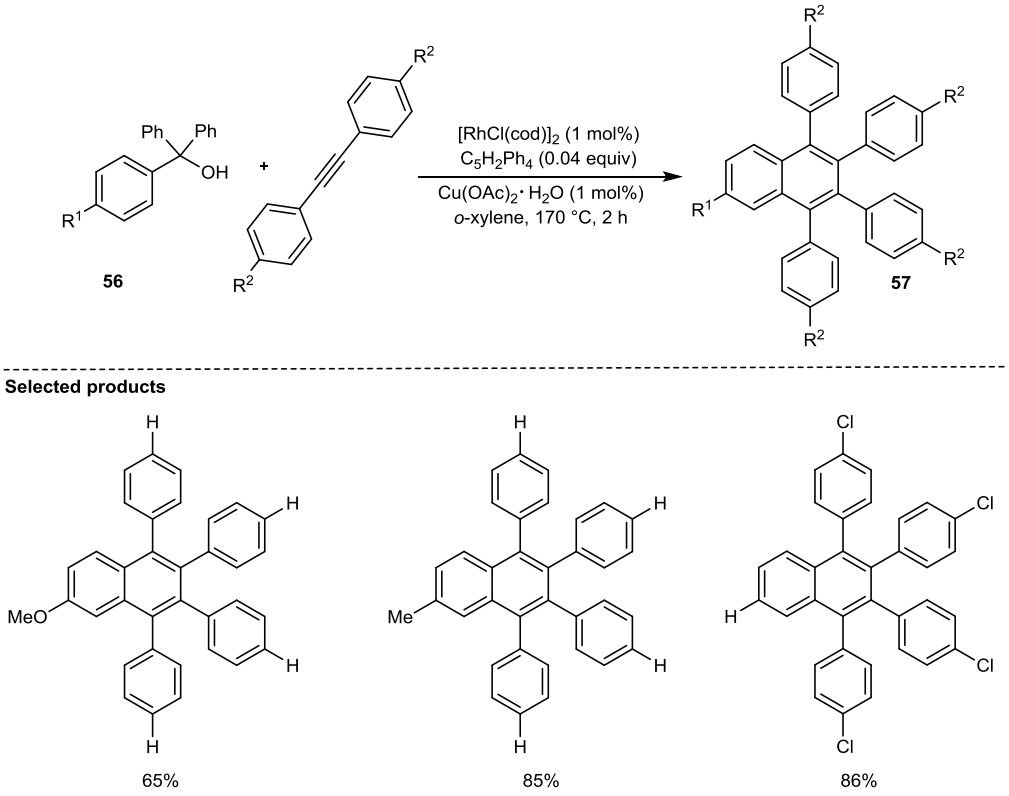


Figure 1.7. Proposed catalytic cycle for isocoumarin formation.

In the following year, the same research group accomplished the synthesis of naphthalene derivatives **57** under rhodium-catalyzed oxidative coupling of triarylmethanols **56** with internal alkynes. Also, the role of the ligand was found to be crucial for this transformation and the presence of a tri- or tetraphenylcyclopentadiene ligand increased the efficiency of the reaction (Scheme 1.11).[38]

The possible catalytic cycle depicted in Figure 1.8 involves the coordination of the alcoholic oxygen to a Rh(III) species generating a rhodium(III) alcoholate intermediate **58**. Subsequently, *ortho*-rhodation generates a five-membered rhodacycle **59**, which on alkyne insertion generates another seven-membered rhodacycle **60** and successive reductive elimination produces another rhodacycle **61** with the elimination of Ph_2CO. The subsequent second alkyne insertion and reductive elimination produces naphthalene **57**. The presence of $Cu(OAc)_2$ may be used for the oxidation of Rh(I) species to regenerate Rh(III) species.



Scheme 1.11. Synthesis of naphthalene derivatives.

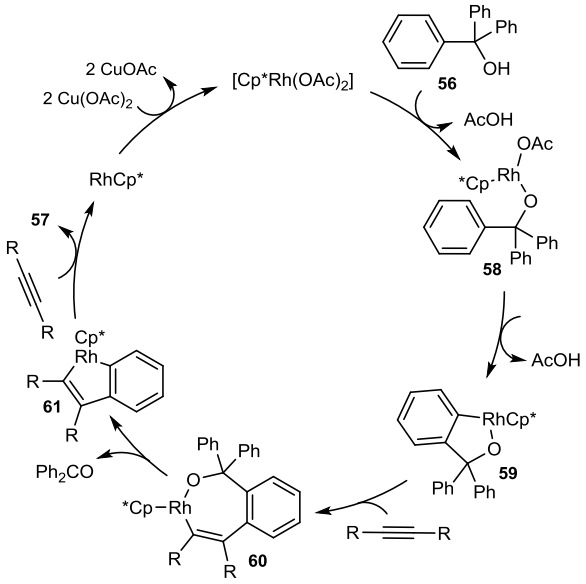
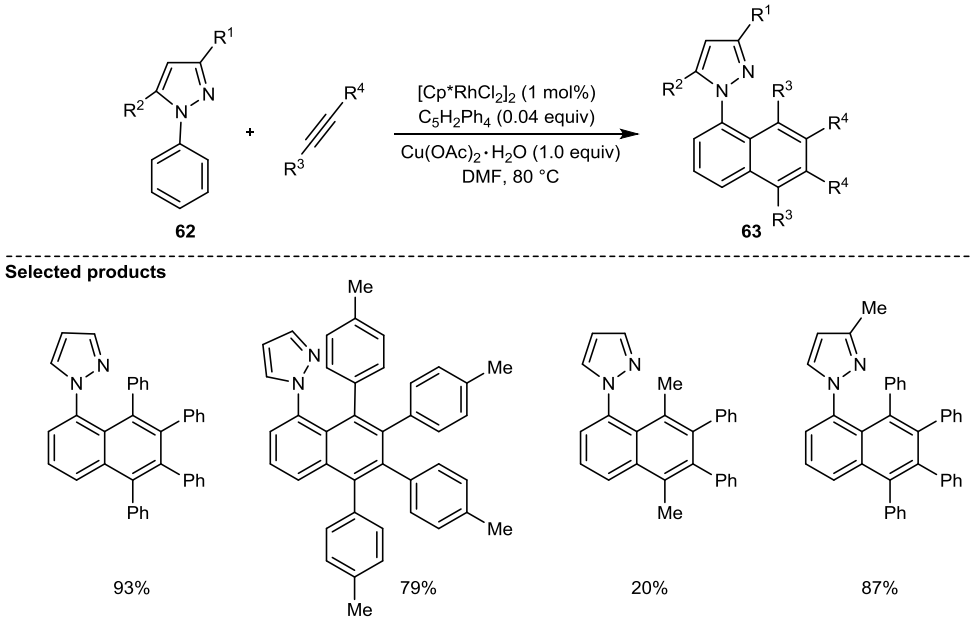


Figure 1.8. Proposed catalytic cycle for naphthalene formation.

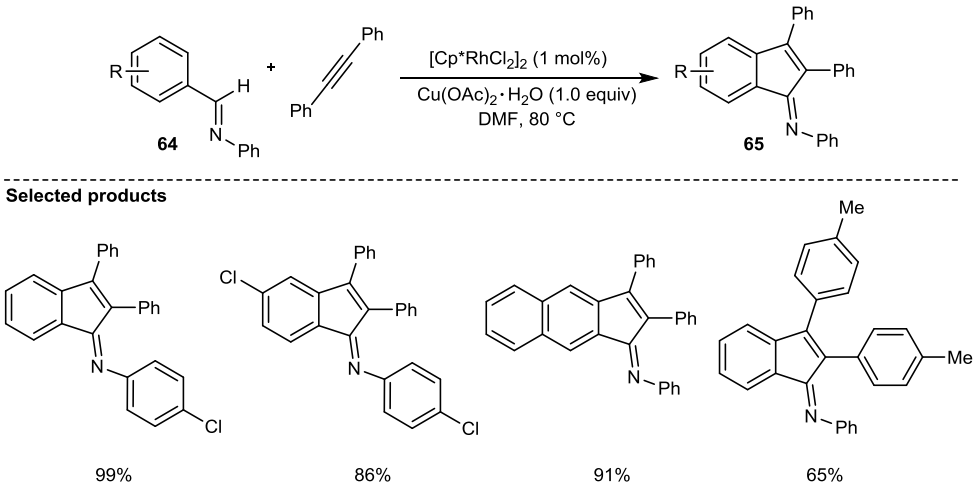
In a continuation of previous studies, the same research group demonstrated new findings that a heterocycle can function as an effective directing group. The use of phenylazoles **62** with internal alkynes under rhodium catalysis and a copper oxidant

produced 1,2,3,4-tetraarylnaphthalen-5-yl-azoles **63** with enhanced fluorescent properties. Furthermore, a suitable phenylazole substrate with four equivalents of an alkyne under similar reaction conditions afforded a highly fluorescent polyarylated anthracene (Scheme 1.12).[39] It is notable that the mechanistic steps for this annulation are consistent with those observed previously.[37]



Scheme 1.12. Synthesis of poly-aromatic compounds.

The research groups of Satoh and Miura, in a continuation of their previous studies, reported rhodium catalyzed oxidative annulation of aromatic imines **64** with internal alkynes. The reaction proceeded effectively *via* regioselective bond cleavage to provide indenone imine derivatives **65** which are valuable intermediates for medicines and organic materials (Scheme 1.13).[40]



Scheme 1.13. Synthesis of indenone imine derivatives.

The possible catalytic approach is illustrated in Figure 1.9. In the first step, coordination of the nitrogen atom of **64** to a Rh(III) species generates intermediate **66**. It is notable that this step is vital for the regioselective C–H bond cleavage. Then, alkyne insertion generates another seven-membered rhodacycle **67**, which on intramolecular insertion of the imino moiety forms **68**. Subsequently, reductive elimination provides access to product **65**. The copper species may be used to regenerate Rh(III) species by oxidation.

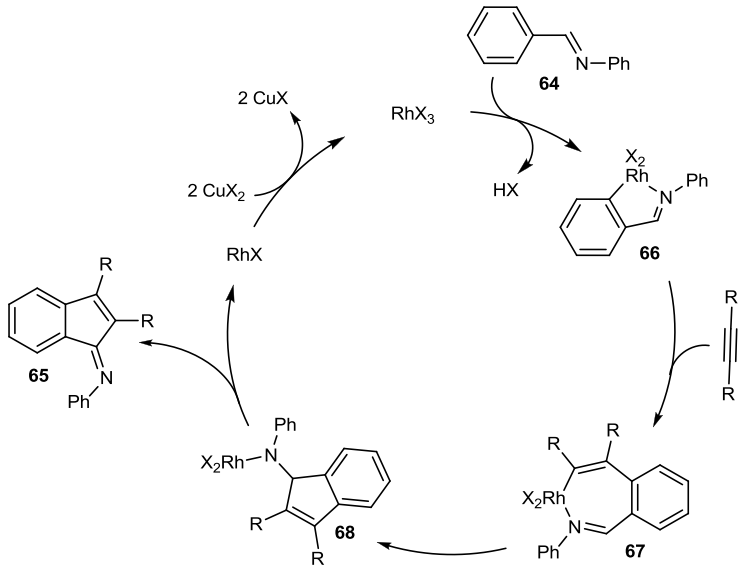
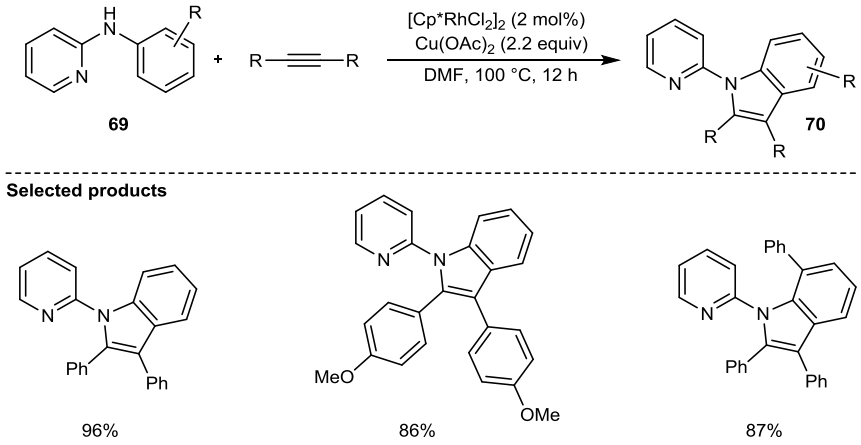


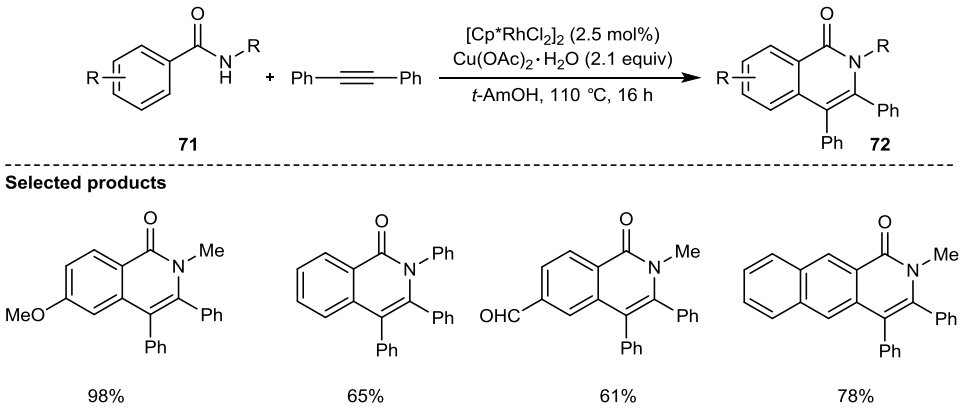
Figure 1.9. Proposed catalytic cycle for indenone imines.

In 2010, Li and co-workers have successfully demonstrated that *N*-aryl-2-aminopyridines **69** are suitable substrates for C–H activation reactions. They have used pyridine as a directing group for the oxidative coupling of these substrates with internal alkynes using $[Cp^*RhCl_2]_2$ as a catalyst and copper acetate as an oxidant. This cyclization furnished *N*-pyridyl substituted indoles **70** that may find applications in the costruction of complex molecules (Scheme 1.14).[41] A range of aminopyridine substrates with a broad substitution pattern was tolerated against a variety of alkynes. The bulkier substrates produced indoles in moderate yields and in case of *meta*-substituents, C–H functionalization occurred at the least sterically hindered position which was consistent with those observed previously in rhodium-catalyzed oxidative couplings.[42]



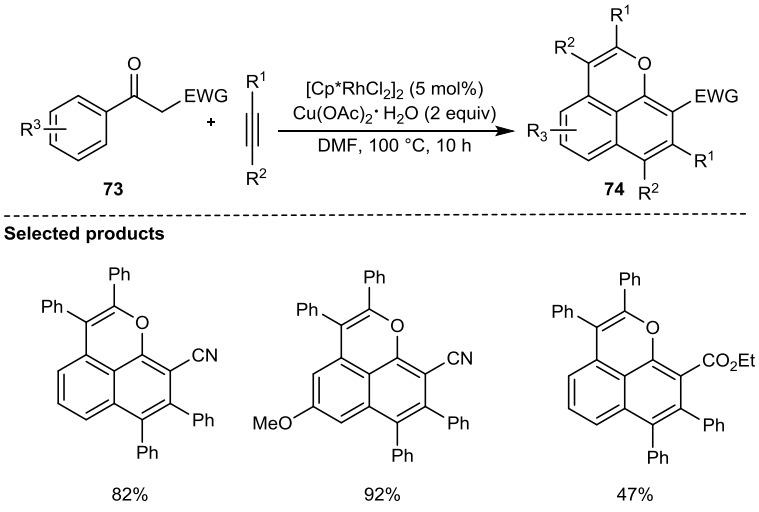
Scheme 1.14. Synthesis of *N*-aryl-2-aminopyridine compounds.

A wide range of isoquinolone derivatives **72** has been accessed by Hyster and Rovis *via* C–H/N–H activation of benzamides **71** and alkynes under rhodium catalysis using $Cu(OAc)_2$ as an oxidant. A variety of substrates with extensive substitution, and symmetrical as well as unsymmetrical alkynes were tolerated to understand the transformation mechanism and reasons for selectivity (Scheme 1.15).[43] The electron-rich tolanes produced compounds in good yield whereas electron-deficient systems were found to be little reluctant towards coupling reaction and gave compounds with moderate yields. Heteroaryl and aliphatic alkynes were also a part of the studies. With unsymmetrical alkynes, the reaction was highly regioselective producing only one isomer in good yield.



Scheme 1.15. Synthesis of isoquinolone derivatives.

In 2012, Wang and co-workers described the cascade oxidative annulation strategy involving benzoacetonitrile **73** and internal alkynes providing access to a number of substituted naphtho[1,8-*bc*]pyrans **74** through cleavages of sp^2, sp^3 and OH bonds under rhodium catalysis and using copper acetate as an oxidant. These cascade annulation reactions showed high levels of regioselectivity with unsymmetrical alkynes. Moreover, a number of these naphtho[1,8-*bc*]pyran derivatives exhibited intense fluorescence in the solid state (Scheme 1.16).[44]



Scheme 1.16. Synthesis of naphtho-pyran derivatives.

On the basis of previous findings related to metal catalyzed C–H functionalizations, they have proposed a possible catalytic cycle to access naphthopyran derivatives (Figure 1.10). Initially, C(sp^3)–H activation process affords a Rh-C(sp^3)–H intermediate **75**, which forms a five membered rhodacycle **76** by *ortho*-C(sp^2)–H

activation (**Path I**), followed by alkyne insertion into Rh-C(sp^2) or Rh-C(sp^3) bond leads to another seven-membered rhodacycle **77** or **78**, respectively. On the other hand, intermediate **75** has been suggested to afford a vinyl activation leading to intermediate **79** (**Path II**). Subsequently, aromatization-driven reductive elimination of **77** or **78** results 1-naphthol **80** as the first-step product. Furthermore, the annulation of 1-naphthol with alkyne adopts the same mechanistic steps as described in literature to afford product **74**.

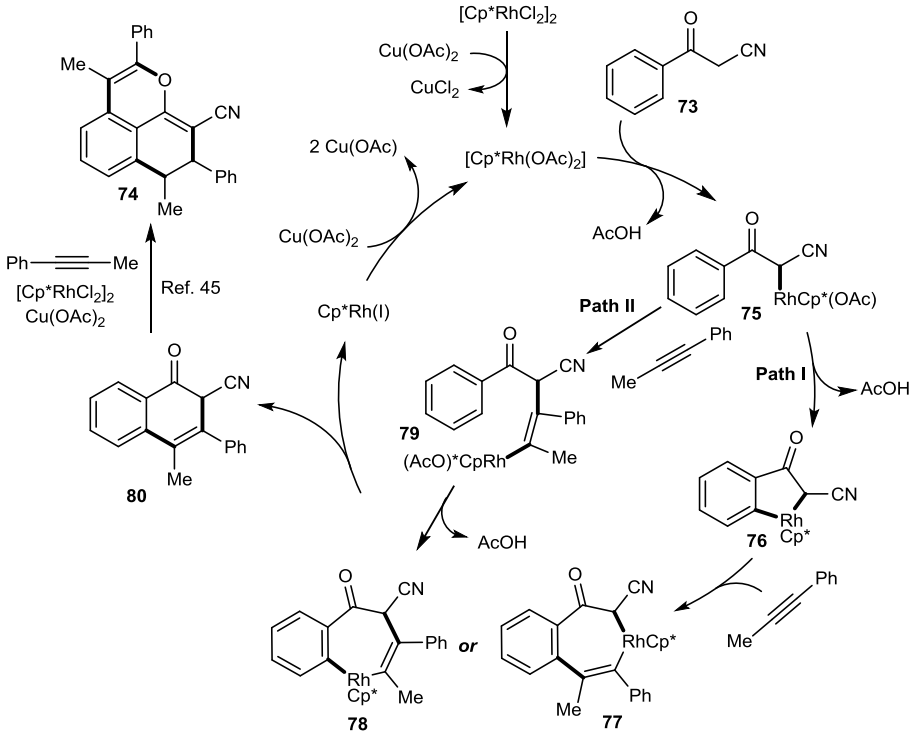
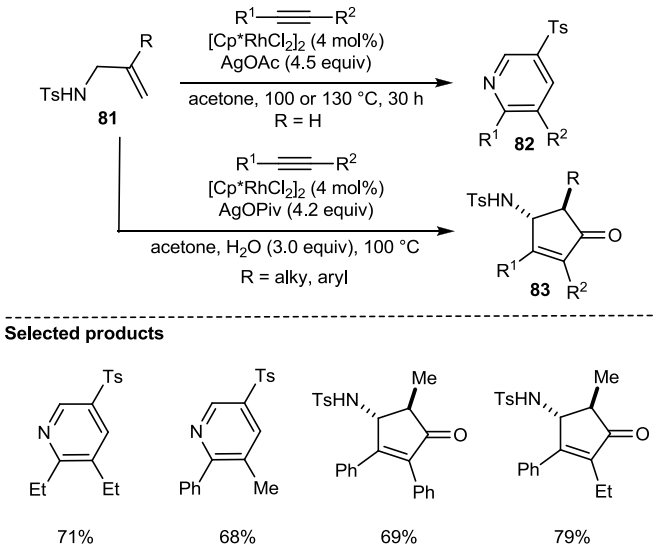


Figure 1.10. Proposed catalytic cycle for naphthopyran formation.

In the same year, the research group of Li developed the synthesis of sulfonylated pyridines **82** and cyclopentenones **83** through the oxidative coupling of *N*-ally arenesulfonamides **81** with internal alkynes under the action of rhodium catalysis.[46] The role of oxidant was found to be crucial for the reaction selectivity. When reaction was performed using AgOAc as an oxidant, pyridines were obtained as final products, whereas, use of AgOPiv led to cyclopentenones. The reaction was observed as highly selective and both the substrates provided broad scope of reactivity (Scheme 1.17). With optimal coupling conditions in hand, dialkyl-substituted alkynes were tolerated against *N*-allyl sulfonamides providing access to pyridine derivatives. When the unsymmetrical alkynes were employed, two separable regioisomers were obtained

which showed a slight preference of bulkier group to be distal to nitrogen. On the other hand, replacement of AgOAc with AgOPiv led to the formation of cyclopentenone derivatives **83** exclusively, with high regio- and diastereoselectivity.



Scheme 1.17. Synthesis of pyridine and cyclopentenone derivatives.

The proposed catalytic cycle for this coupling is illustrated in Figure 1.11, which involves the cyclometallation of **81** to produce five-membered rhodacycle **84** which on subsequent regioselective insertion of alkyne affords another seven-membered rhodium intermediate **85**. This rhodacycle can then proceed through two possible pathways. The pathway I involves the C–N reductive elimination to produce a dihydropyridine derivative **86** in the presence of small amount of Ag^{I} salt. The second pathway involves a *β*-hydride elimination of **85** in the presence of excess Ag^{I} salt to give cyclometalated imine **87** which on migratory insertion of the alkenyl rhodium ligand into the NTs imine produces a rhodium(III) hydride species **88**. At this stage, a second *β*-hydrogen-atom elimination produces intermediate **89** and a rhodium(III) dihydride species, which on oxidation regenerates the Rh(III) active catalyst. The intermediate **89** affords **90** on conjugate addition of water which on cyclopentadiene isomerization produce **91**. The final product **83** could be accessed from **91** by keto–enol tautomerization.

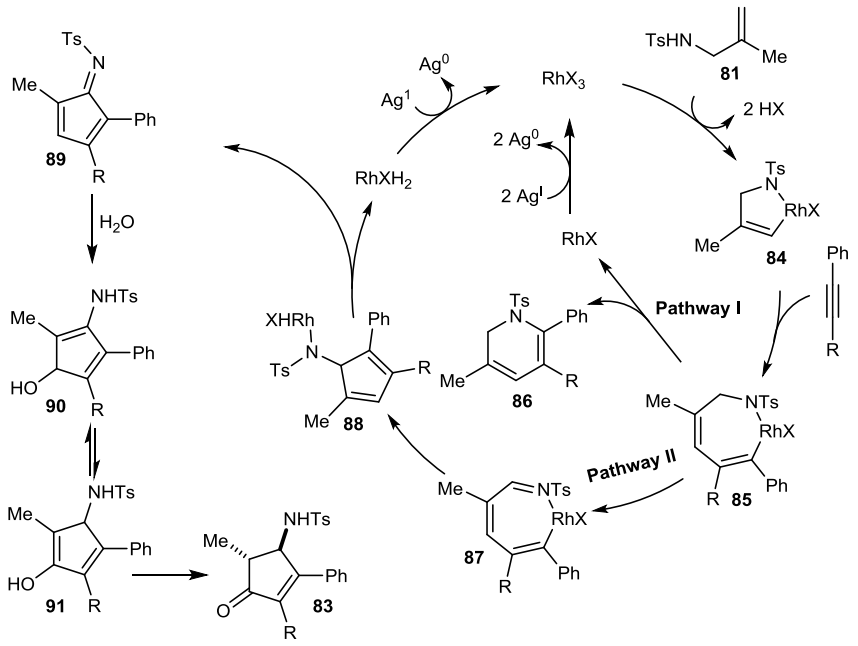
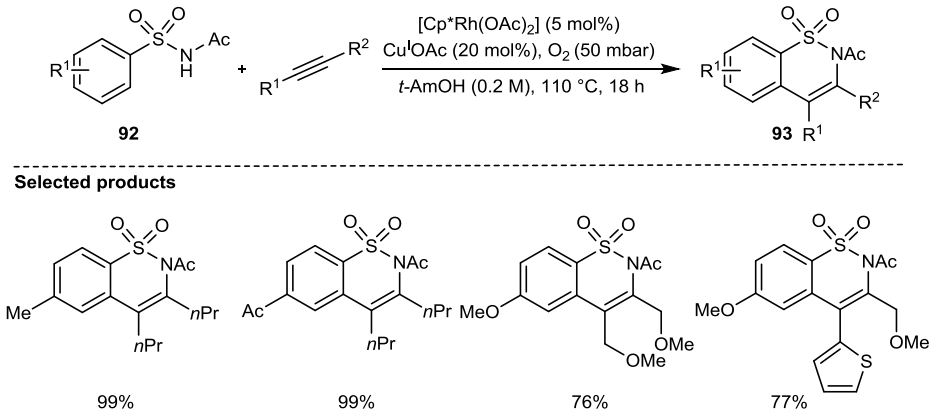


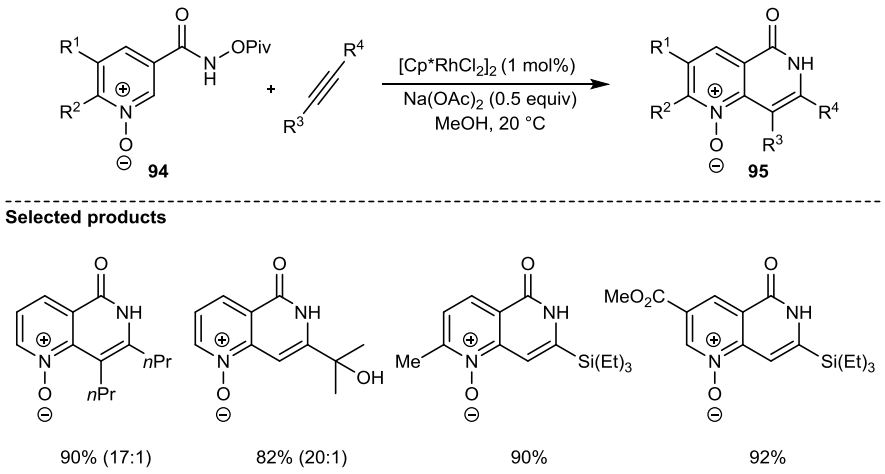
Figure 1.11. Proposed catalytic cycle for pyridine and cyclopentenone formation.

The research group of Cramer made use of acylated sulfonamides **92** as suitable directing groups for C–H functionalization under well-developed rhodium catalysis providing access to a range of structurally diverse aryl sultams **93** in good yields (Scheme 1.18).[47] The reaction was found to be compatible with electron-rich or electron-poor substituents as well as *ortho* and *meta* substitutions producing good results. On the other hand, a range of alkynes were also tolerated and the unsymmetrical alkynes displayed moderate to good regioselectivities.



Scheme 1.18. Synthesis of sultam derivatives.

Huckins *et al*. reported an efficient synthesis of naphthyridinone derivatives **95** catalyzed by Rh(III)-catalyst using nicotinamide *N*-oxides **94** as substrates. This process relies on a double-activation and directing approach affording heterocyclic products in high yields and selectivities using low catalyst loadings under mild reaction conditions (Scheme 1.19).[48] The scope and generality of this method was explored using a range of substituents on the nicotinamide core. The electronic nature of a substituent at the 5-position of the ring had little effect on the outcome of the reaction, providing heterocyclic products in good yield and ≥20:1 regioselectivity. Electron-donating and electron-withdrawing substituents were also tolerated delivering desired products with no effect on the yields. On the other hand, this process proved to be general for a variety of terminal and internal alkynes to afford naphthyridinone *N*-oxides in good yields.



Scheme 1.19. Synthesis of naphthyridinone *N*-oxide derivatives.

A possible catalytic cycle for this annulation is illustrated in Figure 1.12. Initially, C–H activation at the 2-position of the *N*-oxide ring of **94** afforded five-membered metallacycle **96**. Regioselective alkyne insertion into the Rh–C bond would then provide another rhodacycle **97**, which on reductive elimination gave the naphthyridinone *N*-oxide product **95** with concomitant N–O bond cleavage to re-oxidize the rhodium species.

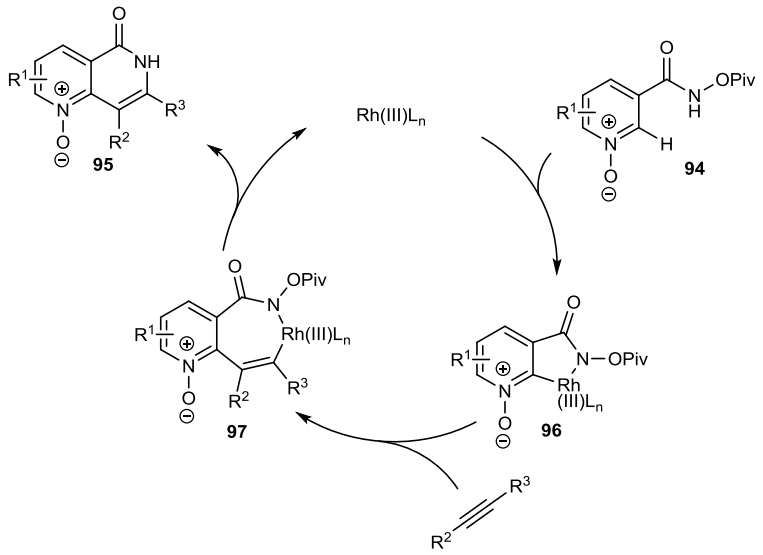
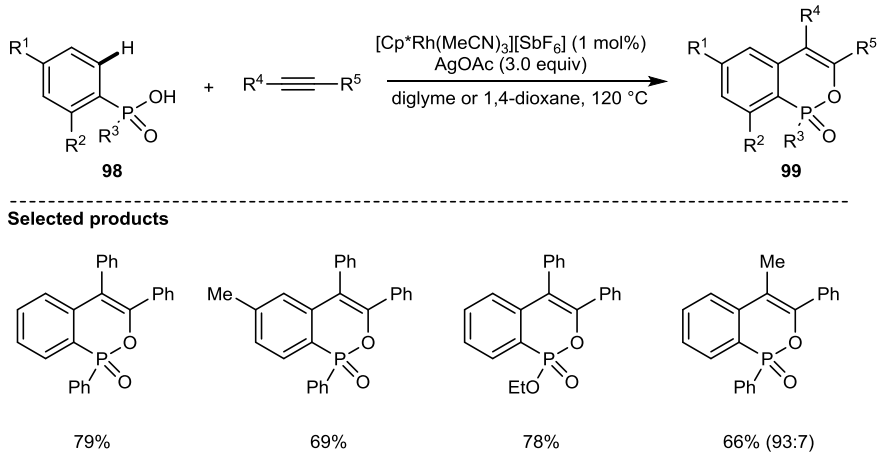


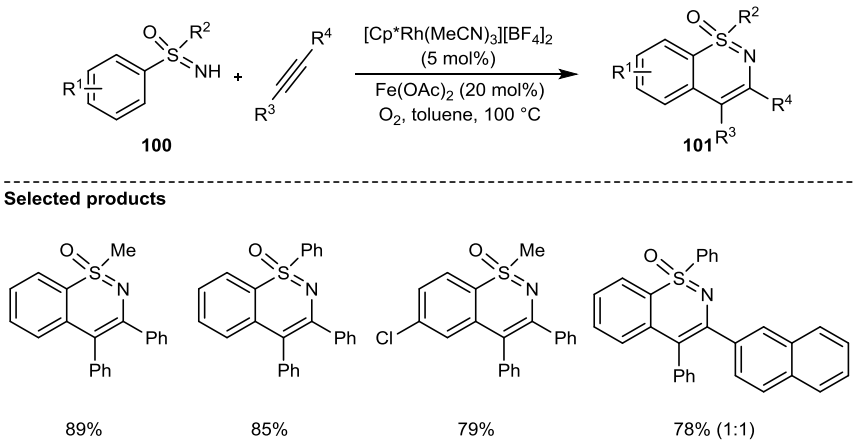
Figure 1.12. Proposed catalytic cycle for naphthyridinone *N*-oxide formation.

The research group of Satoh and Miura developed an efficient protocol for the synthesis of phosphaisocoumarins **99** by the rhodium-catalyzed oxidative annulation of phenylphosphonic acid derivatives **98** with internal alkynes (Scheme 1.20).[49] The scope of the reaction was explored using various phenylphosphonic acids with alkynes. Bis(*para*-substituted phenyl)phosphinic acids also underwent annulation with alkyne to afford the corresponding phosphaisocoumarins in good yields. The reaction of phenylphosphonic acid monoethyl ester also proceeded smoothly to give corresponding heterocycle in 78% yield.



Scheme 1.20. Synthesis of phosphaisocoumarin derivatives.

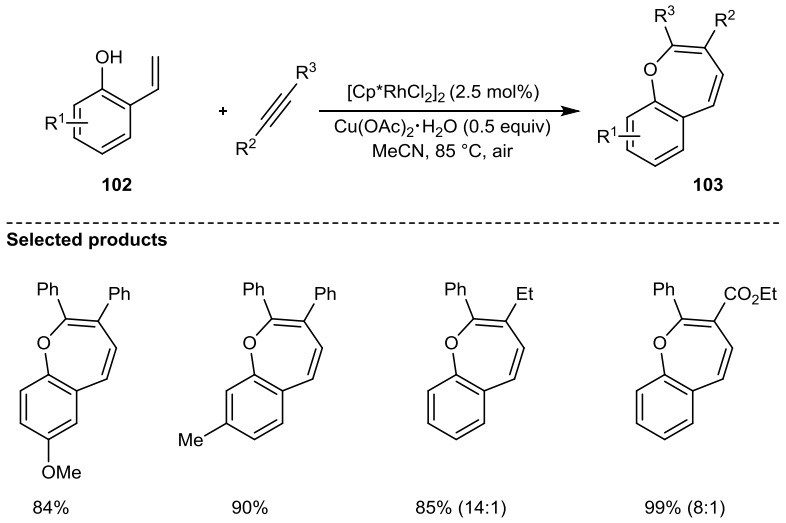
In 2013, Bolm and co-workers demonstrated the synthesis of 1,2-benzothiazines **101** from sulfoximines **100** and alkynes under a rhodium-catalyzed system involving the combination of simple $Fe(OAc)_2$ and O_2 as an oxidant (Scheme 1.21).[50] The scope of this process was evaluated by treating substituted sulfoximines with diphenyl acetylene under the optimized reaction conditions. In general, all transformations proceeded well to afford the corresponding 1,2-benzothiazines in 72–89% yield. The reaction of the *meta*-substituted sulfoximine revealed high regioselectivity in favor of activation of the least hindered C–H bond to provide the two regioisomers in a 90:10 ratio in 88% combined yield. Other alkynes were also tolerated in this process and proved to be the good reaction partners.



Scheme 1.21. Synthesis of 1,2-benzothiazine derivatives.

Mascareñas and co-workers have developed the first example of a metal-catalyzed (5 + 2) cycloaddition involving a C–H activation process. The method provides a fast, efficient, and practical route to benzoxepines **103** using commercial or readily available *o*-vinylphenols **102** and alkynes as starting materials (Scheme 1.22).[51] Having optimized conditions, the scope of this annulation with regard to alkyne and phenol components was then explored. A wide range of symmetrical alkynes bearing electron-rich or electron-deficient aryl substituents afforded the desired products in good yields. Dialkyl-substituted alkynes also participated in a similar manner, but the obtained products were in slightly lower yields. The reaction with unsymmetrical aryl-alkyl alkynes was highly regioselective, leading to products in which the phenyl group is in the carbon tethered to the oxygen group of the product. On the other hand, the reaction is also compatible with a wide range of substituents in the aryl group of

the vinylphenol. In addition, replacement of the alkyne component by carbon monoxide allows assembly of coumarin derivatives in a straightforward fashion.



Scheme 1.22. Synthesis of benzoxepine derivatives.

The proposed catalytic cycle is outlined in Figure 1.13. The process starts with the phenolic substrate **102** replacing one of the acetates of the catalyst **104** to give intermediate **105**.[52,53] This complex might lead to the rhodacycle **107** either through a concerted metalation-deprotonation step (CMD) or by an intramolecular electrophilic attack of the conjugated alkene to the electrophilic rhodium(I) followed by a base-assisted deprotonation to yield the re-aromatized intermediate **107**. Alkyne coordination to the intermediate **107**, followed by migratory insertion then afforded intermediate **108**, which on reductive elimination give the final product **103** and a Rh(I) species **109** which is then reoxidized to generate active Rh species **104**.

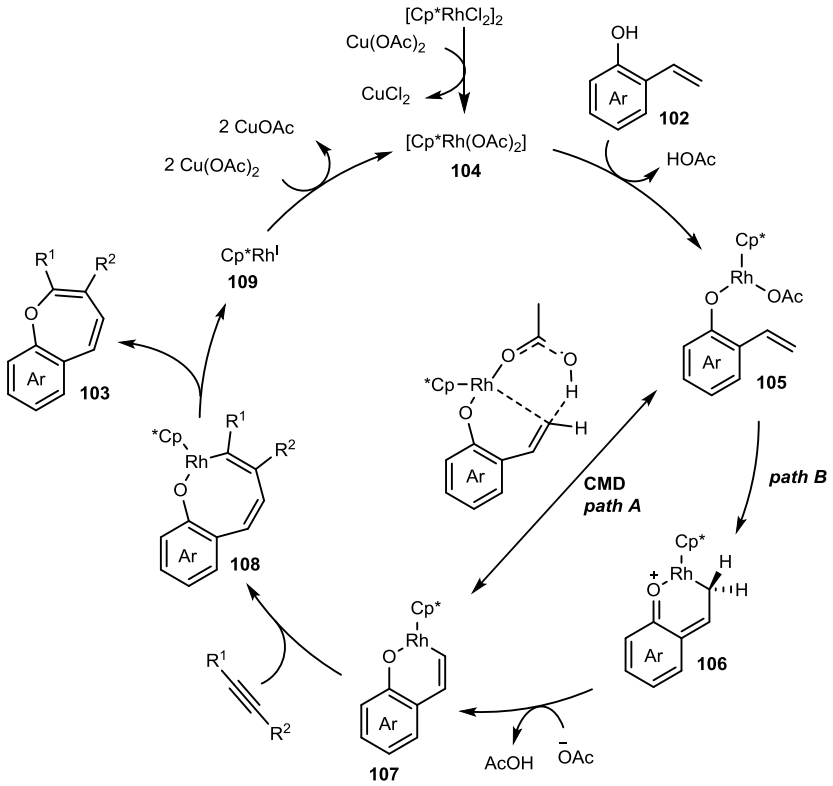
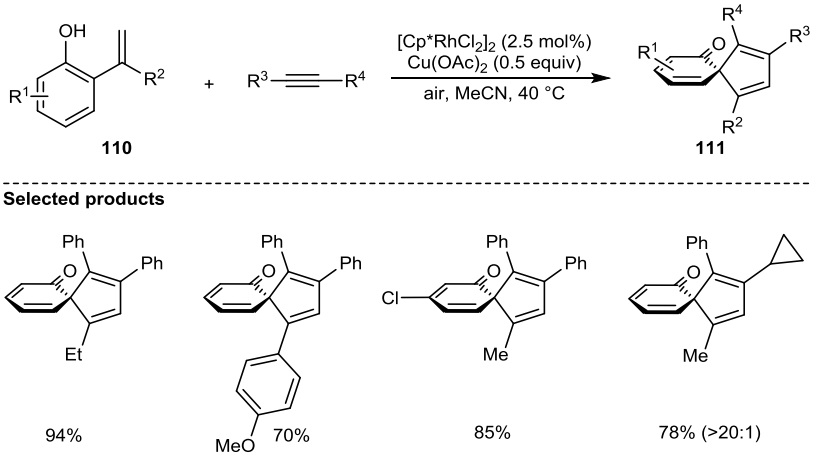


Figure 1.13. Possible catalytic cycle for benzoxepine formation.

In another study, Mascareñas and Lam research groups independently investigated the dearomatizing oxidative annulation of 2-alkenylphenols **110** with alkynes and enynes, respectively. This transformation proceeds with high yields and regioselectivities under Rh(III) catalysis. The process involves the cleavage of the terminal C–H bond of the alkenyl moiety and the dearomatization of the phenol ring, providing a versatile and efficient approach to spirocyclic skeletons **111** (Scheme 1.23).[54,55] Scope of this reaction was assessed using both symmetrical and unsymmetrical alkynes bearing electron-rich or electron-deficient aryl substituents which led to the expected products in good yields. Similar results were obtained with symmetrical dialkyl-substituted alkynes. In case of nonsymmetrical alkynes, the reaction produced spirocyclic products with high regioselectivity (>20:1). The scope of reaction with respect to alkenylphenol was also examined. Several substituents such as methyl, ethyl, phenyl or other aromatic groups at internal position of alkene were tolerated affording desired products in good yields. Substrates with various substituents on the phenol moiety were also found to be the competent partners.



Scheme 1.23. Synthesis of spirocyclic products.

A proposed catalytic pathway for this process is presented in Figure 1.14. Rhodium diacetate complex **104** is formed by the reaction of $[Cp^*RhCl_2]_2$ with $Cu(OAc)_2$ which on phenol-directed C–H functionalization of the alkene of the substrate **110** affords rhodacycle **112**. Coordination and migratory insertion of the alkyne gave another seven-membered rhodacycle intermediate **113**. Here, if the substituent R^1 = H, benzoxepine **103** is accessed by a C–O bond-forming reductive elimination of intermediate **113**, as reported previously.[51] Otherwise, when $R^1 \neq$ H, the rhodacycle **114** is formed by the isomerization of **113**, by relieving an unfavorable steric interaction between R^1 and the phenoxide ring, which on C–C bond-forming reductive elimination gives the spirocyclic enone product **111** along with Cp*Rh(I) **109**, which may be re-oxidized by $Cu(OAc)_2$ to regenerate **104**.

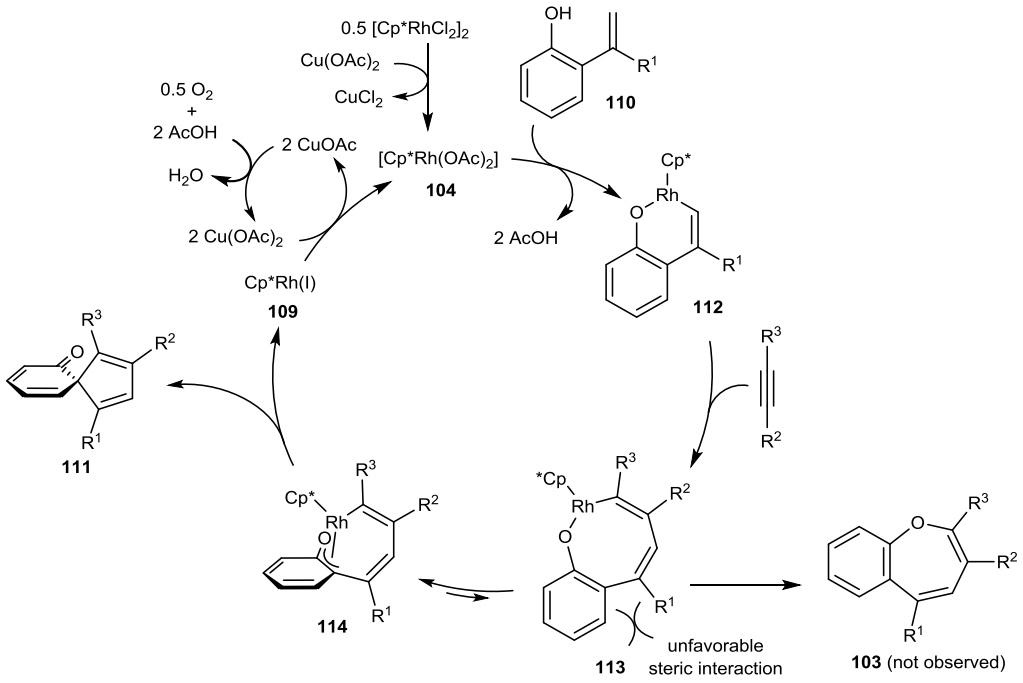
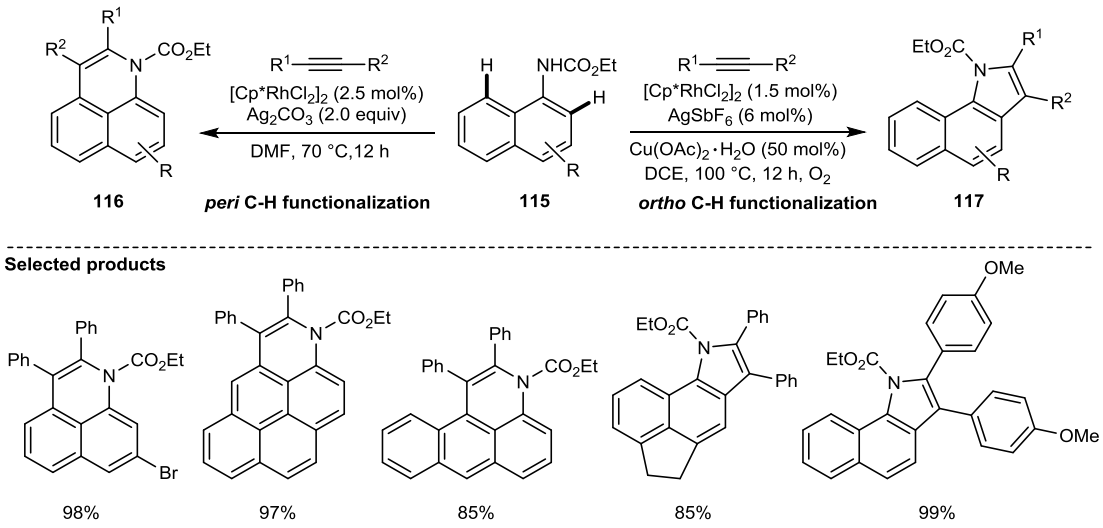


Figure 1.14. Proposed catalytic cycle for spirocyclic compound **111**.

Jin and co-workers reported a facile and unique mode of naphthylcarbamates **115** for the regioselective C–H functionalization involving alkynes as coupling partners under Rh(III)-catalysis. The process undergoes *peri*-C–H bond functionalization of arylcarbamates to give benzoquinoline compounds **116** when neutral rhodium catalyst system is employed, whereas, *ortho*-C–H functionalization affords benzoindole derivatives **117** with cationic rhodium catalyst (Scheme 1.24).[56]



Scheme 1.24. Synthesis of benzoquinoline and benzoindole compounds.

First, scope of *peri*-C–H functionalization with a range of substrates and internal alkynes was investigated and the results demonstrated the good functional group tolerance affording corresponding benzoquinoline derivatives in good yields. The reaction also tolerated ethyl quinolin-5-ylcarbamate, producing the benzo[*ij*][2,7]naphthyridine product in 64% yield under the prolonged reaction time (48 h). It is also worth noting that the process is also applicable to the larger aromatic substrates like fluoranthen-3-ylcarbamate, anthracen-1-ylcarbamate, and pyren-1-ylcarbamate yielding the desired products in higher yields.

Next, the scope was extended to the various arylcarbamates which afforded benzoindole products through *ortho*-C–H functionalization. Pleasingly, the reaction was found to be tolerant of a diverse variety of substituents including electron-donating and electron-withdrawing groups on naphthyl ring and desired products were obtained in high yields. The reaction of polycyclic arylcarbamates with alkyne also proceeded smoothly to produce the resulting polyheterocycles in good to high yields with exclusive selectivity. The key mechanistic step for the regioselective formation of products involve the coordination of neutral Rh(III) complex preferentially to the *N*-atom of carbamate **115** generating a Rh(III)-amine complex,[57] followed by cyclorhodation at the *peri*-C–H bond to afford a five-membered azarhodacycle **118**. Whereas, the cationic Rh(III) complex coordinates to the Lewis basic carbamate oxygen prior to nitrogen presumably due to the Lewis acidity of the Rh(III) catalyst,[46] generating intermediate **119**, followed by cyclorhodation at the *ortho*-C–H bond as depicted in Figure 1.15.

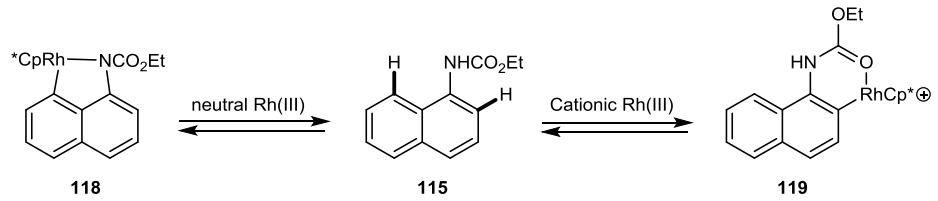
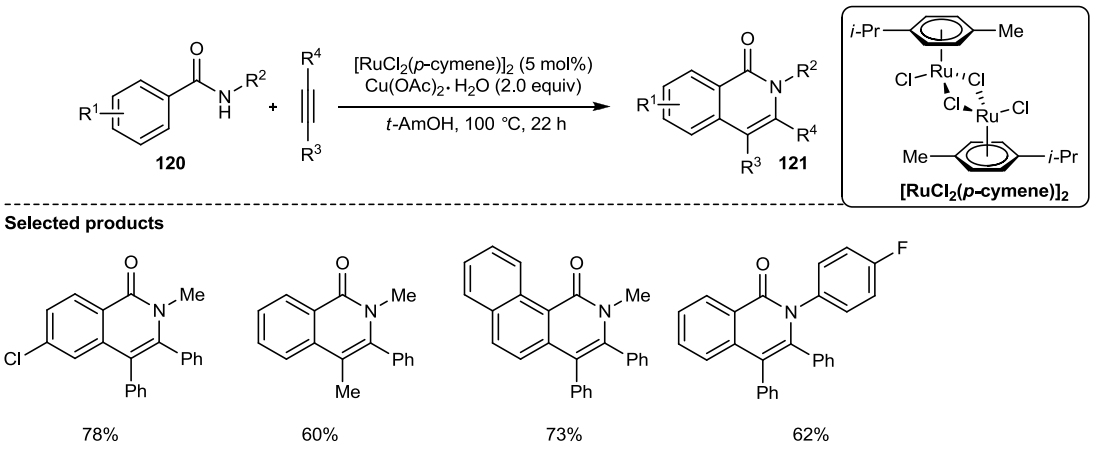


Figure 1.15. Proposed intermediates involved in the regioselective synthesis of benzoquinoline and benzoindole compounds.

1.2.1.5. Ruthenium-Catalyzed Oxidative Annulation of Alkynes

In 2011, the research group of Ackermann developed the first oxidative annulation of internal alkynes with benzamides **120** to access isoquinolones **121** under ruthenium catalysis (Scheme 1.25).[58] The reaction provides ample scope with remarkable high chemo- and regioselectivity. With the standard conditions in hand, a range of aryl-substituted benzamides were tolerated to establish the scope of reaction. Furthermore, *N*-alkyl, *N*-benzyl or *N*-aryl derivatives were also compatible under optimized reaction conditions. Similarly, heteroaromatic benzamides were also found to be viable for this coupling.



Scheme 1.25. Synthesis of isoquinolone derivatives.

Based on mechanistic studies, they proposed the ruthenium-catalyzed oxidative annulation to proceed by an initial intermolecular carboruthenation of alkyne *via* rate-limiting acetate-assisted C–H bond ruthenation to form **123**. Subsequent intramolecular oxidative C–N bond formation gave the desired product **121**.

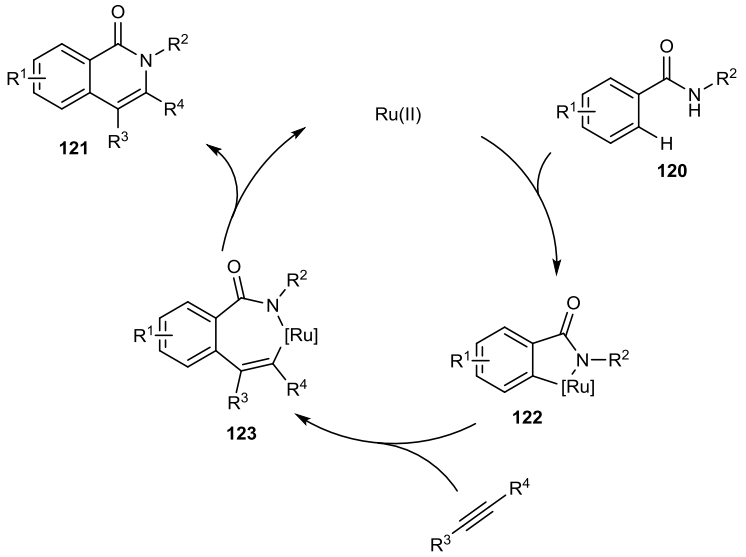
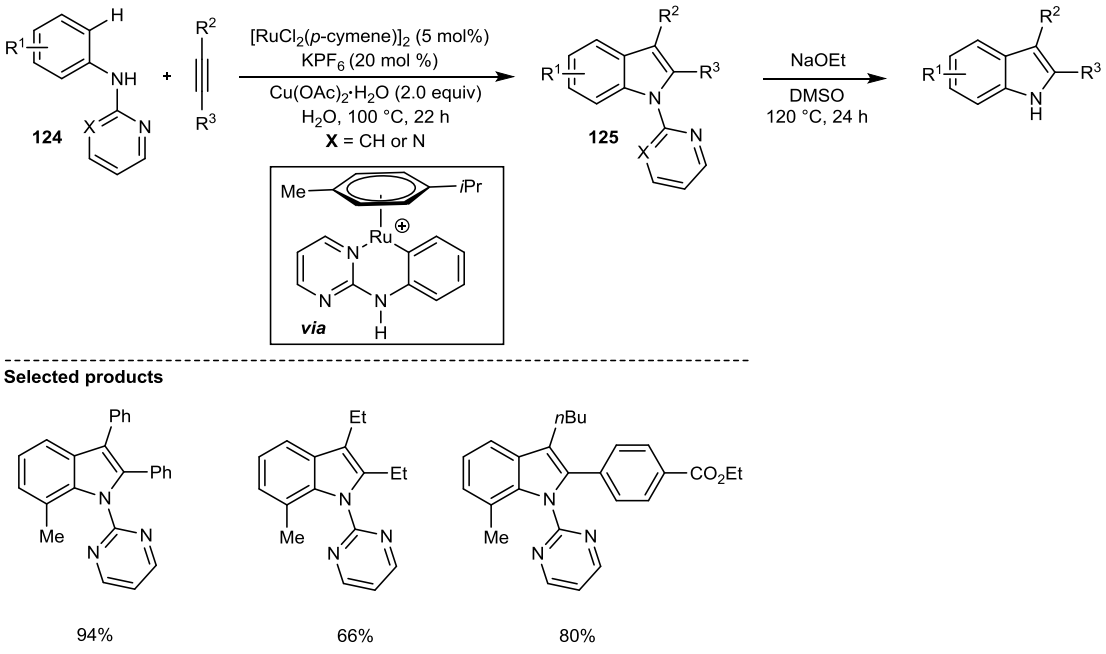


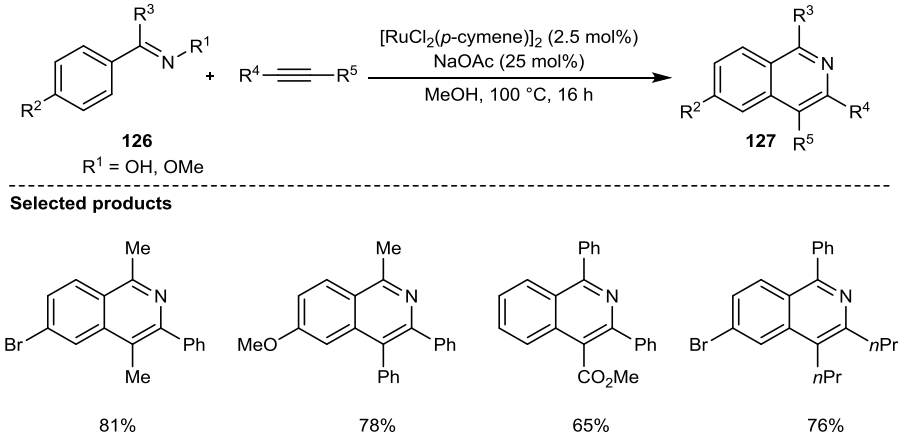
Figure 1.16. Proposed catalytic cycle for isoquinolone formation.

In 2012, Ackermann and Lygin reported the first efficient synthesis of indole derivatives **125** involving internal alkynes and anilines **124** bearing removable directing groups, catalyzed by cationic ruthenium catalyst. The reaction provides ample substrate scope using water as a solvent (Scheme 1.26).[59] The mechanistic studies indicated that the reaction involves the six membered ruthenacycle as a key intermediate.



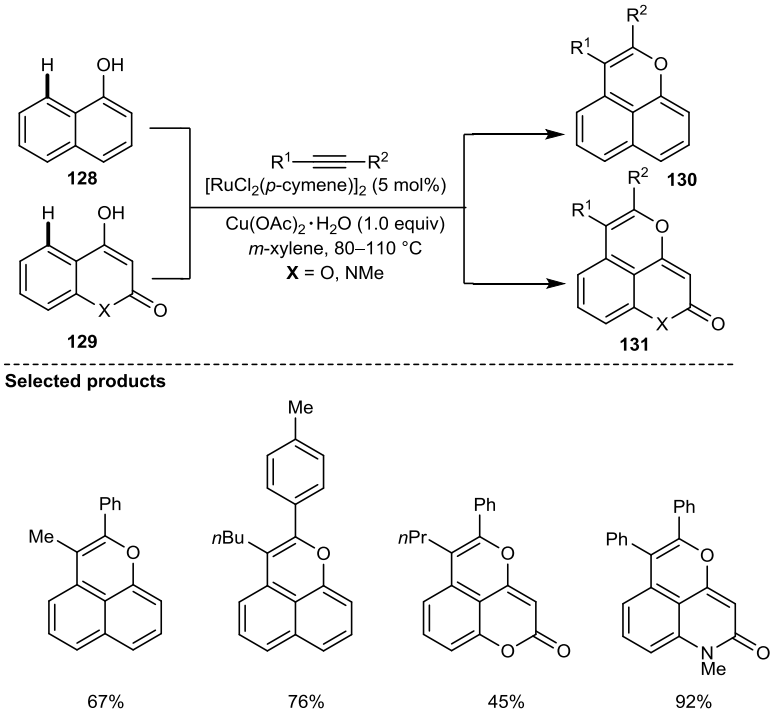
Scheme 1.26. Synthesis of indole derivatives.

In another study, the research group of Jeganmohan demonstrated an inexpensive ruthenium-catalyzed coupling of substituted ketoximes **126** with internal as well as terminal alkynes in a highly regioselective manner to afford the isoquinoline derivatives **127** (Scheme 1.27).[60] A range of ketoximes with a wide substitution pattern was found to be compatible for this cyclization reaction. On the other hand, the effect of changing the methyl group in acetophenone oxime with other groups like ethyl, isopropyl and phenyl were also investigated. In addition, alkyne scope was also studied. The reaction was found to be highly regioselective when unsymmetrical alkynes were used and cyclization takes place at sterically more accessible site exclusively. The mechanistic studies performed for this cyclization were consistent with those observed previously.[58]



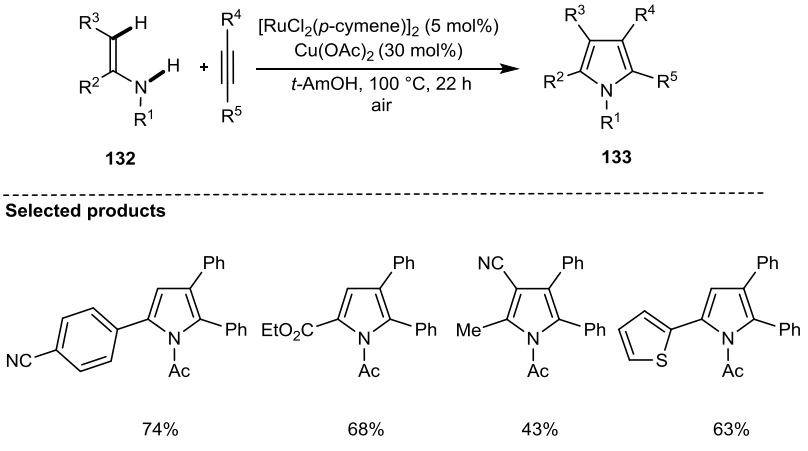
Scheme 1.27. Synthesis of isoquinoline derivatives.

Ackermann and co-workers reported the first inexpensive ruthenium-catalyzed oxidative annulation of internal alkynes with naphthols **128** and **129** through hydroxyl assistance to deliver fluorescent pyrans **130** and **131** (Scheme 1.28).[61] With the optimized catalytic conditions in hand, a range of diversely decorated naphthols were able to undergo coupling reactions. This process displayed a remarkable tolerance of a large number of substituents. Apart from naphthols, 4-hydroxycoumarin and 4-hydroxyquinoline were also examined under the same set of reaction conditions affording annulated products in good yield.



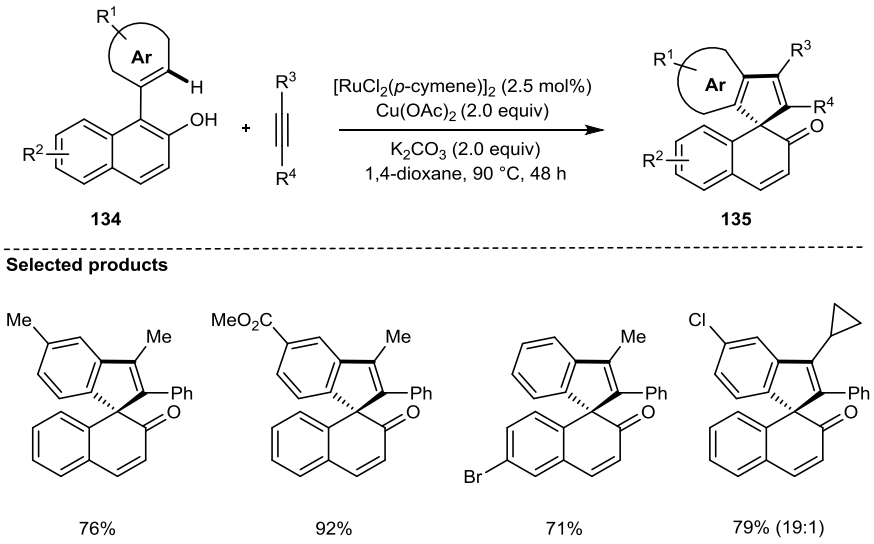
Scheme 1.28. Synthesis of pyran derivatives.

In 2012, Wang and Ackermann reported a versatile synthesis of diversely decorated pyrrole derivatives **133** by the oxidative coupling of electron-rich enamines **132** and internal alkynes under efficient ruthenium catalysis. This C–H/N–H functionalization strategy provided access to pyrrole in the presence of $Cu(OAc)_2$ and air as an oxidant (Scheme 1.29).[62] The scope of this annulation was assessed by making use of numerous electrophilic functional groups including esters, bromo, vinyl, cyano and nitro substituents and gave the desired products in good yields.



Scheme 1.29. Synthesis of pyrrole derivatives.

In 2013, Luan and co-workers reported the first example of intermolecular annulation reactions of 1-aryl-2-naphthols **134** with internal alkynes under ruthenium catalysis using $Cu(OAc)_2$ as an oxidant. The process efficiently generates a library of spirocyclic compounds **135** involving the dearomatization of naphthyl ring (Scheme 1.30).[63] An additional advantage of this method is the formation of an all-carbon quaternary stereocenter in addition to the wide range of functional group tolerance ability. The envisioned oxidative annulation strategy was used to explore the scope of reaction under optimized reaction conditions. Initially, the substituent pattern on naphthol ring was investigated which afforded a number of spirocyclic products in good yields (up to 96%) with excellent levels of regioselectivity in case of unsymmetrical alkynes. A range of substituents including electron-rich and electron-deficient groups on phenyl ring were also taken into account. It is also noteworthy to mention that the replacement of phenyl ring with heteroaryl group did not affect the reaction and products with good yields are obtained. Furthermore, the scope of alkynes with symmetrical as well as unsymmetrical substitution pattern was explored and satisfactory results were obtained.



Scheme 1.30. Synthesis of spirocyclic compounds.

The proposed mechanistic pathway starts with the initial deprotonation and irreversible C–H bond cleavage of substrate affording a six-membered ruthenacycle **136**. The coordination and regioselective migratory insertion of alkyne then produced an eight-membered intermediate **137** which on enol-keto tautomerization of the

phenol ring delivered intermediate **138**. Finally, reductive elimination affords the desired product **135** with concomitant regeneration of Ru(II) catalyst (Figure 1.17).

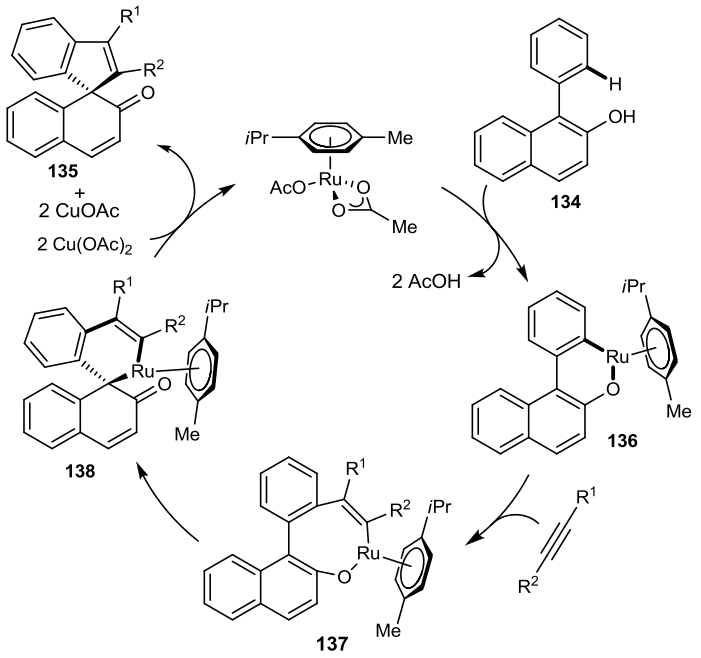
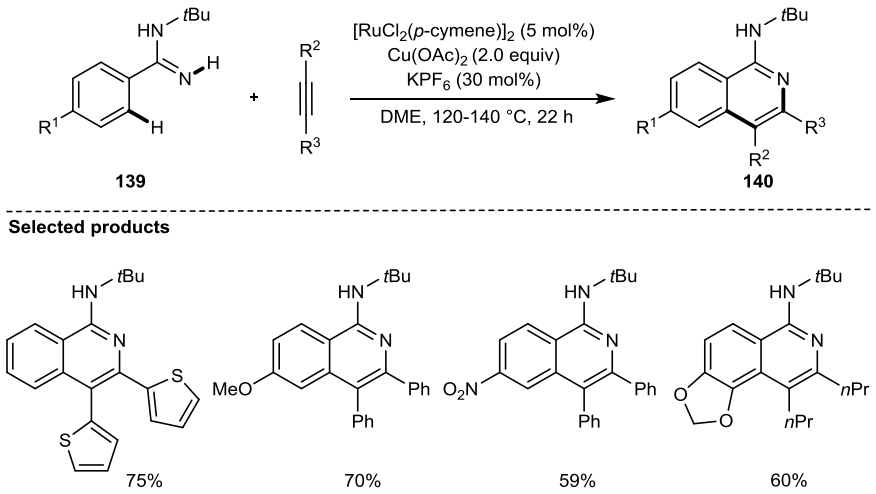


Figure 1.17. Proposed catalytic cycle for spirocyclic product formation.

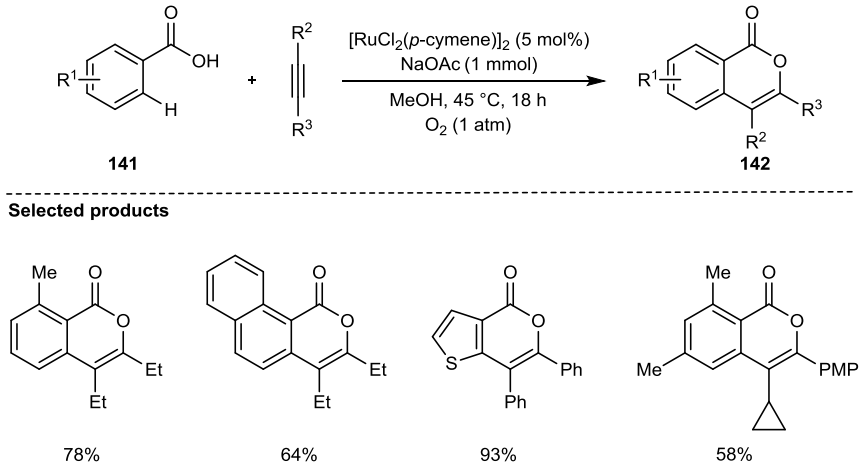
Ackermann and co-workers developed a facile procedure for the synthesis of 1-aminoisoquinolines **140** using amidines **139** and internal alkynes under ruthenium catalysis (Scheme 1.31).[64] This oxidative process was found to be tolerant of diverse functional groups providing desired products in good yields. Based on the optimization studies, they identified a ruthenium(II) *p*-cymene complex with KPF_6 and $Cu(OAc)_2$ as an oxidant works best in DME solvent at 120 °C. Under these set of optimal conditions, they further explored the scope of amidines and internal alkynes. A careful investigation revealed that the arylalkynes bearing various functional groups were tolerated in addition to the alkynes with heteroaryl functional groups. Moreover, this process also afforded desired isoquinolines when symmetrically alkyl substituted alkynes were used as coupling partners. In the case of unsymmetrical alkynes, the corresponding products were obtained in high regioselectivity with the initial C–H functionalization occurring at the sterically least hindered site. With regard to the amidines scope, several useful electrophilic functional groups like nitro, fluoro, chloro, bromo, and iodo were well investigated using ruthenium catalyst. The sterically hindered substrates produced compounds with lower yields. Also, it is

noteworthy to mention that the heterocycles based substrates were also viable starting materials for C–H/N–H functionalization process delivering the corresponding products in moderate yields.



Scheme 1.31. Synthesis of aminoisoquinolines.

Very recently, the same group described an aerobic oxidative C–H functionalizations of benzoic acids **141** using ruthenium(II) biscarboxylates under ambient oxygen or air as an oxidant. This process is advantageous in terms of step- and atom-economy liberating water as the only by-product (Scheme 1.32).[65] Initially, the oxidative C–H/O–H functionalization of 2-methylbenzoic acid with diphenylacetylene occurred in a variety of solvents delivering isocoumarin product **142** but methanol was identified as the best and optimal solvent. Under optimized reaction conditions, the general applicability of this aerobic oxidative annulation was tested and the *in-situ* generated ruthenium(II) biscarboxylate complex broadly tolerated *ortho*-, *meta*-, and *para*-substituted benzoic acids with good conversion to the corresponding isocoumarin products. Several electrophilic substituents like bromo, iodo and amino groups on aryl ring were well tolerated in addition to the heteroaromatic substrates like indoles, thiophenes and furans. In addition, alkynes were also well employed and in case of unsymmetrical alkynes, the desired products were obtained with high levels of regioselectivity placing the aliphatic substituents distal to the oxygen heteroatom.



Scheme 1.32. Synthesis of isocoumarin derivatives.

The proposed mechanistic cycle for the aerobic oxidative annulation initiates with the formation of ruthenium(II) bisacetate complex **143** which on C–H activation of benzoic acid generates ruthena(II)cycle **144** with two equivalents of acetic acid. Subsequent coordination and migratory insertion of an alkyne delivered the seven-membered ruthena(II)cycle **145,**[66] which on reductive elimination yielded the ruthenium(0) sandwich complex **146**. The re-oxidation of this species generates the desired product along with the liberation of H_2O as sole by-product (Figure 1.18).

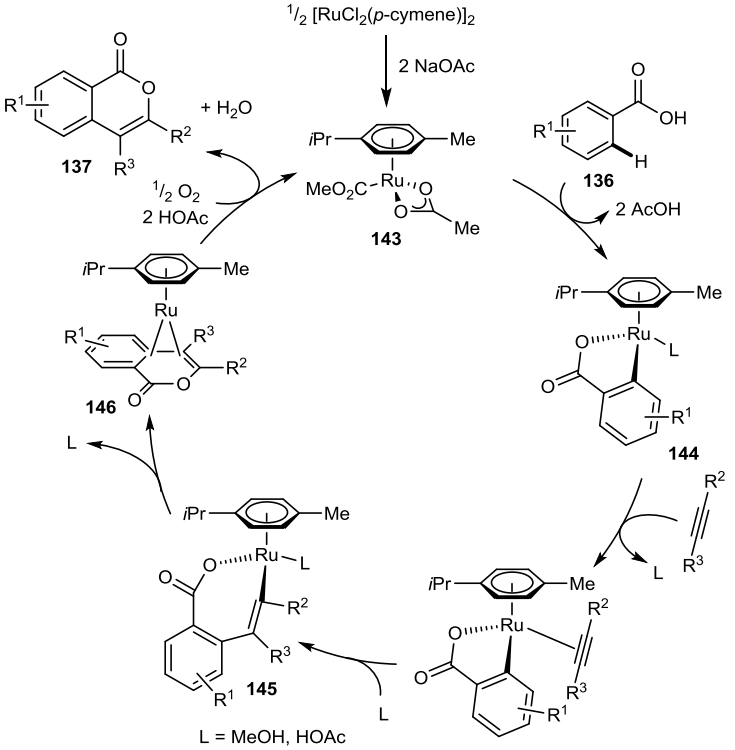
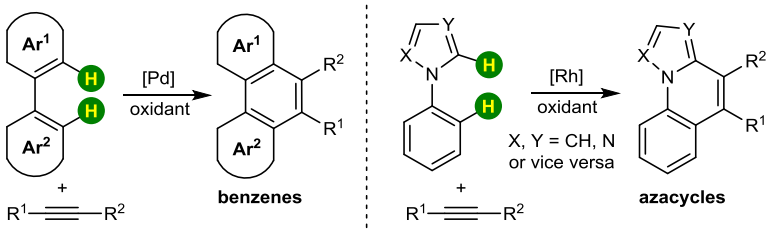


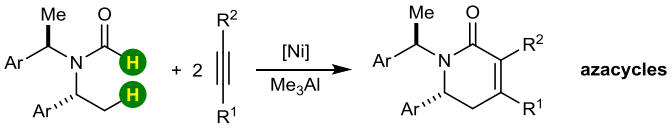
Figure 1.18. Proposed mechanism for isocoumarin formation.

1.3. Aims and Objectives

The activation and subsequent functionalization of aromatic C–H bonds attached to directing groups has emerged as a growing area of research.[67] A wide range of functional groups such as amides, anilides, ketones, imines, azoles, phenols, carbamates, and carboxylic acids were reported, focusing on the utility of the same C–H functionalization concept.[37,43,44,50,60,68] In addition, alkyne oxidative annulation reactions are effective in forming aromatic carbo- and azacycles (Scheme 1.33), the scope and utility of the general process would be considerably enhanced if variants involving the functionalization of C(sp^3)–H bonds could be developed, resulting in partially saturated cyclic products. However, progress in this area has been limited. The only existing report comes from the group of Nakao and Hiyama,[69] who described the oxidative annulation of formamides with alkynes, in which an extra equivalent of alkyne acts as the stoichiometric oxidant (Scheme 1.34). Also, during the course of our investigations, Wang and co-workers published a cascade oxidative annulation strategy using sp^2, sp^3 and OH bonds leading to naphtho[1,8-*bc*]pyran products (Scheme 1.16).[44]



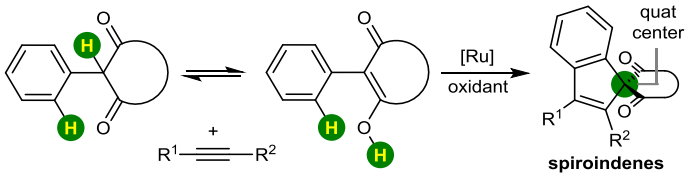
Scheme 1.33. Alkyne oxidative annulations by double C(sp^2)–H bond cleavage.



Scheme 1.34. Alkyne oxidative annulation by C(sp^3)–H/C(sp^2)–H bond cleavage.

In view of these fascinating results, we looked to develop a new mode of catalytic alkyne oxidative annulation involving the (formal) functionalization of one C(sp^3)–H bond and one C(sp^2)–H bond. At the outset of this work, we hypothesized that *α*-arylcarbonyl compounds might be suitable substrates for alkyne oxidative annulations by virtue of the acidic nature of the *α*-protons; deprotonation would generate an

enolate that could serve as an efficient directing group for C(sp^2)–H bond cleavage. 2-Aryl cyclic 1,3-dicarbonyl compounds were selected for investigation on the basis of their high acidity and the permanent close proximity of the aryl and carbonyl groups. This latter feature renders these substrates conformationally predisposed for cyclometallation, forming a six-membered metallacycle in readiness for migratory insertion of the alkyne and spiroindene formation. This ruthenium-catalyzed process would result in the formation of indenes, which are important structures in various biologically active compounds[1-14,70] and functional materials.[71] A notable feature of this process is the formation of an all-carbon quaternary center, which has not been described at the time of beginning of this research in alkyne oxidative annulations (Scheme 1.35).



Scheme 1.35. Synthesis of carbocycles by (formal) C(sp^3)–H/C(sp^2)–H bond cleavage.

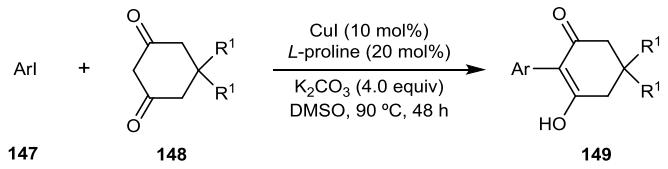
1.4. Results and Discussion

In order to test our hypothesis illustrated in Scheme 1.35, synthesis of appropriate 1,3-dicarbonyl substrates was necessary. A range of these compounds was synthesized using literature reported protocols as described herein in order to undertake the investigation of the proposed mode of catalytic alkyne oxidative annulation.

1.4.1. Preparation of 2-Aryl-1,3-dicarbonyl Substrates

1.4.1.1. Preparation of 3-Hydroxy-2-aryl-cyclohex-2-en-1-one

A variety of 3-hydroxy-2-aryl-cyclohex-2-en-1-ones **149** were synthesized by using a literature protocol (Scheme 1.36).[72] The appropriate aryl iodide **147** was added to a stirred solution of CuI, *L*-proline, K_2CO_3, and the appropriate 1,3-dicarbonyl compound **148** in anhydrous DMSO, and the reaction mixture was then stirred at 90 °C for 48 h. The work-up and purification by column chromatography afforded the corresponding 2-aryl-1,3-dicarbonyl compound **149**.

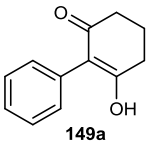
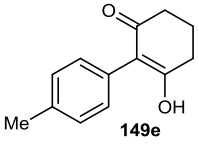
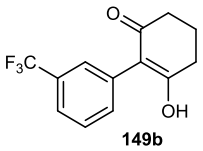
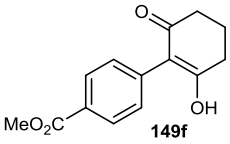
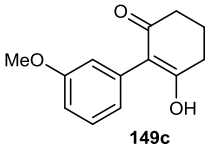
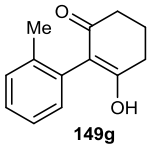
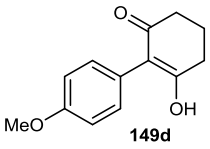
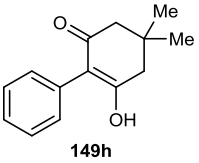


147 148 149

Scheme 1.36. Synthesis of 3-hydroxy-2-aryl-cyclohex-2-en-1-ones.

A range of functional group tolerance has been observed on the synthesized substrates. The substrates with various electron-donating groups as well as electron-withdrawing substituents have been synthesized successfully in moderate to good yields (Table 1.1).

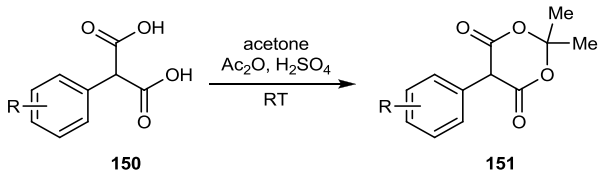
Table 1.1. Synthesis of 1,3-dicarbonyl compounds[a]

Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 **149a**	64	5	 **149e**	65
2	 **149b**	23	6	 **149f**	61
3	 **149c**	73	7	 **149g**	20
4	 **149d**	67	8	 **149h**	35

[a]Substrates synthesized by Dr. Suresh R. Chidipudi and Martin D. Wieczysty. [b]Cited yields are of isolated material.

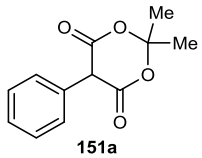
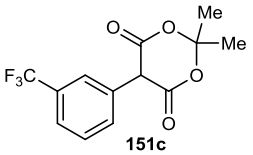
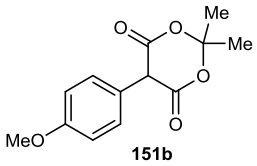
1.4.1.2. Preparation of 2,2-Dimethyl-5-aryl-1,3-dioxane-4,6-dione

The Meldrum's acid derivatives **151** were prepared according to a literature procedure (Scheme 1.37).[73-75] To a stirred suspension of corresponding arylmalonic acid **150** in Ac_2O was added conc. H_2SO_4 dropwise, which caused complete dissolution. The product began to precipitate within one minute after the addition of acetone. The appropriate work-up and purification gave the corresponding 1,3-dicarbonyl compounds **151** (Table 1.2).



Scheme 1.37. Synthesis of 2,2-dimethyl-5-aryl-1,3-dioxane-4,6-dione.

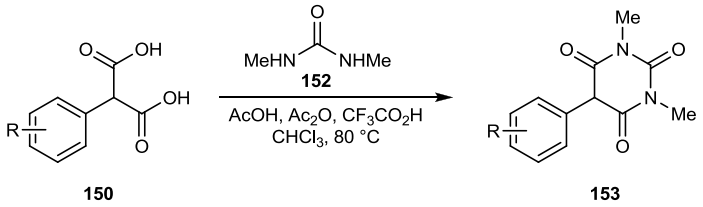
Table 1.2. Synthesis of Meldrum's acid derivatives[a]

Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 **151a**	60	3	 **151c**	55
2	 **151b**	67			

[a]Substrates synthesized by Dr. Suresh R. Chidipudi. [b]Cited yields are of isolated material.

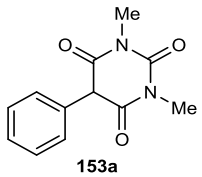
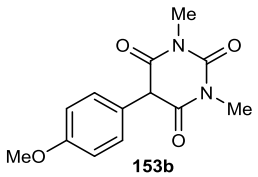
1.4.1.3. Preparation of 1,3-Dimethyl-5-aryl-1,3-diazinane-2,4,6-triones

The 1,3-dimethyl-5-aryl-1,3-diazinane-2,4,6-triones **153a** and **153b** were prepared according to a literature procedure (Scheme 1.38)[76] from 1,3-dimethylurea **152** and appropriate arylmalonic acid **150** (Table 1.3).



Scheme 1.38. Synthesis 1,3-dimethyl-5-aryl-1,3-diazinane-2,4,6-trione.

Table 1.3. Synthesis of Barbituric acid derivatives[a]

Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 **153a**	50	2	 **153b**	42

[a]Substrates synthesized by Dr. Suresh R. Chidipudi. [b]Cited yields are of isolated material.

1.4.2. Preparation of Alkynes

The following alkynes were purchased from commercial sources (Figure 1.19).

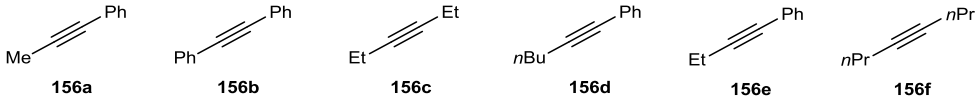
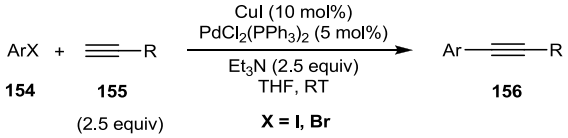


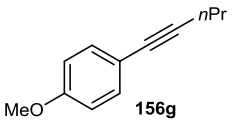
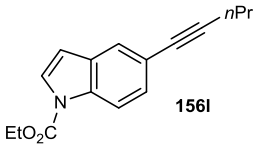
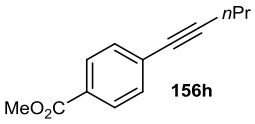
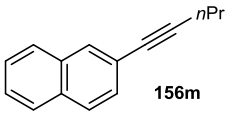
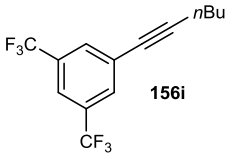
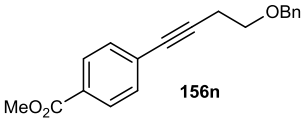
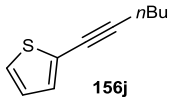
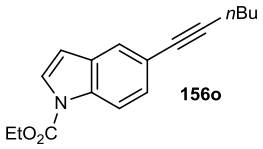
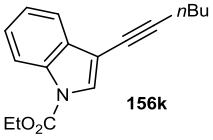
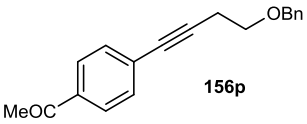
Figure 1.19. Alkynes from commercial sources.

In addition to those commercially available akynes (Figure 1.19), a range of unsymmetrical alkynes **156** were accessed by using Sonogashira coupling procedure from appropriate haloarene **154** and terminal alkyne **155** in THF under palladium catalysis (Scheme 1.39).[77,78] A range of haloarenes has been utilized to produce a diverse variety of alkynes which are used as key coupling partners for oxidative annulation process. The substituents tolerated on aryl part of alkynes include electron-rich and electron-deficient functional groups. Several alkynes with heteroaryl component have also been accessed apart from sterically demanding naphthyl group (Table 1.4).



Scheme 1.39. Synthesis of internal alkynes by Sonogashira coupling.

Table 1.4. Synthesis of internal alkynes

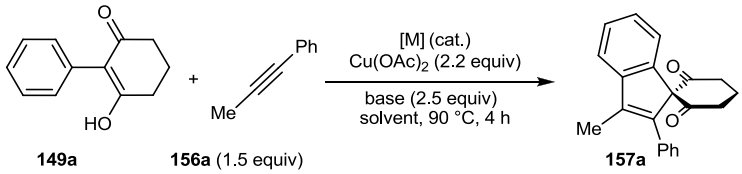
Entry	Alkyne	Yield [%][a]	Entry	Alkyne	Yield [%][a]
1	 **156g**	96	6	 **156l**	99
2	 **156h**	98	7	 **156m**	45
3	 **156i**	90	8	 **156n**	99
4	 **156j**	93	9	 **156o**	98
5	 **156k**	98	10	 **156p**	96

[a]Cited yields are of isolated material.

1.4.3. Reaction Optimization

We began our study with 2-aryl-1,3-diketones, which exist predominantly in the enol tautomer, the feasibility of the coupling reaction was initially examined using 3-hydroxy-2-phenyl-2-cyclohexenone **149a** with 1-phenyl-1-propyne **(157a**; Table 1.5). The reactions were conducted at 90 °C and $Cu(OAc)_2$ (2.2 equivalents) was employed as the stoichiometric oxidant. Although rhodium, ruthenium, and palladium precatalysts have proven to be highly effective in a range of oxidative annulations of alkynes,[25-34,37-65,79-81] the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) was examined first on the basis of its much lower cost compared with rhodium and palladium complexes. In the presence of K_2CO_3 (2.5 equivalents), we were pleased to find that successful formation of spiroindene **157a** occurred in a variety of solvents, (Table 1.5, entries 1–3). Consistent with literature precedent,[58-62,82] the reactions were highly regioselective, with initial C–C bond formation occurring exclusively at the methyl-substituted carbon of the alkyne.[83] The use of NaOAc instead of K_2CO_3 did not help to improve the reaction yield (Table 1.5, entry 4). Subsequently, base was found to be unnecessary; in dioxane as the solvent, the yield of **157a** increased to 80% in the absence of K_2CO_3 or NaOAc (Table 1.5, entry 5). The catalytic reaction in other solvents such as DMF gave lower product yield (Table 1.5, entry 6). The screening of other ruthenium sources such as $[RuCl_2(PPh_3)_3]$ as well as $Pd(OAc)_2$ in 1,4-dioxane proved to be totally ineffective (Table 1.5, entries 7–9). Whereas, the Rh(III) complex $[Cp^*RhCl_2]_2$ provided 88% yield of **157a** in the absence of K_2CO_3 (Table 1.5, entry 11). The use of K_2CO_3 led to the spiroindene product in 74% yield (Table 1.5, entry 10). We noted that there is no catalytic activity with other oxidants such as benzoquinone and AgOAc. We also observed that the formation of spiroindene did not occur below 90 °C and poor reaction yield was obtained at 120 °C. Although $[\{RhCp^*Cl_2\}_2]$ provided the highest yield of **157a**, $[RuCl_2(p\text{-cymene})]_2$ was selected for further experimentation on the basis of its lower cost.

Table 1.5. Optimization of reaction conditions for the synthesis of **157a**[a]



Entry	[M]	[mol%]	Base	Solvent	Yield [%][b]
1	$[RuCl_2(p\text{-cymene})]_2$	2.5	K_2CO_3	*t*-AmOH	60
2	$[RuCl_2(p\text{-cymene})]_2$	2.5	K_2CO_3	THF	55
3	$[RuCl_2(p\text{-cymene})]_2$	2.5	K_2CO_3	dioxane	62
4	$[RuCl_2(p\text{-cymene})]_2$	2.5	NaOAc	dioxane	57
5	**$[RuCl_2(p\text{-cymene})]_2$**	**2.5**	**—**	**dioxane**	**80**
6	$[RuCl_2(p\text{-cymene})]_2$	2.5	—	DMF	15
7	$[RuCl_2(PPh_3)_3]$	5	K_2CO_3	dioxane	—
8	$Pd(OAc)_2$	5	—	dioxane	<5
9	$Pd(OAc)_2$	5	K_2CO_3	dioxane	<5
10	$[RhCp^*Cl_2]_2$	2.5	K_2CO_3	dioxane	74
11	**$[RhCp^*Cl_2]_2$**	**2.5**	**—**	**dioxane**	**88**

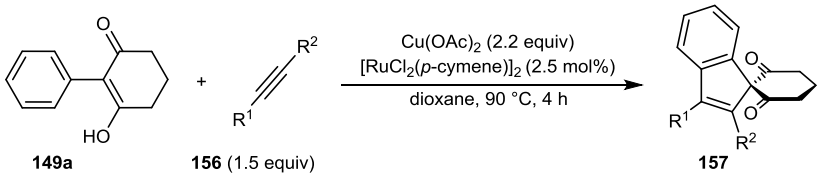
[a]Reactions were conducted using 0.25 mmol of **149a**. [b]Yield of isolated compounds. Cp* = C_5Me_5, DMF = *N*,*N*'-dimethylforamide, *t*-Am = *tert*-amyl, THF = tetrahydrofuran.

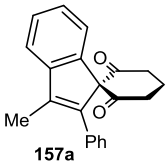
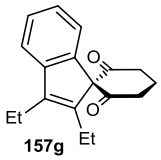
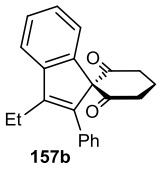
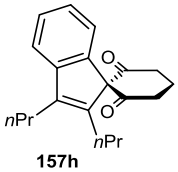
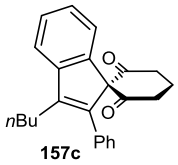
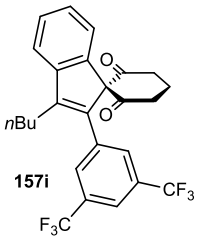
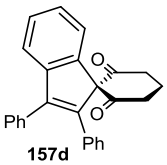
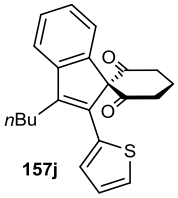
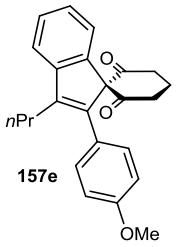
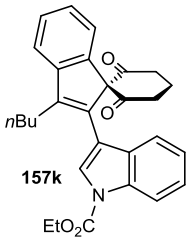
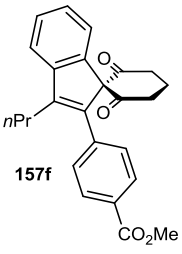
1.4.4. Evaluation of Reaction Scope

With the optimized reaction conditions in hand (Table 1.5, entry 5), an assessment of the reaction scope was conducted by varying the alkyne, and the aryl group of the 3-hydroxy-2-cyclohexenone (Table 1.6). It was noticed that the substituent on the phenyl ring of compound **149** as well as the alkyne partner affected the product′s yield significantly. These experiments revealed that the process demonstrates good generality.

Initially, under standard reaction conditions, a range of internal alkynes including symmetrical and unsymmetrical were tolerated affording moderate to good yields of products. In certain cases, the inclusion of K_2CO_3 (2.5 equivalents) provided higher yields (products **157d**).[84] Oxidative annulation occurred smoothly with various alkyl/(hetero)aryl-substituted alkynes. Again, regioselectivity was high with unsymmetrical alkynes, with initial C–C bond formation occurring at the alkyne carbon bearing the alkyl substituent.[83] With respect to the alkyne substituents, phenyl rings containing methoxy, ester, or trifluoromethyl groups were tolerated (products **157e**, **157f** and **157i**). Heteroarenes on the alkyne, such as 2-thienyl (product **157j**) or indole (product **157k**) were also tolerated resulting in good yield of spiroindenes. However, terminal alkynes were unsuitable substrates, leading to complex mixtures of products.

Table 1.6. Ru-catalyzed oxidative annulation (alkyne scope)[a]

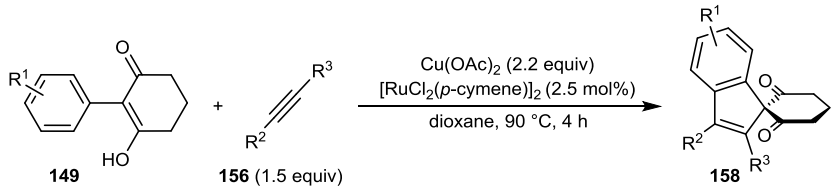


Entry	Spiroindene	Yield [%][b]	Entry	Spiroindene	Yield [%][b]
1	 **157a**	80	7	 **157g**	77
2	 **157b**	76	8	 **157h**	66
3	 **157c**	78	9	 **157i**	71
4	 **157d**	50[c]	10	 **157j**	70
5	 **157e**	70	11	 **157k**	67
6	 **157f**	81			

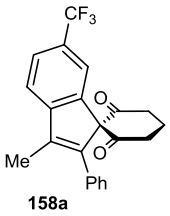
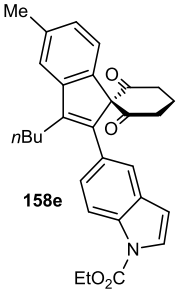
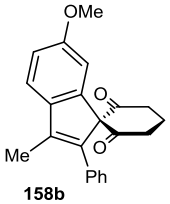
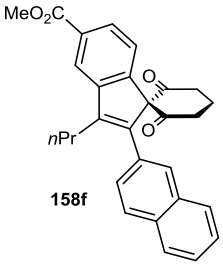
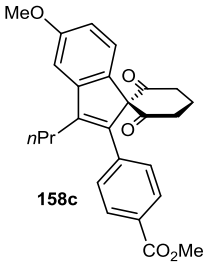
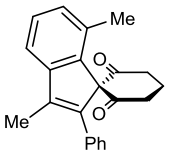
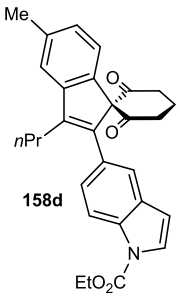
[a]Reactions were conducted using 0.50 mmol of **149a**. [b]Cited yields are of isolated material. [c]Reactions conducted with the addition of K_2CO_3 (2.5 equiv).

Regarding the phenyl group of the 3-hydroxy-2-cyclohexenone, substrates containing *para*-methoxy, *para*-methyl, or *para*-carbomethoxy groups underwent efficient reaction (Table 1.7; products **158c-f**). In these reactions, the inclusion of K_2CO_3 (2.5 equivalents) provided higher yields. With *meta*-substituted phenyl groups, $C(sp^2)$–H functionalization occurred exclusively at the least sterically encumbered site (products **158a** and **158b**).[85] The high site selectivity observed in the formation of **158b** is notable, given that mixtures of isomers were formed when substrates containing *meta*-methoxyphenyl groups were employed in related reactions.[25] We found substrates containing *ortho*-substituted phenyl groups were unreactive (product **158g**). On the other hand, a range of alkynes bearing indole, naphthyl and substituted aryl groups were also found as effective coupling partners.

Table 1.7. Ru-catalyzed oxidative annulation of various alkynes with a range of 2-aryl-3-hydroxy-2-cyclohexenones[a]



149 156 (1.5 equiv) 158

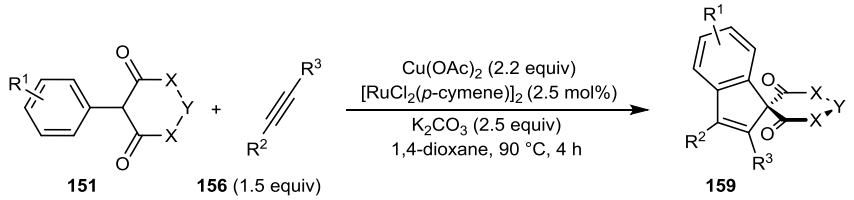
Entry	Spiroindene	Yield [%][b]	Entry	Spiroindene	Yield [%][b]
1	 **158a**	66	5	 **158e**	66[c]
2	 **158b**	64	6	 **158f**	72
3	 **158c**	74[c]	7	 **158g**	0
4	 **158d**	66[c]			

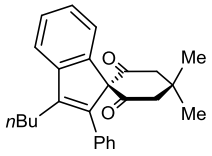
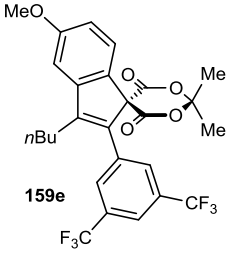
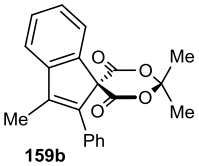
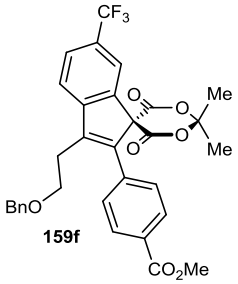
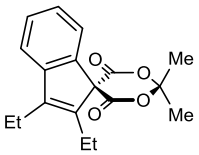
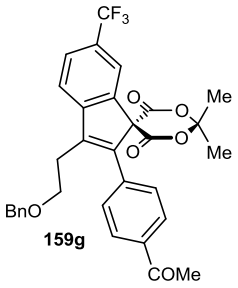
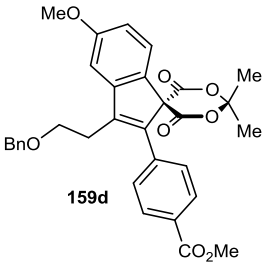
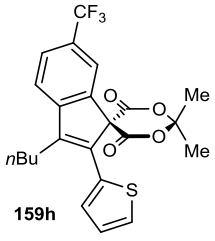
[a]Reactions were conducted using 0.50 mmol of **149a**–**g**. [b]Cited yields are of isolated material. [c]Reactions conducted with the addition of K_2CO_3 (2.5 equiv).

Next, we further extended the reaction scope by varying the 2-aryl cyclic 1,3-dicarbonyl substrates (Table 1.8). Again, a wide range of unsymmetrical alkynes were

tolerated, and the reactions were highly regioselective. While successful formation of product **159a** was not surprising given the results presented in Table 1.7, we were pleased to find that a range of Meldrum's acid derivatives containing various 2-aryl substituents (which exist predominantly in their *β*-dicarbonyl form rather than the enol form) also underwent oxidative annulation (products **159b**-**h**). In these cases, the presence of K_2CO_3 (2.5 equivalents) was required to obtain the products in acceptable yields (products **159b**-**d**; 40–59%).[84] These products incorporate either an unsubstituted aryl ring or a *para*-methoxy substituent in addition to the unsymmetrical, symmetrical alkyl groups at alkyne moiety. Moreover, the aryl groups at alkyne also contain electron-deficient groups like carbomethoxy and bis-trifluoromethyl functionalities. The replacement of *para*-methoxy substituent with a *meta*-trifluoromethyl group also produced spiroindenes (products **159f**-**h**) but the yields were much lower as compared to the products obtained previously.

Table 1.8. Ru-catalyzed oxidative annulation (substrate scope)[a]

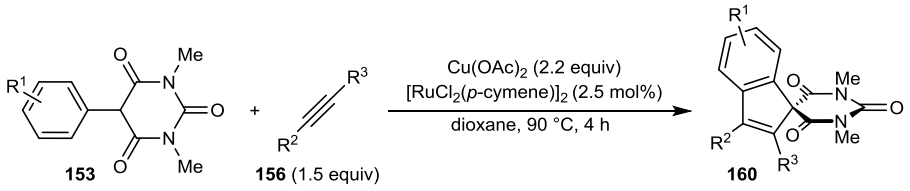


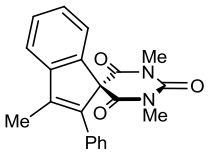
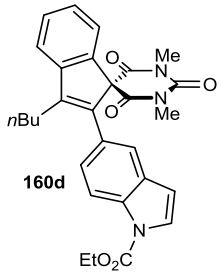
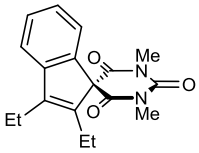
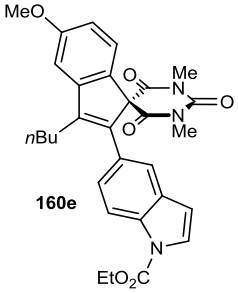
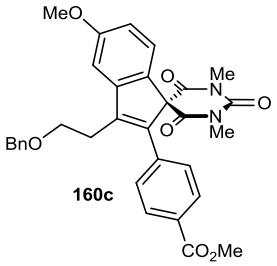
Entry	Spiroindene	Yield [%][b]	Entry	Spiroindene	Yield [%][b]
1	 **159a**	76[c]	5	 **159e**	40
2	 **159b**	54	6	 **159f**	30
3	 **159c**	48	7	 **159g**	28
4	 **159d**	59	8	 **159h**	22

[a]Reactions were conducted using 0.50 mmol of **149h** and **151a-c**. [b]Cited yields are of isolated material. [c]Reaction conducted without K_2CO_3.

Moreover, the reaction scope was further extended by using barbituric acid derivatives, which also exist in the *β*-dicarbonyl form, and were also found to be effective in this process (Table 1.9; products **160a–e** formed in 73–84% yield). Interestingly, substrates containing only one carbonyl group, such as 2-phenylcyclohexanone, do not undergo oxidative annulation under these conditions. Also, acyclic substrates such as diethyl phenylmalonate were unreactive.

Table 1.9. Ru-catalyzed oxidative annulation of various alkynes with 1,3-dimethyl-5-aryl-1,3-diazinane-2,4,6-triones[a]

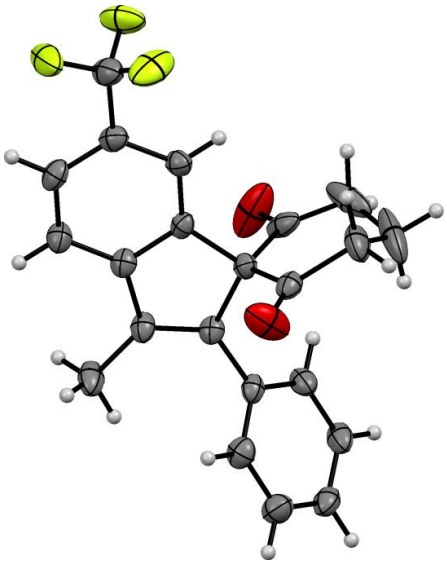


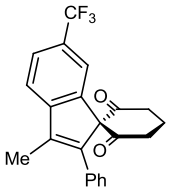
Entry	Spiroindene	Yield [%][b]	Entry	Spiroindene	Yield [%][b]
1	 **160a**	76	4	 **160d**	80
2	 **160b**	75	5	 **160e**	73
3	 **160c**	84			

[a]Reactions were conducted using 0.50 mmol of **153a** and **153b**. [b]Cited yields are of isolated material.

1.4.5. Regiochemical Determination

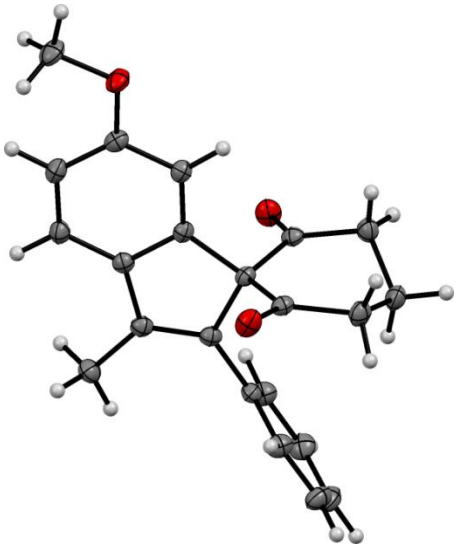
The structures of compounds **158a** and **158b** were determined by X-ray crystallography in order to confirm the regioselectivity of the *meta*-substituted spiroindenes (Figure 1.20). The structures of other *meta*-substituted compounds were assigned by analogy.

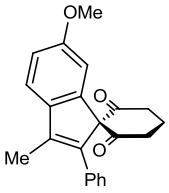




158a

CCDC: 894550





158b

CCDC: 897478

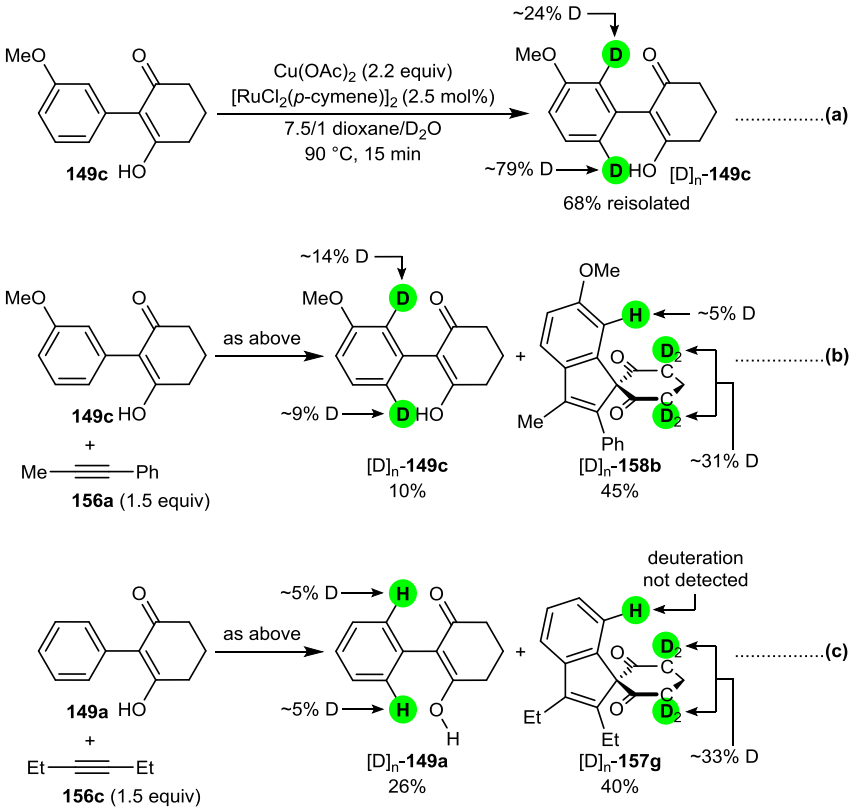
Figure 1.20. Crystal structures of spiroindenes **158a** and **158b**.

1.4.6. Deuterium Labeling Experiments

To gain insight into the mechanism and regioselectivity of these reactions, deuteration experiments were carried out. First, substrate **149c** was subjected to the standard reaction conditions with the inclusion of D_2O, but in the absence of alkyne [Scheme 1.40 (a)]. After only 15 min, recovered **149c** contained significant deuteration (~79%) at the eventual site of spiroindene formation, as expected. Deuteration was also observed at the more sterically hindered site, albeit to a lower extent (~24%). This experiment suggests that in the presence of D_2O and the absence of alkyne, cycloruthenation is rapid, reversible, and faster at the more sterically accessible site. The recovery was relatively modest (68% yield) due to competitive substrate decomposition.

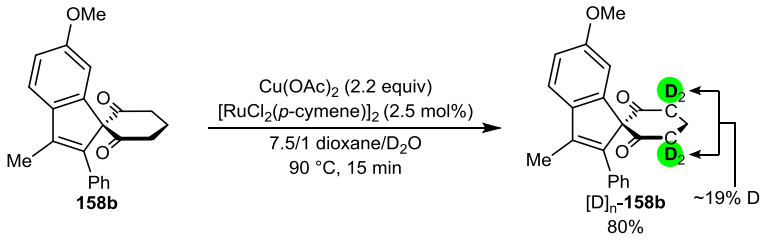
Repeating this experiment in the presence of alkyne **156a** gave spiroindene $[D]_n$-**158b** (45% yield) that contained minimal (~5%) deuteration at the indene, but was partially deuterated in the cyclohexane [Scheme 1.40 (b)]. In addition, recovered starting material was partially deuterated. These observations are consistent with cycloruthenation being partially reversible in the presence of alkyne. Slightly higher deuterium incorporation was observed at the more hindered site of $[D]_n$-**149c** from Scheme 1.40 (b), which is in contrast with $[D]_n$-**149c** obtained from Scheme 1.40 (a); this is consistent with migratory insertion of the alkyne being more rapid with the ruthenacycle derived from functionalization at the least hindered site of **149c**, thus depleting deuterium at this site preferentially.

Finally, cycloruthenation was found to be largely irreversible in the reaction of **149a** with **156c**, as evidenced by a reaction run to partial completion in the presence of D_2O, in which no deuteration was detected at the indene of the annulation product, and only minimal deuteration (~5% at each site) was observed in recovered $[D]_n$-**149a** [Scheme 1.40 (c)].



Scheme 1.40. Deuterium labeling experiments.

On the other hand, deuteration at the cyclohexane ring most likely occurs by reversible enolization after the formation of spiroindene **158b**, as evidenced by the control experiment shown in Scheme 1.41.



Scheme 1.41. Control experiment involving **158b**.

1.4.7. Possible Catalytic Cycle

In line with catalytic cycles put forth for related processes,[58-62,82] a possible mechanism for these oxidative annulations is illustrated in Figure 1.21. Under the reaction conditions, deprotonation of the cyclic 1,3-dicarbonyl substrate **149a** generates an enolate, which is then able to direct cycloruthenation with complex **161** to form six-membered ruthenacycle **162**. It should be noted that with one exception,[59] all ruthenium-catalyzed alkyne oxidative annulations reported to date involve initial cyclometallation to form five-membered ruthenacycles. Coordination and migratory insertion of the alkyne **156** with **162** then occurs with preference for C–C bond formation at the alkyne carbon bearing the alkyl substituent to form a second ruthenacycle **163**, which although depicted as an oxa-π-allylruthenium species, could exist in the O- or C-bound forms.[86] Finally, C–C reductive elimination of **163**, with concomitant Cu^{II}-promoted oxidation of Ru^0 back to the Ru^{II} species **161**, releases the product **157**.[87]

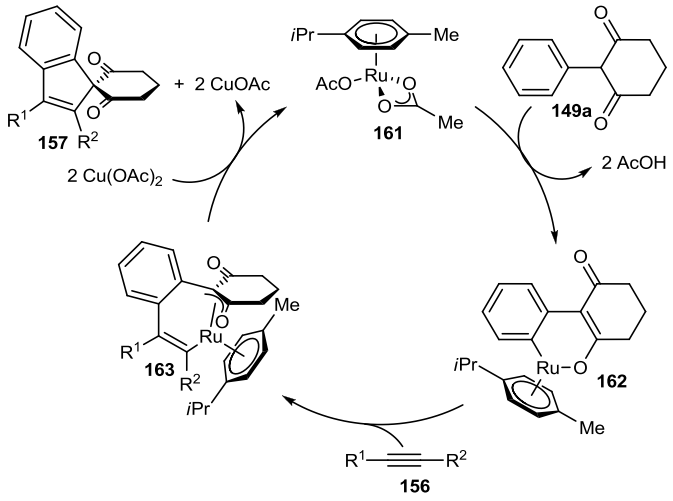


Figure 1.21. Possible catalytic cycle for spiroindene formation.

1.4.8. Photocatalytic Rearrangement of Benzoxazepine

In addition to the mechanism presented in Figure 1.21, another possibility is that reductive elimination of **163** occurs to first generate benzoxepine **164**, which then rearranges to spiroindene **157** under the reaction conditions (Figure 1.22). The conversion of benzoxazepines to indenes, along with related rearrangements, have been observed previously under photochemical conditions.[88] However, oxidative annulations conducted with the rigorous exclusion of light still led to the formation of spiroindenes rather than the corresponding benzoxazepines, which suggests that this pathway is less likely.

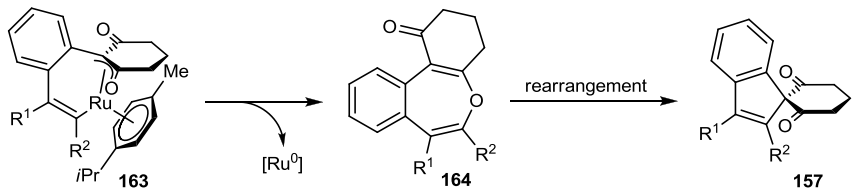
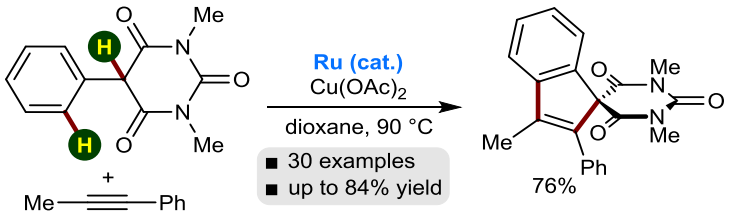


Figure 1.22. Alternate possible mechanism for spiroindene formation.

1.5. Conclusions and Future Work

In summary, we have developed an inexpensive ruthenium-catalyzed oxidative annulation of alkynes involving (formal) functionalization of C(sp^3)–H and C(sp^2)–H bonds. Under the action of ruthenium catalysis, the process provides a diverse range of spiroindenes with high levels of regioselectivity. A notable feature of this process is the formation of products with all-carbon quaternary centers. These experiments revealed that the process demonstrates good substrate generality and functional group tolerance as well. Our future work will involve the development of diastereo- and enantioselective variants of this process as well as the utilization of enolate directing group into other types of carbo- and heterocycle-forming oxidative annulations.



Chapter 2: Synthesis of Benzopyrans by Pd(II)- or Ru(II)-Catalyzed C–H Alkenylation of 2-Aryl-3-hydroxy-2-cyclohexenones

2. Introduction

2.1. The Significance of Benzopyrans

Heterocycles are of immense importance and exhibit a key role for the design and discovery of new chemical structures with broad spectrum biological profile.[89] In this perspective, an important class of oxygenated heterocyclic scaffolds such as benzopyrans represents key structural units of diversified natural compounds with useful biological activities.[90] These moieties possess diverse biological activities,[91] and are used as key intermediates in organic and natural product synthesis.[92] Certain benzopyrans possess photochromic and thermochromic properties.[93] Some representative examples of biologically active benzopyran derivatives **165-167** are shown in Figure 2.1.[94-96]

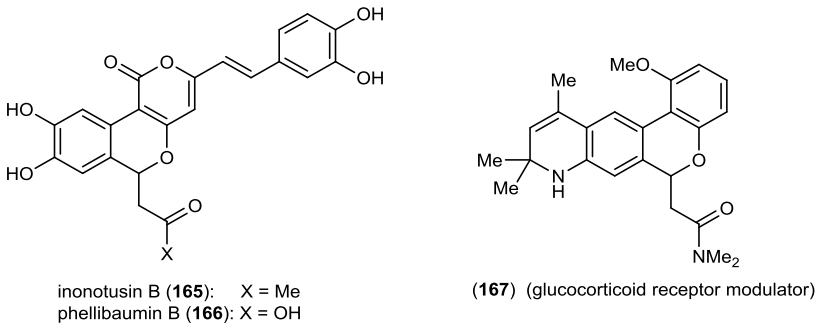


Figure 2.1. Some representative examples of biologically active benzopyrans.

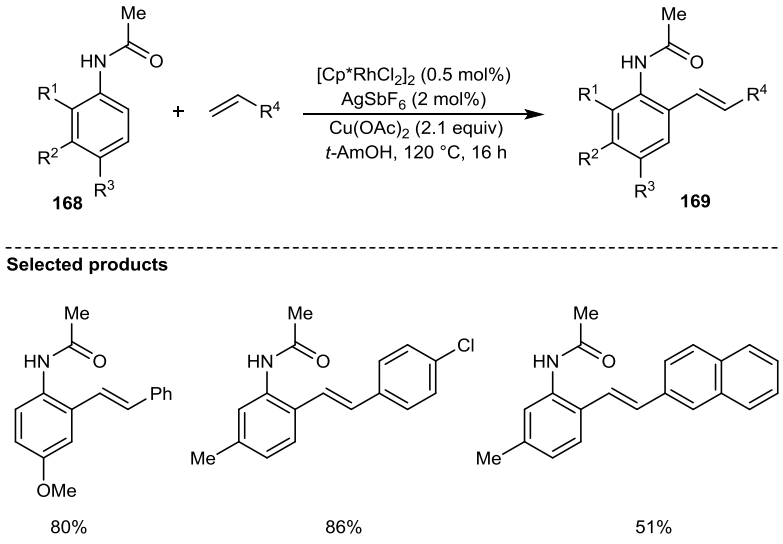
2.2. Dehydrogenative Olefination Reactions

Atom-economical construction of carbon-carbon and carbon-heteroatom bonds under oxidative conditions is of vital significance and has emerged as an increasingly important synthetic strategy.[97] Among these, the metal-catalyzed alkenylation of aromatic C(sp^2)–H bonds, directed by a coordinating functional group, has proven to be a versatile strategy in organic synthesis[98] successfully complementing alternatives such as the Mizoroki–Heck reaction,[99] and the Fujiwara–Moritani reaction.[100] The use of directing groups not only offers enhanced reactivity but also provides reaction products with high site-selectivity, by minimizing the formation of positional

isomers.[101] Strategically, however, the use of directing groups can also be a limitation, especially if several steps are required to convert the directing group into the final desired functional group.[102] Nevertheless, this drawback is mitigated by the continued development of new procedures that employ an ever expanding range of directing groups, thus increasing the toolbox of methods available for catalytic C–H alkenylation and allowing access to a greater diversity of products. The literature investigations have revealed that there is a diverse range of directing groups that have been involved to perform these transformations, however, in the following discussion, we will highlight some representative examples of C–H olefination reactions using various metal precatalysts.

2.2.1. Rhodium-Catalyzed Dehydrogenative Olefination Reactions

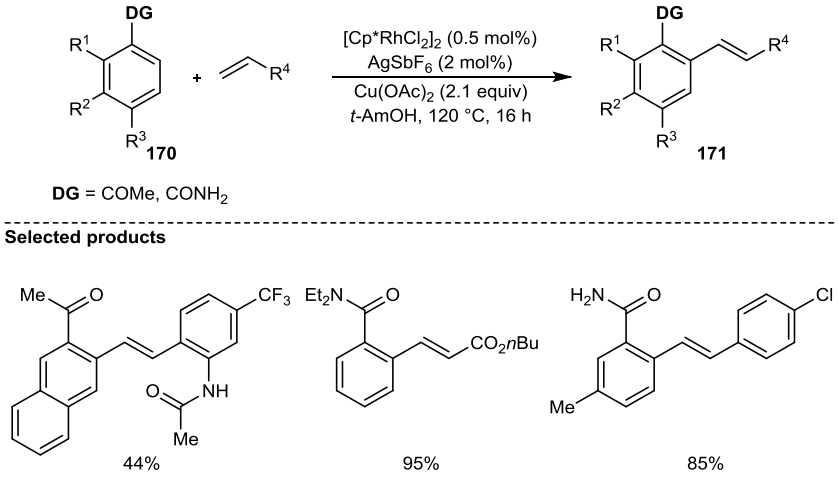
Glorius and Patureau developed an efficient and attractive strategy affording the direct *ortho*-olefination of acetanilides **168** under the action of rhodium catalysis. Low catalytic loadings, good yields of products **169**, hydrolysis of acetanilides to corresponding anilines and high levels of regio- and chemoselectivity make this methodology useful and may find many applications in natural product and total synthesis in the future (Scheme 2.1).[103]



Scheme 2.1. Alkenylation of acetanilide derivatives.

In 2011, the same research group carried out a selective rhodium-catalyzed oxidative *ortho*-olefination of benzamides and acetophenones **170** (Scheme 2.2).[104] A variety of

electron-donating and electron-withdrawing styrenes were tolerated. They have also shown that the high yields and high selectivities are strongly dependent on the nature of the aromatic system. On the other hand, a benzamide core bearing both electron-rich and electron-deficient groups was proved to be an effective substrate for C–H alkenylation. The reaction of tertiary benzamide with *n*-butyl acrylate led to the desired oxidative Heck product in 95% yield with good selectivity.



Scheme 2.2. Alkenylation of acetophenone and benzamide derivatives.

The proposed mechanism for the olefination reaction is illustrated in Figure 2.2. The initial step is the activation of C–H bond of **170** by coordinating with rhodium complex generating a 5-membered rhodacycle **172**, which on alkene insertion generates another intermediate **173**. Subsequently, *β*-hydrogen elimination gives the desired olefinated product **171**.

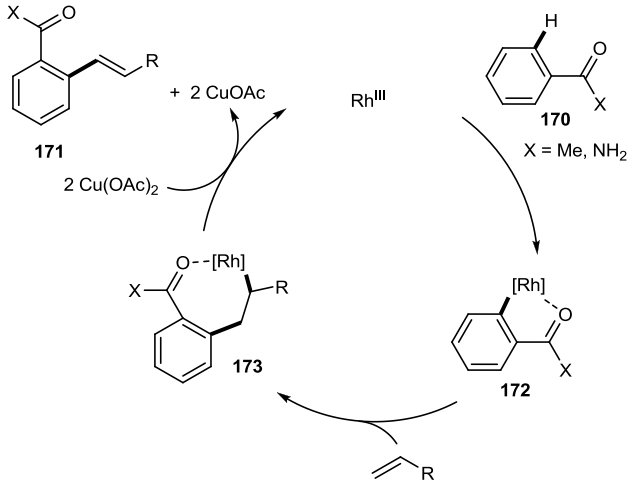
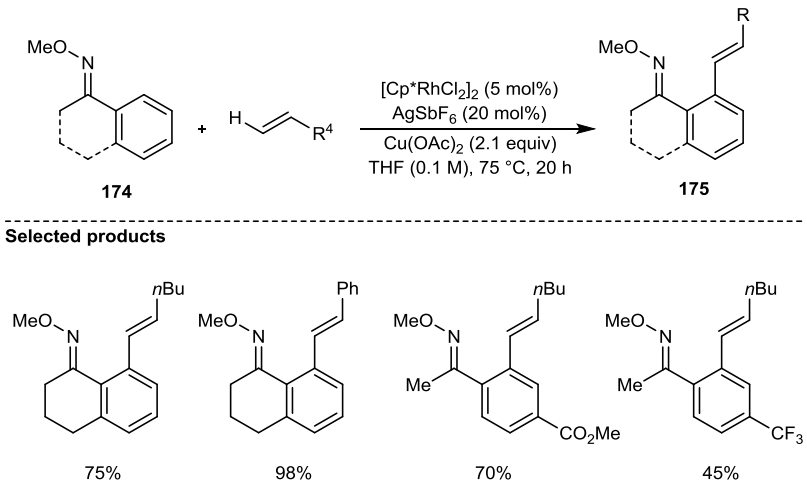


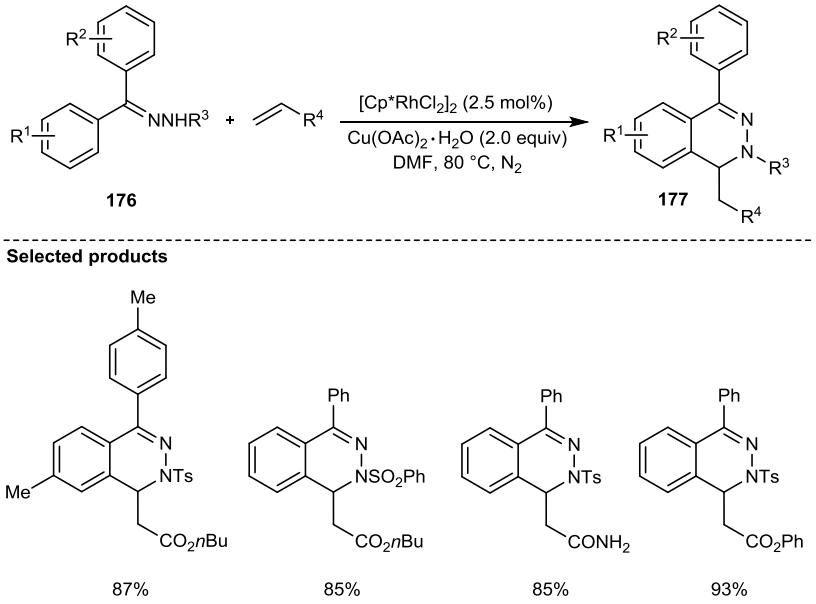
Figure 2.2. Possible catalytic cycle for acetophenone and benzamide alkenylation.

Bergman, Ellman and co-workers demonstrated an efficient strategy for the oxidative coupling of unactivated alkenes to oximes **174** involving C–H bond functionalization using a cationic rhodium catalyst. This process provides access to a diverse range of olefinated products **175** in good yields (Scheme 2.3).[105] Under optimal reaction conditions, oximes with diverse substitution pattern were tolerated against a variety of alkenes to afford a range of products. The substrates with electron-donating and electron-withdrawing substituents at the *meta*- and *para*-positions were found to be the effective coupling partners. Alkene scope was also explored and *β*-branched alkenes were found to be more productive compared to *α*-branched alkenes. The reaction was also compatible with activated olefins such as ethyl acrylate affording olefinated products in good yields.



Scheme 2.3. Alkenylation of oxime derivatives.

In 2012, Xu and co-workers demonstrated an efficient tandem C–H olefination of sulfonylhydrazones **176** with alkenes under rhodium catalysis. This process involves a copper acetate promoted intramolecular C–N bond formation, leading to a variety of l,2-dihydrophthalazines **177** in good to excellent yields (Scheme 2.4).[106] Under the optimized conditions, a variety of hydrazones with electron-rich and electron-deficient substituents at *meta*- and *para*-position proved to be efficient substrates yielding products in good to excellent yields. The regioselectivity of this reaction was shown to be dependent on the steric hindrance of the substrates, however, alkenes conjugated with alkyl or aryl acrylates were found to be effective coupling partners affording products in good yields.



Scheme 2.4. Alkenylation of sulfonylhydrazone derivatives.

A possible catalytic cycle for this reaction is depicted in Figure 2.3. The reaction was initiated with the coordination of hydrazone to the Rh(III) species generating rhodacycle **178**, which, on insertion, of alkene give another eight-membered rhodacycle **179**. Subsequently, reductive elimination of **179** affords intermediate **180** and a Rh(I) species which is oxidized to regenerate the active Rh(III) species. The intermediate **180** on reaction with copper acetate gives intermediate **181** which on Michael addition afforded **182** followed by subsequent enolate protonation to give final product **177**.

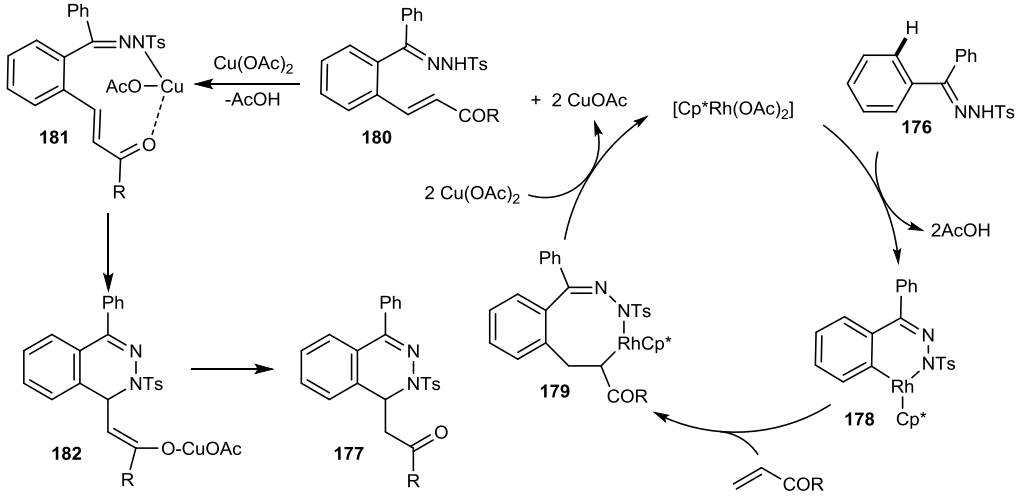
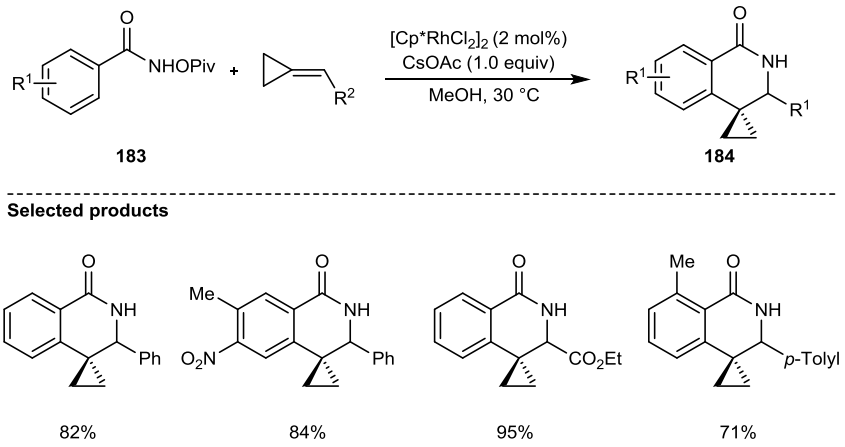
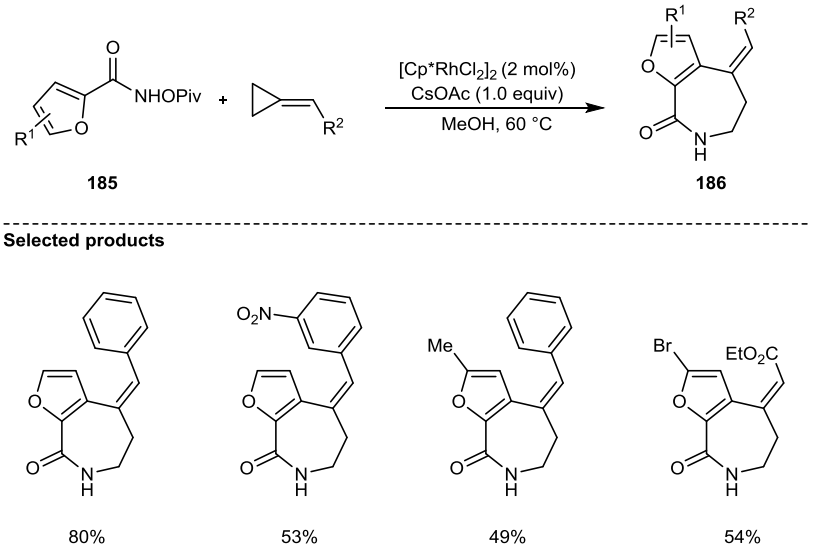


Figure 2.3. Possible catalytic cycle for dihydrophthalazine formation.

Cui and co-workers developed a Rh(III)-catalyzed C–H activation/cycloaddition of benzamides **183** and methylenecyclopropanes, with C–C double bonds and C–C proximal bonds as selective coupling partners, for the divergent synthesis of biologically interesting spiro dihydroisoquinolinones **184** (Scheme 2.5) and furan-fused azepinones **186** (Scheme 2.6).[107] This process features simple starting materials, mild conditions, and high efficiency and is external oxidant free. Under the optimized reaction conditions, generality of the reaction was investigated. Various benzamides with valuable functional groups, such as methoxy, bromo, cyano and nitro, reacted smoothly with the olefins to afford the corresponding spiro dihydroisoquinolinone products in moderate to excellent yields (55–90%). Electron-withdrawing groups on the benzamides somewhat retarded the reaction, however, worked efficiently by elevating the reaction temperature to 60 °C. In addition, various polysubstituted furan-fused azepinones **186** were obtained in moderate to good yields using various furan-based substrates.



Scheme 2.5. Synthesis of spiro dihydroisoquinolinones.



Scheme 2.6. Synthesis of furan-fused azepinones.

The proposed mechanism for this transformation is illustrated in Figure 2.4. It suggests that the initial rhodium dicarboxylate was obtained from the reaction between $[Cp^*RhCl_2]_2$ and CsOAc. A carboxylate-assisted C–H activation of substrate **183** *via* a concerted metalation/deprotonation (CMD) pathway then generates rhodacycle **187**,[108] which on coordination and insertion to C=C double bond delivers another rhodacycle **188**. C–N bond formation takes place to afford **189** along with N–O bond cleavage. Finally, product **184** is obtained by the protonation of **189** with the release of active Rh(III) species.[109]

For the azepinone formation, the first step is also a CMD involving C–H activation generating intermediate **190** which, on coordination and subsequent insertion, forms rhodacycle **192**. This intermediate **192** undergoes a cyclopropylcarbinyl-butenyl rearrangement to generate **193**.[110] C–N bond formation affords **194** along with N–O bond cleavage. The final step is protonation of **194** to furnish the product **186** with Rh(III) catalyst regeneration.[109] For this reaction, the ring opening of (cyclopropylcarbinyl)rhodium **192** to give (3-butenyl) rhodium moiety **193** is faster than the generation of a Rh(III) intermediate. The fused electron-rich furan moiety must slow down the Rh(III) generation making the rearrangement relatively the faster step while formation of the azepinone product becomes the limiting step.

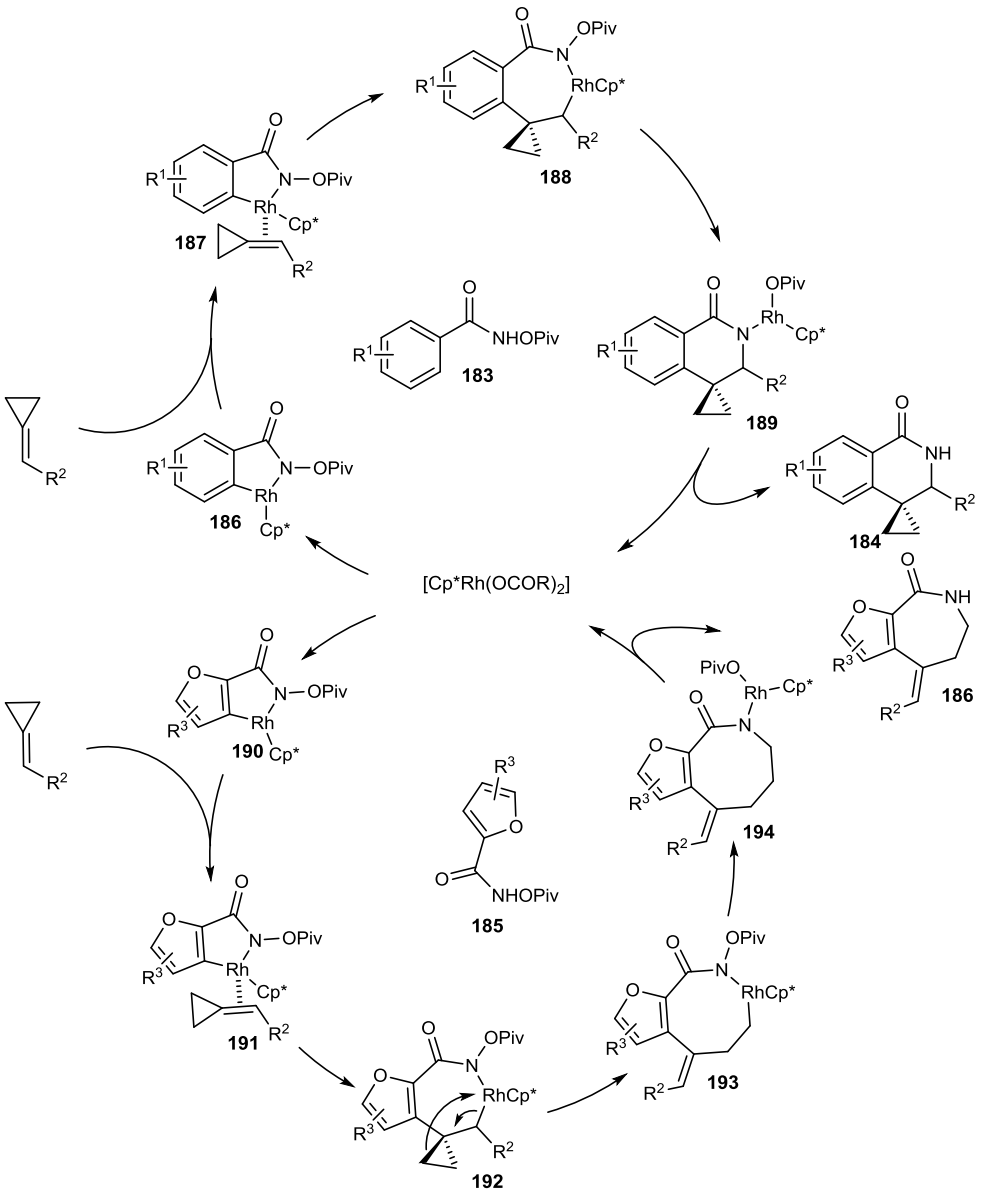
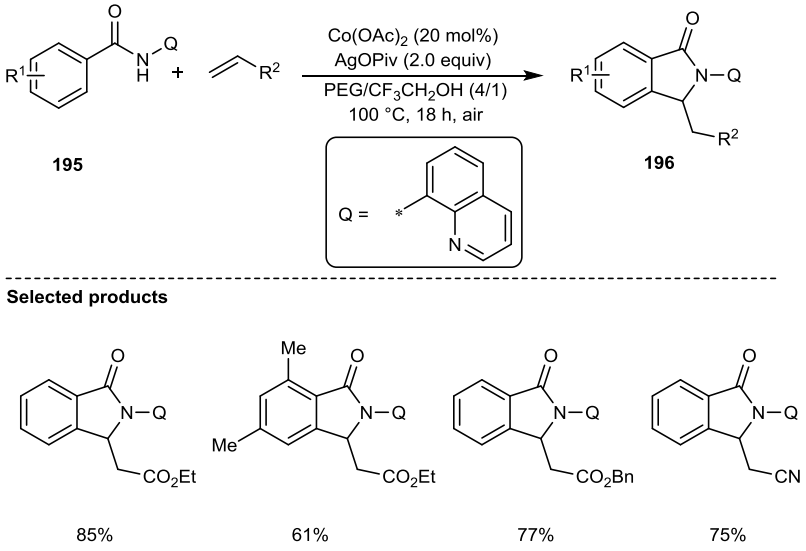


Figure 2.4. Proposed mechanism for dihydroisoquinolinone and azepinone formation.

2.2.2. Cobalt-Catalyzed Dehydrogenative Olefination Reactions

Recently, Ackermann and Ma reported the first example of cobalt-catalyzed C–H alkenylation of benzamides **195** using electron-deficient alkenes and $Mn(OAc)_2$ or AgOPiv as the oxidant. The process affords a range of isoindolin-1-one derivatives **196** with good regio- and site-selectivity (Scheme 2.7).[111] With optimized catalytic reaction conditions, the general scope of this oxidative annulation strategy was tested with a range of substituted amides. The results revealed that the catalytic system efficiently transforms *para*-substituted substrates as well as sterically hindered *ortho*-substituted arenes. A variety of electrophilic functional groups, such as chloro, bromo, iodo, cyano or nitro substituents were tolerated affording the desired cyclized products in good yields. In addition, several electron-deficient alkenes were found as compatible coupling partners.



Scheme 2.7. Synthesis of isoindolinone derivatives.

The proposed mechanistic cycle is illustrated in Figure 2.5. The initial carboxylate-assisted[112] C–H cobaltation of benzamide **195** affords intermediate **197** which on migratory insertion of the olefin, along with *β*-hydride-elimination, delivers the alkenylated benzamide **199**. Compound **199** undergoes an intramolecular alkene hydroamidation[113] to furnish the desired isoindolinones.

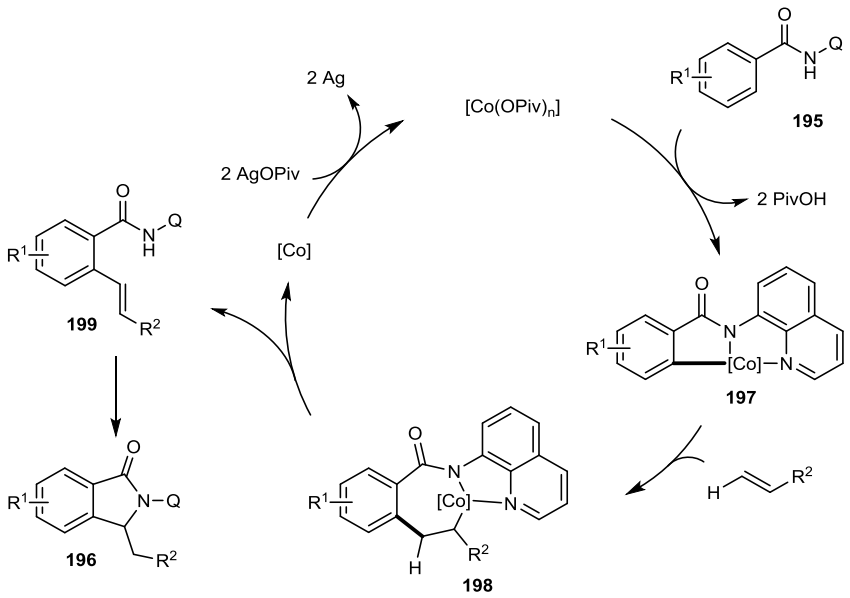
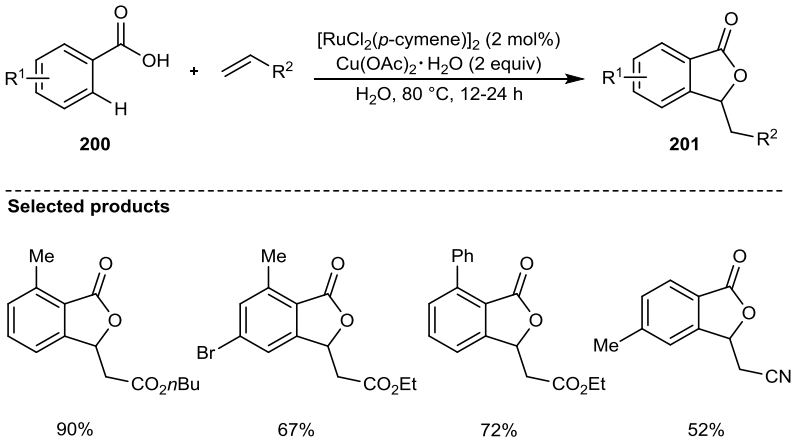


Figure 2.5. Proposed mechanism for isoindolinone formation.

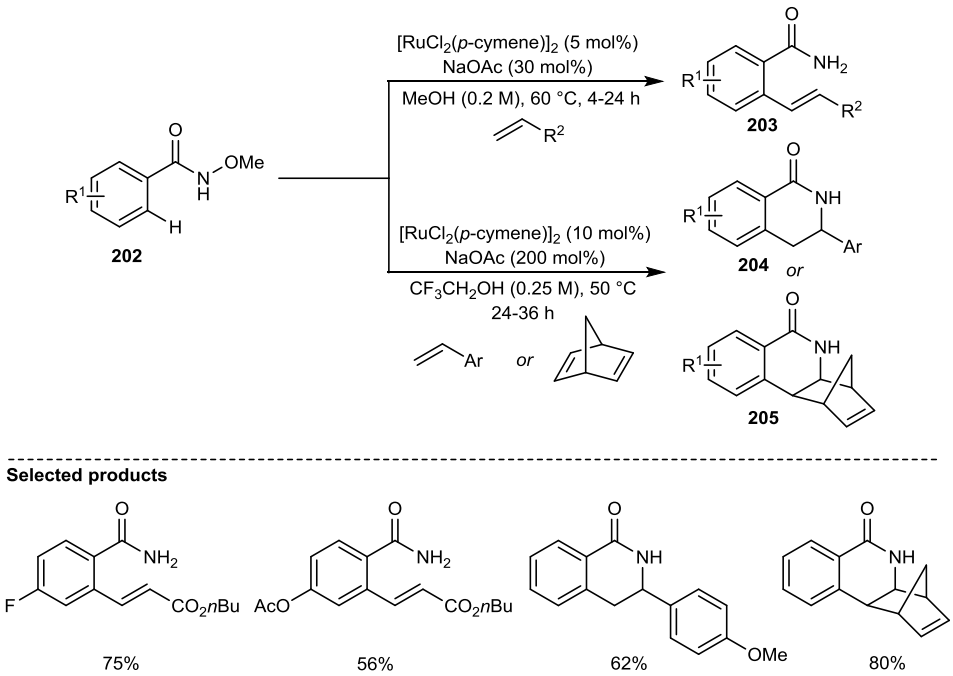
2.2.3. Ruthenium-Catalyzed Dehydrogenative Olefination Reactions

In 2011, Ackermann and Pospech disclosed an efficient C–H alkenylation of benzoic acids **200** providing access to versatile phthalide derivatives **201** under ruthenium catalysis. Additionally, the reaction is environment friendly owing to the use of H_2O as a solvent (Scheme 2.8).[114] It is noteworthy that a variety of benzoic acids bearing substituents with electrophilic functional group such as fluoro and bromo as well as sterically hindered *ortho*-substituted acids were found to be viable for this oxidative coupling.



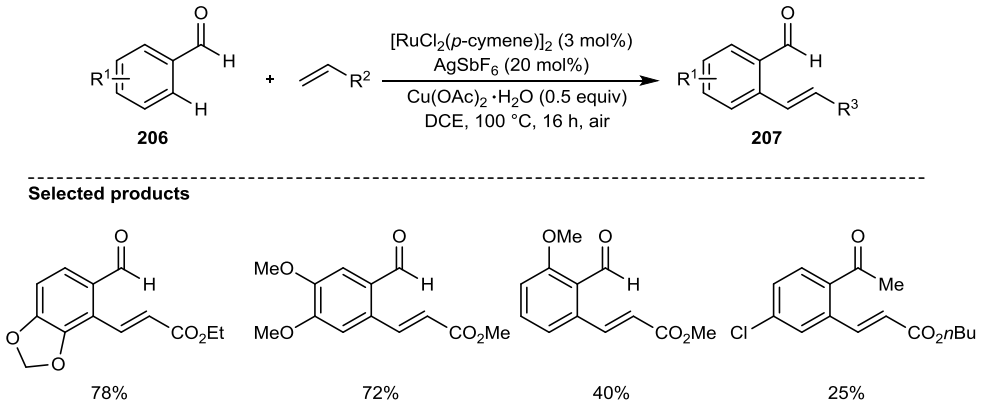
Scheme 2.8. Alkenylation of benzoic acid derivatives.

Li, Wang and co-workers reported an oxidative C–H alkenylation of *N*-methoxybenzamides **202**. They have performed the studies using an oxidizing directing group using an inexpensive ruthenium catalyst (Scheme 2.9).[115] The reaction provided good results and a broad substrate scope with only mono- and *ortho*-olefination selectively. Both electron-rich and electron-poor benzamides performed equally in this reaction. The reaction afforded benzamides with acrylate esters whereas with styrenes or norbornadiene dihydroisoquinolinone derivatives **204** and **205** were obtained.



Scheme 2.9. Alkenylation of *N*-methoxybenzamide derivatives.

To further broaden the scope of alkenylation, the Jeganmohan and Padala made use of the aromatic as well as heteroaromatic aldehydes **206** under the same reaction conditions to afford alkenylated products **207** in highly regio- and stereoselective fashion (Scheme 2.10).[116] The corresponding alkenes were further transformed into four-membered cyclic ketones or a polycyclic isochromanones *via* a photochemical rearrangement.



Scheme 2.10. Alkenylation of aldehyde derivatives.

The proposed catalytic cycle is illustrated in Figure 2.6. Initially, the reaction is initiated by the removal of chloride ligand by the silver salt from ruthenium complex.

Then, coordination of the carbonyl oxygen of **206** to the ruthenium cationic species followed by *ortho*-metalation generates a five-membered ruthenacycle **208**. Coordinative insertion of alkene into the Ru-carbon bond of ruthenacycle **208** affords intermediate **209** which, on *β*-hydride elimination, gives the final product **207**.

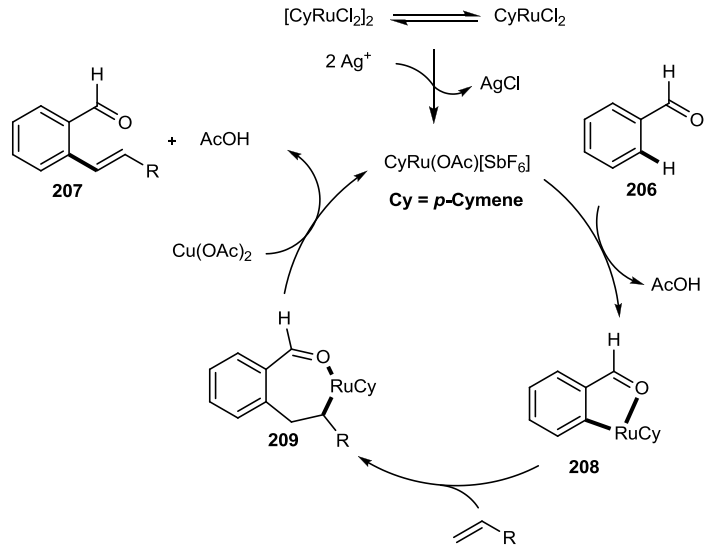
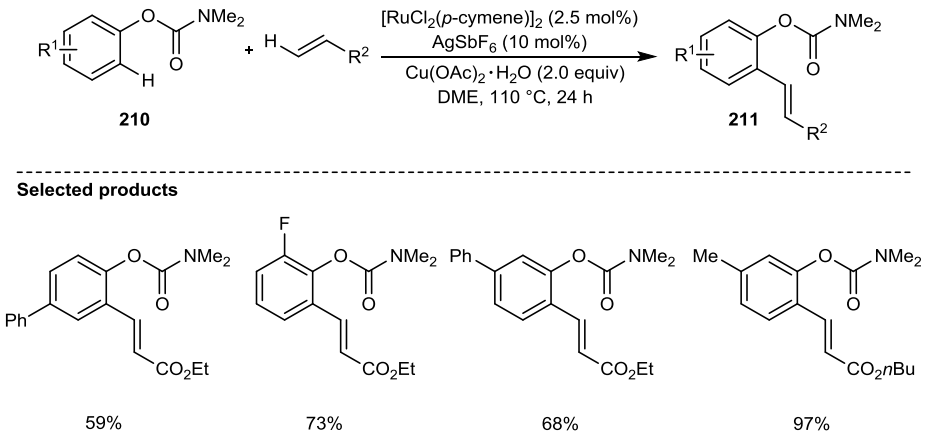


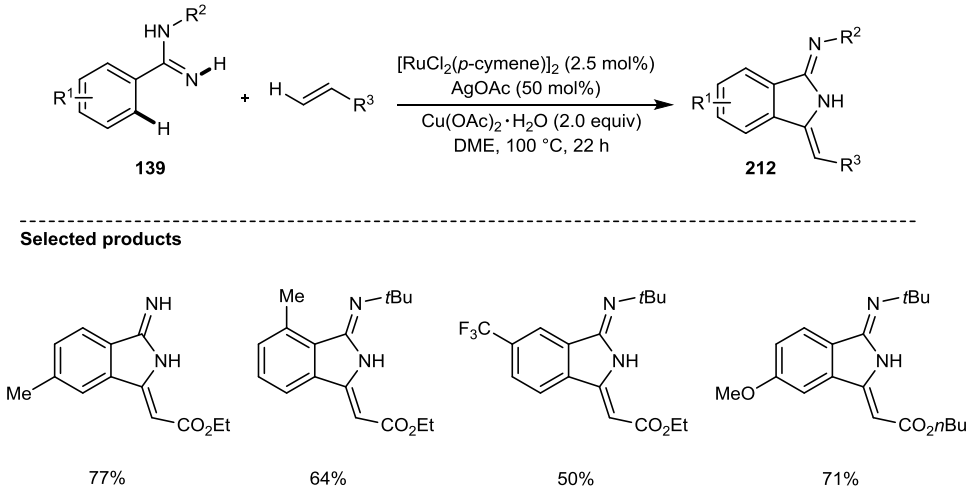
Figure 2.6. Possible catalytic cycle for aldehyde alkenylation.

Ackermann and co-workers developed an oxidative alkenylation of aryl carbamates **210** using ruthenium catalysis. The reaction produces good results under aerobic conditions with ambient air as an external oxidant (Scheme 2.11).[117] The ruthenium catalyst was found to be highly valuable and tolerated a range of functional groups including alkyl, aryl fluorides, chlorides and bromides. Additionally, electron-rich and electron-deficient arenes were also proved to be effective counterparts delivering their corresponding products in good yield.



Scheme 2.11. Alkenylation of aryl carbamate derivatives.

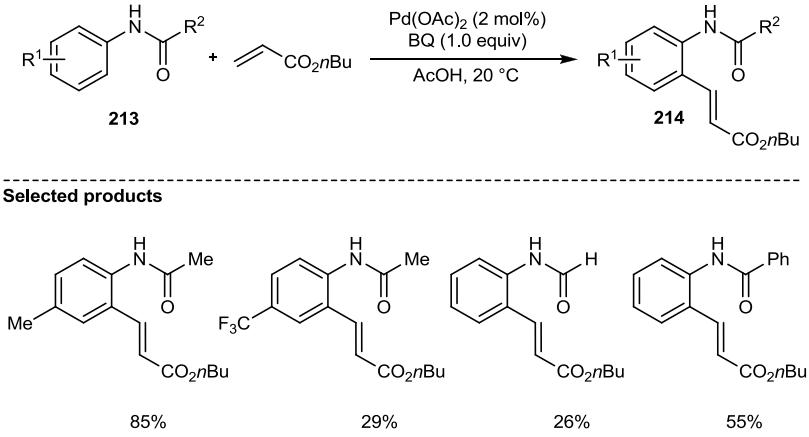
In 2014, Ackermann and co-workers developed an efficient Ru-catalyzed C–H activation protocol using amidine substrates **139** with substituted acrylates affording a diverse range of new 1-iminoisoindoline derivatives **212** (Scheme 2.12).[64] With the optimized reaction conditions, the scope of the ruthenium(II)-catalyzed process was examined with differently substituted benzamidines and alkenes. Several valuable electrophilic functional groups, such as fluoro, chloro, bromo, and nitro substituents were tolerated. The C–H-bond functionalization also occurred efficiently with *para*- and more sterically-hindered *ortho*-substituted amidines.



Scheme 2.12. Synthesis of iminoisoindoline derivatives.

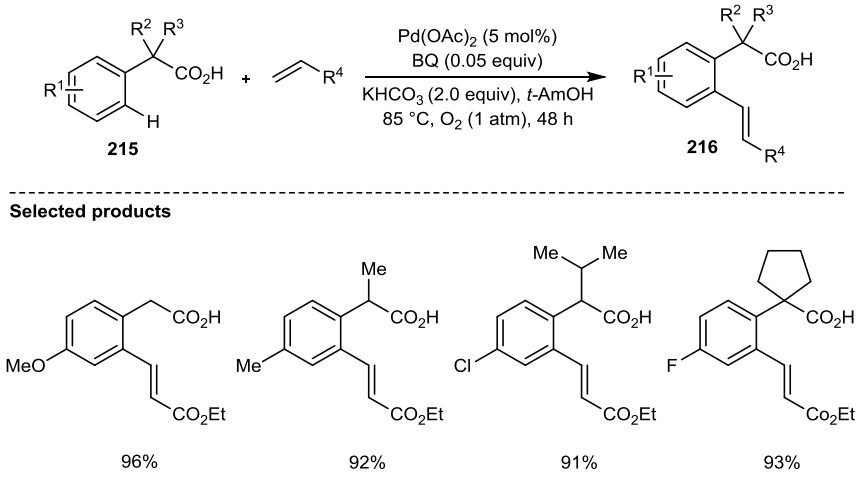
2.2.4. Palladium-Catalyzed Dehydrogenative Olefination Reactions

Vries, Leeuwen and co-workers carried out a selective and oxidative olefination of aniline derivatives **213** under palladium catalysis conditions. The reaction produced products **214** with good yields at room temperature with the use of benzoquinone as an oxidant (Scheme 2.13).[118] It is notable that the substituents on the aryl ring of the acetanilide substrate influence the coupling reaction significantly. *Ortho*-substitution hampered the reaction whereas the substrates with electron-rich substituents were significantly higher yielding, compared to the substrates with electron-deficient substituents.



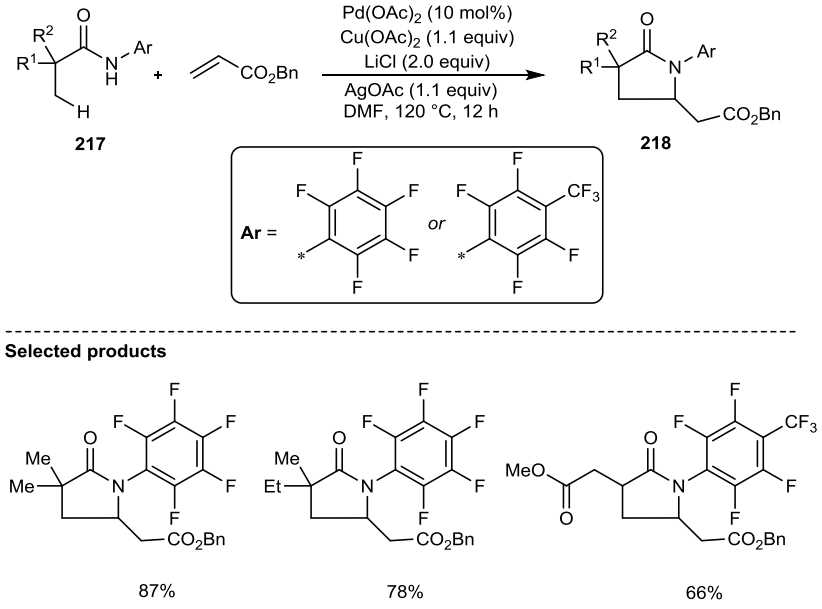
Scheme 2.13. Alkenylation of aniline derivatives.

Yu and co-workers demonstrated a simple and atom-economical C–H olefination reaction of phenylacetic acid and phenylpropionic acid substrates **215** under palladium catalysis using oxygen as an oxidant at room temperature (Scheme 2.14).[119] A wide range of phenylacetic acid substrates were found to be operative under this protocol, affording alkenylated products **216** in good yields. Several drugs, including ketoprufen, naproxen, and ibuprofen were found to react under these conditions. A variety of alkenes were also compatible with this protocol as coupling partners.



Scheme 2.14. Alkenylation of phenylacetic and phenylpropionic acids.

The same group developed an efficient protocol for direct olefination of C(sp^3)–H bonds using palladium catalysis. The reaction provides a diverse scope of lactam compounds **218** in good yield (Scheme 2.15).[120] Using optimized reaction conditions, an array of α-hydrogen containing substrates **217** were tolerated affording olefinated products in good to excellent yields.



Scheme 2.15. Alkenylation of amide derivatives.

2.3. Aims and Objectives

Olefins represent basic organic building blocks, and stereoselective methods for their preparation are highly valued. A promising method for the preparation of alkenes combines C–H bond functionalization with a Heck-type alkenylation.[121]

The aim of our present study was based on our previous finding that 2-aryl-3-hydroxy-2-cyclohexenones are effective substrates for ruthenium-catalyzed oxidative annulations with alkynes producing a range of spiroindenes *via* sequential C(sp^2)–H and C(sp^3)–H functionalization in generally good yields.[122] In light of these results, we speculated whether replacement of the alkyne with a terminal alkene would enable the corresponding C(sp^2)–H alkenylation of these substrates to proceed (Figure 2.7). If successful, the initially formed product **219** would likely undergo cyclization of an enolate oxygen atom onto an electron-deficient alkene. This process would be attractive as the resulting benzopyrans **220** resemble the core structures of a number of biologically active natural products and drug candidates.[94-96]

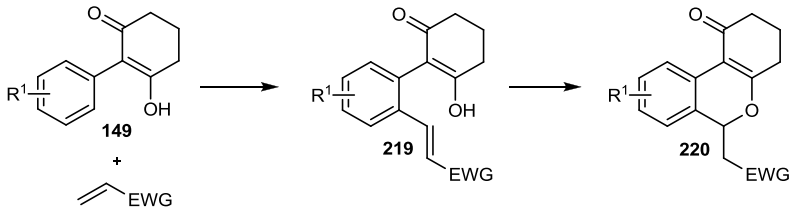


Figure. 2.7. Proposed benzopyran synthesis by C–H alkenylation.

Recently, the synthesis of benzopyrans under metal-catalyzed processes has been developed by using palladium,[123-125] ruthenium,[126] rhodium,[127] gold,[128] and copper complexes,[129] with a range of alkynes as coupling partners. The direct and related precedent for an alkenylation approach comes in the form of a study by Miura and co-workers, who demonstrated that a range of benzopyrans could be easily accessed by the palladium-catalyzed C–H alkenylation of 2-phenylphenols **221** (Figure 2.8).[130]

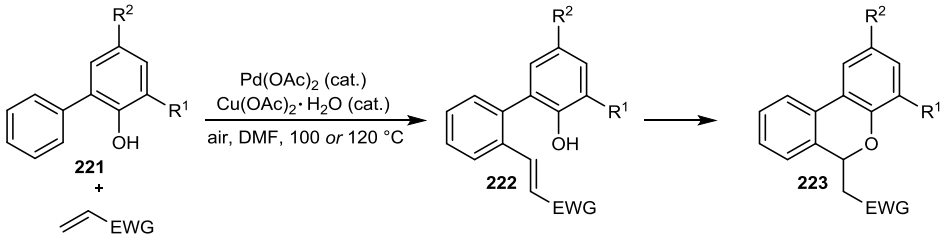


Figure 2.8. Palladium-catalyzed C–H alkenylation of 2-phenylphenols.

Yu and co-workers also reported an efficient palladium-catalyzed hydroxyl-directed C–H alkenylation using a tertiary alcohol as a directing group and an inexpensive menthol-leucine carbamate ligand (Figure 2.9).[131]

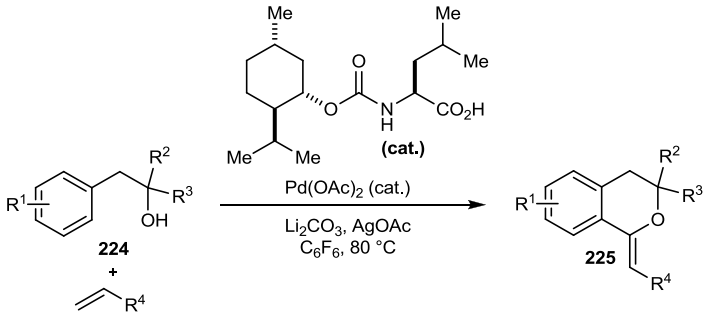


Figure 2.9. Palladium-catalyzed hydroxyl-directed C–H alkenylation.

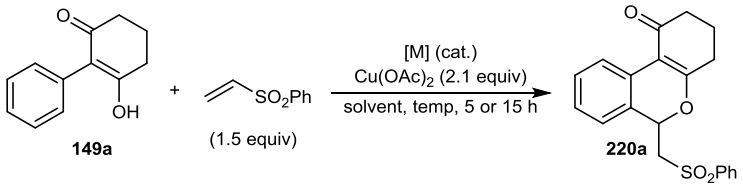
To our knowledge, the use of 2-aryl-3-hydroxy-2-cyclohexenones as substrates for metal-catalyzed directed C–H alkenylation has not been reported previously. Herein, we demonstrate the successful use of these substrates in the strategy presented in Figure 2.7. Furthermore, these reactions proceed using not only well-established palladium catalysis,[118-120] but also with more recently developed ruthenium catalysis.[114-117]

2.4. Results and Discussion

2.4.1. Reaction Optimization

Our investigation began with the study of metal precatalysts and reaction conditions using 3-hydroxy-2-phenyl-2-cyclohexenone **149a** as a standard substrate with phenyl vinyl sulfone as an alkenylation partner to give the corresponding benzopyran product. Based on the previous understanding of substrate reactivity, $Cu(OAc)_2$ (2.1 equiv) was used as the oxidant (Table 2.1). A range of metal precatalysts, solvents, temperatures and additives were screened to obtain the desired benzopyran product in good yield. Pleasingly, the initial experiment of substrate **149a** with olefin using $Pd(OAc)_2$ (5 mol%) was successful providing benzopyran **220a** in 78% yield in DMF at 120 °C (entry 1). The reaction conducted using $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), which had proven successful in our previous study of spiroindene synthesis,[122] was less effective, and led to a decrease in chemical yield (30%) of **220a** (entry 2). The use of base (K_2CO_3, 2.0 equiv) as an additive also had a detrimental effect on the reaction producing benzopyran in only 7% yield (Entry 3). Although, the exchange of DMF for *t*-AmOH as the solvent offered no improvement in the reaction efficiency (entry 4), the addition of K_2CO_3 (2.0 equiv) to these reaction conditions led to the isolation of **220a** in a significant yield (61%, entry 5). In addition, the use of rhodium precatalysts also afforded benzopyran in an isolated yield of 69% using DMF as the reaction solvent. The beneficial effect of K_2CO_3 was not replicated using *t*-AmOH as the solvent (entry 7, compare with entry 5). Although, rhodium precatalysts provided comparable results to palladium, further experimentation was carried out by using palladium and ruthenium catalysts due to their lower cost.

Table 2.1. Evaluation of reaction conditions[a,d]

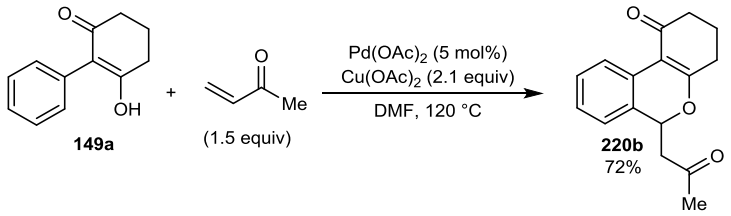


Entry	[M]	[mol%]	Solvent	Temp [°C]	Time [h]	Yield [%][b]
1	**$Pd(OAc)_2$**	**5**	**DMF**	**120**	**5**	**78**
2	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	120	15	30
3[c]	$[RuCl_2(p\text{-cymene})]_2$	2.5	DMF	120	15	7
4	$[RuCl_2(p\text{-cymene})]_2$	2.5	*t*-AmOH	90	15	8
5[c]	**$[RuCl_2(p\text{-cymene})]_2$**	**2.5**	***t*-AmOH**	**90**	**15**	**61**
6	$[RhCp^*Cl_2]_2$	2.5	DMF	120	15	69
7[c]	$[RhCp^*Cl_2]_2$	2.5	*t*-AmOH	90	15	51

[a]Reactions were conducted using 0.50 mmol of **149a**. [b]Cited yields are of isolated material. *t*-Am = *tert*-amyl. [c]Reaction conducted in the presence of K_2CO_3 (2.0 equiv). [d]Experiments performed by Dr. Suresh R. Chidipudi & Martin D. Wieczysty.

2.4.2. Comparison of Ruthenium- and Palladium-Catalyzed Alkenylations

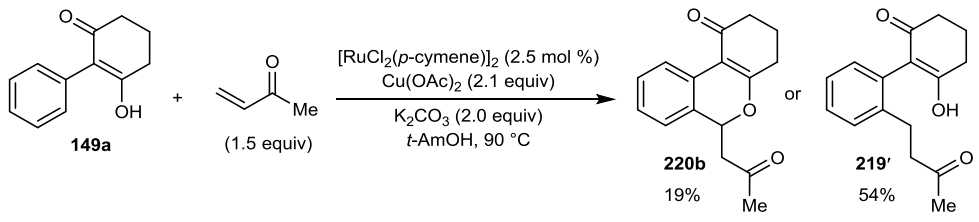
From the optimized conditions, we pleasingly observed that the C–H olefination reaction proceeded both under the ruthenium and palladium catalysis affording the benzopyran product in good yield. It was therefore our aim to investigate the reaction scope under both sets of conditions. With the optimized reaction conditions for palladium (Table 2.1, Entry 1) and ruthenium (Table 2.1, Entry 5) catalysis, a study was established to assess the difference in catalytic reactivity between the two precatalysts using a range of terminal olefins. Initially, the reaction of substrate **149a** and methyl vinyl ketone was conducted under palladium conditions (Scheme 2.16).
On examination of the reaction, it was observed that the corresponding benzopyran **220b** was successfully obtained in 72% yield. The remaining mass balance of the reaction was a complex mixture of unidentified by-products which is possibly due to substrate decomposition under the reaction conditions. Further examination of the reaction at lower temperatures resulted in a decreased yield of the desired benzopyran **220b**.



Reaction performed by Dr. Suresh R. Chidipudi/Martin D. Wieczysty

Scheme 2.16. Pd-catalyzed alkenylation of substrate **149a** with methyl vinyl ketone.

When the same reaction was conducted using $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst, the formation of benzopyran product **220b** was inefficient (19%) delivering addition product **219′** as the major product (54% yield, Scheme 2.17).



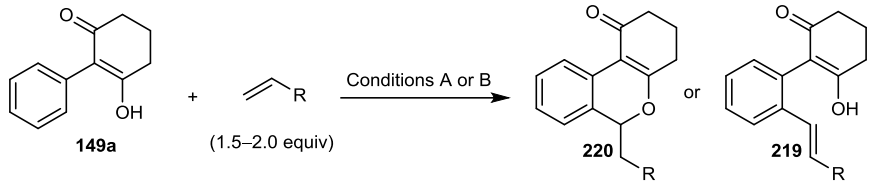
Reaction performed by Dr. Suresh R. Chidipudi/Martin D. Wieczysty

Scheme 2.17. Ru-catalyzed alkenylation of substrate **149a** with methyl vinyl ketone.

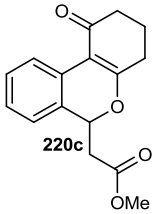
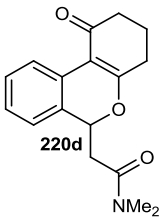
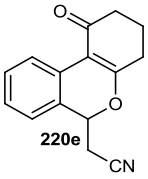
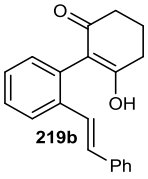
Based on these observations, substrate **149a** was then subjected to palladium and ruthenium reaction conditions with a range of other terminal alkenes (Table 2.2). Electron-deficient alkenes including methyl acrylate (entry 1), *N*,*N*-dimethylacrylamide (entry 3), and acrylonitrile (entry 5) were effective in the C–H alkenylation of **149a** using palladium catalysis. In general, the yields of annulated products were slightly higher when the reactions were conducted under ruthenium catalysis. The use of methyl acrylate as coupling partner afforded corresponding benzopyran in 65% yield using palladium catalysis, whereas a 76% yield was observed using ruthenium conditions. Similarly, in case of *N*,*N*-dimethylacrylamide and acrylonitrile, the corresponding benzopyrans were obtained in 47% and 45% isolated yields respectively. The same coupling partners were more efficient under ruthenium conditions affording desired products in 64% and 61% yields.

In the case of styrene as a reaction partner, the reaction temperature (palladium catalysis) was unfavorable leading to lower chemical yields, however, when the reaction temperature was lowered to 90 °C, product **219b** was obtained in higher yield. In this case, the unsaturated alkenylation addition product was obtained in 59% and 52% yield, respectively, under both palladium and ruthenium conditions (entries 7 and 8). The formation of the non-cyclized addition product is most probably due to the minimal electron-withdrawing properties of the benzene ring which reduces the oxa-cyclization efficiency to form the benzopyran.

Table 2.2. Catalytic C–H alkenylation of **149a**[a,f]



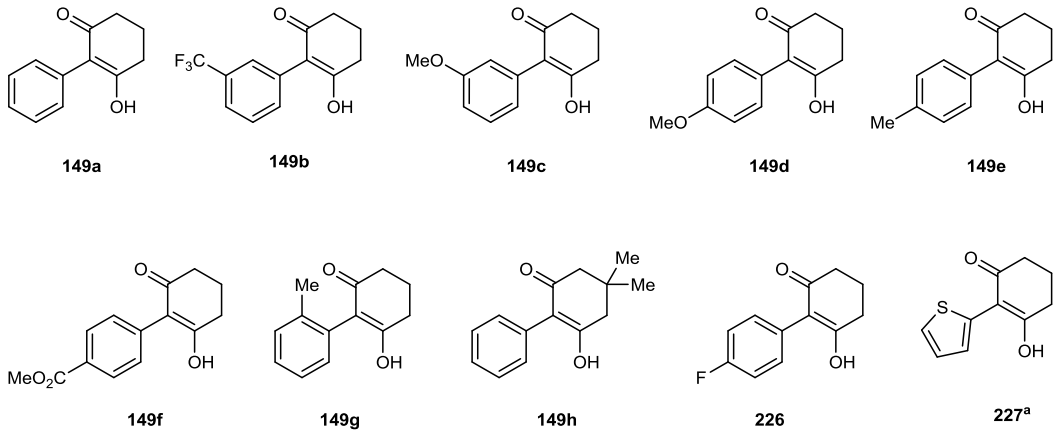
Conditions A: $Pd(OAc)_2$ (5 mol %)
$Cu(OAc)_2$ (2.1 equiv), DMF, 120 °C, 2–24 h
Conditions B: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2$ (2.1 equiv)
K_2CO_3 (2.0 equiv), *t*-AmOH, 90 °C, 2–24 h

Entry	Product(s)	Conditions	Yield[%][b]
1		A	65
2		B	76
3		A	47
4		B	64
5		A	45
6		B	61
7[c]		A	59
8		B	52

[a]Reactions were conducted using 0.50 mmol of **149a**. [b]Cited yields are of isolated material. [c]Reaction conducted at 90 °C as the reaction conducted at 120 °C led to a complex mixture. [f]Experiments performed by Dr. Suresh R. Chidipudi & Martin D. Wieczysty.

2.4.3. Preparation of 2-Aryl-1,3-dicarbonyl Compounds

Based on the initial investigations, the 1,3-dicarbonyl compounds showed general reactivity under palladium- and ruthenium catalysis. To further probe the reaction scope, it was proposed to investigate a range of 2-aryl cyclic 1,3-dicarbonyl substrates and couple them with electron-deficient olefins under palladium- and ruthenium conditions to generate a library of benzopyran compounds. A range of previously accessed 1,3-dicarbonyl substrates were investigated in addition to newly synthesized aryl substituted analogues (Figure 2.10).



[a]Experiment performed by Martin D. Wieczysty

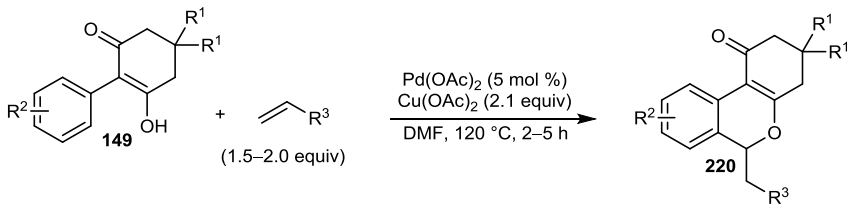
Figure 2.10. Synthesis of 1,3-dicarbonyl compounds.

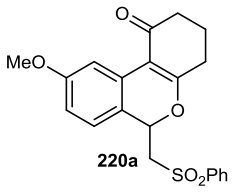
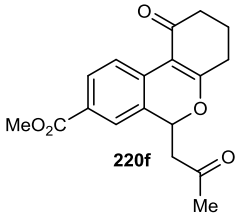
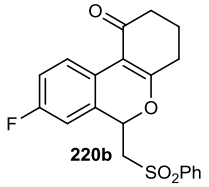
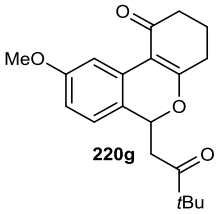
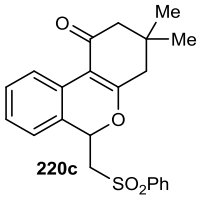
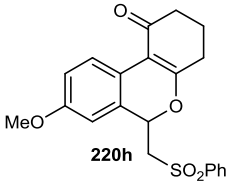
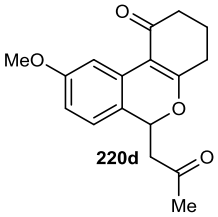
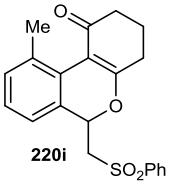
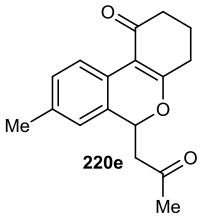
2.4.4. Evaluation of Reaction Scope

2.4.4.1. Pd-Catalyzed C–H Alkenylation of 2-Aryl-1,3-dicarbonyl Compounds

Having established the C–H alkenylation protocol, the reactions of a range of 2-aryl-3-hydroxy-2-cyclohexenones were carried out using a number of different electron-deficient alkenes under the optimized palladium conditions (Table 2.3). Pleasingly, a range of substituents were well tolerated with phenyl vinyl sulfone, methyl vinyl ketone and *tert*-butyl vinyl ketone producing desired benzopyran products (**220a-220h**) in moderate to good yields. The substrate **149c** featuring a *meta*-methoxy substituent delivered benzopyran **220a** in 64% yield as a single regioisomer. In this case, C–H functionalization occurred exclusively at the more sterically accessible site (product **220a**), which is consistent with our previous study.[122] X-ray crystallography allowed unambiguous confirmation of the site-selectivity in the formation of **220a**. In addition to *meta*-substituted substrates, *para*-substituents were also tolerated well. In case of *para*-fluoro substituted substrate **226**, the intended benzopyran **220b** was produced in 50% yield. Additional *para*-substituents include electron-rich methyl and electron-deficient methyl ester and were also well tolerated delivering corresponding benzopyrans in 73% and 68% yield, respectively. The coupling of substrate **149d** with phenyl vinyl sulfone was inefficient, producing the desired benzopyrans **220h** in 26% yield. In addition, a dimedone-derived substrate was also effective, providing benzopyran **220c** in 65% yield. No C–H alkenylation occurred with a substrate containing an *ortho*-methylphenyl group (product **220i**).

Table 2.3. Pd(II)-catalyzed alkenylation (reaction scope)[a]



Entry	Benzopyran	Yield [%][b]	Entry	Benzopyran	Yield [%][b]
1[c]		64	6[c]		68
2		50	7		47
3[c]		65	8[c]		26
4[c]		70	9		0
5		73			

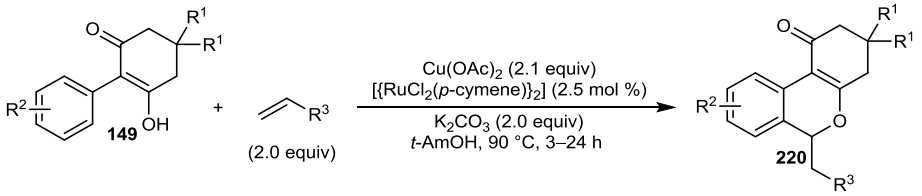
[a]Reactions were conducted with 0.50 mmol of **149c**, **149d–149h**, and **226**. [b]Cited yields are of isolated material. [c]Experiments performed by Dr. Suresh R. Chidipudi & Martin D. Wieczysty.

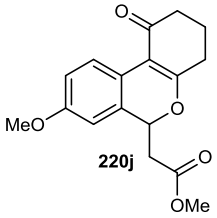
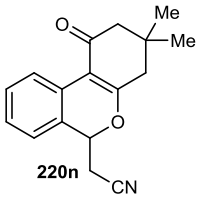
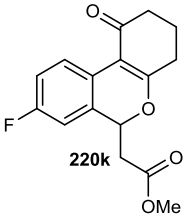
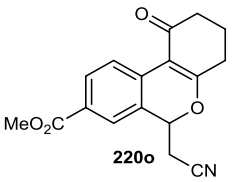
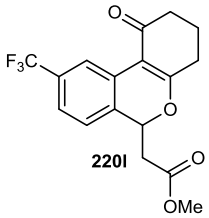
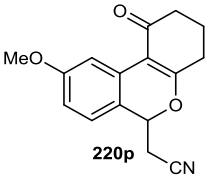
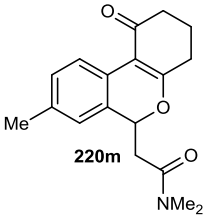
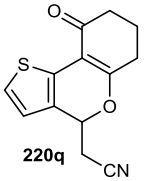
2.4.4.2. Ru-Catalyzed C–H Alkenylation of 2-Aryl-1,3-dicarbonyl Compounds

Pleased with the synthesis of benzopyrans with good functional group tolerance and generality in terms of substrate diversity and olefins as coupling partners under palladium catalysis, further examination of the scope of the process was performed. Methyl acrylate, *N*,*N*-dimethyl acrylamide, and acrylonitrile as the alkene reaction partner was used under ruthenium catalysis (Table 2.4), utilizing the previously optimized conditions (Table 2.1, entry 5).

The *para*-methoxy aryl substrate **149d** successfully underwent the alkenylation reaction with methyl acrylate, producing benzopyran **220j** in 66% yield. Other *para*-substituted substrates for example *para*-fluoro aryl afforded corresponding benzopyran **220k** in acceptable yield when reacted with the electron-deficient methyl acrylate. The substrates with carbomethoxy group (**149f**) and methyl substituent (**149e**) were also efficient under the standard reaction conditions delivering the corresponding benzopyran products in 74% and 45% yield, respectively. In this case, however, the reaction was performed without addition of K_2CO_3, as under the previously optimized conditions, lower yield of products was observed. With the *meta*-methoxy and *meta*-(trifluoromethyl)phenyl-containing substrate, C–H alkenylation occurred exclusively at the more sterically accessible site (product **220p** and **220l**). A poor yield of 30% was obtained with substrate **149c** using an acrylonitrile coupling partner to produce benzopyran **220p**. The reaction of a dimedone-derived substrate with acrylonitrile gave benzopyran **220n** in 64% yield. This result implies that a delicate balance of the electronic nature of both coupling partners is required in some cases to obtain high yields. Substrate **227** bearing a thiophene moiety also underwent similar cyclization with acrylonitrile but the yield was quite poor (product **220q**, 13%). The remaining mass balance was substrate recovery with a complex, inseparable mixture of by-products.

Table 2.4. Ru(II)-catalyzed alkenylation (reaction scope)[a]

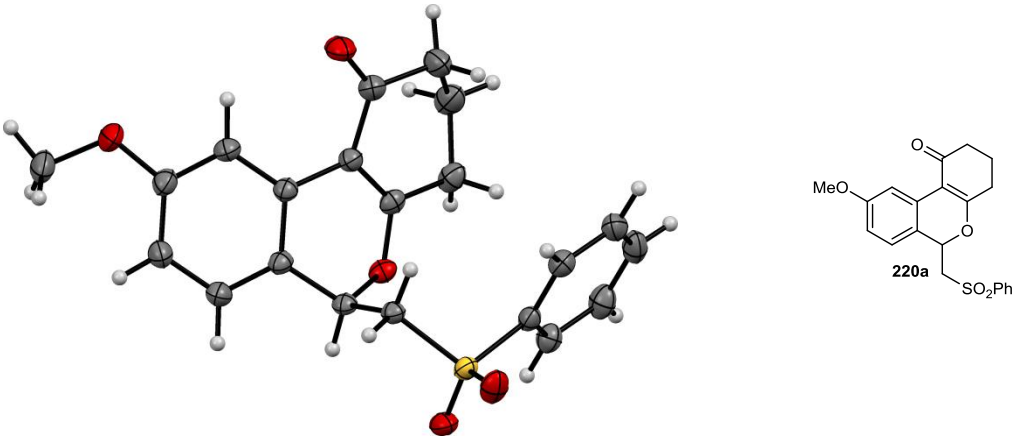


Entry	Benzopyran	Yield [%][b]	Entry	Benzopyran	Yield [%][b]
1[d]		66	5[d]		64
2		57	6		74[c]
3[d]		55	7		30
4		45	8[d]		13

[a]Reactions were conducted with 0.50 mmol of **149b–149h** and **227**. [b]Cited yields are of isolated material. [c]Reaction conducted in the absence of K_2CO_3, as **220o** was formed in a low yield when K_2CO_3 was employed. [d]Experiments performed by Dr. Suresh R. Chidipudi & Martin D. Wieczysty.

2.4.5. Site-Selectivity Determination

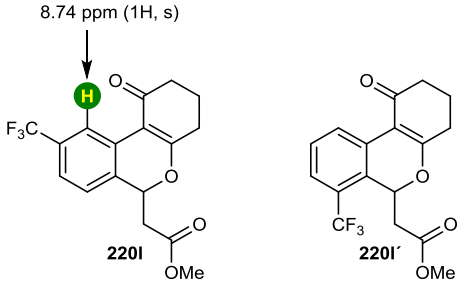
The structure of compound **220a** was determined by X-ray crystallography (Figure 2.11), and the structures of compounds **220d**, **220g**, **220l** and **220p** were assigned by analogy. This structure demonstrated the occurrence of C–H functionalization at the more sterically accessible site.



Reaction performed by Dr. Suresh R. Chidipudi

Figure 2.11. Crystal structure of benzopyran **220a**.

The structure of compound **220l** was assigned on the basis of the ^{1}H NMR spectrum, in which the indicated proton gave rise to a singlet. The alternative product **220l´** would not give rise to such a signal.



2.4.6. Proposed Catalytic Cycle

A possible catalytic cycle for this process was proposed based on previously reported mechanisms (Figure 2.12). It is assumed that reaction of **149a** with the metal acetate complex **228**[132] leads to deprotonation to generate the corresponding enolate, which is able to direct cyclometallation to form metallacycle **229**. This complex then coordinate with the alkene and a migratory insertion step then provides a second metallacycle **230**,[122] which is protonated by AcOH to give species **231**. *β*-Hydride elimination of **231** releases metal hydride species **232** and furnishes the alkenylated product **219** which then cyclizes to the benzopyran **220**. Reductive elimination of **232** and $Cu(OAc)_2$-promoted oxidation of the resulting Pd(0) or Ru(0) species **233** regenerates the metal acetate complex **228**.

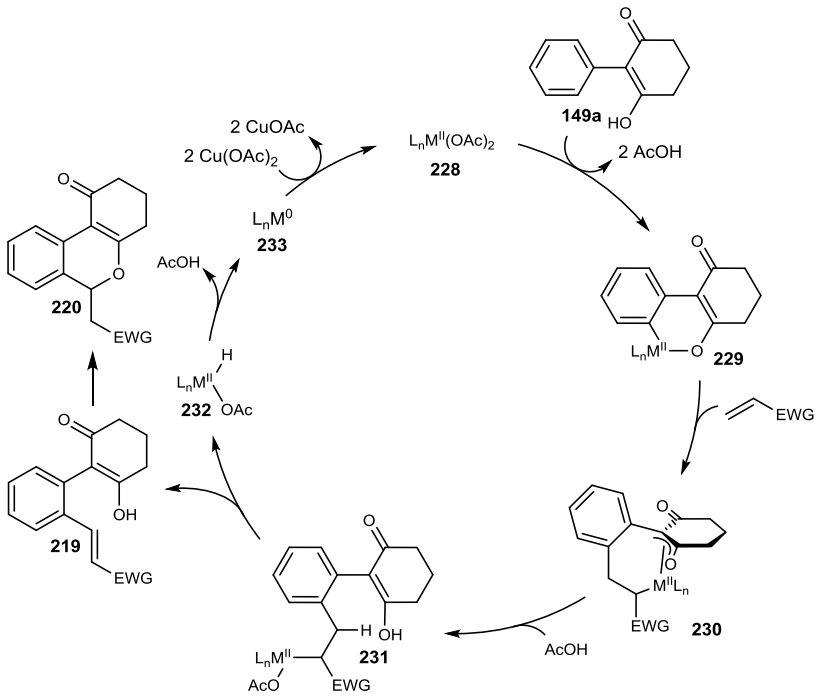
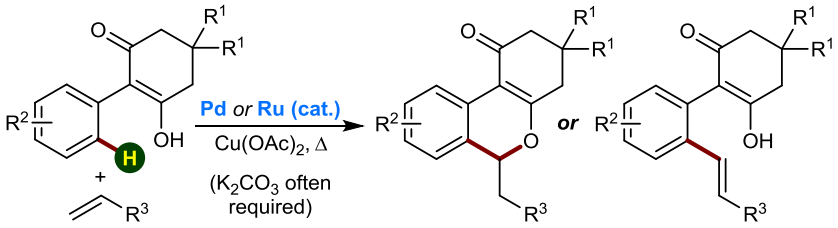


Figure 2.12. Proposed catalytic cycle for benzopyran formation.

2.5. Conclusions and Future Work

In summary, we have demonstrated that 2-aryl-3-hydroxy-2-cyclohexenones, which have been reported to undergo metal-catalyzed oxidative annulations with alkynes,[122] are also highly effective substrates in catalytic C–H alkenylation reactions. These reactions proceed not only under the action of well-established palladium catalysis, but also with more recently developed ruthenium catalysis to provide benzopyrans. A variety of 2-aryl cyclic 1,3-dicarbonyl compounds were successfully coupled with a range of electron-deficient olefins to form benzopyrans with high levels of functional group tolerance. Future investigations will focus on the variation of coupling partners in order to expand the directing ability of enolates in C–H functionalization chemistry to access a variety of heterocycles as well as carbocycles.



Chapter 3: Synthesis of Spiroindanes by Palladium-Catalyzed Oxidative Annulations of 1,3-Dienes Involving C–H Functionalization

3. Introduction

3.1. The Significance of Indanes

Indane ring frameworks are considered as diverse and significant scaffolds in the carbocyclic chemistry domain because these structural motifs have been found to possess outstanding biological properties and a wide range of utility in pharmaceutical industry, and as synthetic intermediates.[133] These derivatives exhibit promising levels of biological potential like anticancer, antitumor, anti-allergenic and significant increased mast cell stabilization activities.[134,135] Moreover, these structures also act as aspartic protease inhibitors, smooth muscle relaxants, and antiretroviral agents and are involved in the melatonin receptor agonism, inhibition of the production of inflammation factor TNF-α, inhibition of HIV integrease independent of COX-inhibitors and treatment of Alzheimer′s disease and asthma.[136] Some representative examples **234-237** are depicted in Figure 3.1.

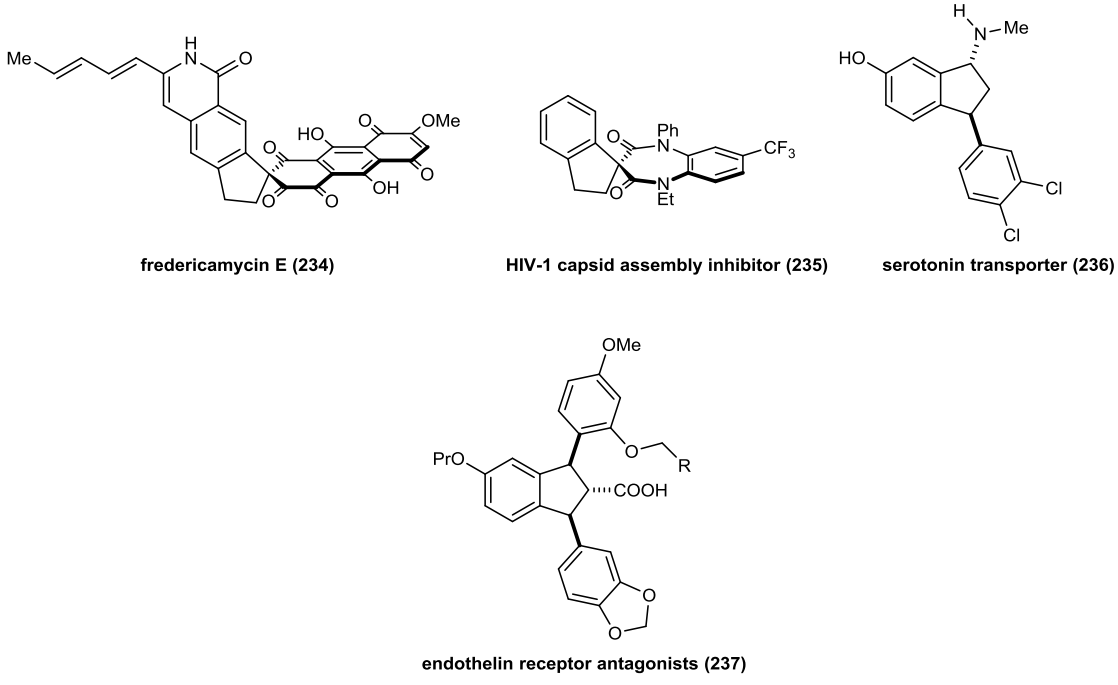


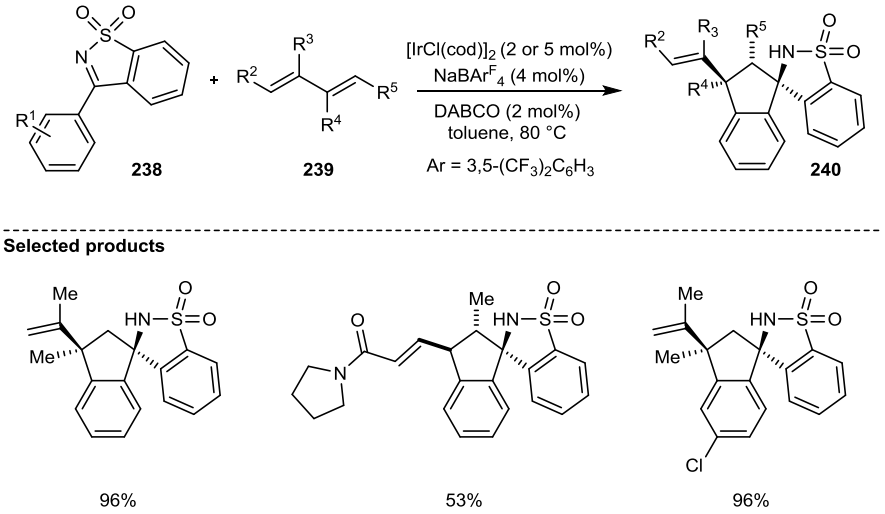
Figure 3.1. Representative examples of some biologically active indanes.

3.2. 1,3-Dienes in Organic Chemistry

1,3-Dienes are important structural motifs in organic chemistry due to their great potential to be readily transformed into a diverse range of synthetic products. These include carbo- and heterocycles,[137-139] peroxides,[140] mono-[141] and biscyclopropanes,[142] and *β*-lactams.[143] 1,3-Dienes also serve as important synthetic intermediates, finding particular application in the Diels-Alder reaction.[144] In the recent years, 1,3-dienes have also been shown to act as efficient coupling partners in C–H functionalization chemistry for the synthesis of useful compounds in a step-economic fashion.[145-148]

3.3. Metal-Catalyzed Annulation of 1,3-Dienes

Nishimura and co-workers reported an efficient synthesis of aminoindane derivatives **240** by Ir-catalyzed [3 + 2] annulation of cyclic *N*-sulfonyl ketimines **238** with 1,3-dienes **239** (Scheme 3.1).[145] This transformation was found to involve an aryliridium intermediate *via* C–H activation. The obtained products were in high yields with high regio- and diastereoselectivity. Under optimized reaction conditions, a diverse range of 1,3-dienes participated efficiently in this annulation reaction. Also, several ketimines were investigated having diverse substitution pattern on the aryl ring.



Scheme 3.1. Ir-catalyzed synthesis of spirocyclic compounds.

The proposed catalytic cycle (Figure 3.2) suggests that ketimine **238** coordinates to iridium and undergoes cyclometalation to form arylhydridoiridium(III) species **241**.[149] Deprotonation of **241** promoted by DABCO forms aryliridium(I) species **242**.

Nucleophilic attack of the electron-rich terminal carbon of diene at the imine carbon in intermediate **243**, where the other double bond of the diene coordinates to Ir, forms π-allyliridium(III) intermediate **244** *via* oxidative cyclization.[150] The intermediate **244** undergoes reductive elimination to form a carbon-carbon bond, giving imidoiridium(I) species **245**. Subsequent protonolysis gives aminoindane **240** and regenerates the cationic Ir complex. Alternatively, protonation of **244** to form a cationic π-allyliridium(III) species and subsequent reductive elimination would give the annulation product.

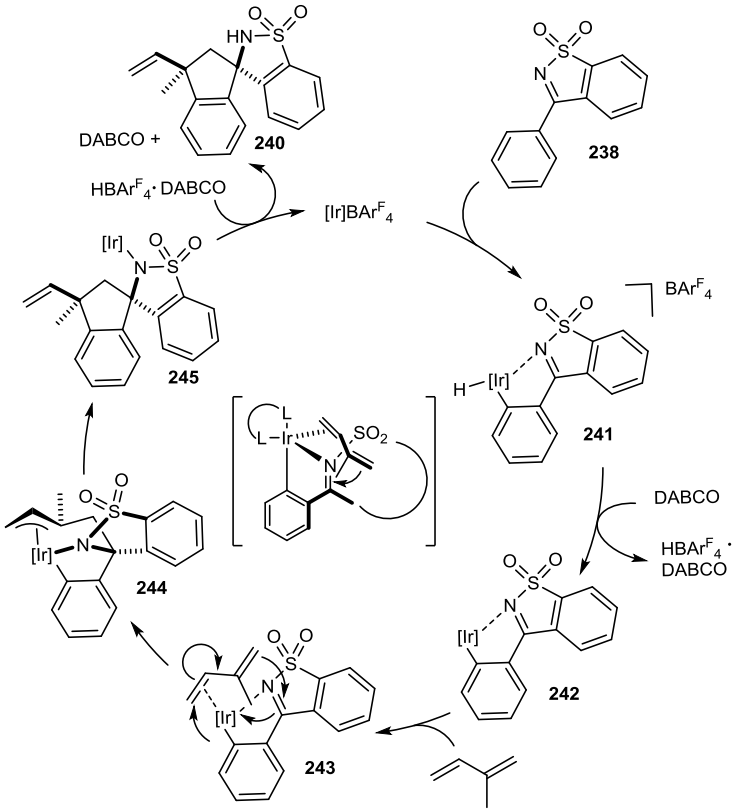
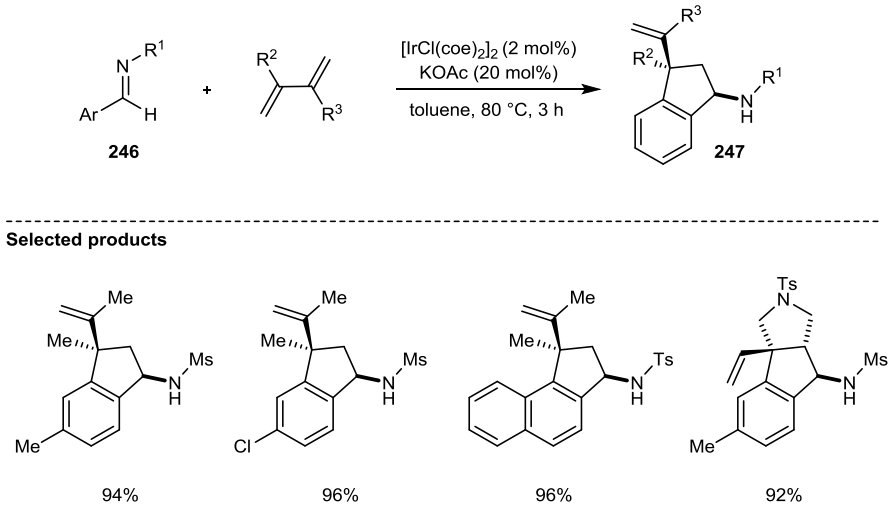


Figure 3.1. Proposed catalytic cycle for spiroindane synthesis.

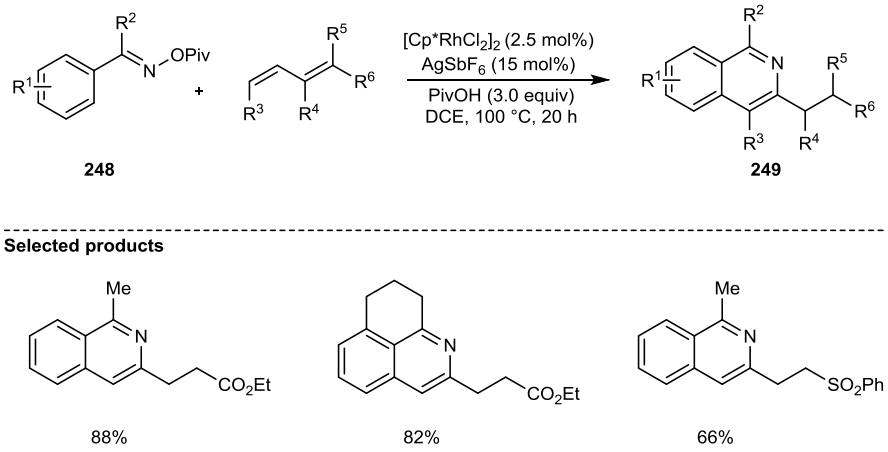
The same group developed the annulation of aromatic aldimines **246** with 1,3-dienes using an iridium catalyst to give aminoindanes **247** in good yields (Scheme 3.2).[146] The scope of the reaction was explored using a range of aromatic imines substituted at the *para*-position with electron-donating groups (Me, MeO and NMe_2) and electron-withdrawing groups (F, Cl, Br, and CF_3) gave good yields of the corresponding annulation products. In case of *meta*-substituted substrates, the reaction occured at the least sterically hindered C–H bond of the phenyl ring. Also, in case of 1-

naphthylimine, the annulation occurred at the 2-position affording product in 96% yield.



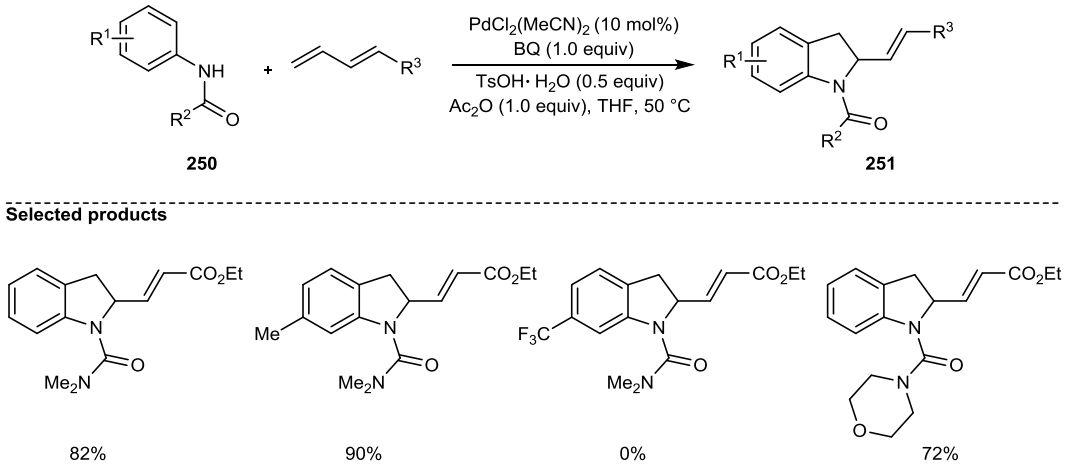
Scheme 3.2. Synthesis of aminoindanes.

Glorius and co-workers developed an efficient strategy for the preparation of isoquinolines **249** from aromatic oxime esters **248** and 1,3-dienes under rhodium(III)-catalyzed redox-neutral C–H activation/cyclization/isomerization sequence (Scheme 3.3).[147] This transformation proceeded without using any external oxidant under simple and convenient conditions and delivered annulated products in good yields with complete regioselectivity. The process was also tolerant to a wide range of substrates. Under standard reaction conditions, a range of substituents at various positions (5-, 6-, 7- and/or 8-) were tolerated affording isoquinoline products in good to excellent yields. Substrates with electron-rich, electron-poor, or sterically encumbered substituents were also tested. In addition, a variety of mono-substituted electron-deficient dienes bearing ester, ketone, sulfone, cyano and phosphonate functional groups could be efficiently used as reaction coupling partners.



Scheme 3.3. Synthesis of isoquinolines.

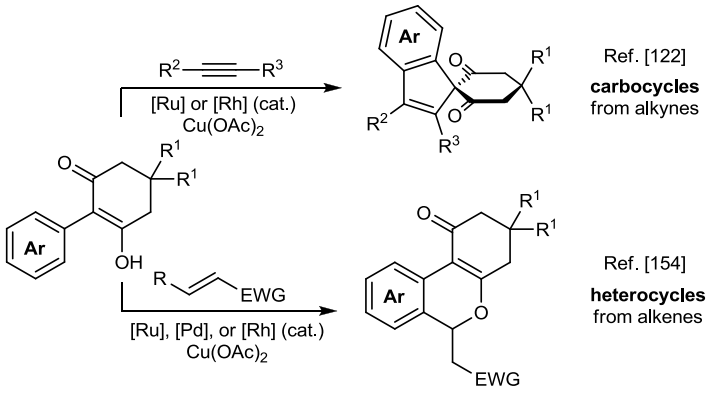
Booker-Milburn, Lloyd-Jones, and co-workers developed a new route towards the synthesis of indolines **251** by Pd(II)-catalyzed diene 1,2-carboamination reaction, involving an *ortho* C–H insertion/carbopalladation/cyclization sequence (Scheme 3.4).[148] The products **251** were obtained in high yields from readily available *N*-aryl ureas **250** in a single step. Under optimized reaction conditions, a variety of electron-deficient dienes were successfully reacted leading to the desired products in moderate to good yields. In addition, different aryl ring substitutions were also well tolerated. In case of *meta*-substitution with electron-donating groups, a single regioisomer of the corresponding indoline product was obtained. However, electron-withdrawing (CF_3) substitution in the *meta*-position as well as *ortho*-substitution retarded the reaction completely.



Scheme 3.4. Synthesis of indolines.

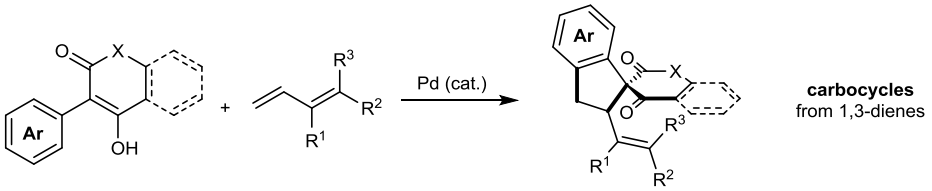
3.4. Aims and Objectives

The site-selective metal-catalyzed oxidative C–H functionalization of aromatic C(sp^2)−H bonds with alkynes and alkenes, directed by a heteroatom-containing functional group, is now a well-established strategy for the preparation of a diverse range of heterocycles.[151-153] In this context, we have demonstrated the utility of cyclic 1,3-dicarbonyls as directing groups in catalytic oxidative annulations that produce carbocyclic,[122] and heterocyclic products.[154] Using ruthenium or rhodium catalysis, these reactions resulted in the formation of spiroindenes when alkynes were used as the reaction partners (Scheme 3.5, top, see chapter 1).[122] However, the use of electron-deficient alkenes in place of alkynes led to the formation of heterocycles (Scheme 3.5, bottom)[154] resulting from intramolecular oxa-conjugate addition of the initially formed alkenylation products, which is in line with literature precedent (see chapter 2).[155] The ability to utilize other unsaturated compounds in oxidative annulations to prepare further types of carbocycles would represent a useful advance.[156]



Scheme 3.5. Synthesis of spiroindenes and benzopyrans.

However, 1,3-dienes have rarely been used as annulation partners in these types of reactions (see section 3.3). Although currently limited in number, these processes demonstrate the significant potential of 1,3-dienes as annulation partners in C–H functionalization reactions. The development of new types of annulations involving 1,3-dienes to increase the range of products that can be accessed, is therefore an important objective. So in view of these literature reports, we have developed the synthesis of carbocycles (spiroindanes) from the oxidative annulation of 2-aryl cyclic-1,3-dicarbonyls with 1,3-dienes under palladium catalysis (Scheme 3.6).



Scheme 3.6. Pd-catalyzed synthesis of spiroindanes from 1,3-dienes.

3.5. Results and Discussion

Pleased with the synthesis of spiroindenes and benzopyrans by the catalytic C–H functionalization of 2-aryl cyclic 1,3-dicarbonyl compounds using internal alkynes and electron-deficient alkenes, we hypothesized that these compounds might be suitable substrates for oxidative annulations when less explored 1,3-dienes are used as reaction coupling partners, resulting in the formation of carbocycles (spiroindanes) which have not been accessed in the previously reported annulation processes.

3.5.1. Preparation of 2-Aryl-1,3-dicarbonyl Substrates

In previous investigations, 2-aryl-1,3-dicarbonyl compounds showed general reactivity under various metal precatalysts. To undertake this new mode of oxidative annulation of 1,3-dienes, a range of previously accessed 1,3-dicarbonyl substrates were investigated (Figure 3.3).[122,154]

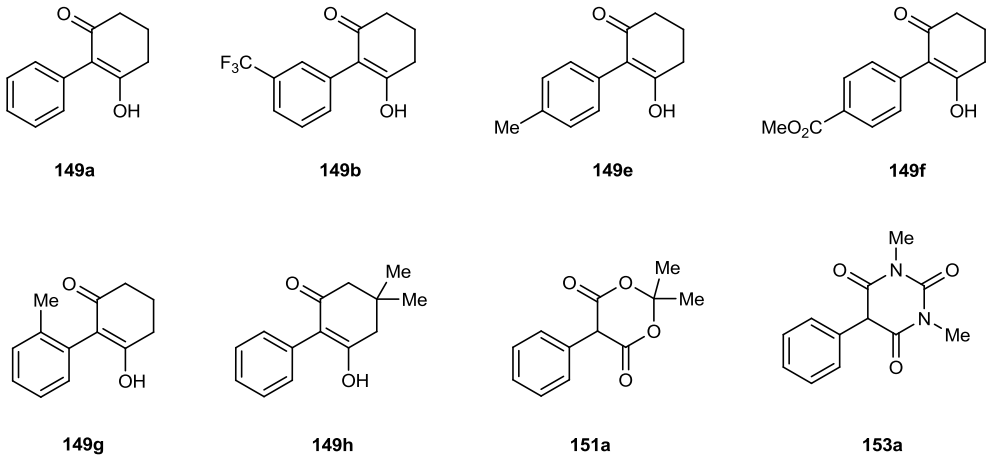
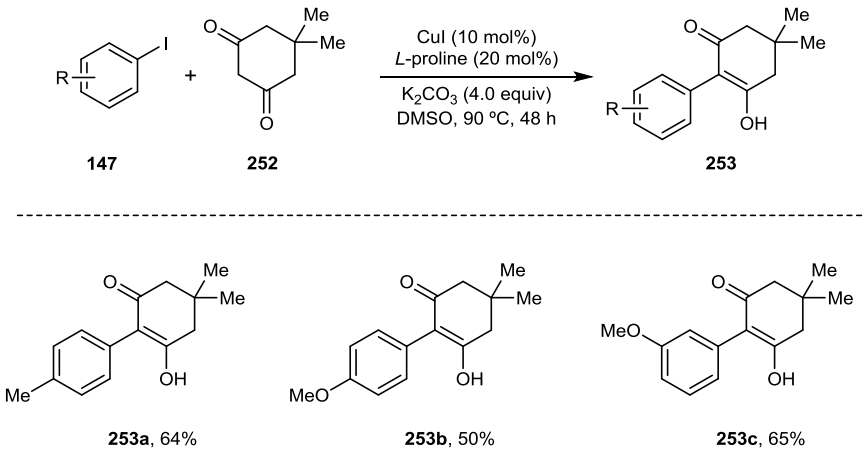


Figure 3.3. 1,3-Dicarbonyl substrates investigated herein.

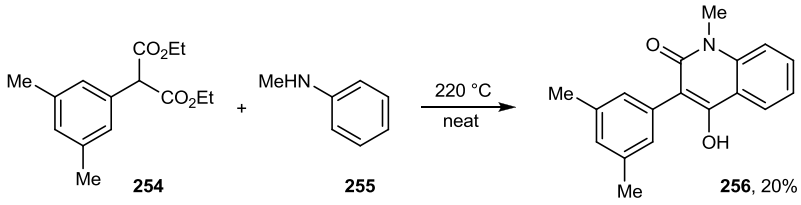
Several dimedone-derived 2-aryl dimedones (Scheme 3.7) were also synthesized using previously described procedure.[122,154]



Scheme 3.7. Synthesis of dimedone-derived 1,3-dicarbonyl compounds.

3.5.1.1. Preparation of Unsymmetrical 1,3-Dicarbonyl Substrate

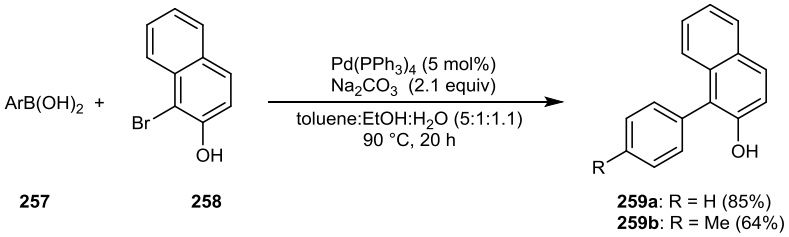
To expand the substrate scope, unsymmetrical 1,3-dicarbonyl compound **256** was synthesized from diethyl 2-(3,5-dimethylphenyl)malonate **254** (1.0 equiv) and *N*-methylaniline **255** (1.0 equiv) by heating at 220 °C (Scheme 3.8).[157]



Scheme 3.8. Synthesis of unsymmetrical 1,3-dicarbonyl compound.

3.5.2. Preparation of 1-Aryl-2-naphthols

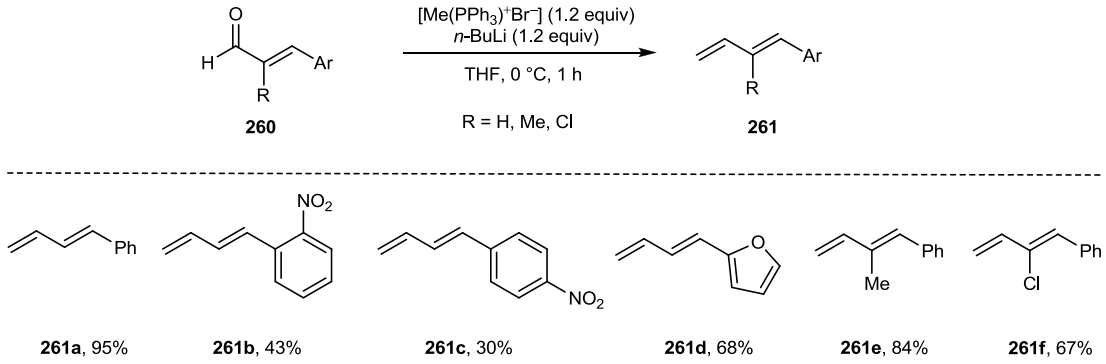
1-Aryl-2-naphthols **259** have also been applied as substrates in oxidative annulation reactions in the literature.[158] These compounds were obtained from the reaction of 1-bromonaphthalen-2-ol **258** and corresponding arylboronic acid **257**, under palladium catalysis in a mixture of solvents (Scheme 3.9).



Scheme 3.9. Synthesis of 1-aryl-2-naphthols.

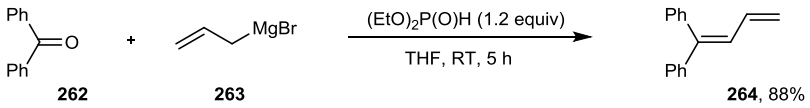
3.5.3. Preparation of 1,3-Dienes

Several synthetic pathways have been used to prepare a large variety of 1,3-dienes. The Wittig olefination of *α,β*-unsaturated aldehydes with methyl triphenylphosphonium ylide was used to synthesize terminal olefins. The *α,β*-unsaturated aldehydes were purchased from commercial sources and 1,3-dienes **261a**,[159] **261b**,[160] **261c**,[160] **261d**,[160] **261e**,[161] and **261f**,[162] were prepared according to previously reported procedures using the following representative synthetic pathway (Scheme 3.10).



Scheme 3.10. Synthesis of 1,3-dienes by Wittig olefination.

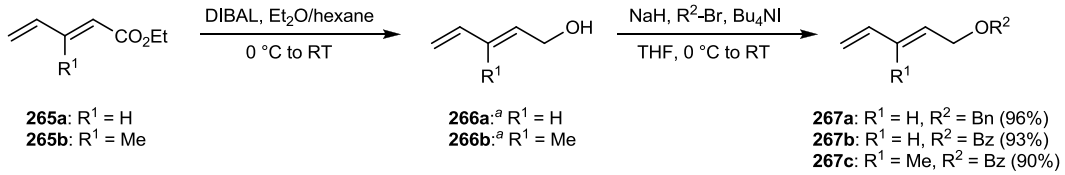
In addition, diene **264** was prepared by the olefination of benzophenone **262** with allyl magnesium bromide **263** in the presence of diethyl phosphite as depicted in Scheme 3.11.[163]



Reaction performed by Dr. Suresh Reddy Chidipudi

Scheme 3.11. Synthesis of buta-1,3-diene-1,1-diyldibenzene.

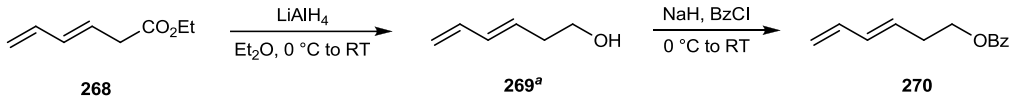
Several other 1,3-dienes (**267a-c**) were also synthesized by the synthetic pathway illustrated in Scheme 3.12. The diene esters **265** were reduced to corresponding allylic alcohols **266** using DIBAL and subsequent protection using benzyl or benzoyl bromide under basic conditions afforded the desired 1,3-dienes.



[a]Reactions performed by Dr. Suresh Reddy Chidipudi

Scheme 3.12. Synthesis of 1,3-dienes (**267a**-**c**).

Similarly, compound **270** was synthesized using the following synthetic pathway (Scheme 3.13). The homoallylic alcohol **269** was obtained by the $LiAlH_4$ reduction of allylic ester **268**. The subsequent benzoylation of **269** affords compound **269**.



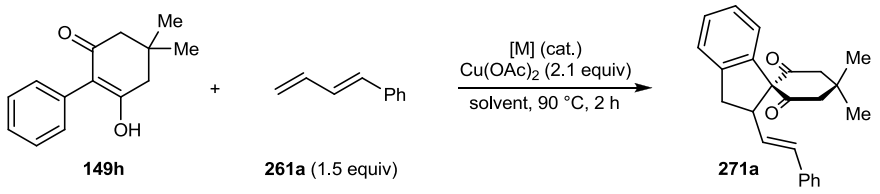
[a]Reaction performed by Dr. Suresh Reddy Chidipudi

Scheme 3.13. Synthesis of 1,3-diene **270**.

3.5.4. Reaction Optimization

The feasibility of the coupling reaction was initially examined by reacting 2-phenyldimedone (**149h**) with 1,3-diene **261a** (1.5 equiv) in the presence of various metal precatalysts and $Cu(OAc)_2$ (2.1 equiv) as an oxidant in DMF at 90 °C (Table 3.1). In the initial screening, the well-established ruthenium and rhodium complexes for C–H functionalizations were found to be inactive (Table 3.1, entries 1 and 2). However, the palladium-*N*-heterocyclic carbene complex PEPPSI-IPr that was previously employed for oxidative annulation of unsymmetrical 2-aryl cyclic 1,3-dicarbonyls[157] furnished spiroindane **271a** in 60% yield (Table 3.1, entry 3). Subsequent, optimization of solvents (*t*AmOH, 1,4-dioxane and MeCN) (entries 4-6) and base did not improve the yield (Table 3.1, entries 10 and 11). To our delight, a slightly enhanced yield (66%) of **271a** was observed when the reaction was conducted in degassed DMF (Table 3.1, entry 7).[164] The remaining mass balance of the reaction is the complex mixture of by-products due to substrate decomposition. Use of 2.5 mol% of PEPPSI-IPr gave **271a** in a more modest yield of 54% (entry 12), while increasing the catalyst loading from 5 mol% to 10 mol% led only to a minimal increase in yield (entry 13, compare with entry 7).

Table 3.1. Evaluation of reaction conditions for the synthesis of **271a**[a]



Entry	[M]	[mol%]	Solvent	Base	Yield [%][b]
1	[{$RuCl_2$(*p*-cymene)}$_2$]	2.5	DMF	—	—
2	[{Cp^*RhCl_2}$_2$]	2.5	DMF	—	—
3	PEPPSI-IPr	5	DMF	—	60
4	PEPPSI-IPr	5	*t*AmOH	—	39
5	PEPPSI-IPr	5	1,4-dioxane	—	46
6	PEPPSI-IPr	5	MeCN	—	38
7[c]	**PEPPSI-IPr**	**5**	**DMF**	**—**	**66**
8[d]	PEPPSI-IPr	5	DMF	—	48
9[e]	PEPPSI-IPr	5	DMF	—	—
10	PEPPSI-IPr	5	DMF	NaOAc	36
11	PEPPSI-IPr	5	DMF	K_2CO_3	25
12[c]	PEPPSI-IPr	2.5	DMF	—	54
13[c]	PEPPSI-IPr	10	DMF	—	68

[a]Using 0.25 mmol of **149h**. [b]Yield of isolated product. [c]Using degassed DMF. [d]With 1.1 equiv of diene. [e]Without $Cu(OAc)_2$. *t*Am = *tert*-amyl.

3.5.5. Evaluation of Reaction Scope

With the optimized catalytic system in hand (Table 3.1, entry 7), the scope of palladium-catalyzed annulation reaction was explored by using substrate **149h** with a range of 1,3-dienes. Table 3.2 illustrates the scope of substituents present on the various positions on 1,3-dienes we tested. Various aryl (Table 3.2, products **271a** and **271b**) or alkyl substituents (Table 3.2, products **271c-e**) at the 1-position were successfully tolerated and gave moderate to good yields. Dienes with a 1,1-diphenyl-substitution also smoothly underwent the annulation reaction and afforded corresponding spiroindane product in 73% yield (Table 3.2, product **271f**). Moreover, we found that dienes with electron-donating (-Me) or electron-withdrawing (-Cl) groups at the 3-position are also competent reaction partners affording the desired products in good yields (Table 3.2, products **271g-i**). The stereochemistry of the internal olefin was preserved in the products and was confirmed through X-ray crystallography (Figure 3.4).[165] The highly activated 1,3-dienes were found to be unsuccessful coupling partners in these annulation reactions resulting recovered starting materials (product **271j**).[166]

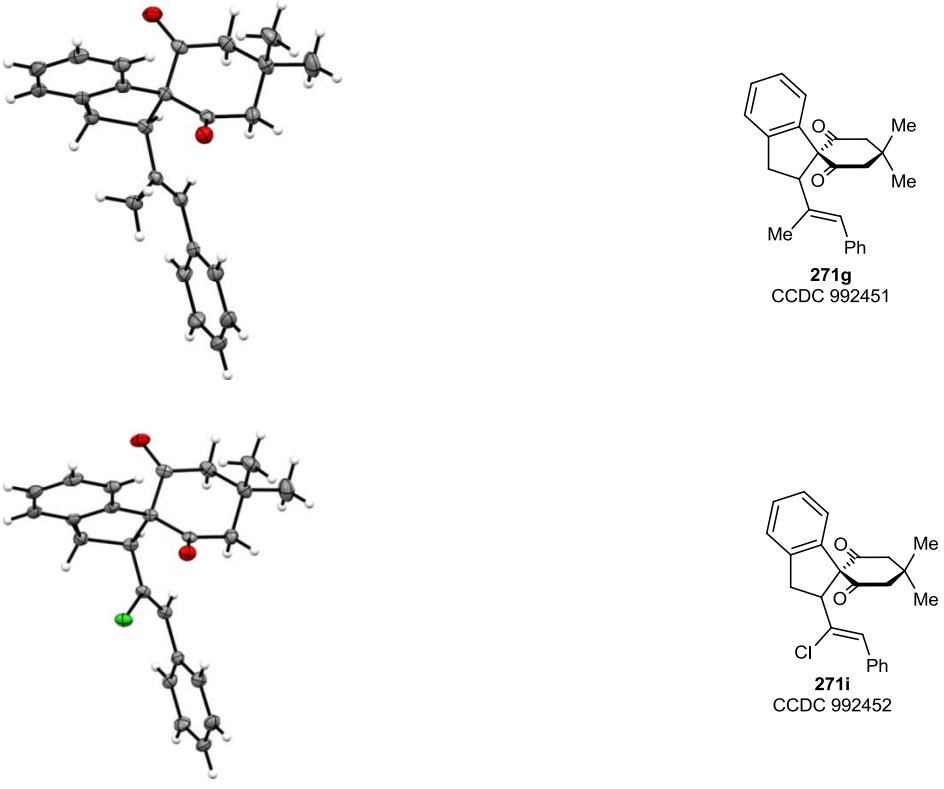
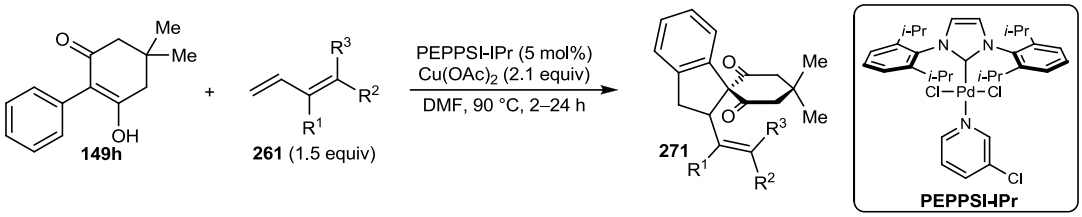
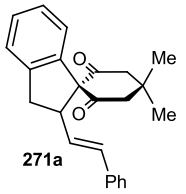
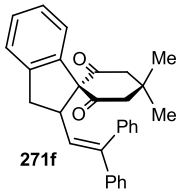
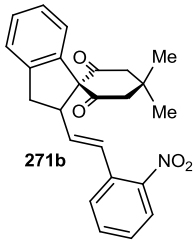
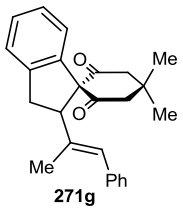
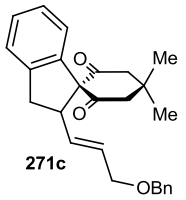
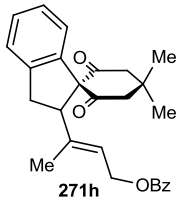
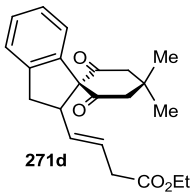
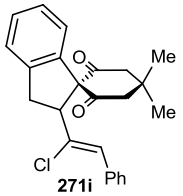
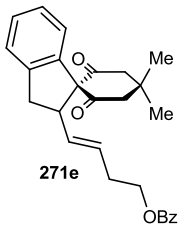
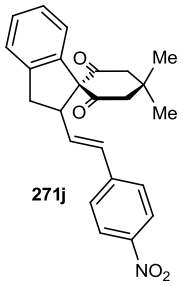


Figure 3.4. Crystal structure of compounds **271i** and **271j**.

Table 3.2. Oxidative annulation of **149h** with various 1,3-dienes[a]

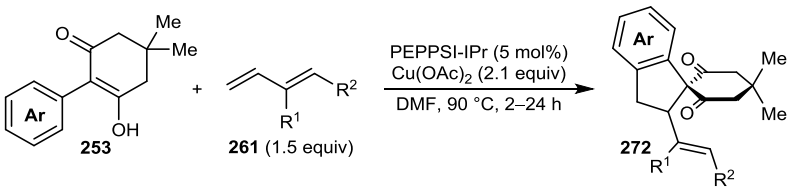


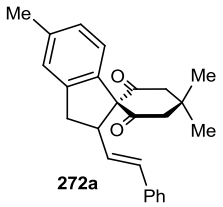
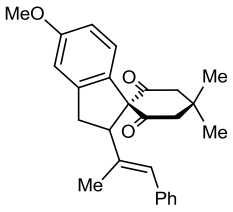
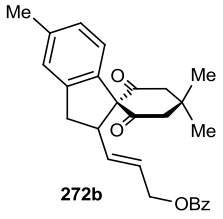
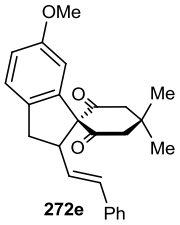
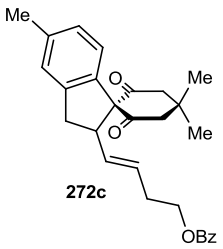
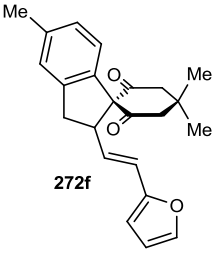
Entry	Spiroindane	Yield [%][b]	Entry	Spiroindane	Yield [%][b]
1	 271a	66	6	 271f	73
2	 271b	66	7	 271g	70
3	 271c	74	8	 271h	60
4	 271d	63	9	 271i	67
5	 271e	73	10	 271j	0

[a]Using 0.50 mmol of **149h** in degassed DMF. [b]Yield of isolated product.

Next, various substituted 2-aryl-cyclic 1,3-dicarbonyl substrates were applied to this process. As can be seen from Table 3.3, the substrates derived from dimedone successfully underwent the oxidative annulation reaction (products **272a-f**). Several substituents including methyl (products **272a-c** and **272f**) and methoxy (products **272d** and **272e**) at the *para*- and *meta*-position of the 2-phenyl ring were well tolerated affording the desired spiroindane products in 40-81% yield. Also, several 1,3-dienes with aryl and alkyl substituent were proved as efficient coupling partners. Diene with a methyl substitution at 3-position was also successfully employed giving spiroindane **272d** in 61% yield. However, the methoxy substituent at *meta*-position gave the desired product **272e** in comparatively lower yield (46%) due to the formation of complex mixture of by-products. Similarly, when a diene with a heteroaryl group was coupled to substrate **253a**, the resulting product **272f** was obtained in 40% yield only. The remaining mass balance of the reaction was a complex mixture of the by-products.

Table 3.3. Oxidative annulation of various dimedone-derived substrates with various 1,3-dienes[a]

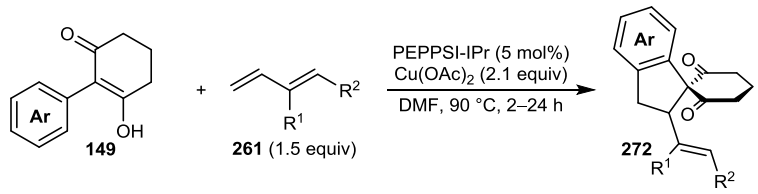


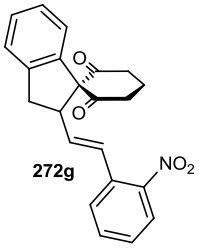
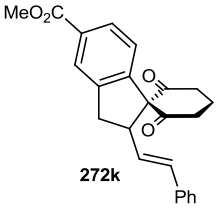
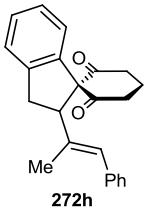
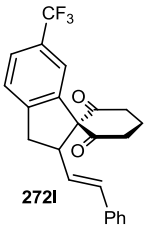
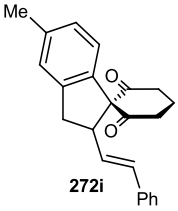
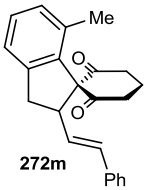
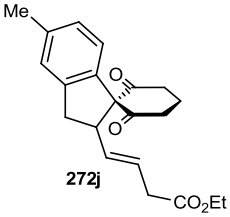
Entry	Spiroindane	Yield [%][b]	Entry	Spiroindane	Yield [%][b]
1		81	4		61
2		74	5		46
3		79	6[c]		40

[a]Reactions were conducted with 0.50 mmol of **253a-c** in degassed DMF. [b]Yield of isolated product. [c]Reaction performed by Dr. Suresh R. Chidipudi.

To further explore the reaction scope, the substrate derived from cyclohexane-1,3-dione were also tested in this process where the resulting products (Table 3.4, products **272g-m**), are of comparatively lower yields.[167] This is probably due to the lower stability of these substrates toward acid-catalyzed decomposition. Several substituents including methyl (products **272i** and **272j**), and carbomethoxy groups (product **272k**) at the *para*-position of the 2-phenyl ring were tolerated in this process. The substrates bearing a substituent at *meta*-position of the phenyl ring offered annulated product **272l** preferentially at the least sterically hindered position, which is consistent with previous observations.[122,154] The lower yield (34%) was obtained in this case due to the formation of additional complex by-products. This process is also found to be tolerant of *ortho*-substituted substrate, affording C–H functionalization product (**272m**) in 60% yield, which is in contrast with the Ru-catalyzed oxidative annulations we reported previously (chapter 1 & 2).[122,154]

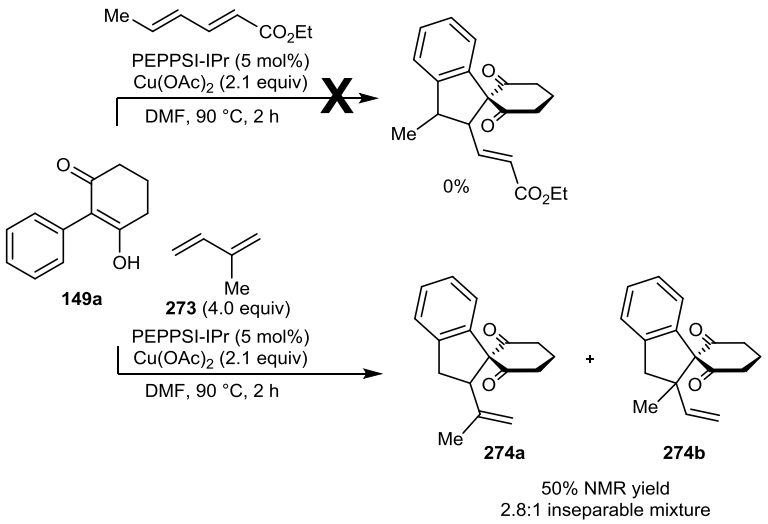
Table 3.4. Oxidative annulation of various 2-aryl-1,3-dicarbonyl compounds with various 1,3-dienes[a]



Entry	Spiroindane	Yield [%][b]	Entry	Spiroindane	Yield [%][b]
1	 272g	61	5	 272k	54
2	 272h	47	6	 272l	34
3	 272i	73	7	 272m	60
4	 272j	59			

[a]Reactions were conducted with 0.50 mmol of **149** in degassed DMF. [b]Yield of isolated product.

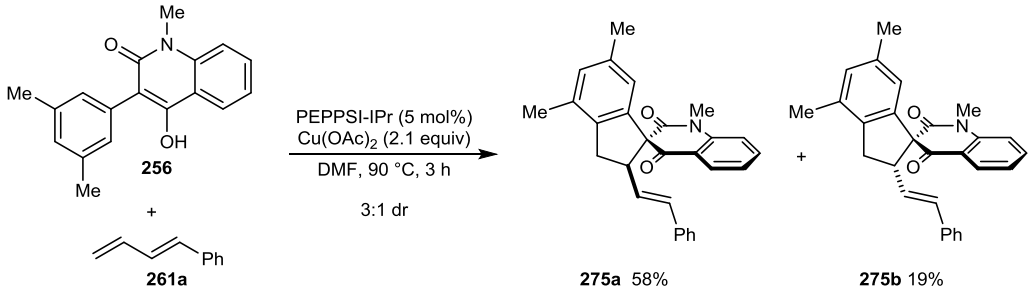
1,3-Dienes that do not contain a terminal alkene, such as 1,4-disubstituted-1,3-dienes, were unreactive in this process (Scheme 3.14, top). However, isoprene **273** reacted with **149a** to provide a 2.8:1 inseparable mixture of two isomers **274a** and **274b** (Scheme 3.14).[168]



Reaction performed by Dr. Suresh R. Chidipudi

Scheme 3.14. Oxidative annulation of isoprene with **149a**.

To further expand the substrate scope, the same catalytic system was applied to the oxidative annulation of an unsymmetrical 2-aryl cyclic 1,3-dicarbonyl substrate (**256**) with 1,3-diene **261a**. The reaction afforded a mixture of diastereomeric spiroindanes **275a** and **275b** in 58% and 19% yields, respectively (Scheme 3.15). The X-ray crystallography unambiguously confirmed the diastereomeric product **275a** (Figure 3.5).



Scheme 3.15. Oxidative annulation of unsymmetrical 1,3-dicarbonyl substrate.

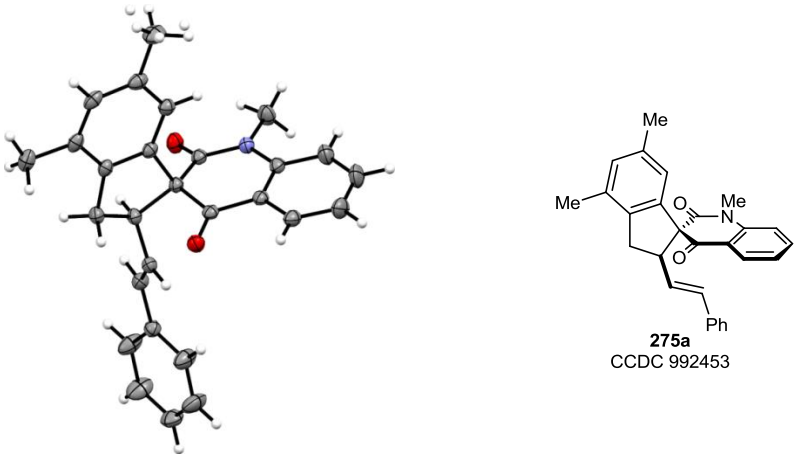
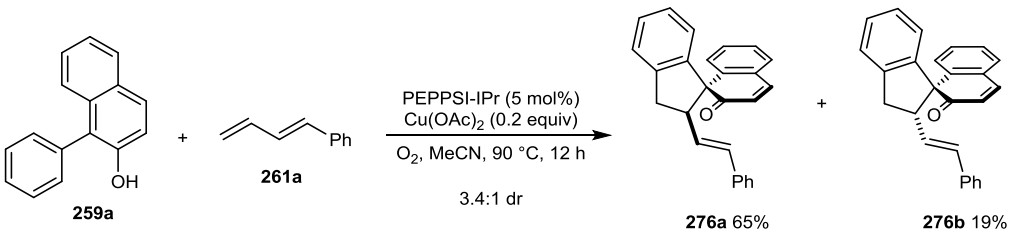


Figure 3.5. Crystal structure of **275a**.

In addition to 1,3-dicarbonyl substrates, we have also found that 1-phenyl-2-naphthol (**259a**) undergo Pd-catalyzed oxidative annulation with 1,3-diene **261a** to afford a diastereomeric mixture of the dearomatized products **276a** and **276b**, under a slight change to the previously optimized reaction conditions (Scheme 3.16).[169] In this case, the highest yields were observed when stoichiometric amount of $Cu(OAc)_2$ was applied in the presence of oxygen atmosphere as the terminal oxidant, using MeCN as the solvent. The dearomatized annulated product **276a** was confirmed through X-ray crystallography (Figure 3.6).



Scheme 3.16. Dearomatized oxidative annulation of 1-phenyl-2-naphthol.

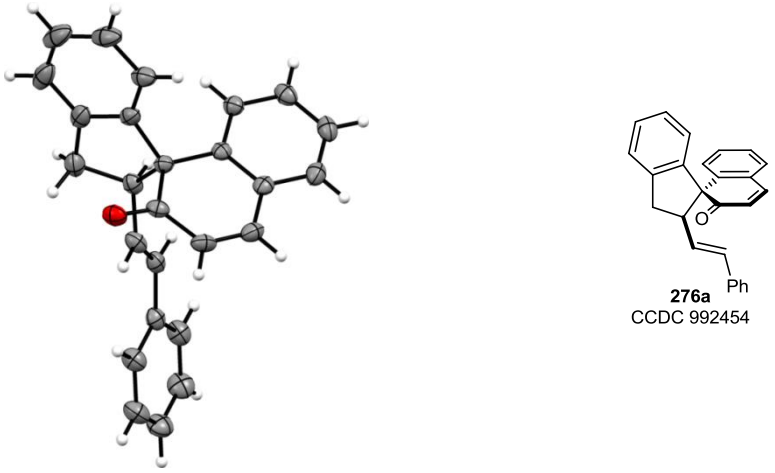
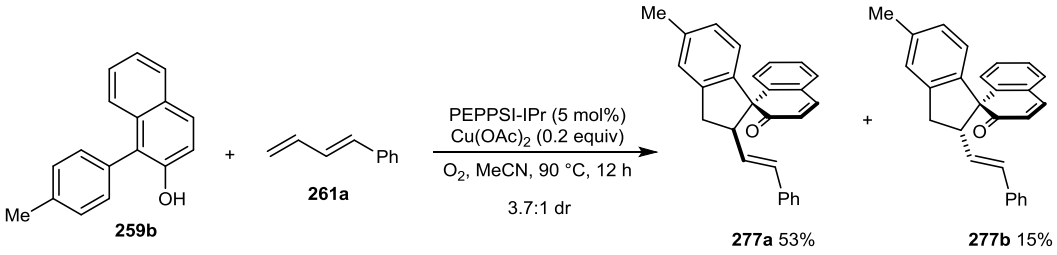


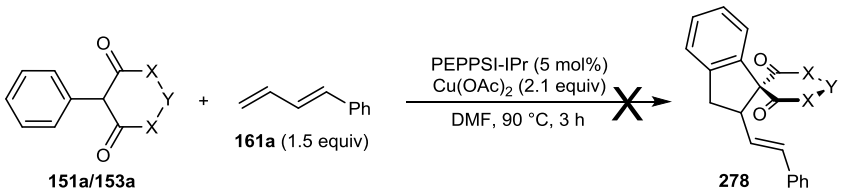
Figure 3.6. Crystal structure of **276a**.

Similar results were obtained when a *para*-substituted 1-aryl-2-naphthol was reacted under same conditions leading to a diastereomeric mixture of the dearomatized products **277a** and **277b** (Scheme 3.17).



Scheme 3.17. Dearomatized oxidative annulation of 1-*p*-tolyl-2-naphthol.

Some other Barbituric acid- and Meldrum′s acid-derived substrates were also investigated in this process but were found as unreactive resulting in returned starting materials or a complex mixture of unidentifiable products (Scheme 3.18).



Scheme 3.18. Attempted oxidative annulation of Barbituric and Meldrum′s-acid derived substrates.

3.5.6. Possible Catalytic Cycle

A possible catalytic cycle for these reactions is shown in Figure 3.7. Initially, PEPPSI-IPr forms a palladium diacetate complex **279**, from reaction with $Cu(OAc)_2$. This complex then reacts with **149h** in a cyclometallation reaction to deliver palladacycle **280**, liberating two equivalents of acetic acid. Migratory insertion of the 1,3-diene **261a** with **280** would give a new palladacycle **281**. An inner sphere C–C bond-forming reductive elimination[170] of **281** then provides the spiroindane **271a** and a palladium(0) species, which then undergoes oxidation by $Cu(OAc)_2$ to regenerate **279**. Computational studies on the enantioselective Tsuji allylation of enolates, which proceed *via* intermediates similar to **281**, suggests that in those reactions, reductive elimination by a 3,3' pathway is lowest in energy.[171] However, in the reactions presented herein, where the palladium enolate and allylpalladium components are tethered to each other, the mechanism of reductive elimination may well be different. A possible alternative is that the product could be formed by outer sphere nucleophilic attack of an enol onto a π-allylpalladium species such as in **282**.[172] This could in turn be formed by protonolysis of **281** by AcOH. Further studies will be required to shed more light on the mechanism.

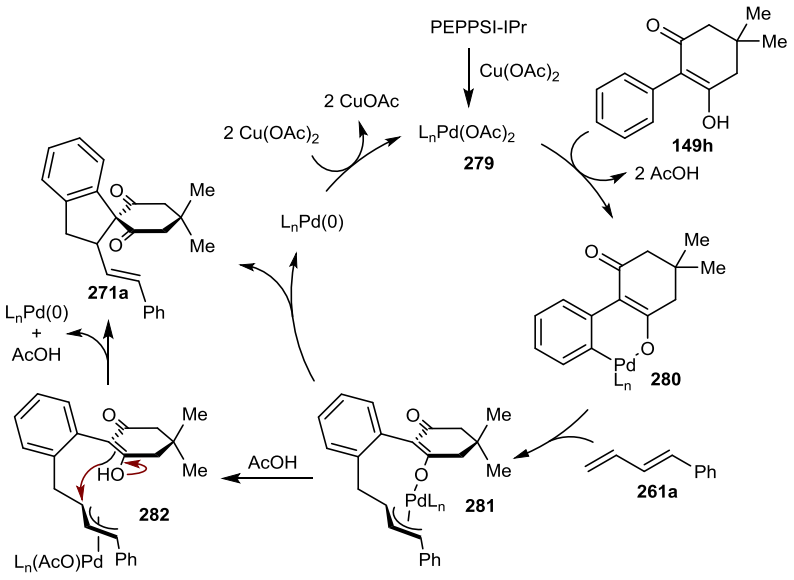
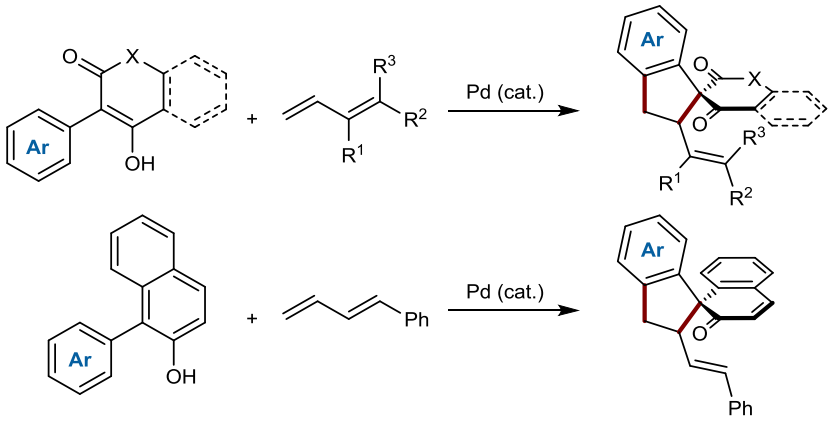


Figure 3.7. Possible catalytic cycle for spiroindane formation.

3.6. Conclusions and Future Work

In summary, we have developed an efficient synthesis of spiroindanes through palladium-catalyzed oxidative annulation of cyclic 2-aryl-1,3-dicarbonyl compounds with non- or weakly activated 1,3-dienes in moderate to good yields. The reactions have broad scope in terms of both 1,3-dicarbonyl and 1,3-diene substrates. In this process, the stereochemistry of the internal alkene is preserved in the products. The reaction was also found to proceed with 1-aryl-2-naphthols affording dearomatized annulated products. This work demonstrates the broad utility of palladium catalysis in oxidative annulations involving C–H functionalization, and increases the scope of carbocyclic products that can be prepared using these reactions. Future work will involve the development of diastereo- and enantioselective variants of these processes.

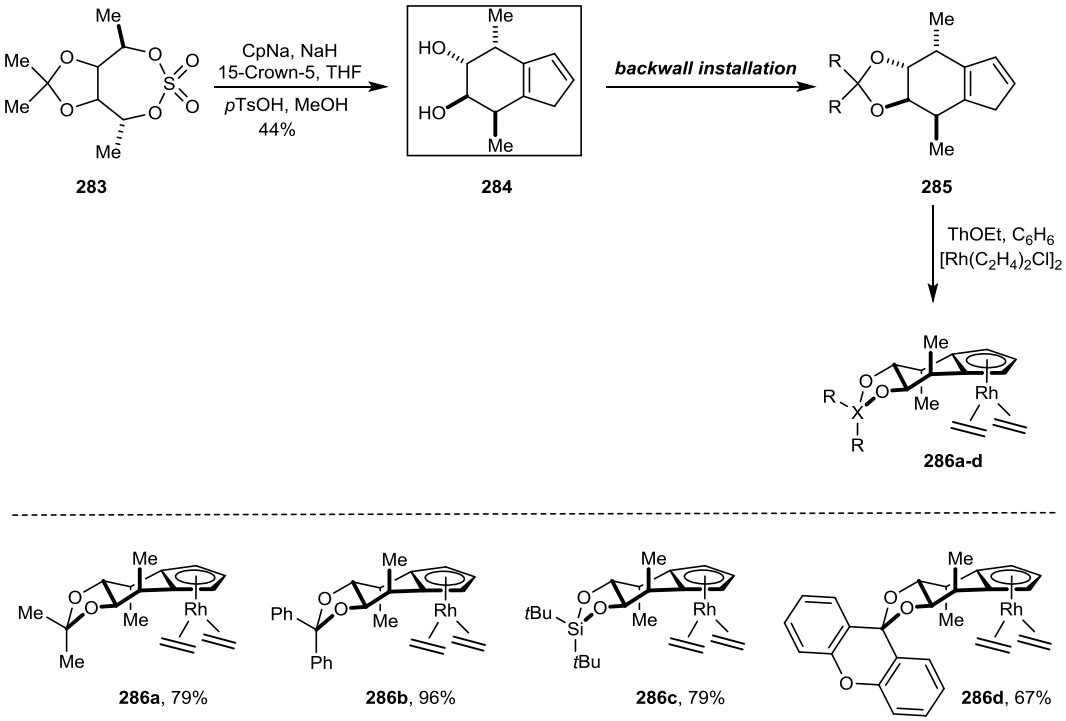


Chapter 4: Enantioselective Spiroindene Formation *via* C–H Functionalization Using Chiral Cyclopentadienyl Rhodium Catalysts

4. Introduction

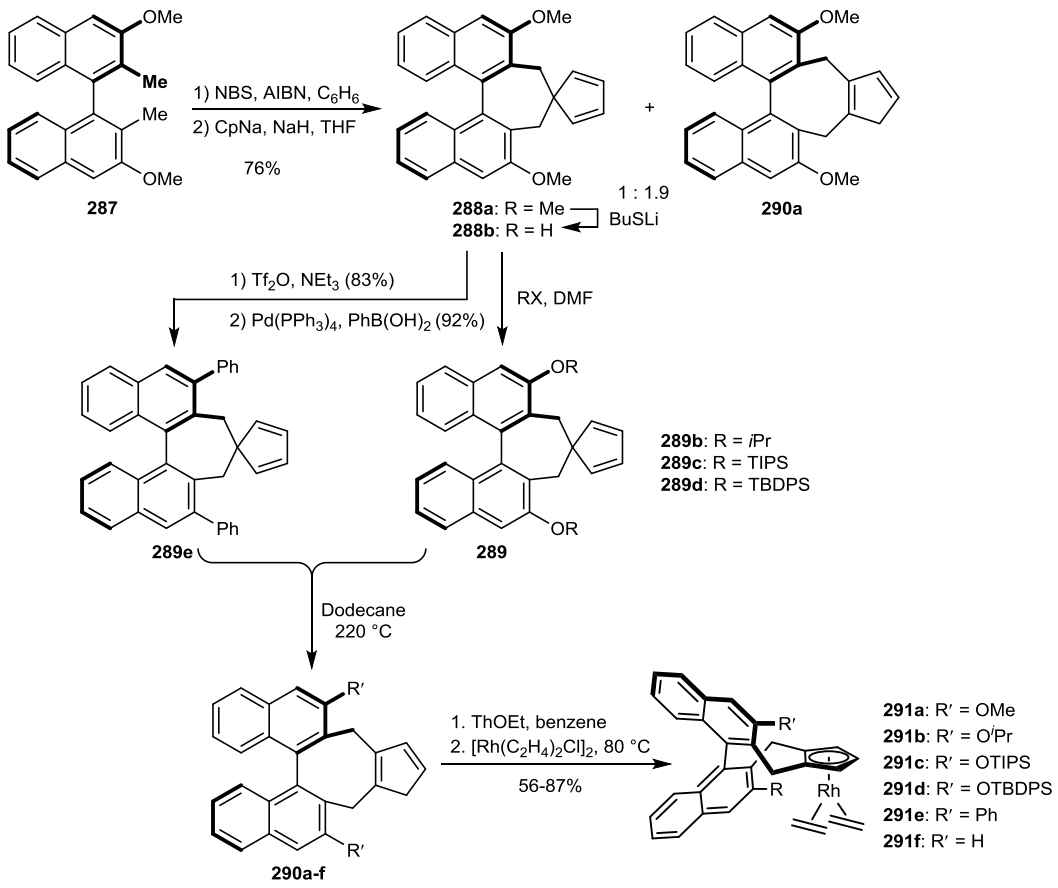
Transition-metal-catalyzed C–H functionalization has proven an important and complementary synthetic tool for the rapid and efficient construction of complex molecules.[173] In this domain, Cp*Rh(III) complexes played a powerful role for the transformation of simple starting materials into a broad range of synthetically useful building blocks.[174] Despite their high synthetic potential, the corresponding catalytic enantioselective transformations remain underexplored due to the lack of suitable ligands.[175,176] In achieving this goal, chiral versions of the cyclopentadienyl (Cp) and pentamethylcyclopentadienyl (Cp*) ligands hold a great promise and two independent and complementary strategies for chiral Cp-type ligands have been reported independently by the Cramer group[177,178] and Rovis, Ward and co-worker.[179] These ligands have been applied in a range of Rh-catalyzed asymmetric C–H functionalization reactions.

The first class of ligands was derived from the chiral pool using D-mannitol as starting material to access cyclic sulfate **283** which on alkylation of sodium cyclopentadienide and subsequent ketal cleavage afforded diol **284** as a common intermediate for further modifications. The installation of sterically different ketals and cyclic silylethers affords a range of ligands precursors **285**. Deprotonation with thallium ethoxide gave corresponding cyclopentadienyl anions which were reacted with rhodium(I) ethylene chloride to give chiral $Cp^{x}Rh(I)$ complexes (**286a-d**) in good yields (Scheme 4.1).[177]



Scheme 4.1. Synthesis of the first generation of chiral Cp^x ligands and their Rh(I) complexes.

Complementary to this ligand family, the second class of chiral Cp ligands was based on the C_2-symmetric atrop-chiral biaryl backbone, originating from Binol. This was previously accessed by Halterman for the parent chiral Cp ligand skeleton without its critical 3,3′ substituents.[180] The synthesis started with the compound **287**, previously accessed by Maruoka, for the synthesis of chiral phase-transfer catalysts.[181] Radical bromination followed by double alkylation of sodium cyclopentadienide produced a mixture of the 1,2-disubstituted cyclopentadiene **288** and spirocyclic diene **290a** (Scheme 4.2). Independently, the cleavage of the methoxy groups gave a common intermediate **289b** to access the different *ortho*-substituted members (**289**) of the second class of the ligands. Conversion of the **289b** to the corresponding triflate and subsequent Pd-mediated phenyl boronic acid cross coupling gave diene **289e**. Alternatively, ether formation gave **289b-d**. The thermal rearrangement of **289** affords **290a-f**, which on deprotonation and rhodium(I) complexation delivered the chiral Cp^xRh(I) complexes **291a-f**.



Scheme 4.2. Synthesis of the second generation of chiral Cp^x ligands and their Rh(I) Complexes.

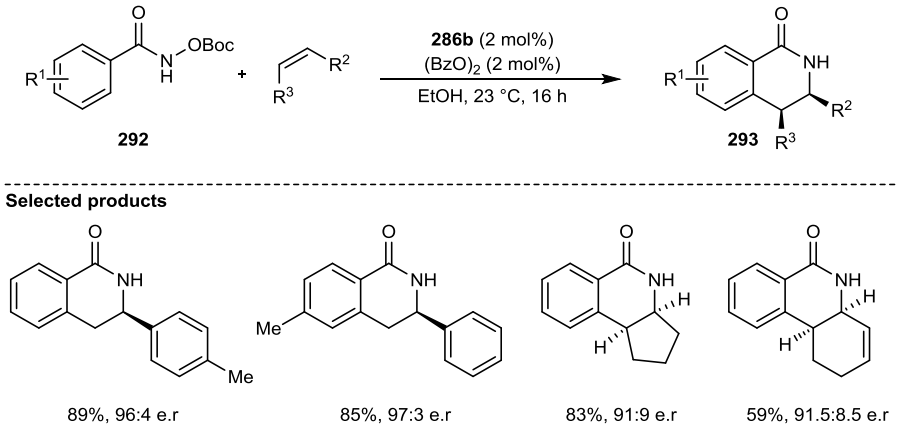
4.1. Applications of the Chiral Cyclopentadienyl Rhodium Complexes in Catalysis

A range of different Rh(III)-catalyzed enantioselective reactions have been explored using these two classes of ligands. Some examples will be highlighted in our subsequent discussion.

4.1.1. Asymmetric Cp^xRh(III)-Catalyzed Dihydroisoquinolone Synthesis

Ye and Cramer developed an enantioselective Cp^xRh(III)-Catalyzed C–H functionalization of hydroxamic acids **292**. This process generates dihydroisoquinolone derivatives **293** with generally good yield and enantioselectivity (Scheme 4.3).[177] The use of dibenzoylperoxide for the reaction to oxidize the complex **286b** *in-situ* was necessary to deliver a competent Rh(III) catalyst. The scope of this

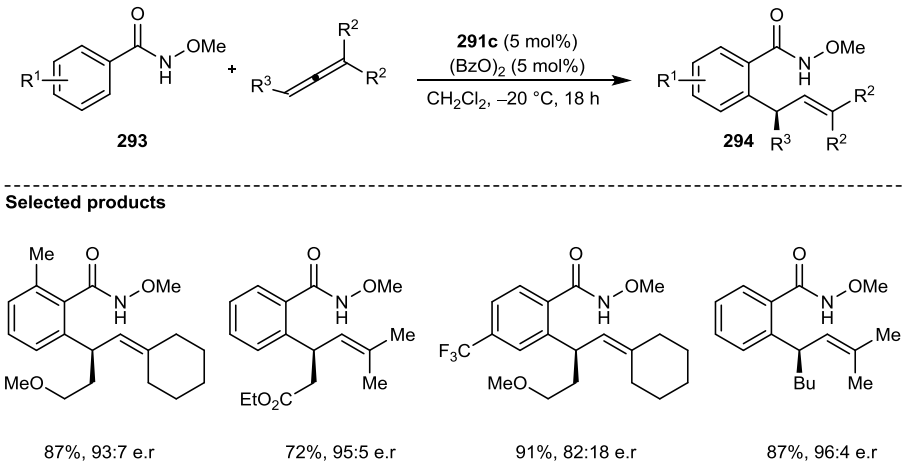
enantioselective reaction was explored under optimized conditions where a range of styrenes were reacted successfully affording dihydroisoquinolone products in excellent enantioselectivities. However, with some structurally and electronically different terminal and cyclic olefins produced products with slightly reduced enantioselectivity. On the aryl hydroxamate, different electronic and steric variations showed little influence on product yield and selectivity.



Scheme 4.3. Asymmetric synthesis of dihydroisoquinolones.

4.1.2. Asymmetric C-H Allylations of Benzamides

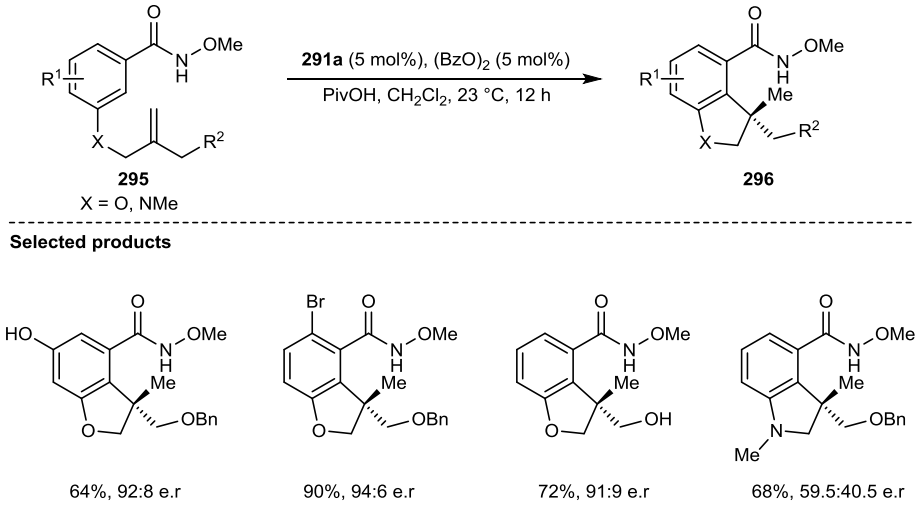
The same group demonstrated the utility of Cp^xRh complexes in the enantioselective allylation of *N*-methoxybenzamides **294** involving C–H functionalization (Scheme 4.4).[178]. The process used allenes as coupling partners affording the allylated products **295** with stereogenic center at the benzylic position. Benzamide substrates with a range of substitution pattern underwent smooth transformation. Also, the electronic nature of the substituents showed generally little influence on the reactivity and selectivity of the allylation reaction except *para*-CF_3 group for which a reduced enantioselectivity was observed. The variations on the allene component including free or protected hydroxyl groups and esters were also shown to work efficiently. Simple unfunctionalized allenes provided similar selectivity.



Scheme 4.4. Asymmetric C–H allylations of benzamides.

4.1.3. Asymmetric Synthesis of Benzofurans by Hydroarylation Reaction

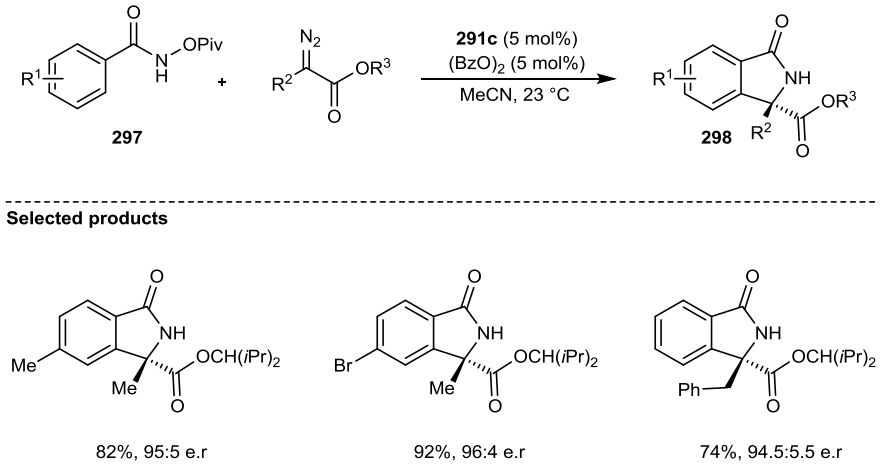
Cramer and co-workers demonstrated the utility of chiral $Cp^{x}Rh(III)$ catalyst system for the efficient intramolecular enantioselective hydroarylation of aryl hydroxamates **295** (Scheme 4.5).[182] The process affords a range of dihydrobenzofurans **296** featuring methyl-substituted quaternary stereocenters by C–H functionalization under mild conditions. The enantioselective hydroarylation reaction tolerated both electron-rich and electron-poor arenes. Functional groups like a free phenol or a nitro substituent were compatible with the reaction conditions. A broad range of variations on the alkene moiety were also tested. The reaction also tolerates different allylic ethers and free allylic alcohol leading to the desired products in good yield and enantioselectivities. Moreover, hydrocarbon substituents on the olefin moiety, including ethyl and benzyl groups afforded benzofuran products with good enantioselectivities. A substrate with a nitrogen tether displayed comparable reactivity for the cyclization (68%), but the corresponding product was formed with poor enantioselectivity (59.5:40.5 e.r).



Scheme 4.5. Asymmetric synthesis of benzofurans.

4.1.4. Asymmetric Synthesis of Isoindolone by Enantioselective Carbene Insertions

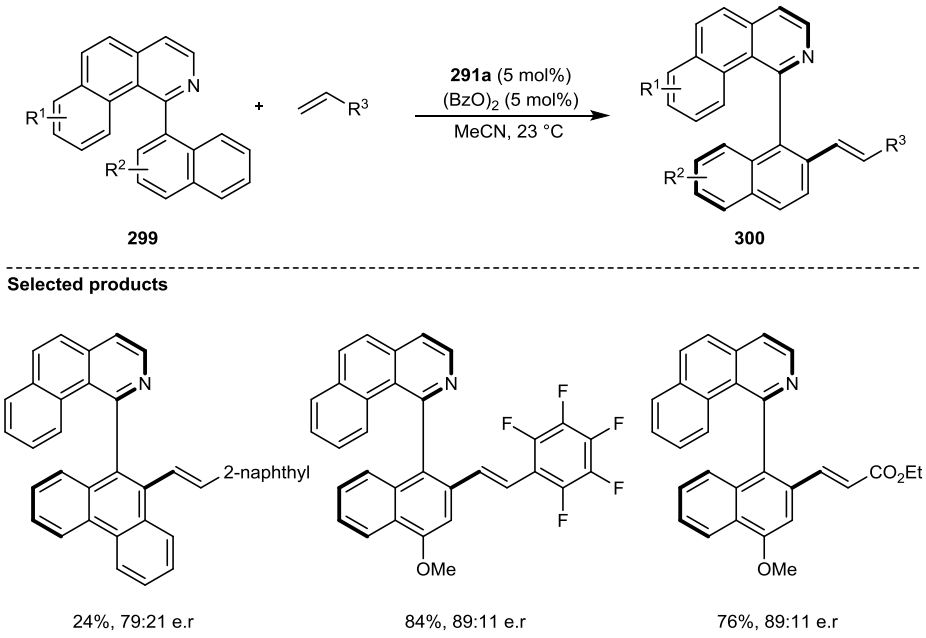
Ye and Cramer developed a $Cp^{x}Rh(III)$-catalyzed asymmetric synthesis of isoindolones **298** from arylhydroxamates **297** and diazo ester compounds as one-carbon annulation partners under mild conditions (Scheme 4.6).[183] The process generally affords chiral isoindolones in good yields and high enantioselectivities. The extended scope of this transformation includes a broad tolerance of the aryl hydroxamate substrates, bearing electron-rich and electron-poor, and halogenated substituents. The report also evaluates a range of diazo esters incorporating alkyl or aryl substituents delivering the desired isoindolone products with excellent enantioselectivities.



Scheme 4.6. Asymmetric synthesis of isoindolones.

4.1.5. Synthesis of Axially Chiral Biaryl Compounds

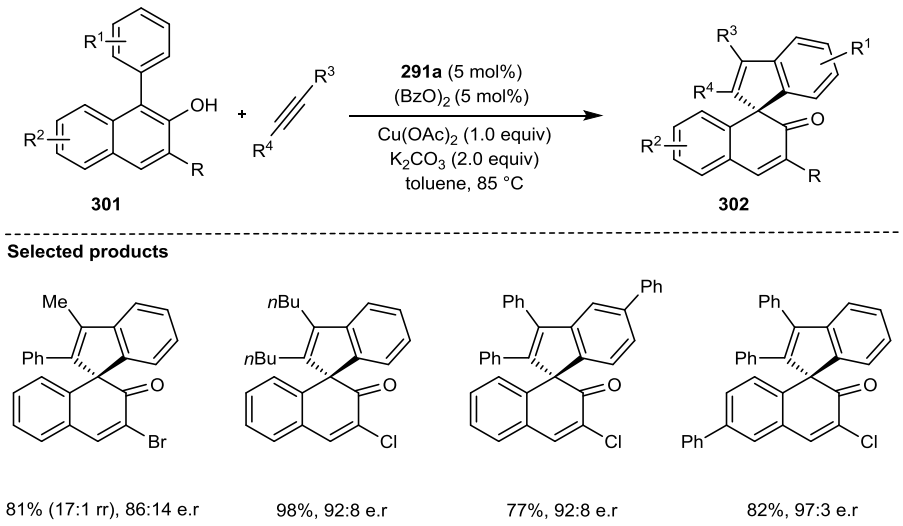
Zheng and You reported the use of chiral $Cp^xRh(III)$ catalyst for the successful synthesis of novel axially chiral biaryls **300** by the direct C–H bond olefination of biaryl compounds **299**, in good to excellent yields and enantioselectivities (Scheme 4.7).[184] A variety of biaryls underwent smooth olefination with 2-vinylnaphthalene, thus generating the desired alkenylated products in moderate to excellent yields and enantioselectivities. Introduction of both electron-donating and electron-withdrawing groups onto the naphthalene ring produced alkenylated products without affecting the enantioselectivity. However, substrate endowed with sterically hindered substituents on the naphthalene ring gave a poor yield (24%) of the product and reduced enantoselectivity (79:21 e.r). The nature of the olefin acceptor can also be varied over a wide range (styrenes, acrylates, acrylamides, vinyl phosphate, ethylene) with minor influence on the enantioselectivity.



Scheme 4.7. Synthesis of axially chiral biaryl compounds.

4.1.6. Asymmetric Dearomatization of Naphthols

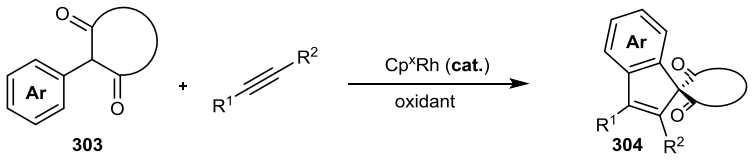
Recently, You and co-workers developed an asymmetric Rh-catalyzed dearomatization of 1-aryl-2-naphthols **301** with internal alkynes involving C–H functionalization. A range of highly enantienriched spirocyclic enones **302** bearing an all-carbon quaternary stereogenic center have been accessed with the use of a chiral Cp^xRh catalyst and a combination of $Cu(OAc)_2$ and air (oxygen) as an oxidant (Scheme 4.8).[185] Several 3-substituted (halogen and methyl) naphthols were tested to validate the scope and generality of the reaction. Various alkynes including symmetrical and unsymmetrical substituents were also examined in the reaction leading to their corresponding dearomatized products in excellent enantioselectivities, good yields and, moderate to good regioselectivity. Also, both aromatic and aliphatic substituted alkynes underwent annulation reaction successfully. Various substituted 1-aryl-2-naphthol derivatives bearing electron-donating or electron-withdrawing groups at the *para*-position of the phenyl ring were well tolerated, and the desired products were obtained in good yields and enantioselectivity. The limitation of the reaction include the longer reaction time (up to 72 h) as well as the substrates with the substituents at the 3-position of naphthols.



Scheme 4.8. Asymmetric dearomatization of naphthols.

4.2. Aims and Objectives

Keeping in view the recent applications of Cp^xRh complexes, and our continued interest in C–H functionalization chemistry,[122,154,] we aimed to develop the asymmetric synthesis of spiroindenes **304** using enolate as a directing group under the action of chiral Cp^xRh complexes (Scheme 4.9). This builds on our previous findings where 2-aryl-1,3-dicarbonyl compounds were reacted with alkynes affording the racemic products in good yield and regioselectivity.[122]

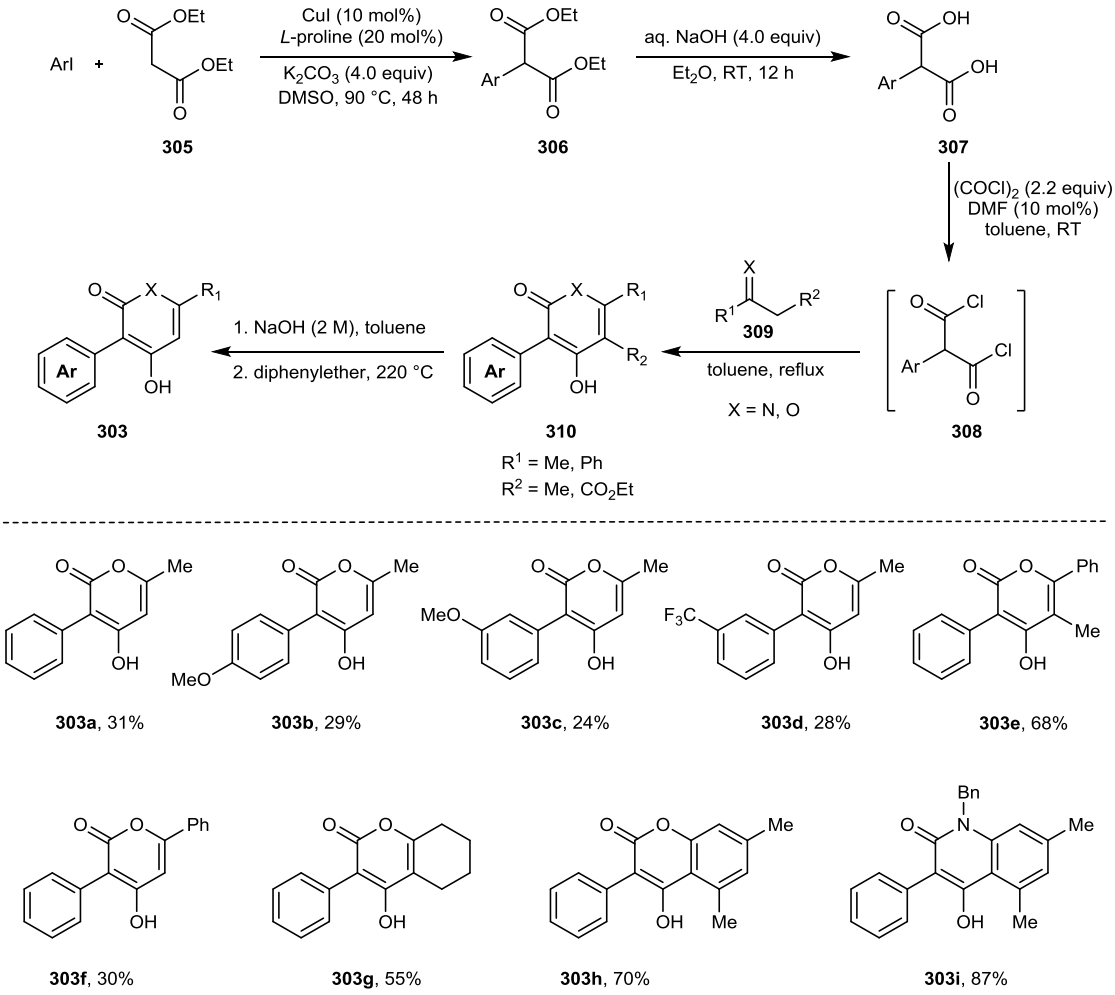


Scheme 4.9. Asymmetric synthesis of spiroindenes.

4.3. Results and Discussion

4.3.1. Preparation of 2-Aryl-1,3-dicarbonyl Compounds

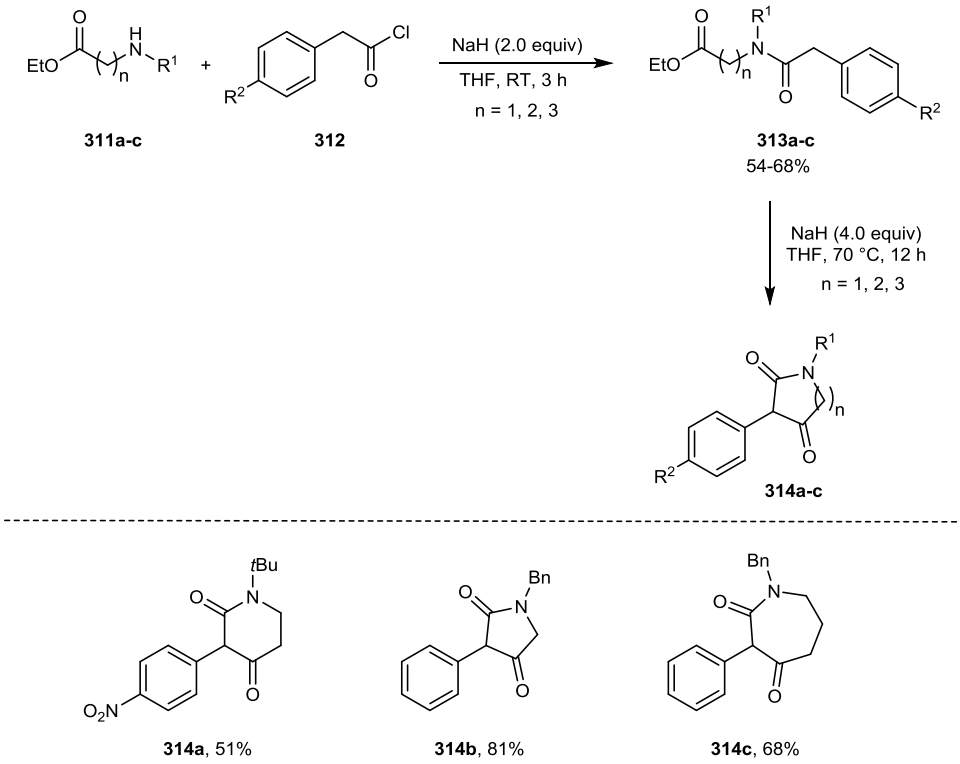
In order to undertake the envisioned process, a range of different 1,3-dicarbonyl substrates were synthesized. Initial Cu-catalyzed α-arylation of diethyl malonate **305** afforded the corresponding 2-aryl diethylmalonate derivatives **306**, which upon hydrolysis gave 2-aryl malonic acid **307**. The malonic acid derivatives were converted to the corresponding aryl chloride **308** and reacted with compound **309** to give substrates **310**. The substrates bearing ester group were hydrolyzed and decarboxylated to generate compounds **303** in 24-87% overall yield (Scheme 4.10).



Substrates synthesized by Dr. Suresh R. Chidipudi

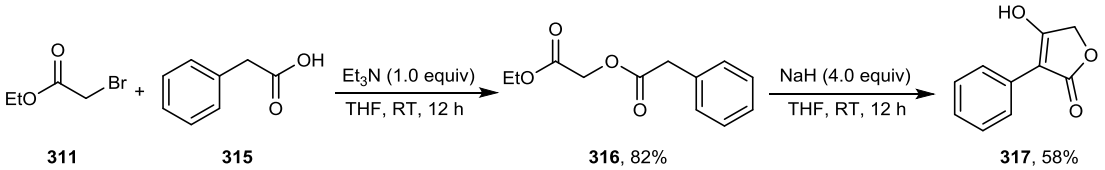
Scheme 4.10. Synthesis of 2-aryl-1,3-dicarbonyl compounds.

Keto-amide substrates **314** were synthesized by using the protocol illustrated in Scheme 4.11. The amino ester compounds **311**[186-188] were reacted with the aryl chloride **312** under basic conditions to afford the intermediate **313**. Cyclization, using NaH, gave the desired keto-amide compounds **314**.



Scheme 4.11. Synthesis of keto-amide substrates.

In addition, 4-hydroxy-2(5*H*)-furanone **317** was synthesized by cyclization of ethoxycarbonylmethyl phenylacetate **316** using triethylamine as a base (Scheme 4.12).[189] Intermediate **316** was obtained by the condensation of a phenylacetic acid **315** with ethyl bromoacetate **311** using NaH in THF.

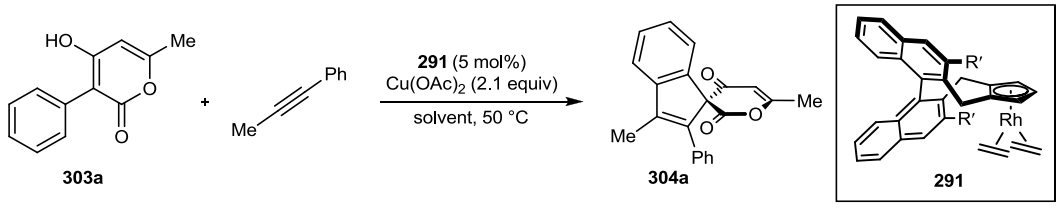


Scheme 4.12. Synthesis of the 4-hydroxy-2(5*H*)-furanone.

4.3.2. Reaction Optimization

We began our study by utilizing 4-hydroxy-6-methyl-3-phenyl-2*H*-pyran-2-one **303a** and 1-phenyl propyne as the model substrates to optimize the reaction conditions (Table 4.1). In the presence of 5 mol% of chiral Rh complex **291f** and 2.1 equiv of $Cu(OAc)_2$, the annulation reaction proceeded efficiently in DMF at 50 °C to provide **304a** in 93% NMR yield and 58% ee (entry 1). A lower yield (41%) but an improved selectivity (88% ee) was observed when the reaction was conducted using Rh complex **291e** (entry 2). The use of Rh complex **291a** bearing methoxy substituents at the *ortho* positions of the biaryl scaffold significantly improved the selectivity and the product **304a** was obtained in 97% yield and 90% ee (entry 3). Using a Rh complex with a larger isopropoxy ether (O*i*Pr; **291b**, entry 4) resulted in diminished yield (38%) and enantiselectivity (78% ee). However, the use of Rh complex with bulky silyl ethers (**291c** and **291d**) at 3,3′-position of biaryl ring produced spiroindene **304a** in high yield and excellent enantiselectivities (entries 5 and 6). Lowering the reaction temperature to 23 °C led to a slight decrease in product yield without increasing e.e. (entry 7). The reaction solvent was found to have a significant influence on the enantioselectivity of the reaction (entries 8-10).

Table 4.1. Optimization of reaction conditions for the synthesis of **304a**[a,e]



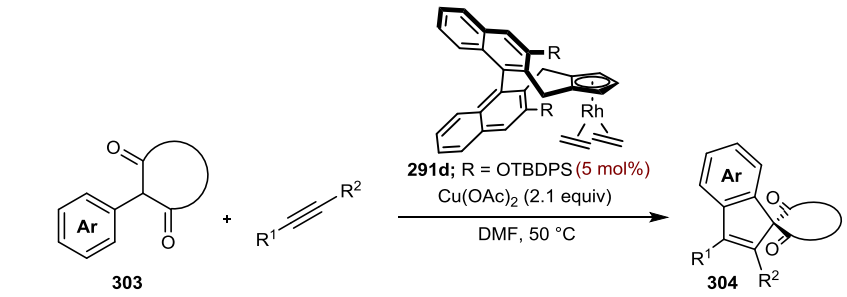
Entry	[RhL]	Solvent	Yield [%][b]	ee [%][c]
1	**291f** R′ = H	DMF	93	58
2	**291e** R′ = Ph	DMF	41	88
3	**291a** R′ = OMe	DMF	97	90
4	**291b** R′ = O*i*Pr	DMF	33	78
5	**291c** R′ = OTIPS	DMF	84	92
6	**291d R′ = OTBDPS**	**DMF**	**98**	**95**
7[d]	**291d** R′ = OTBDPS	DMF	91	95
8	**291d** R′ = OTBDPS	1,4-dioxane	92	69
9	**291d** R′ = OTBDPS	DMC	93	55
10	**291d** R′ = OTBDPS	toluene	93	59

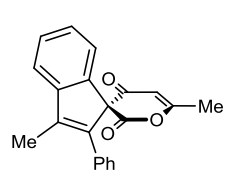
[a]Reactions were conducted using 0.05 mmol of **303a**. [b]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by a chiral HPLC. [d]At 23 °C. [e]Reactions performed by Dr. Suresh R. Chidipudi & Dr. David. J. Burns. DMF = *N*,*N*'-dimethylforamide. DMC = dimethyl carbonate.

4.3.3. Evaluation of Reaction Scope

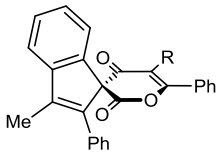
The scope of the enantioselective spiroindene formation was explored under the optimized reaction conditions (Table 4.1, entry 6). The results are summarized in Table 4.2. The reaction worked efficiently for substrates bearing substituents at various positions of the pyran-dione ring, and products (**304b** and **304c**) were formed in good yields and excellent enantioselectivity. The substrates with electron-donating and electron-withdrawing groups on the aryl ring were also compatible with the standard reaction conditions and gave desired spiroindenes in good yield and enantiselectivities (products **304d-f**). Notably, *meta*-substituted arene (**303c**) having two unequal *ortho* C(sp^2)–H bonds resulted in a mixture of two regioisomeric products with good levels of stereoselectivities (product **304d**). However, substrate **303d** bearing a *meta*-CF_3 group delivered the annulated product as a single regioisomer with the utilization of the sterically less hindered C–H functionalization site (product **304d**) which is consistent with previous observations.[153] The substrates with a benzannulation of dione ring also displayed comparable reactivity for the cyclization, but the corresponding products were obtained with slightly reduced enantioselectivities (products **304g** and **304h**). However, substrate with a saturated ring afforded spiroindene in 85% yield and 94% ee (product **304i**). Moreover, the keto-amide substrates with different ring sizes were tolerated well, affording products in good yield and enantioselectivities (products **304j** and **304k**). The 4-hydroxy-2(5*H*)-furanone **317** also participated efficiently in the annulation reaction. However, the desired product (**304l**) was obtained in lower yield (22%) with excellent enantioselectivity (90%). The lower yield obtained is probably due to the competing substrate decomposition. Also, the substrate with a *para*-NO_2 group on the aryl ring and a bulky *t*-Bu protected amide, gave spiroindene **304m** in 80% yield and 97% ee. In this case, the *para*-NO_2 substituent is necessary for the reaction to occur, as the reaction did not proceed without a nitro group on the phenyl ring.

Table 4.2. Evaluation of reaction scope[a-c]

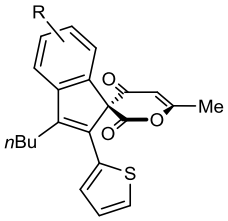




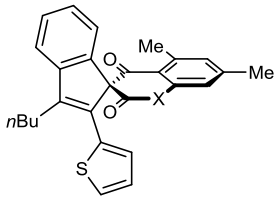
304a: 84%, 95% ee



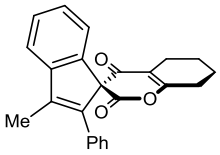
304b: R = Me 94%, 95% ee
304c: R = H 74%, 94% ee



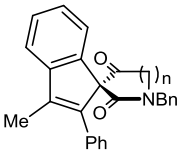
304d: R = 4-OMe 85%, 95% ee
304e: R = 3-OMe 91% (4:1), 94%:96% ee
304f: R = 3-CF_3 67%, 96% ee



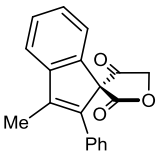
304g: X = O, 66%, 81% ee
304h: X = NBn, 84%, 68% ee



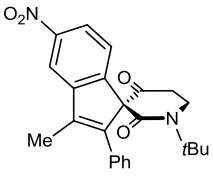
304i: 82%, 94% ee



304j: n = 1, 80%, 84% ee
304k: n = 3, 73%, 94% ee



304l: 22%, 90% ee

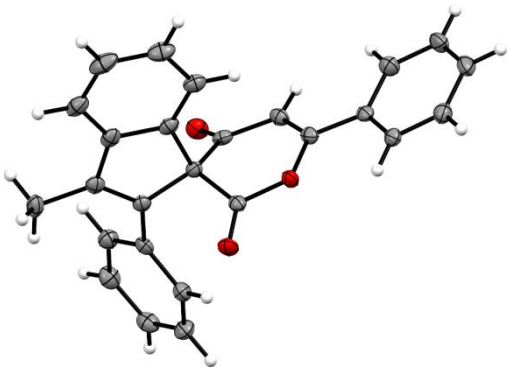


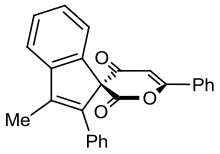
304m: 80%, 97% ee

[a]Reactions were conducted using 0.2 mmol of **303**, **314** and **317**. [b]Yields are of isolated materials. [c]Enantiomeric excess was determined by a chiral HPLC.

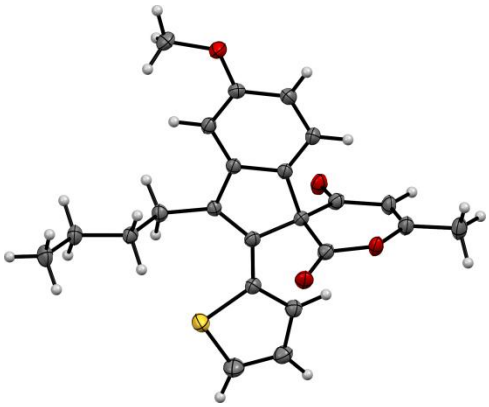
4.3.4. Stereochemical Determinations

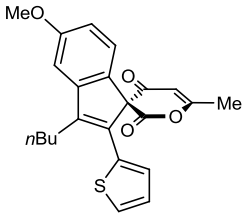
The absolute stereochemistries of **304c**, **304d**, **304f**, **304i**, and **304k** were determined by single crystal X-ray crystallography using a copper radiation source. All crystals were obtained by recrystallization from EtOAc/petroleum ether. The stereochemistries of the remaining products were assigned by analogy.



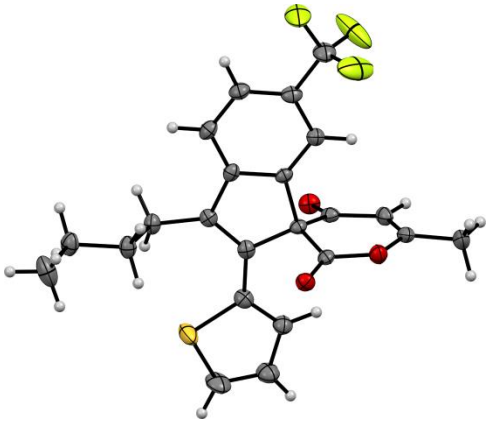


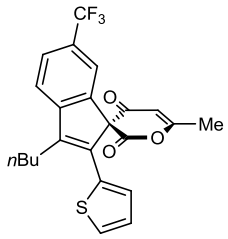
304c
CCDC 1415393
Flack parameter 0.13(19)



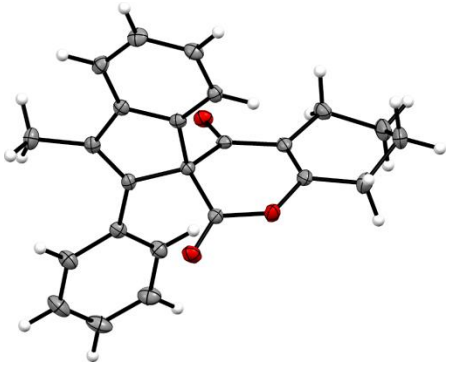


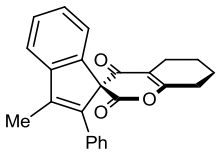
304d
CCDC 1415391
Flack parameter 0.10(3)
Hooft parameter 0.10(2)



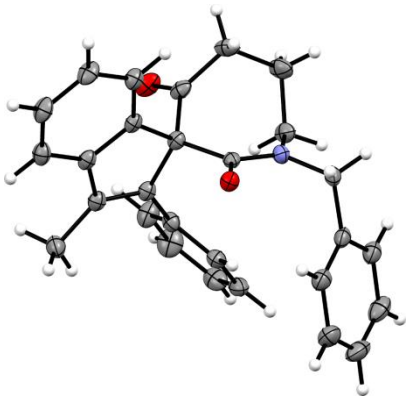


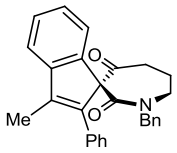
304f
CCDC 1415390
Flack parameter –0.020(15)





304i
CCDC 1415395
Flack parameter 0.02(8)





304k
CCDC 1415394
Flack parameter –0.03(9)

Figure 4.1. Stereochemical Determinations by X-ray Crystallography.

4.3.5. Proposed Catalytic Cycle and Stereochemical Model

A proposed catalytic cycle and stereochemical model for the spiroindene formation is shown in Figure 4.2, using **303a** and **156a** as representative substrates. After formation of rhodium diacetate complex **305**, we assume that cyclorhodation of **303a** is promoted by the most enolizable of the two possible directing groups, which is the enol derived from the ketone rather than the ester, to give rhodacycle **306a**. Coordination and migratory insertion of the alkyne would then give rhodacycle **307a**. The alternative conformations **306b** and **307b** appear to be disfavored because of steric interactions between the side wall of the cyclopentadienyl ligand with the metallated arene of **306b** or the phenyl substituent of **307b** (Figure 4.3). The next step is the isomerization of the *O*-bound rhodium enolate **307a** into the *C*-bound tautomer **308a**, presumably through an oxa–π-allylrhodium species, which requires a rotation of the 4-alkoxypyran-2-one moiety. Because the alkoxy group of this moiety is in closest

proximity to the chiral ligand, it experiences the greatest steric interactions, and we propose there is a preference for this group to rotate away from the ligand to give **308a**. Reductive elimination of **308a** gives spiroindene **304a** and Rh(I) species **309**, which is oxidized by $Cu(OAc)_2$ to regenerate **305**. The formation of the minor enantiomer from **307a** requires an unfavorable rotation of the alkoxy group towards the back wall of the chiral ligand (Figure 4.4).

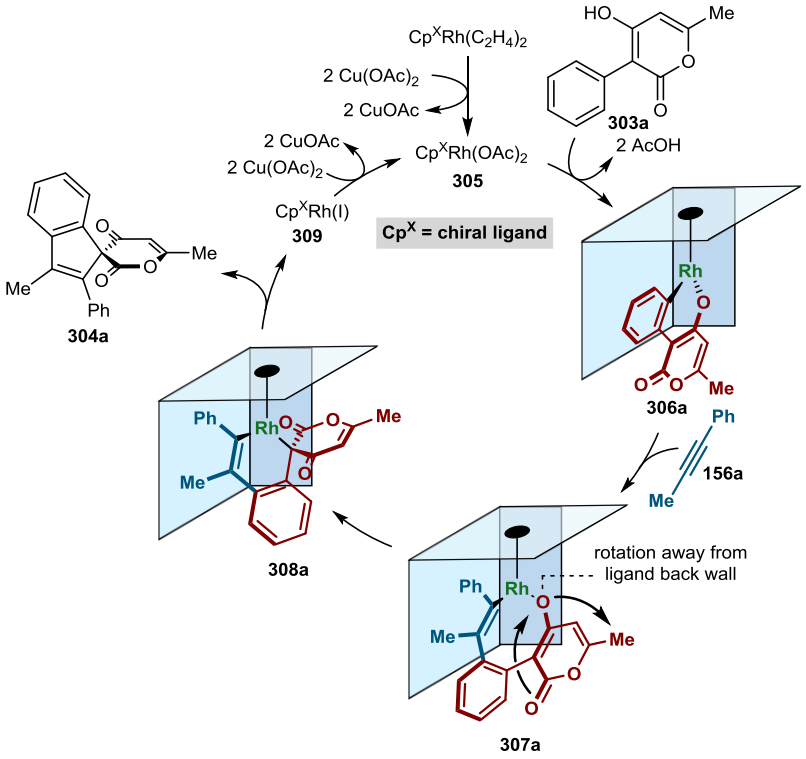


Figure 4.2. Proposed catalytic cycle.

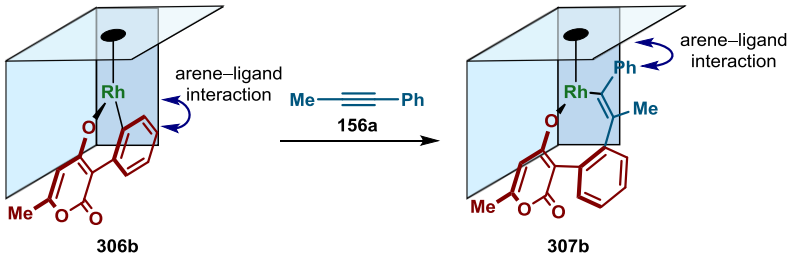


Figure 4.3. Disfavored conformations of the intermediate rhodacycles.

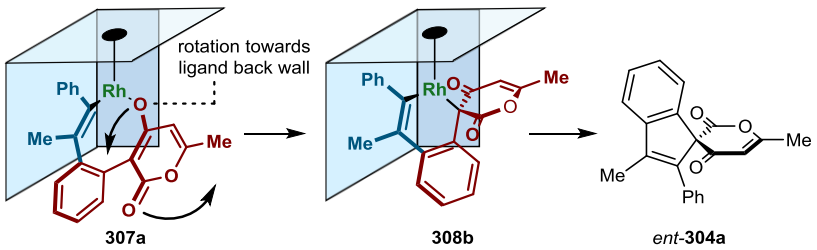
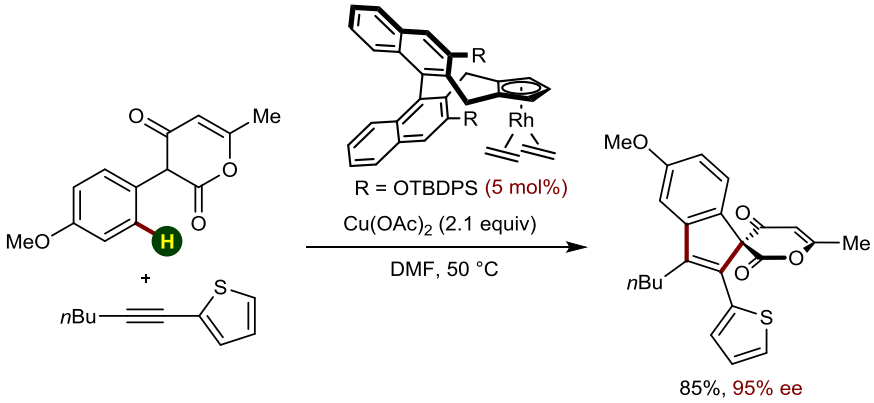


Figure 4.4. Disfavored rotation leading to the minor enantiomer.

An alternative explanation that cannot be excluded is that migratory insertion of **306a** with the alkyne directly produces a rhodacycle with a conformation closely related to that of **307a**, but with the alkoxide already partially rotated away from the chiral ligand. Continued rotation of the 4-alkoxypyran-2-one moiety in the same direction, according to the principle of least motion, would then give **308a**.

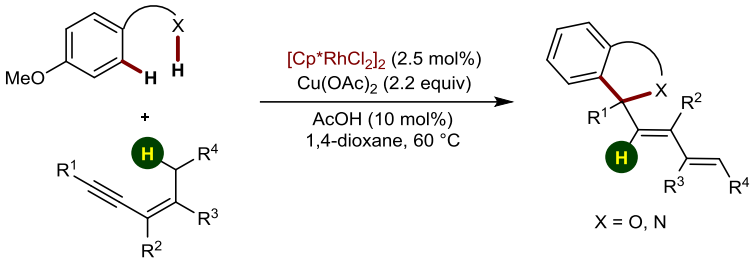
4.4. Conclusions

In summary, we have developed an enantioselective Rh(III)-catalyzed oxidative annulation of 2-aryl-1,3-dicarbonyl compounds (or their enol tautomers) with alkynes as coupling partners. The process affords a range of spiroindenes possessing an all-carbon quaternary sterogenic center in good yields and high enantiselectivities. The good functional group tolerance and broad substrate generality are advantages of this reaction.



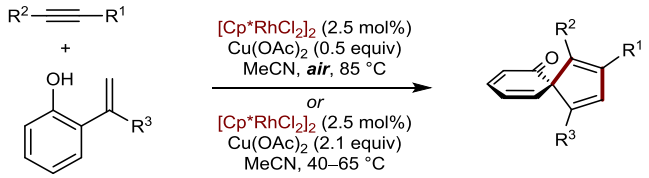
4.5. Future Work

The current work in the Lam group is focused on the extension of the scope for the spiroindene formation reaction in terms of substrate generality and the use of different alkynes as the reaction partners. Also, the Lam group has previously developed the rhodium-catalyzed oxidative annulation strategies involving C–H functionalization using 1,3-enynes as coupling partners. This process tolerates a diverse variety of substrates, and provides a broad range of heterocyclic products (Scheme 4.13).[190]



Scheme 4.13. Rh-catalyzed oxidative annulation involving 1,3-enynes.

In addition, the group also succeeded to develop a catalytic C-H functionalization method for the dearomatizing spiroannulation of 2-alkenylphenols with alkynes and enynes. The process delivers a diverse range of highly functionalized spirocyclic compounds demonstrating good functional group tolerance and the generality of the reaction (Scheme 4.14).[55]



Scheme 4.14. Rh-catalyzed spirocyclic enone formation.

Taken together, these strategies offer an appropriate platform for the broad application of chiral $Cp^{x}Rh$ complexes in the oxidative annulation processes. Also, the development of enantioselective variants of carbo- and heterocycle-forming oxidative annulations will be the subject of our future work.

5. Experimental

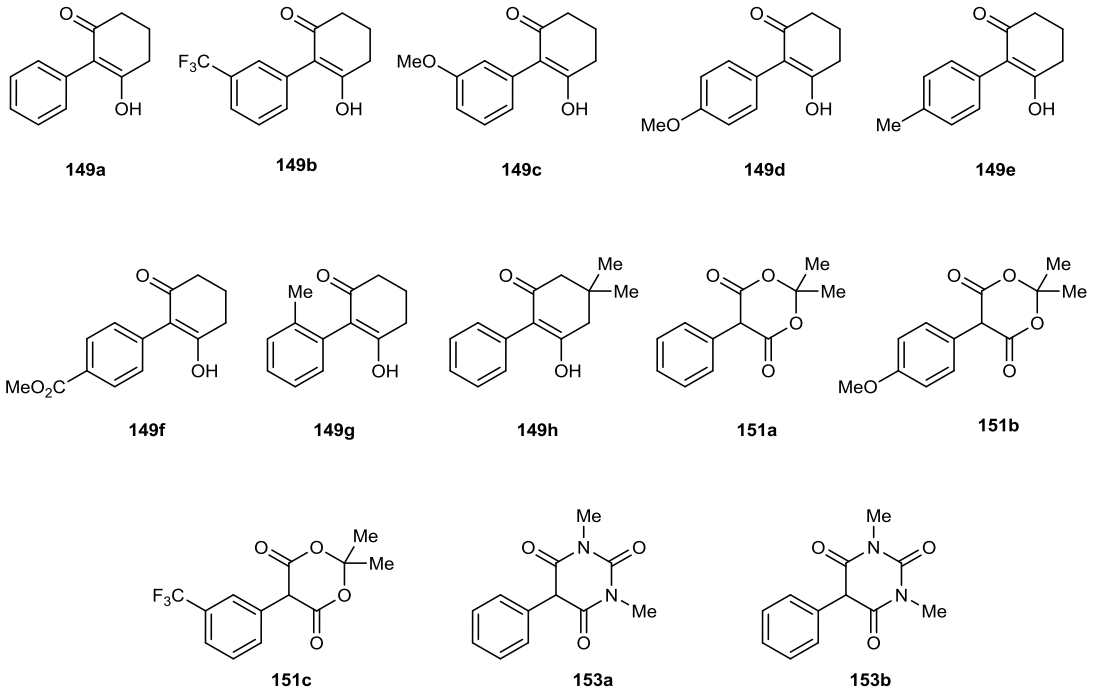
5.1. General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere using oven-dried apparatus. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60 F_{254} 0.2 mm precoated plates. Product spots were visualized under UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[191] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument or Nicolet Avatar 360 FT instrument on the neat compound, using the attenuated total reflectance (ATR) technique. ^{1}H NMR spectra were recorded on a Bruker AVA500 (500 MHz) spectrometer or a Bruker AVA400 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm, d^6-DMSO at 2.50 ppm, CD_3CN at 1.94 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), quin (quintet), app (apparent), br (broad), m (multiplet). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) or AVA400 (100.6 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, d^6-DMSO at 39.52 ppm, CD_3CN at 118.26 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$ (δ = 0 ppm), using fluorobenzene (C_6H_5F at –113.5 ppm) or trifluoroacetic acid (CF_3CO_2H at –76.55 ppm), as internal standard. High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact (EI) techniques at the EPSRC National Mass Spectrometry Service Centre, Swansea University, at the School of Chemistry, The University of Edinburgh or at The University of Nottingham, UK. Optical rotations were performed on a

Bellingham and Stanley ADP 400 polarimeter. Chiral HPLC analysis was performed on an Agilent 1290 series instrument using 4.6 x 250 mm columns.

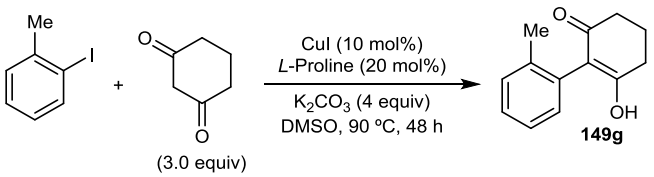
5.2. Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds

5.2.1. Synthesis of 2-Aryl-1,3-dicarbonyl Compounds[a]



[a]Substrates synthesized by Dr. Suresh R. Chidipudi/Martin D. Wieczysty

5.2.1.1. Synthesis of 3-Hydroxy-2-(2-methylphenyl)cyclohex-2-en-1-one (149g)

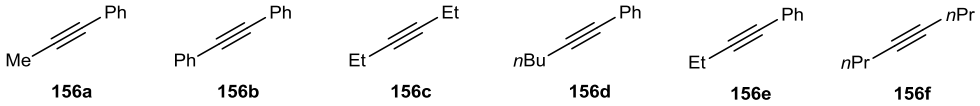


2-Iodotoluene (5.00 g, 22.9 mmol) was added to a stirred solution of CuI (436 mg, 2.29 mmol), *L*-proline (527 mg, 4.58 mmol), K_2CO_3 (12.7 g, 91.6 mmol), and cyclohexane-1,3-dione (7.72 g, 68.8 mmol) in anhydrous DMSO (90 mL), and the reaction mixture was then stirred at 90 °C for 48 h. The reaction was cooled to 0 °C and acidified with 2 *N* HCl to pH 3–4 and the aqueous layer was separated and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed

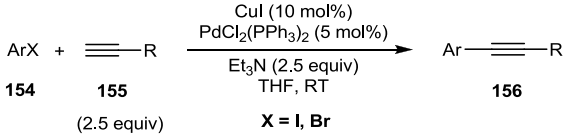
with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (25% acetone/hexane) gave the 2-aryl-3-hydroxy-2-cyclohexenone **149g** as a white solid (932 mg, 20%). R_f = 0.20 (30% acetone/hexane); m.p. 148-150 °C (EtOAc/hexane); IR 2945, 2916, 1610 (C=O), 1583, 1571, 1330, 1271, 1195, 1066, 983, 761, 725, 590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.21 (3H, m, Ar**H**), 7.05 (1H, t, J = 6.9 Hz, Ar**H**), 6.00 (1H, br s, O**H**), 2.53 (4H, t, J = 6.5 Hz, 2 × C**H**$_2$), 2.15-2.05 (5H, m, C**H**$_3$ and C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.5 (C), 131.0 (CH), 130.7 (CH), 130.1 (C), 128.7 (CH), 126.5 (CH), 117.5 (C), 20.6 (CH_2), 19.4 (CH_3), some signals not observed due to keto–enol tautomerism; HRMS (EI) Exact mass calcd for $C_{13}H_{14}O_2$ $[M]^+$: 202.0989, found: 202.0989.

5.2.2 Preparation of Alkynes

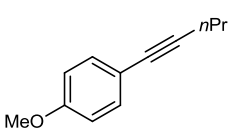
The following alkynes were purchased from commercial sources:



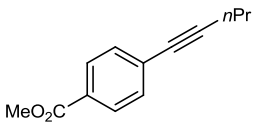
5.2.2.1. Preparation of Alkynes by Sonogashira Coupling: General Procedure A



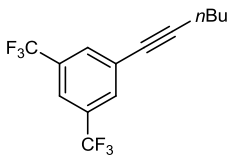
To a solution of the appropriate haloarene (1.0 equiv), appropriate terminal alkyne (2.5 equiv), and Et_3N (2.5 equiv) in THF (3 mL/mmol) at room temperature was added $PdCl_2(PPh_3)_2$ (5 mol%). The mixture was stirred for 5 min, and CuI (10 mol%) was added. The reaction mixture was then stirred at room temperature until the reaction had stopped progressing as observed by TLC analysis. After cooling to room temperature, the mixture was filtered to room the ammonium salt, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography gave the alkyne.



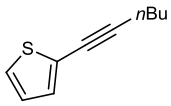
1-Methoxy-4-(pent-1-yn-1-yl)benzene (156g). The title compound was prepared according to General Procedure A from 4-iodoanisole (500 mg, 2.14 mmol) and 1-pentyne (0.53 mL, 5.35 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (357 mg, 96%) that displayed spectroscopic data consistent with those observed previously.[77]



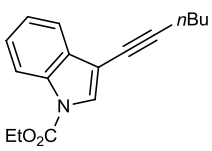
Methyl 4-(pent-1-yn-1-yl)benzoate (156h). The title compound was prepared according to General Procedure A from methyl 4-iodobenzoate (500 mg, 1.91 mmol) and 1-pentyne (0.47 mL, 4.77 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (378 mg, 98%). R_f = 0.52 (10% EtOAc/hexane); IR (film) 1720 (C=O), 1606, 1435, 1307, 1273, 1174, 1107, 856, 769, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.5 Hz, Ar**H**), 7.44 (2H, d, J = 8.5 Hz, Ar**H**), 3.90 (3H, s, OC**H**$_3$), 2.40 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$CH$_3$), 1.60 (2H, sextet, J = 7.2 Hz, CH$_2$C**H**$_2$CH$_3$), 1.05 (3H, t, J = 7.4 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.6 (C), 131.4 (2 × CH), 129.3 (2 × CH), 128.9 (C), 128.8 (C), 93.7 (C), 80.2 (C), 52.1 (CH_3), 22.0 (CH_2), 21.4 (CH_2), 13.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067, found: 203.1067.



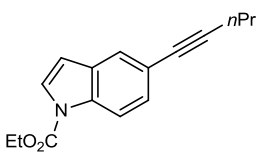
1-(Hex-1-yn-1-yl)-3,5-bis(trifluoromethyl)benzene (156i). The title compound was prepared according General Procedure A from 1-iodo-3,5-bis(trifluoromethyl)benzene (88 μL, 0.50 mmol) and 1-hexyne (0.14 mL, 1.25 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (132 mg, 90%). R_f = 0.4 (5% EtOAc/hexane); IR (film) 2974, 2881, 1382, 1280, 1143, 1089, 1047, 881, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (2H, s, Ar**H**), 7.78 (1H, s, Ar**H**), 2.47 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.70-1.60 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.59-1.48 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 1.00 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 131.7 (2 × C, q, J = 33.5 Hz), 131.5 (2 × CH, q, J = 4.0 Hz), 126.5 (C), 123.1 (2 × C, q, J = 272.7 Hz), 120.8 (CH, septet, J = 4.0 Hz), 94.6 (C), 78.1 (C), 30.5 (CH_2), 22.1 (CH_2), 19.0 (CH_2), 13.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.2 (6F, 2 × CF_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{13}F_6$ $[M+H]^+$: 295.0916, found: 295.0918.



2-(Hex-1-yn-1-yl)thiophene (156j). The title compound was prepared according to General Procedure A from 2-iodothiophene (0.53 mL, 4.76 mmol) and 1-hexyne (1.36 mL, 11.9 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (725 mg, 93%) that displayed spectroscopic data consistent with those observed previously.[78]

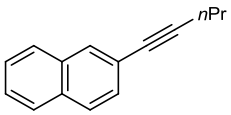


Ethyl 3-(hex-1-yn-1-yl)-1*H*-indole-1-carboxylate (156k). The title compound was prepared according to General Procedure A from 3-iodo-1-ethylcarboxylate indole (157 mg, 0.50 mmol) and 1-hexyne (0.14 mL, 1.25 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (132 mg, 98%). R_f = 0.42 (10% EtOAc/hexane); IR (film) 2972, 2881, 1712 (C=O), 1435, 1379, 1276, 1089, 1047, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 7.8 Hz, Ar**H**), 7.72 (1H, s, Ar**H**), 7.67 (1H, dd, J = 7.6, 0.6 Hz, Ar**H**), 7.40-7.29 (2H, m, Ar**H**), 4.50 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.50 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.70-1.61 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.60-1.50 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 1.47 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 0.99 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.5 (C), 134.6 (C), 130.9 (C), 127.6 (CH), 125.2 (CH), 123.2 (CH), 120.1 (CH), 115.1 (CH), 104.8 (C), 94.1 (C), 71.7 (C), 63.4 (CH_2), 30.9 (CH_2), 22.0 (CH_2), 19.3 (CH_2), 14.4 (CH_3), 13.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{20}O_2N$ $[M+H]^+$: 270.1489, found: 270.1489.

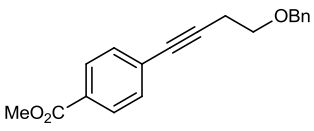


Ethyl 5-(pent-1-yn-1-yl)-1*H*-indole-1-carboxylate (156l). The title compound was prepared according to General Procedure A from 5-iodo-1-ethylcarboxylate indole (315 mg, 1.0 mmol) and 1-pentyne (0.25 mL, 2.50 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (252 mg, 99%). R_f = 0.44 (5% EtOAc/hexane); IR (film) 2972, 2881, 1712 (C=O), 1379, 1274, 1087, 1047, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (1H, d, J = 7.8 Hz, Ar**H**), 7.63 (1H, d, J = 1.1 Hz, Ar**H**), 7.39 (1H, d, J = 1.5 Hz, Ar**H**), 7.38 (1H, dd, J = 8.5, 1.5 Hz, Ar**H**), 6.55 (1H, dd, J = 3.7, 0.5 Hz, Ar**H**), 4.50 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.41 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$CH$_3$), 1.65 (2H, sextet, J = 7.2 Hz, CH$_2$C**H**$_2$CH$_3$), 1.47 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 1.08 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.9 (C), 134.3 (C), 130.4 (C),

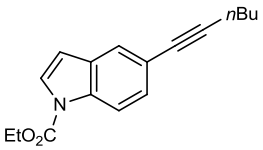
128.0 (CH), 126.2 (CH), 124.2 (CH), 118.6 (C), 114.9 (CH), 107.7 (C), 88.8 (C), 81.0 (C), 63.3 (CH_2), 22.3 (CH_2), 21.4 (CH_2), 14.4 (CH_3), 13.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{18}O_2N$ $[M+H]^+$: 256.1332, found: 256.1333.



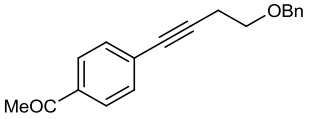
2-(Pent-1-yn-1-yl)naphthalene (156m). The title compound was prepared according to General Procedure A from 2-bromonaphthalene (500 mg, 2.43 mmol) and 1-pentyne (0.69 mL, 6.07 mmol) the product was purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (300 mg, 45%). IR (film) 2970, 2827, 1670, 1440, 1423, 1375, 1029, 754, 717, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (1H, s, Ar**H**), 7.83-7.75 (3H, m, Ar**H**), 7.51-7.45 (3H, m, Ar**H**), 2.46 (2H, t, J = 7.0 Hz, C**H**$_2$$CH_2CH_3$), 1.70 (2H, sextet, J = 7.2 Hz, CH_2C**H**$_2$$CH_3$), 1.11 (3H, t, J = 7.3 Hz, CH_2CH_2C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 133.1 (C), 132.4 (C), 131.0 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 126.3 (CH), 126.2 (CH), 121.4 (C), 90.7 (C), 81.0 (C), 22.2 (CH_2), 21.5 (CH_2), 13.6 (CH_3); HRMS (EI) Exact mass calcd for $C_{15}H_{14}$ $[M]^+$: 194.1090, found: 194.1089.



Methyl 4-[4-(benzyloxy)but-1-yn-1-yl]benzoate (156n). The title compound was prepared according to General Procedure A from methyl-4-iodobenzoate (786 mg, 3.00 mmol) and benzyl 3-butynyl ether (1.20 g, 7.50 mmol), and purified by column chromatography (3% EtOAc/hexane) to give a white solid (878 mg, 99%). R_f = 0.50 (5% EtOAc/hexane); m.p. 70-72 °C; IR (film) 1712 (C=O), 1440, 1274, 1176, 1107, 1097, 1016, 860, 771, 746, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 8.5 Hz, Ar**H**), 7.46 (2H, d, J = 8.5 Hz, Ar**H**), 7.40-7.34 (4H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 4.61 (2H, s, OC**H**$_2$Ph), 3.92 (3H, s, OC**H**$_3$), 3.70 (2H, t, J = 6.9 Hz, OC**H**$_2$$CH_2$), 2.76 (2H, t, J = 6.9 Hz, OCH_2C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.6 (C), 138.0 (C), 131.5 (2 × CH), 129.4 (2 × CH), 129.1 (C), 128.4 (2 × CH and C), 127.72 (CH), 127.69 (2 × CH), 90.3 (C), 81.0 (C), 73.0 (CH_2), 68.2 (CH_2), 52.2 (CH_3), 21.0 (CH_2); HRMS (ESI) Exact mass calcd for $C_{19}H_{19}O_3$ $[M+H]^+$: 295.1334, found: 295.1335.

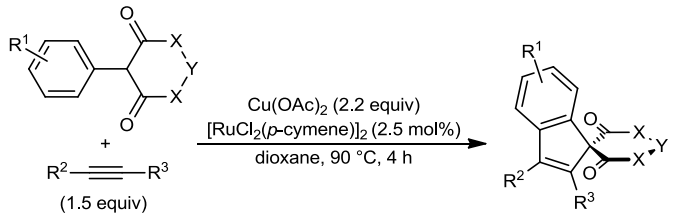


Ethyl 5-(hex-1-yn-1-yl)-1*H*-indole-1-carboxylate (156o). The title compound was prepared according to General Procedure A from 5-iodo-1-ethylcarboxylate indole (315 mg, 1.00 mmol) and 1-hexyne (0.35 mL, 2.50 mmol), and purified by column chromatography (1% EtOAc/hexane) to give a colorless oil (263 mg, 98%). R_f = 0.43 (5% EtOAc/hexane); IR (film) 2972, 2879, 1712 (C=O), 1433, 1379, 1087, 1047, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (1H, d, J = 7.8 Hz, Ar**H**), 7.63 (1H, d, J = 1.1 Hz, Ar**H**), 7.61 (1H, d, J = 3.7 Hz, Ar**H**), 7.37 (1H, dd, J = 8.6, 1.5 Hz, Ar**H**), 6.55 (1H, dd, J = 3.7, 0.6 Hz, Ar**H**), 4.50 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.44 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.66-1.58 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.56-1.45 (5H, m, CH$_2$C**H**$_2$CH$_3$ and OCH$_2$C**H**$_3$), 0.97 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 150.8 (C), 134.3 (C), 130.4 (C), 128.0 (CH), 126.2 (CH), 124.2 (CH), 118.6 (C), 114.9 (CH), 107.7 (C), 89.0 (C), 80.8 (C), 63.3 (CH$_2$), 30.9 (CH$_2$), 22.0 (CH$_2$), 19.1 (CH$_2$), 14.4 (CH$_3$), 13.6 (CH$_3$); HRMS (EI) Exact mass calcd for $C_{17}H_{19}O_2N$ $[M]^+$: 269.1410, found: 269.1408.

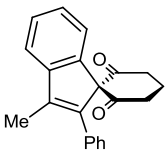


1-{4-[4-(Benzyloxy)but-1-yn-1-yl]phenyl}ethan-1-one (156p). The title compound was prepared according to General Procedure A from 4-iodoacetophenone (369 mg, 1.5 mmol) and benzyl 3-butynyl ether (600 mg, 3.75 mmol), and purified by column chromatography (3% EtOAc/hexane) to give an off-white solid (400 mg, 96%). R_f = 0.23 (10% EtOAc/hexane); m.p. 90-92 °C; IR (film) 2229, 1679 (C=O), 1599, 1266, 1095, 834, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 8.6 Hz, Ar**H**), 7.49 (2H, d, J = 8.6 Hz, Ar**H**), 7.41-7.34 (4H, m, Ar**H**), 7.33-7.28 (1H, m, Ar**H**), 4.61 (2H, s, OC**H**$_2$Ph), 3.71 (2H, t, J = 6.9 Hz, OC**H**$_2$CH$_2$), 2.77 (2H, t, J = 6.9 Hz, OCH$_2$C**H**$_2$), 2.59 (3H, s, C**H**$_3$C=O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.3 (C), 138.0 (C), 135.8 (C), 131.7 (2 × CH), 128.6 (C), 128.4 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 127.6 (2 × CH), 90.7 (C), 80.9 (C), 72.9 (CH$_2$), 68.1 (CH$_2$), 26.5 (CH$_3$), 20.9 (CH$_2$); HRMS (ESI) Exact mass calcd for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1380, found: 279.1380.

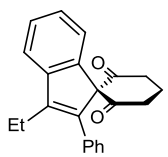
5.2.3. Ruthenium-Catalyzed Oxidative Annulation Reactions: General Procedure B



To a mixture of the appropriate 2-aryl-1,3-dicarbonyl compound (0.50 mmol), $Cu(OAc)_2$ (200 mg, 1.10 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) in dioxane (1.0 mL) was added the appropriate alkyne (0.75 mmol) in dioxane (0.5 mL), and the resulting mixture was stirred at 90 ºC for 4 h. The reaction was filtered through a pad of silica gel eluting with Et_2O (100 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the spiroindene.

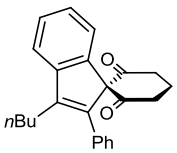


3'-Methyl-2'-phenylspiro[cyclohexane-1,1'-indene]-2,6-dione (157a). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156a** (94 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (121 mg, 80%). R_f = 0.74 (40% EtOAc/hexane); m.p. 184-186 °C; IR (film) 1716 (C=O), 1687, 1263, 1207, 1087, 1033, 1018, 798, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.18 (9H, m, Ar**H**), 2.97 (2H, ddd, J = 16.6, 11.4, 5.5 Hz, 2 × C**H**C=O), 2.74 (2H, dt, J = 16.6, 5.0 Hz, 2 × C**H**C=O), 2.30-2.18 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 2.19 (3H, s, C**H**$_3$), 2.00-1.87 (1H, m, $CH_2C\mathbf{H}_2CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.1 (2 × C), 146.8 (C), 142.8 (C), 142.3 (C), 140.7 (C), 135.6 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 127.5 (CH), 125.8 (CH), 121.2 (CH), 120.8 (CH), 85.2 (C), 40.0 (2 × CH_2), 16.8 (CH_2), 11.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{19}O_2$ $[M+H]^+$: 303.1380, found: 303.1385.

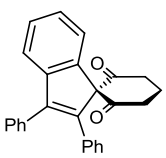


3'-Ethyl-2'-phenylspiro[cyclohexane-1,1'-indene]-2,6-dione (157b). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156e** (106 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane)

to give a white solid (120 mg, 76%). R_f = 0.60 (40% EtOAc/hexane); m.p. 120-122 °C; IR (film) 2970, 2931, 2870, 1720 (C=O), 1687, 1263, 1207, 767, 736, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (4H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 7.20 (1H, td, *J* = 7.4, 1.3 Hz, Ar**H**), 2.93 (2H, ddd, *J* = 16.4, 10.8, 5.4 Hz, C**H**$_2$C=O), 2.67 (2H, ddd, *J* = 16.6, 6.0, 4.7 Hz, C**H**$_2$C=O), 2.56 (2H, q, *J* = 7.6 Hz, C**H**$_2$CH$_3$), 2.22-2.11 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.93-1.80 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.23 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.28 (2 × C), 146.73 (C), 145.89 (C), 143.53 (C), 141.95 (C), 135.87 (C), 129.31 (CH), 128.44 (CH), 128.35 (CH), 127.69 (CH), 125.75 (CH), 121.68 (CH), 121.07 (CH), 85.33 (C), 40.14 (CH_2), 19.40 (CH_2), 16.82 (CH_2), 13.62 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{21}O_2$ $[M+H]^+$: 317.1541, found: 317.1542.

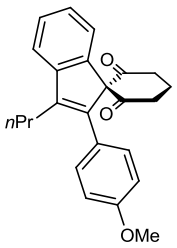


3'-Butyl-2'-phenylspiro[cyclohexane-1,1'-indene]-2,6-dione (157c). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156d** (131 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (134 mg, 78%). R_f = 0.62 (40% EtOAc/hexane); m.p. 102-104 °C; IR (film) 2964, 2875, 1716 (C=O), 1687, 1463, 1259, 746, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.34 (4H, m, Ar**H**), 7.33-7.27 (2H, m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 7.19 (1H, td, *J* = 7.4, 1.3 Hz, Ar**H**), 2.91 (2H, ddd, *J* = 16.3, 10.7, 5.4 Hz, C**H**$_2$C=O), 2.66 (2H, ddd, *J* = 16.6, 6.1, 4.8 Hz, C**H**$_2$C=O), 2.57-2.43 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.23-2.08 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.92-1.75 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.65-1.53 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.41-1.26 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.85 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.35 (2 × C), 146.20 (C), 145.39 (C), 143.57 (C), 142.42 (C), 135.94 (C), 129.43 (CH), 128.39 (CH), 128.31 (CH), 127.65 (CH), 125.73 (CH), 121.63 (CH), 121.14 (CH), 85.36 (C), 40.17 (CH_2), 30.83 (CH_2), 25.76 (CH_2), 22.62 (CH_2), 16.80 (CH_2), 13.88 (CH_3); HRMS (EI) Exact mass calcd for $C_{24}H_{24}O_2$ $[M]^+$: 344.1771, found: 344.1770.

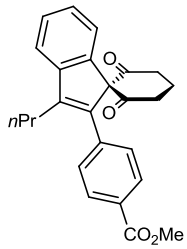


2',3'-Diphenylspiro[cyclohexane-1,1'-indene]-2,6-dione (157d). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from dione **149a** (94 mg, 0.50 mmol) and alkyne **156b** (133 mg, 0.75 mmol), and purified by column

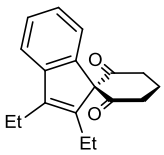
chromatography (20% EtOAc/hexane) to give a white solid (91 mg, 50%). R_f = 0.52 (40% EtOAc/hexane); m.p. 190-192 °C; IR (film) 1685 (C=O), 746, 732, 692, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.40 (3H, m, Ar**H**), 7.39-7.29 (5H, m, Ar**H**), 7.25-7.21 (1H, m, Ar**H**), 7.20-7.14 (3H, m, Ar**H**), 7.08-7.04 (2H, m, Ar**H**), 3.07 (2H, ddd, *J* = 17.4, 12.1, 5.6 Hz, 2 × C**H**C=O), 2.84 (2H, dt, *J* = 16.6, 4.7 Hz, 2 × C**H**C=O), 2.37-2.29 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 2.09-1.99 (1H, m, $CH_2C\mathbf{H}_2CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.4 (2 × C), 146.0 (C), 145.0 (C), 143.4 (C), 142.6 (C), 135.1 (C), 134.2 (C), 129.5 (2 × CH), 129.3 (2 × CH), 128.5 (3 × CH), 128.1 (2 × CH), 127.7 (CH), 127.3 (CH), 125.9 (CH), 122.2 (CH), 121.5 (CH), 85.3 (C), 39.8 (2 × CH_2), 16.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{26}H_{21}O_2$ $[M+H]^+$: 365.1536, found: 365.1539.



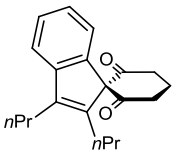
2'-(4-Methoxyphenyl)-3'-propylspiro[cyclohexane-1,1'-indene]-2,6-dione (157e). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156g** (130 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (126 mg, 70%). R_f = 0.46 (40% EtOAc/hexane); m.p. 154-156 °C; IR (film) 1716 (C=O), 1689, 1278, 1265, 1111, 750, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (2H, m, Ar**H**), 7.26 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.18 (1H, dd, *J* = 7.2, 1.5 Hz, Ar**H**), 7.15 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.89 (2H, d, *J* = 8.8 Hz, Ar**H**), 3.83 (3H, s, $OC\mathbf{H}_3$), 2.90 (2H, ddd, *J* = 16.2, 10.6, 5.4 Hz, 2 × C**H**C=O), 2.65 (2H, ddd, *J* = 16.6, 6.3, 4.7 Hz, 2 × C**H**C=O), 2.52-2.46 (2H, m, $C\mathbf{H}_2CH_2CH_3$), 2.21-2.12 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.91-1.81 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.68-1.60 (2H, m, $CH_2C\mathbf{H}_2CH_3$), 0.92 (3H, t, *J* = 7.3 Hz, $CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.5 (2 × C), 158.9 (C), 146.3 (C), 144.8 (C), 143.4 (C), 142.4 (C), 130.6 (2 × CH), 128.2 (CH), 128.1 (C), 125.5 (CH), 121.6 (CH), 120.9 (CH), 113.7 (2 × CH), 85.4 (C), 55.1 (CH_3), 40.1 (2 × CH_2), 27.9 (CH_2), 21.8 (CH_2), 16.8 (CH_2), 14.1 (CH_3); HRMS (EI) Exact mass calcd for $C_{24}H_{24}O_3$ $[M]^+$: 360.1720, found: 360.1718.



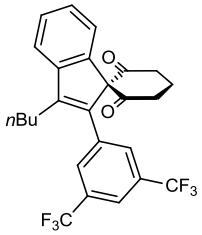
Methyl 4-[2,6-dioxo-3'-propylspiro(cyclohexane-1,1'-indene)-2'-yl]benzoate (157f). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156h** (151 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (157 mg, 81%). R_f = 0.51 (40% EtOAc/hexane); m.p. 140-142 °C; IR (film) 1716 (C=O), 1689, 1278, 1265, 1203, 1111, 750, 734, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (2H, t, J = 8.6 Hz, Ar**H**), 7.41-7.37 (1H, m, Ar**H**), 7.36-7.32 (4H, m, Ar**H**), 7.22-7.18 (1H, m, Ar**H**), 3.92 (3H, s, OC**H**$_3$), 2.97 (2H, ddd, J = 17.1, 11.8, 5.5 Hz, 2 × C**H**C=O), 2.71 (2H, dt, J = 16.6, 4.9 Hz, 2 × C**H**C=O), 2.56-2.51 (2H, m, C**H**$_2$CH$_2$CH$_3$), 2.27-2.18 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.89-1.79 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.70-1.61 (2H, m, CH$_2$C**H**$_2$CH$_3$), 0.92 (3H, t, J = 7.4 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.5 (2 × C), 166.8 (C), 146.3 (C), 145.6 (C), 142.9 (C), 141.5 (C), 141.0 (C), 129.52 (2 × CH), 129.45 (2 × CH), 129.1 (C), 128.4 (CH), 125.9 (CH), 121.4 (CH), 121.3 (CH), 85.6 (C), 52.1 (CH$_3$), 39.8 (2 × CH$_2$), 28.0 (CH$_2$), 21.8 (CH$_2$), 16.7 (CH$_2$), 14.0 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{25}H_{25}O_4$ $[M+H]^+$: 389.1747, found: 389.1747.



2',3'-Diethylspiro[cyclohexane-1,1'-indene]-2,6-dione (157g). The title compound was prepared according to General Procedure B from dione **149a** (109 mg, 0.50 mmol) and alkyne **156c** (61 μL, 0.75 mmol), and purified by column chromatography (5% acetone/hexane) to give a white solid (103 mg, 77%). R_f = 0.30 (10% acetone/hexane); m.p. 104-106 °C; IR (film) 2964, 2927, 2875, 1718 (C=O), 1687, 1463, 1313, 1259, 752 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.46 (1H, d, J = 7.6 Hz, Ar**H**), 7.31 (1H, td, J = 7.4, 1.0 Hz, Ar**H**), 7.26 (1H, dd, J = 7.5, 0.6 Hz, Ar**H**), 7.13 (1H, td, J = 7.5, 1.3 Hz, Ar**H**), 3.10-3.03 (2H, m, 2 × C**H**C=O), 2.77 (2H, dt, J = 16.6, 4.5 Hz, 2 × C**H**C=O), 2.50 (2H, q, J = 7.6 Hz, C**H**$_2$CH$_3$), 2.35 (2H, q, J = 7.6 Hz, C**H**$_2$CH$_3$), 2.33-2.27 (1H, m, CH$_2$C**H**$_2$CH$_2$), 2.10-1.99 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.16 (3H, t, J = 7.6 Hz, CH$_2$C**H**$_3$), 1.01 (3H, t, J = 7.6 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (118.26 MHz, CD_3CN) δ 206.6 (2 × C), 147.1 (C), 146.3 (C), 144.5 (C), 143.5 (C), 129.1 (CH), 125.7 (CH), 122.7 (CH), 120.4 (CH), 85.3 (C), 40.3 (2 × CH$_2$), 21.5 (CH$_2$), 19.1 (CH$_2$), 18.1 (CH$_2$), 13.8 (CH$_3$), 13.7 (CH$_3$); HRMS (EI) Exact mass calcd for $C_{18}H_{20}O_2$ $[M]^+$: 268.1458, found: 268.1456.

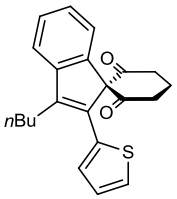


2',3'-Dipropylspiro[cyclohexane-1,1'-indene]-2,6-dione (157h). The title compound was prepared according to General Procedure B from dione **149a** (109 mg, 0.50 mmol) and alkyne **156f** (110 μL, 0.75 mmol), and purified by column chromatography (40% EtOAc/hexane) to give a white solid (98 mg, 66%). R_f = 0.67 (20% EtOAc/hexane); m.p. 105-107 °C; IR (film) 2966, 2929, 2864, 1720 (C=O), 1687, 1465, 1311, 1263, 1211, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (2H, m, Ar**H**), 7.22 (1H, d, J = 6.9 Hz, Ar**H**), 7.09 (1H, td, J = 7.5, 1.2 Hz, Ar**H**), 3.09-2.98 (2H, m, C**H**$_2$C=O), 2.86 (2H, dt, J = 16.4, 4.4 Hz, C**H**$_2$C=O), 2.61-2.51 (2H, m, C**H**$_2$CH$_2$), 2.41-2.29 (3H, m, C**H**$_2$C**H**$_2$), 2.07 (1H, dtt, J = 14.1, 12.7, 4.4 Hz, CH$_2$C**H**$_2$), 1.71-1.56 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.46-1.35 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.05-0.98 (3H, m, CH$_2$CH$_2$C**H**$_3$), 0.95 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.90 (2 × C), 146.45 (C), 144.19 (C), 142.92 (C), 141.88 (C), 128.26 (CH), 124.57 (CH), 121.07 (CH), 120.09 (C), 84.60 (C), 39.68 (CH$_2$), 30.66 (CH$_2$), 27.54 (CH$_2$), 22.25 (CH$_2$), 21.70 (CH$_2$), 17.59 (CH$_2$), 14.90 (CH$_3$), 14.06 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{20}H_{25}O_2$ $[M+H]^+$: 297.1849, found: 297.1855.

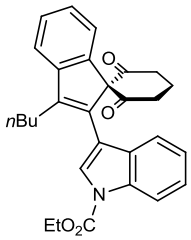


2'-[3,5-Bis(trifluoromethyl)phenyl]-3'-butylspiro[cyclohexane-1,1'-indene]-2,6-dione (157i). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156i** (220 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (170 mg, 71%). R_f = 0.73 (40% EtOAc/hexane); m.p. 116-118 °C; IR (film) 1697 (C=O), 1384, 1276, 1166, 1138, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (1H, s, Ar**H**), 7.79 (2H, s, Ar**H**), 7.49 (1H, d, J = 7.6 Hz, Ar**H**), 7.45-7.38 (2H, m, Ar**H**), 7.28-7.24 (1H, m, Ar**H**), 3.09 (2H, ddd, J = 16.3, 13.4, 5.8 Hz, 2 × C**H**C=O), 2.81 (2H, dt, J = 16.4, 4.0 Hz, 2 × C**H**C=O), 2.56-2.51 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.37-2.29 (1H, m, C**H**$_2$CH$_2$C=O), 1.89-1.78 (1H, m, C**H**$_2$CH$_2$C=O), 1.67-1.59 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.42-1.33 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.86 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 203.7 (2 × C), 148.1 (C), 144.8 (C), 141.6 (C), 139.2 (C), 138.5 (C), 131.5 (2 × C, q, J = 33.2 Hz), 130.0 (2 × CH, q, J = 3.5 Hz), 128.7 (CH), 126.3 (CH), 123.3 (2 × C, q, J = 272.7 Hz), 121.7 (CH), 121.5 (CH), 121.1 (CH, septet, J = 3.9 Hz), 86.5 (C), 39.4 (2 × CH$_2$), 30.7 (CH$_2$), 25.8 (CH$_2$), 22.5 (CH$_2$), 17.0 (CH$_2$), 13.7 (CH$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.8 (6F,

s, 2 × CF_3); HRMS (EI) Exact mass calcd for $C_{26}H_{22}O_2F_6$ $[M]^+$: 480.1519, found: 480.1524.

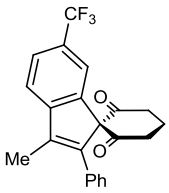


3'-Butyl-2'-(thiophen-2-yl)spiro[cyclohexane-1,1'-indene]-2,6-dione (157j). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156j** (123 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (123 mg, 70%). R_f = 0.53 (40% EtOAc/hexane); m.p. 134-136 °C; IR (film) 2954, 2852, 1720 (C=O), 1687, 1263, 1199, 1039, 744, 688, 567 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 7.6 Hz, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.29 (1H, dd, J = 5.1, 1.0 Hz, Ar**H**), 7.20-7.16 (1H, m, Ar**H**), 7.03 (1H, dd, J = 5.1, 3.6 Hz, Ar**H**), 6.85 (1H, dd, J = 3.6, 1.0 Hz, Ar**H**), 3.08 (2H, ddd, J = 16.5, 13.2, 5.7 Hz, 2 × C**H**C=O), 2.91 (2H, dt, J = 16.5, 4.1 Hz, 2 × C**H**C=O), 2.87-2.83 (2H, m, C**H**$_2$$CH_2CH_2CH_3$), 2.40-2.32 (1H, m, CH_2C**H**$_2$$CH_2$), 2.17-2.06 (1H, m, CH_2C**H**$_2$$CH_2$), 1.75-1.66 (2H, m, CH_2C**H**$_2$$CH_2CH_3$), 1.56-1.47 (2H, m, CH_2CH_2C**H**$_2$$CH_3$), 0.97 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 203.8 (2 × C), 145.7 (C), 145.1 (C), 141.6 (C), 137.3 (C), 135.5 (C), 128.6 (CH), 127.1 (CH), 126.5 (CH), 125.6 (CH), 125.3 (CH), 121.3 (CH), 121.2 (CH), 85.7 (C), 39.4 (2 × CH_2), 30.5 (CH_2), 26.3 (CH_2), 22.9 (CH_2), 17.2 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{23}O_2S$ $[M+H]^+$: 351.1413, found: 351.1418.

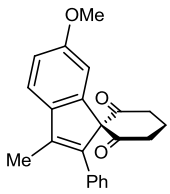


Ethyl 3-{3'-butyl-2,6-dioxospiro[cyclohexane-1,1'-indene]-2'-yl}-1*H*-indole-1-carboxylate (157k). The title compound was prepared according to General Procedure B from dione **149a** (94 mg, 0.50 mmol) and alkyne **156k** (201 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (152 mg, 67%). R_f = 0.49 (40% EtOAc/hexane); m.p. 121-123 °C; IR (film) 1739, 1724 (C=O), 1697, 1452, 1379, 1249, 1228, 1062, 761, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (1H, d, J = 8.2 Hz, Ar**H**), 7.54 (1H, d, J = 7.7 Hz, Ar**H**), 7.48 (1H, s, Ar**H**), 7.43-7.34 (4H, m, Ar**H**), 7.29-7.21 (2H, m, Ar**H**), 4.51 (2H, q, J = 7.1 Hz, OC**H**$_2$), 2.94 (2H, ddd, J = 16.4, 10.9, 5.4 Hz, 2 × C**H**C=O), 2.66 (2H, dt, J = 10.6, 5.6 Hz, 2 × C**H**C=O), 2.47 (2H, t, J = 7.6 Hz, C**H**$_2$$CH_2CH_2CH_3$), 2.22-2.13 (1H, m, CH_2C**H**$_2$$CH_2$), 1.90-1.79 (1H, m, CH_2C**H**$_2$$CH_2$), 1.58-1.51 (2H, m,

$CH_2C\mathbf{H}_2CH_2CH_3$), 1.49 (3H, t, J = 7.1, Hz, $OCH_2C\mathbf{H}_3$), 1.32-1.21 (2H, m, $CH_2CH_2C\mathbf{H}_2CH_3$), 0.77 (3H, t, J = 7.3, Hz, $CH_2CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.8 (2 × C), 150.9 (C), 147.9 (C), 145.6 (C), 143.0 (C), 135.0 (C), 134.1 (C), 130.2 (C), 128.4 (CH), 125.7 (CH), 124.8 (CH), 124.3 (CH), 123.1 (CH), 121.9 (CH), 121.1 (CH), 121.0 (CH), 116.8 (C), 115.0 (CH), 86.2 (C), 63.3 (CH_2), 39.9 (2 × CH_2), 30.5 (CH_2), 26.3 (CH_2), 22.4 (CH_2), 17.0 (CH_2), 14.4 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{29}H_{30}O_4N$ $[M+H]^+$: 456.2169, found: 456.2164.

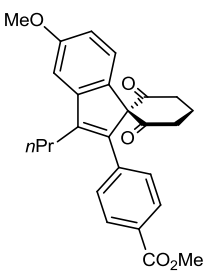


3'-Methyl-2'-phenyl-6'-(trifluoromethyl)spiro[cyclohexane-1,1'-indene]-2,6-dione (158a). The title compound was prepared according to General Procedure B from dione **149b** (128 mg, 0.50 mmol) and alkyne **156a** (94 μL, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a white solid (122 mg, 66%). R_f = 0.48 (20% EtOAc/hexane); m.p. 210-212 °C; IR (film) 1712 (C=O), 1697, 1321, 1155, 1116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 7.9 Hz, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.42-7.37 (2H, m, Ar**H**), 7.36-7.32 (1H, m, Ar**H**), 7.23-7.20 (2H, m, Ar**H**), 2.94 (2H, ddd, J = 16.3, 10.7, 5.3 Hz, 2 × C**H**C=O), 2.73 (2H, ddd, J = 16.7, 6.0, 4.9 Hz, 2 × C**H**C=O), 2.28-2.19 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 2.17 (3H, s, $C\mathbf{H}_3$), 1.98-1.88 (1H, m, $CH_2C\mathbf{H}_2CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.5 (2 × C), 150.5 (C, d, J = 1.0 Hz), 145.3 (C), 143.4 (C), 140.0 (C), 134.9 (C), 129.0 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 127.8 (C, q, J = 32.3 Hz), 126.0 (CH, q, J = 4.0 Hz), 124.2 (C, q, J = 271.5 Hz), 120.7 (CH), 118.1 (CH, q, J = 3.7 Hz), 84.8 (C), 40.2 (2 × CH_2), 16.7 (CH_2), 11.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.6 (3F, s, CF_3); HRMS (EI) Exact mass calcd for $C_{22}H_{17}O_2F_3$ $[M]^+$: 370.1175, found: 370.1174.

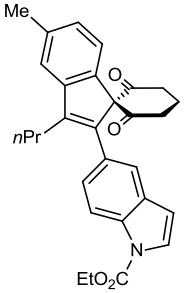


6'-Methoxy-3'-methyl-2'-phenylspiro[cyclohexane-1,1'-indene]-2,6-dione (158b). The title compound was prepared according to General Procedure B from dione **149c** (109 mg, 0.50 mmol) and alkyne **156a** (94 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (110 mg, 64%). R_f = 0.10 (20% EtOAc/hexane); m.p. 185-187 °C; IR (film) 2970, 2937, 2843, 1720 (C=O), 1687, 1282, 1211, 1188, 1132, 1026, 889, 723, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (2H, m, Ar**H**), 7.31-7.25 (2H, m, Ar**H**), 7.24-7.20 (2H, m, Ar**H**), 6.91-6.87 (2H, m, Ar**H**), 3.82 (3H, s, $OC\mathbf{H}_3$), 2.94 (2H, ddd, J = 16.4, 11.0, 5.3 Hz, 2

× C**H**C=O), 2.71 (2H, dt, *J* = 16.5, 5.2 Hz, 2 × C**H**C=O), 2.24-2.14 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 2.15 (3H, s, $C\mathbf{H}_3$), 2.00-1.86 (1H, m, $CH_2C\mathbf{H}_2CH_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.2 (2 × C), 158.3 (C), 144.4 (C), 140.23 (C), 140.17 (C), 139.6 (C), 135.7 (C), 129.1 (2 × CH), 128.4 (2 × CH), 127.3 (CH), 121.1 (CH), 112.1 (CH), 109.7 (CH), 84.8 (C), 55.6 (CH_3), 39.9 (2 × CH_2), 16.7 (CH_2), 11.8 (CH_3); HRMS (EI) Exact mass calcd for $C_{22}H_{20}O_3$ $[M]^+$: 332.1407, found: 332.1407.

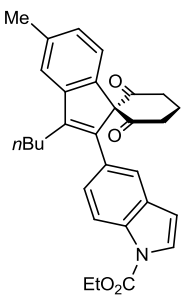


Methyl 4-(5'-methoxy-2,6-dioxo-3'-propylspiro[cyclohexane-1,1'-indene]-2'-yl)benzoate (158c). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from dione **149d** (109 mg, 0.50 mmol) and alkyne **156h** (151 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (155 mg, 74%). R_f = 0.38 (40% EtOAc/hexane); m.p. 137-139 °C; IR (film) 1720 (C=O), 1693, 1433, 1276, 1261, 1242, 1207, 1182, 1111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.24 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.90 (1H, d, *J* = 2.4 Hz, Ar**H**), 6.70 (1H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 3.92 (3H, s, $OC\mathbf{H}_3$), 3.84 (3H, s, $OC\mathbf{H}_3$), 2.95 (2H, ddd, *J* = 17.0, 11.8, 5.5 Hz, 2 × C**H**C=O), 2.70 (2H, dt, *J* = 16.5, 4.8 Hz, 2 × C**H**C=O), 2.54-2.47 (2H, m, $C\mathbf{H}_2CH_2CH_3$), 2.27-2.17 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.90-1.77 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.70-1.59 (2H, m, $CH_2C\mathbf{H}_2CH_3$), 0.91 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.8 (2 × C), 166.8 (C), 160.3 (C), 147.3 (C), 146.0 (C), 142.8 (C), 141.0 (C), 135.2 (C), 129.5 (2 × CH), 129.4 (2 × CH), 129.1 (C), 122.0 (CH), 110.7 (CH), 107.8 (CH), 84.8 (C), 55.5 (CH_3), 52.1 (CH_3), 39.8 (2 × CH_2), 28.0 (CH_2), 21.9 (CH_2), 16.8 (CH_2), 14.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{27}O_5$ $[M+H]^+$: 419.1853, found: 419.1855.



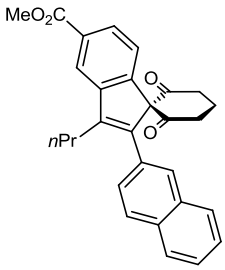
Ethyl 5-(5'-methyl-2,6-dioxo-3'-propylspiro[cyclohexane-1,1'-indene]-2'-yl)-1*H*-indole-1-carboxylate (158d). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from dione **149e** (101 mg, 0.50 mmol) and alkyne

156l (191 mg, 0.75 mmol) and K_2CO_3 (172.7 mg, 1.25 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (150 mg, 66%). R_f = 0.44 (40% EtOAc/hexane); m.p. 128-130 °C; IR (film) 1722 (C=O), 1710, 1687, 746, 732, 692, 580, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 8.0 Hz, Ar**H**), 7.65 (1H, d, J = 3.6 Hz, Ar**H**), 7.43 (1H, d, J = 1.1 Hz, Ar**H**), 7.22-7.19 (2H, m, Ar**H**), 7.15 (1H, d, J = 7.7 Hz, Ar**H**), 7.03-7.00 (1H, m, Ar**H**), 6.60 (1H, dd, J = 3.7, 0.5 Hz, Ar**H**), 4.50 (2H, q, J = 7.1 Hz, OC**H**$_2$), 2.87 (2H, ddd, J = 15.6, 10.2, 5.3 Hz, 2 × C**H**C=O), 2.59 (2H, ddd, J = 16.5, 6.7, 4.8 Hz, 2 × C**H**C=O), 2.51-2.45 (2H, m, C**H**$_2$CH$_2$CH$_3$), 2.41 (3H, s, ArC**H**$_3$), 2.15-2.06 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.84-1.74 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.69-1.60 (2H, m, CH$_2$C**H**$_2$CH$_3$), 1.49 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 0.91 (3H, t, J = 7.4 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.8 (2 × C), 150.9 (C), 146.3 (C), 145.0 (C), 143.1 (C), 141.0 (C), 138.0 (C), 134.5 (C), 130.7 (C), 130.5 (C), 126.3 (CH), 126.1 (CH), 125.9 (C), 121.9 (CH), 121.8 (CH), 121.4 (CH), 114.9 (CH), 108.1 (CH), 85.2 (C), 63.2 (CH_2), 40.2 (2 × CH_2), 27.9 (CH_2), 21.8 (CH_2), 21.5 (CH_3), 16.7 (CH_2), 14.3 (CH_3), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{29}H_{29}O_4N$ $[M]^+$: 455.2091, found: 455.2093.

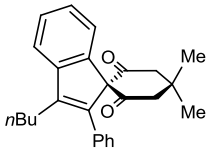


Ethyl 5-(5'-methyl-2,6-dioxo-3'-butylspiro[cyclohexane-1,1'-indene]-2'-yl)-1*H*-indole-1-carboxylate (158e). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from dione **149e** (101 mg, 0.50 mmol) and alkyne **156o** (201 mg, 0.75 mmol) and K_2CO_3 (172.7 mg, 1.25 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (155 mg, 66%). R_f = 0.50 (40% EtOAc/hexane); m.p. 99-101 °C; IR (film) 2926, 2856, 1737 (C=O), 1693 (C=O), 1647, 1604, 1462, 1398, 1336, 1257, 1085, 1045, 804, 763, 732, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 8.4 Hz, Ar**H**), 7.65 (1H, d, J = 3.7 Hz, Ar**H**), 7.42 (1H, d, J = 1.3 Hz, Ar**H**), 7.21 (1H, d, J = 1.5 Hz, Ar**H**), 7.18 (1H, d, J = 1.7 Hz, Ar**H**), 7.15 (1H, d, J = 7.7 Hz, Ar**H**), 7.01 (1H, dd, J = 7.6, 0.6 Hz, Ar**H**), 6.60 (1H, d, J = 3.7 Hz, Ar**H**), 4.51 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.87 (2H, ddd, J = 15.6, 10.1, 5.3 Hz, C**H**$_2$C=O), 2.59 (2H, ddd, J = 16.5, 6.7, 4.8 Hz, C**H**$_2$C=O), 2.52-2.46 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.41 (3H, s, ArC**H**$_3$), 2.16-2.04 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.86-1.73 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.65-1.53 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.49 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 1.32 (2H, tt, J = 9.6, 4.8 Hz,

$CH_2CH_2C\mathbf{H}_2CH_3$), 0.83 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.9 (2 × C), 151.0 (C), 146.4 (C), 145.3 (C), 142.9 (C), 141.1 (C), 138.2 (C), 134.6 (C), 130.7 (C), 130.6 (C), 126.4 CH, 126.1 (CH), 126.0 (CH), 122.0 (CH), 121.9 (CH), 121.4 (CH), 115.0 (CH), 108.2 (CH), 85.2 (C), 63.3 (CH_2), 40.3 (CH_2), 30.8 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 21.6 (CH_3), 16.8 (CH_2), 14.4 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{30}H_{32}O_4N$ $[M+H]^+$: 470.2326, found: 470.2320.

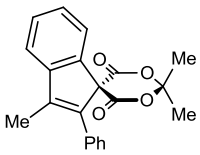


Methyl 2'-(naphthalen-2-yl)-2,6-dioxo-3'-propylspiro[cyclohexane-1,1'-indene]-5'-carboxylate (158f). The title compound was prepared according to General Procedure B from dione **149f** (123 mg, 0.50 mmol) and alkyne **156m** (146 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (158 mg, 72%). R_f = 0.47 (40% EtOAc/hexane); m.p. 177-179 °C; IR (film) 1724 (C=O), 1689, 1422, 1290, 1261, 1246, 1201, 1114, 981, 831, 756, 563 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, d, J = 1.1 Hz, Ar**H**), 7.95 (1H, dd, J = 7.8, 1.5 Hz, Ar**H**), 7.89-7.82 (3H, m, Ar**H**), 7.67 (1H, s, Ar**H**), 7.55-7.50 (2H, m, Ar**H**), 7.35-7.31 (2H, m, Ar**H**), 3.96 (3H, s, $OC\mathbf{H}_3$), 2.88 (2H, ddd, J = 16.5, 9.8, 5.2 Hz, 2 × C**H**C=O), 2.62 (2H, ddd, J = 16.6, 7.0, 4.8 Hz, 2 × C**H**C=O), 2.57-2.52 (2H, m, $C\mathbf{H}_2CH_2CH_3$), 2.17-2.08 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.87-1.77 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.72-1.62 (2H, m, $CH_2C\mathbf{H}_2CH_3$), 0.90 (3H, t, J = 7.3 Hz, $CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.8 (2 × C), 166.9 (C), 148.4 (C), 146.7 (C), 145.1 (C), 143.6 (C), 133.1 (C), 133.0 (C), 132.7 (C), 130.3 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.7 (2 × CH), 127.3 (CH), 126.4 (CH), 126.3 (CH), 121.9 (CH), 121.7 (CH), 85.5 (C), 52.3 (CH_3), 40.3 (2 × CH_2), 27.9 (CH_2), 21.8 (CH_2), 16.7 (CH_2), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{29}H_{26}O_4$ $[M]^+$: 438.1825, found: 438.1822.

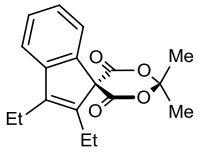


3'-Butyl-4,4-dimethyl-2'-phenylspiro[cyclohexane-1,1'-indene]-2,6-dione (159a). The title compound was prepared according to General Procedure B from dione **149h** (108 mg, 0.50 mmol) and alkyne **156d** (0.13 mL, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a white solid (141 mg, 76%). R_f = 0.71 (40% EtOAc/hexane); m.p. 173-175 °C; IR (film) 1712 (C=O), 1693, 1220, 750, 704, 551 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (8H, m, Ar**H**), 7.23-7.18 (1H, m, Ar**H**), 2.91 (2H, d, J

= 15.3 Hz, 2 × C**H**C=O), 2.52 (2H, d, *J* = 15.3 Hz, 2 × C**H**C=O), 2.48-2.43 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.61-1.54 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.38-1.27 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 1.19 (3H, s, C(C**H**$_3$)$_2$), 0.83 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$), 0.70 (s, 3H, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 204.8 (2 × C), 145.7 (C), 145.6 (C), 142.3 (C), 142.2 (C), 136.0 (C), 130.3 (2 × CH), 128.3 (CH), 127.9 (2 × CH), 127.5 (CH), 125.5 (CH), 121.6 (CH), 121.0 (CH), 84.9 (C), 53.5 (2 × CH$_2$), 30.7 (CH$_2$), 30.3 (C), 30.0 (CH$_3$), 27.3 (CH$_3$), 25.6 (CH$_2$), 22.5 (CH$_2$), 13.8 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{26}H_{29}O_2$ $[M+H]^+$: 373.2162, found: 373.2163.

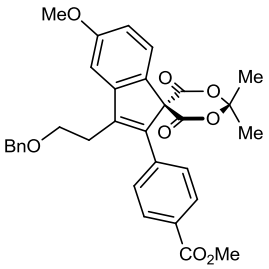


3',6,6-Trimethyl-2'-phenylspiro[1,5-dioxane-3,1'-indene]-2,4-dione (159b). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from 1,3-dicarbonyl compound **151a** (109 mg, 0.50 mmol) and alkyne **156a** (94 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (90 mg, 54%). R_f = 0.71 (40% EtOAc/hexane); m.p. 196-198 °C; IR (film) 1735 (C=O), 1716, 1296, 1271, 1253, 1222, 1195, 1105, 1008, 914, 744, 702 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48-7.32 (8H, m, Ar**H**), 7.29 (1H, dd, *J* = 7.4, 1.0 Hz, Ar**H**), 2.15 (3H, s, CC**H**$_3$), 1.88 (3H, s, C(C**H**$_3$)$_2$), 1.33 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 165.8 (2 × C), 146.1 (C), 143.4 (C), 143.3 (C), 139.1 (C), 134.1 (C), 129.6 (2 × CH), 129.5 (CH), 128.7 (2 × CH), 128.5 (CH), 126.9 (CH), 121.1 (CH), 121.0 (CH), 106.1 (C), 68.2 (C), 30.2 (CH$_3$), 28.7 (CH$_3$), 11.4 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{21}H_{22}O_4N$ $[M+NH_4]^+$: 352.1543, found: 352.1548.

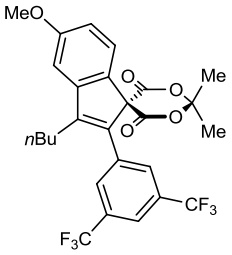


2',3'-Diethyl-6,6-dimethylspiro[1,5-dioxane-3,1'-indene]-2,4-dione (159c). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from 1,3-dicarbonyl compound **151a** (109 mg, 0.50 mmol) and alkyne **156c** (85 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (72 mg, 48%). R_f = 0.60 (40% EtOAc/hexane); m.p. 112-114 °C; IR (film) 1741 (C=O), 1712, 1300, 1269, 1247, 1228, 1199, 1010, 914, 750 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.38 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), δ 7.34-7.28 (2H, m, Ar**H**), 7.20 (1H, td, *J*

= 7.5, 1.2 Hz, Ar**H**), 2.62 (2H, q, *J* = 7.6 Hz, C**H**$_2$CH$_3$), 2.48 (2H, q, *J* = 7.7 Hz, C**H**$_2$CH$_3$), 2.00 (3H, s, C(C**H**$_3$)$_2$), 1.91 (3H, s, C(C**H**$_3$)$_2$), 1.25 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$), 1.18 (3H, t, *J* = 7.7 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.0 (2 × C), 146.4 (C), 146.0 (C), 142.4 (C), 141.2 (C), 129.3 (CH), 126.0 (CH), 121.3 (CH), 120.3 (CH), 105.8 (C), 66.7 (C), 30.0 (CH_3), 29.6 (CH_3), 20.3 (CH_2), 18.8 (CH_2), 13.6 (CH_3), 13.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{24}O_4N$ $[M+NH_4]^+$: 318.1700, found: 318.1706.

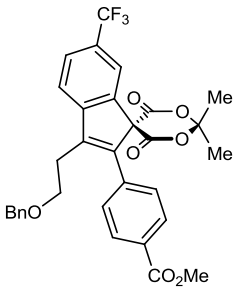


Methyl 4-{3'-[2-(benzyloxy)ethyl]-5'-methoxy-6,6-dimethyl-2,4-dioxospiro[1,5-dioxane-3,1'-indene]-2'-yl}benzoate (159d). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from 1,3-dicarbonyl compound **151b** (125 mg, 0.50 mmol) and alkyne **156n** (220 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give an off-white solid (160 mg, 59%). R_f = 0.53 (40% EtOAc/hexane); m.p. 132-134 °C; IR (film) 1743 (C=O), 1724, 1294, 1271, 1249, 1224, 1201, 1097, 1028, 912, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.43 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.32-7.25 (6H, m, Ar**H**), 7.00 (1H, d, *J* = 2.4 Hz, Ar**H**), 6.79 (1H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 4.47 (2H, s, OC**H**$_2$Ph), 3.95 (3H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 3.68 (2H, t, *J* = 7.0 Hz, OC**H**$_2$CH$_2$), 2.82 (2H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_2$), 1.83 (3H, s, C(C**H**$_3$)$_2$), 1.29 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.6 (C), 165.5 (2 × C), 161.1 (C), 146.5 (C), 145.2 (C), 140.8 (C), 138.8 (C), 138.0 (C), 135.3 (C), 130.3 (C), 129.9 (2 × CH), 129.8 (2 × CH), 128.3 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 121.9 (CH), 112.3 (CH), 107.8 (CH), 106.0 (C), 73.0 (CH_2), 68.2 (C), 67.7 (CH_2), 55.6 (CH_3), 52.2 (CH_3), 30.4 (CH_3), 28.4 (CH_3), 27.1 (CH_2); HRMS (ESI) Exact mass calcd for $C_{32}H_{34}O_8N$ $[M+NH_4]^+$: 560.2279, found: 560.2274.



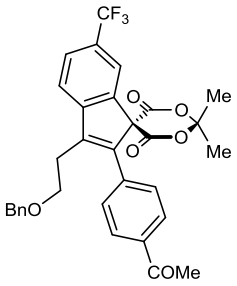
2'-[3,5-Bis(trifluoromethyl)phenyl]-3'-butyl-5'-methoxy-6,6-dimethyl-2',3'-dihydrospiro[1,5-dioxane-3,1'-indene]-2,4-dione (159e). The title compound was prepared according to a slight modification of General Procedure B (in that the reaction

was conducted in the presence of K_2CO_3 (173 mg, 1.25 mmol)) from 1,3-dicarbonyl compound **151b** (125 mg, 0.50 mmol) and alkyne **156i** (220 μL, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a white solid (108 mg, 40%). R_f = 0.77 (40% EtOAc/hexane); m.p. 128-130 °C; IR (film) 2927, 2860, 1739 (C=O), 1463, 1377, 1274, 1087, 906, 680, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (1H, s, Ar**H**), 7.83 (2H, s, Ar**H**), 7.32 (1H, d, J = 8.4 Hz, Ar**H**), 7.01 (1H, d, J = 2.4 Hz, Ar**H**), 6.84 (1H, dd, J = 8.4, 2.4 Hz, Ar**H**), 3.88 (3H, s, OC**H**$_3$), 2.51 (2H, t, J = 7.3 Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.91 (3H, s, C(C**H**$_3$)$_2$), 1.68-1.59 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.39 (3H, s, C(C**H**$_3$)$_2$), 1.35 (3H, t, J = 7.5 Hz, CH$_2$C**H**$_2$CH$_2$CH$_3$), 0.85 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 165.5 (C), 161.2 (C), 150.2 (C), 145.9 (C), 136.8 (C), 136.4 (C), 135.1 (C), 132.1 (2 × C, q, J = 33.6 Hz), 129.99 (CH), 129.97 (CH), 123.0 (2 × C, q, J = 273.0 Hz), 122.21 (C), 122.20 (2 × CH), 112.1 (CH), 108.4 (CH), 106.2 (C), 67.8 (C), 55.7 (CH_3), 30.6 (CH_2), 30.5 (CH_3), 28.3 (CH_3), 25.8 (CH_2), 22.4 (CH_2), 13.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.9 (6F, s, 2 × CF_3); HRMS (EI) Exact mass calcd for $C_{27}H_{24}O_5F_6Na$ $[M]^+$: 565.1420, found: 565.1424.

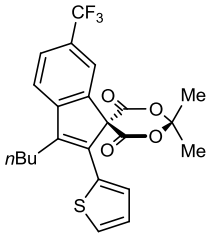


4-{3'-[2-(Benzyloxy)ethyl]-6,6-dimethyl-2,4-dioxo-6'-(trifluoromethyl)spiro[1,5-dioxane-3,1'-indene]-2'-yl}benzoate (159f). The title compound was prepared according to General Procedure C from dione **151c** (144 mg, 0.50 mmol) and alkyne **156n** (220 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a light yellow solid (87 mg, 30%). R_f = 0.61 (40% EtOAc/hexane); m.p. 102-103 °C; IR (film) 1752, 1726 (C=O), 1606, 1437, 1275, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (2H, m, Ar**H**), 7.68 (1H, dd, J = 11.8, 3.7 Hz, Ar**H**), 7.55 (2H, d, J = 7.5 Hz, Ar**H**), 7.43-7.38 (2H, m, Ar**H**), 7.32-7.20 (5H, m, Ar**H**), 4.45 (2H, s, OC**H**$_2$Ph), 3.94 (3H, s, OC**H**$_3$), 3.66 (2H, t, J = 6.8 Hz, OC**H**$_2$CH$_2$), 2.83 (2H, t, J = 6.8 Hz, OCH$_2$C**H**$_2$), 1.89 (3H, s, C(C**H**$_3$)$_2$), 1.27 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.44 (C), 164.4 (2 × C), 148.6 (C), 144.9 (C), 143.4 (C), 142.5 (C), 137.9 (C), 137.8 (C), 130.7 (C), 129.9 (CH), 129.8 (CH), 128.8 (C, q, J = 33.0 Hz), 128.3 (CH), 127.6 (2 × CH), 127.1 (CH, q, J = 3.8 Hz), 124.3 (C, q, J = 275.1 Hz), 121.9 (CH), 118.1 (CH, q, J = 3.0 Hz), 106.6 (C), 73.0 (CH_2), 68.4 (C), 67.9 (CH_2), 52.3 (CH_3), 30.2 (CH_3), 29.5

(C), 28.5 (CH_2), 27.0 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.9 (3F, CF_3); HRMS (EI) Exact mass calcd for $C_{32}H_{27}F_3O_7Na$ $[M]^+$: 603.1601, found: 603.1598.

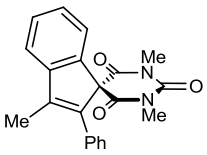


2'-(4-Acetylphenyl)-3'-[2-(benzyloxy)ethyl]-6,6-dimethyl-6'-(trifluoromethyl)spiro[1,5-dioxane-3,1'-indene]-2,4-dione (159g). The title compound was prepared according to General Procedure C from dione **151c** (144 mg, 0.50 mmol) and alkyne **156p** (208 mg, 0.75 mmol), and purified by column chromatography (15% EtOAc/hexane) to give an off-white solid (79 mg, 28%). R_f = 0.53 (40% EtOAc/hexane); m.p. 134-135 °C; IR (film) 1749, 1683 (C=O), 1603, 1326, 1281, 1127, 1097, 1013, 761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.3 Hz, Ar**H**), 7.69 (1H, d, J = 8.1 Hz, Ar**H**), 7.59-7.53 (2H, m, Ar**H**), 7.44 (2H, d, J = 8.3 Hz, Ar**H**), 7.33-7.20 (5H, m, Ar**H**), 4.47 (2H, s, OC**H**$_2$Ph), 3.68 (2H, t, J = 6.7 Hz, OC**H**$_2$CH$_2$), 2.84 (2H, t, J = 6.7 Hz, OCH$_2$C**H**$_2$), 2.63 (3H, s, C**H**$_3$C=O), 1.91 (3H, s, C(C**H**$_3$)$_2$), 1.29 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.4 (C), 164.4 (2 × C), 148.5 (C), 145.0 (C), 143.4 (C), 142.4 (C), 138.1 (C), 137.8 (C), 137.3 (C), 130.1 (2 × CH), 129.2 (C, q, J = 32.8 Hz), 128.6 (2 × CH), 128.3 (2 × CH), 127.6 (2 × CH), 127.1 (CH, q, J = 3.7 Hz), 124.1 (C, q, J = 271.2 Hz), 121.9 (CH), 118.1 (CH, q, J = 3.7 Hz), 106.6 (C), 73.1 (CH_2), 68.4 (C), 67.9 (CH_2), 30.3 (CH_3), 28.6 (CH_3), 27.1 (CH_2), 26.6 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.9 (3F, CF_3); HRMS (EI) Exact mass calcd for $C_{32}H_{27}F_3O_6Na$ $[M]^+$: 587.1652, found: 587.1644.

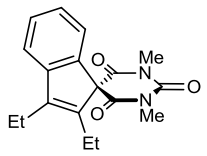


3'-Butyl-6,6-dimethyl-2'-(thiophen-2-yl)-6'-(trifluoromethyl)spiro[1,5-dioxane-3,1'-indene]-2,4-dione (159h). The title compound was prepared according to General Procedure C from dione **151c** (144 mg, 0.50 mmol) and alkyne **156j** (123 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a light yellow solid (49.5 mg, 22%). R_f = 0.79 (40% EtOAc/hexane); m.p. 131-132 °C; IR (film) 1748 (C=O), 1683, 1603, 1326, 1282, 1160, 1097, 761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, ddd, J = 8.0, 1.5, 0.7 Ar**H**), 7.54 (2H, dt, J = 12.8, 2.8 Ar**H**), 7.43 (1H, dd, J = 4.9, 1.4 Hz, Ar**H**), 7.12-7.07 (2H, m, Ar**H**), 2.71 (2H, t, J = 7.9, Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.96 (3H,

s, C(C**H**$_3$)$_2$), 1.71-1.63 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.55 (3H, s, C(C**H**$_3$)$_2$), 1.48-1.39 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 0.92 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 164.4 (2 × C), 149.2 (C), 148.6 (C), 143.3 (C), 135.3 (C), 133.4 (C), 129.0 (C, q, J = 32.8 Hz), 128.4 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH, q, J = 3.7 Hz), 123.8 (C, q, J = 271.1 Hz), 121.5 (CH), 118.3 (CH, q, J = 3.7 Hz), 106.9 (C), 68.4 (C), 30.5 (CH$_2$), 30.3 (CH$_3$), 28.8 (CH$_3$), 26.1 (CH$_2$), 22.6 (CH$_2$), 13.8 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –62.0 (3F, CF$_3$); HRMS (EI) Exact mass calcd for $C_{23}H_{21}F_3O_4SNa$ [M]$^+$: 473.1005, found: 473.0995.

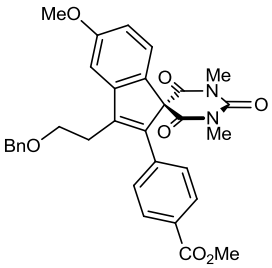


1,3',5-Trimethyl-2'-phenylspiro[1,5-diazinane-3,1'-indene]-2,4,6-trione (160a). The title compound was prepared according to General Procedure B from 1,3-dicarbonyl compound **153a** (116 mg, 0.50 mmol) and alkyne **156a** (94 μL, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (132 mg, 76%). R$_f$ = 0.57 (40% EtOAc/hexane); m.p. 118-120 °C; IR (film) 1712 (C=O), 1678 (C=O), 1417, 1365, 742, 723, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46-7.32 (5H, m, Ar**H**), 7.28-7.22 (3H, m, Ar**H**), 7.17 (1H, d, J = 7.5 Hz, Ar**H**), 3.32 (6H, s, 2 × *N*C**H**$_3$), 2.22 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 166.8 (2 × C), 151.3 (C), 146.6 (C), 142.6 (C), 142.1 (C), 140.1 (C), 134.0 (C), 129.5 (CH), 128.8 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 126.7 (CH), 121.1 (CH), 120.6 (CH), 70.4 (C), 29.2 (2 × CH$_3$), 11.8 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{21}H_{19}O_3N_2$ [M+H]$^+$: 347.1390, found: 347.1395.

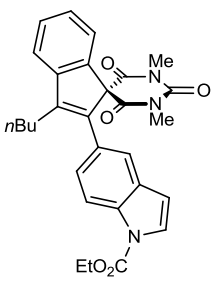


2',3'-Diethyl-1,5-dimethylspiro[1,5-diazinane-3,1'-indene]-2,4,6-trione (160b). The title compound was prepared according to General Procedure B from 1,3-dicarbonyl compound **153a** (116 mg, 0.50 mmol) and alkyne **156c** (85 μL, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a white solid (117 mg, 75%). R$_f$ = 0.73 (40% EtOAc/hexane); m.p. 170-172 °C; IR (film) 1712 (C=O), 1674 (C=O), 1435, 1363, 1278, 1114, 748 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (1H, td, J = 7.4, 0.7 Hz, Ar**H**), 7.29 (1H, d, J = 7.4 Hz, Ar**H**), 7.13 (1H, td, J = 7.4, 0.9 Hz, Ar**H**), 7.07 (1H, d, J = 7.5 Hz, Ar**H**), 3.40 (6H, s, 2 × *N*C**H**$_3$), 2.62 (2H, q, J = 6.2 Hz, C**H**$_2$CH$_3$), 2.45 (2H, q, J = 7.7 Hz, C**H**$_2$CH$_3$), 1.25 (3H, t, J = 7.6 Hz, CH$_2$C**H**$_3$), 1.07 (3H, t, J =

7.7 Hz, CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.1 (2 × C), 151.7 (C), 146.1 (C), 145.8 (C), 142.6 (C), 141.6 (C), 129.2 (CH), 125.6 (CH), 120.23 (CH), 120.22 (CH), 68.9 (C), 29.3 (2 × CH_3), 20.2 (CH_2), 18.9 (CH_2), 13.2 (CH_3), 13.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{21}O_3N_2$ $[M+H]^+$: 313.1547, found: 313.1547.

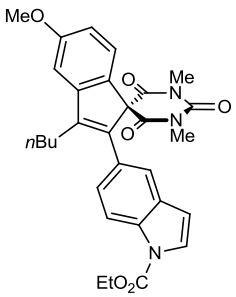


Methyl 4-{3'-[2-(benzyloxy)ethyl]-5'-methoxy-1,5-dimethyl-2,4,6-trioxospiro[1,5-diazinane-3,1'-indene]-2'-yl}benzoate (160c). The title compound was prepared according to General Procedure B from 1,3-dicarbonyl compound **153b** (131 mg, 0.50 mmol) and alkyne **156n** (220 mg, 0.75 mmol), and purified by column chromatography (20% EtOAc/hexane) to give a white solid (233 mg, 84%). R_f = 0.50 (40% EtOAc/hexane); m.p. 118-120 °C; IR (film) 1726 (C=O), 1714 (C=O), 1680 (C=O), 1436, 1367, 1273, 1230, 1101, 752, 738, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (2H, d, J = 8.4 Hz, Ar**H**), 7.37 (2H, d, J = 8.4 Hz, Ar**H**), 7.35-7.25 (5H, m, Ar**H**), 7.06 (1H, d, J = 8.3 Hz, Ar**H**), 7.00 (1H, d, J = 2.3 Hz, Ar**H**), 6.76 (1H, dd, J = 8.3, 2.3 Hz, Ar**H**), 4.49 (2H, s, OC**H**$_2$Ph), 3.94 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 3.71 (2H, t, J = 7.1 Hz, OC**H**$_2$CH$_2$), 3.32 (6H, s, 2 × *N*C**H**$_3$), 2.88 (2H, t, J = 7.1 Hz, OCH$_2$C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (2 × C), 161.0 (C), 151.2 (C), 146.9 (C), 144.2 (C), 141.8 (C), 138.8 (C), 138.1 (C), 134.7 (C), 130.0 (C), 1 29.8 (2 × CH), 129.3 (2 × CH), 128.3 (2 × CH), 127.64 (2 × CH), 127.56 (CH), 121.4 (CH), 112.1 (CH), 108.0 (CH), 73.0 (CH_2), 69.9 (C), 68.3 (CH_2), 55.6 (CH_3), 52.2 (CH_3), 29.2 (2 × CH_3), 27.2 (CH_2); HRMS (ESI) Exact mass calcd for $C_{32}H_{34}O_7N_3$ $[M+NH_4]^+$: 572.2391, found: 572.2387.



Ethyl 5-(3'-butyl-1,5-dimethyl-2,4,6-trioxospiro[1,5-diazinane-3,1'-indene]-2'-yl)-1*H*-indole-1-carboxylate (160d). The title compound was prepared according to General Procedure B from 1,3-dicarbonyl compound **153a** (116 mg, 0.50 mmol) and alkyne **156o** (201 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give an off-white solid (200 mg, 80%). R_f = 0.72 (40% EtOAc/hexane); m.p. 144-146 °C; IR (film) 1737 (C=O), 1680 (C=O), 1465, 1436, 1365, 1226, 1045, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (1H, d, J = 7.9 Hz, Ar**H**), 7.66 (1H, d, J = 3.6 Hz, Ar**H**), 7.48-7.40

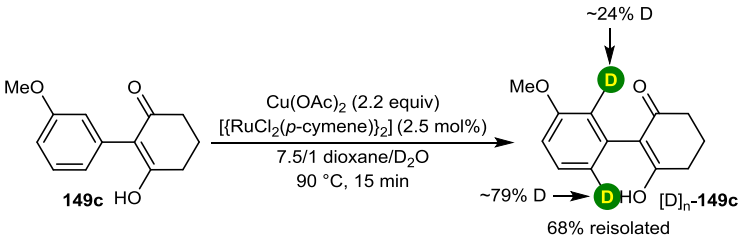
(3H, m, Ar**H**), 7.28-7.17 (3H, m, Ar**H**), 6.60 (1H, d, *J* = 3.7 Hz, Ar**H**), 4.52 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.29 (6H, s, 2 × *N*C**H**$_3$), 2.56 (2H, t, *J* = 7.7 Hz, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.67-1.58 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.49 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.35 (2H, sextet, *J* = 7.4 Hz, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.84 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 166.9 (2 × C), 151.2 (C), 150.9 (C), 146.6 (C), 146.1 (C), 143.0 (C), 140.7 (C), 134.9 (C), 130.6 (C), 129.2 (CH), 128.8 (C), 126.4 (CH), 126.2 (CH), 125.6 (CH), 121.7 (CH), 121.3 (CH), 121.0 (CH), 115.2 (CH), 108.0 (CH), 71.0 (C), 63.3 (CH$_2$), 30.6 (CH$_2$), 29.1 (2 × CH$_3$), 25.8 (CH$_2$), 22.5 (CH$_2$), 14.4 (CH$_3$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{29}H_{30}O_5N_3$ $[M+H]^+$: 500.2180, found: 500.2171.



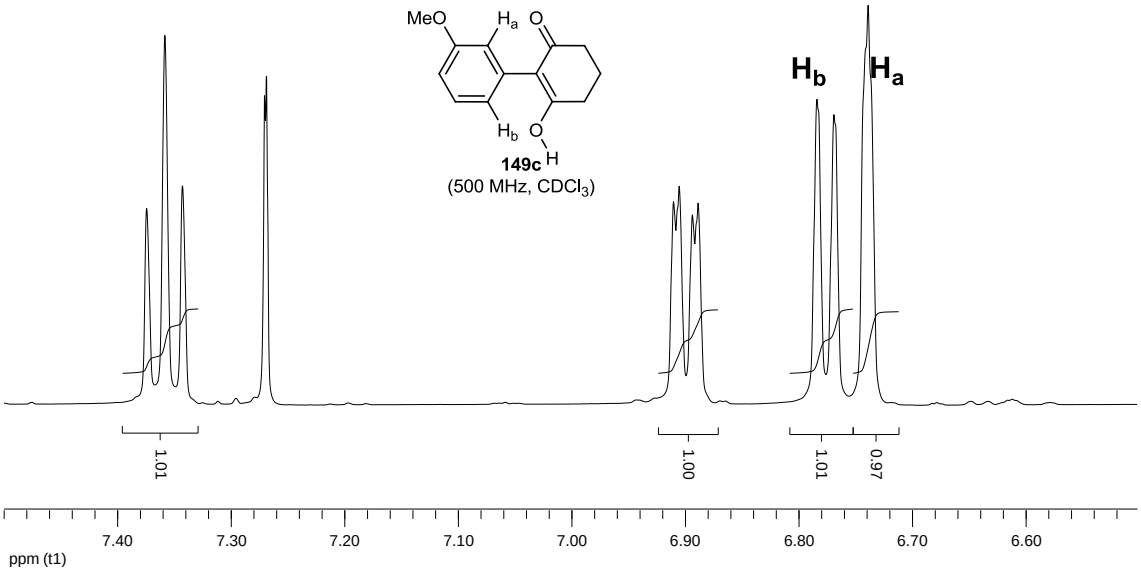
Ethyl 5-(3'-butyl-5'-methoxy-1,5-dimethyl-2,4,6-trioxospiro[1,5-diazinane-3,1'-indene]-2'-yl)-1*H*-indole-1-carboxylate (160e). The title compound was prepared according to General Procedure B from 1,3-dicarbonyl compound **153b** (131 mg, 0.50 mmol) and alkyne **156o** (201 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give an off-white solid (193 mg, 73%). R_f = 0.61 (40% EtOAc/hexane); m.p. 96-98 °C; IR (film) 1739 (C=O), 1680, 1363, 1338, 1224 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.65 (1H, d, *J* = 3.6 Hz, Ar**H**), 7.44 (1H, d, *J* = 1.4 Hz, Ar**H**), 7.20 (1H, dd, *J* = 8.5, 1.6 Hz, Ar**H**), 7.07 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.98 (1H, d, *J* = 2.4 Hz, Ar**H**), 6.75 (1H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 6.59 (1H, d, *J* = 3.7 Hz, Ar**H**), 4.51 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.86 (3H, s, OC**H**$_3$), 3.28 (6H, s, 2 × *N*C**H**$_3$), 2.55-2.50 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.65-1.56 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.49 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$), 1.38-1.29 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.83 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 167.1 (2 × C), 160.9 (C), 151.3 (C), 150.9 (C), 147.7 (C), 146.4 (C), 141.9 (C), 135.1 (C), 134.9 (C), 130.6 (C), 128.8 (C), 126.2 (CH), 125.6 (CH), 121.6 (2 × CH), 115.1 (CH), 111.0 (CH), 108.1 (CH), 108.0 (CH), 70.2 (C), 63.3 (CH$_2$), 55.6 (CH$_3$), 30.6 (CH$_2$), 29.1 (2 × CH$_3$), 25.8 (CH$_2$), 22.5 (CH$_2$), 14.4 (CH$_3$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{30}H_{32}O_6N_3$ $[M+H]^+$: 530.2286, found: 530.2277.

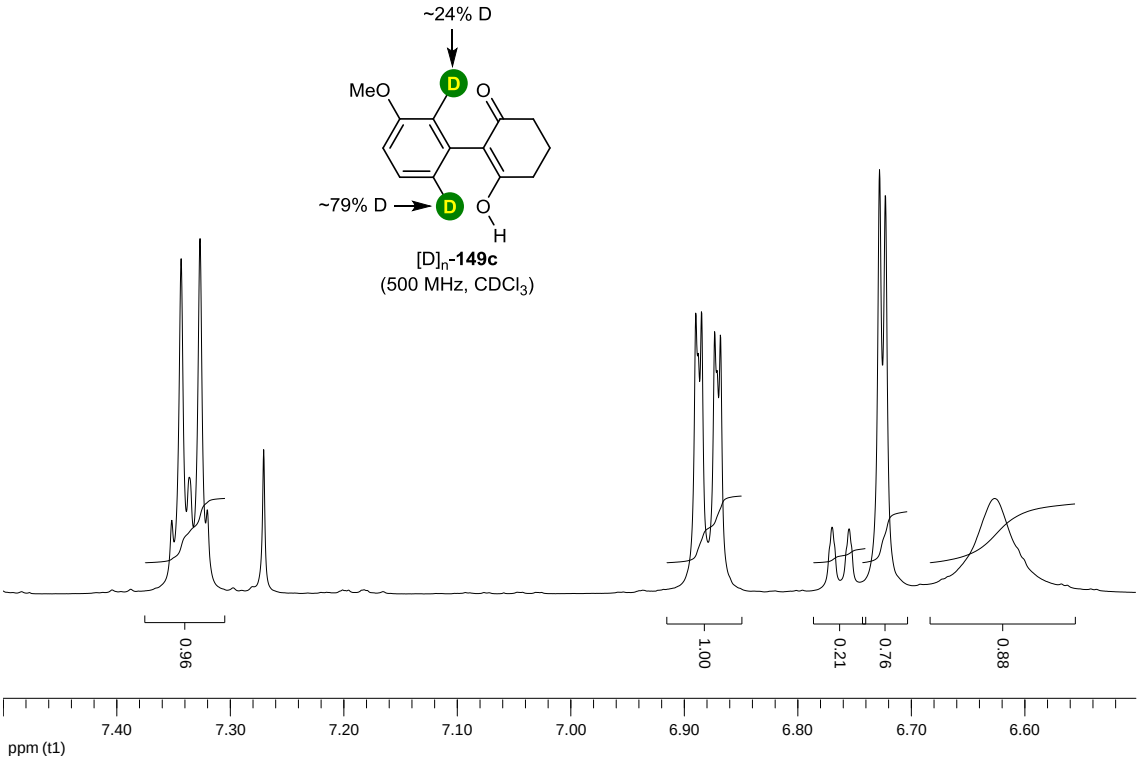
5.2.4. Deuterium-Labeling Experiments

5.2.4.1. H/D Scrambling of 149c in the Absence of Alkyne

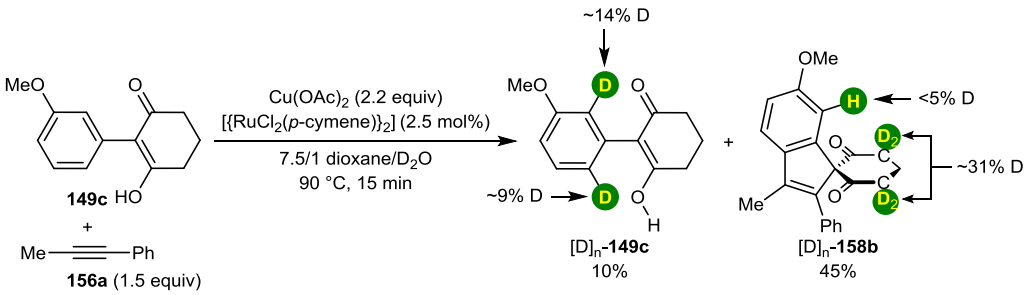


A mixture of **149c** (109 mg, 0.50 mmol), $Cu(OAc)_2$ (200 mg, 1.10 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) in dioxane (1.5 mL) and D_2O (0.2 mL) was stirred at 90 °C for 15 min. The reaction was filtered through a pad of silica gel eluting with EtOAc (100 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography (25% acetone/hexane) to give $[D]_n$-**149c** as a white solid (74 mg, 68%).

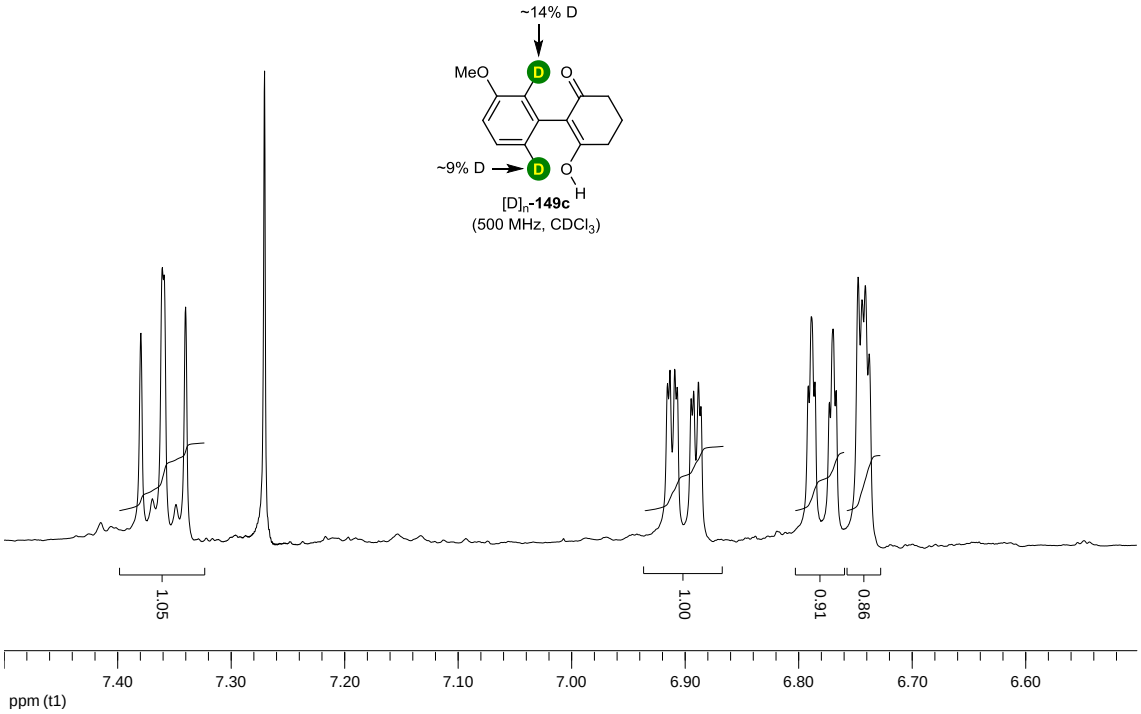




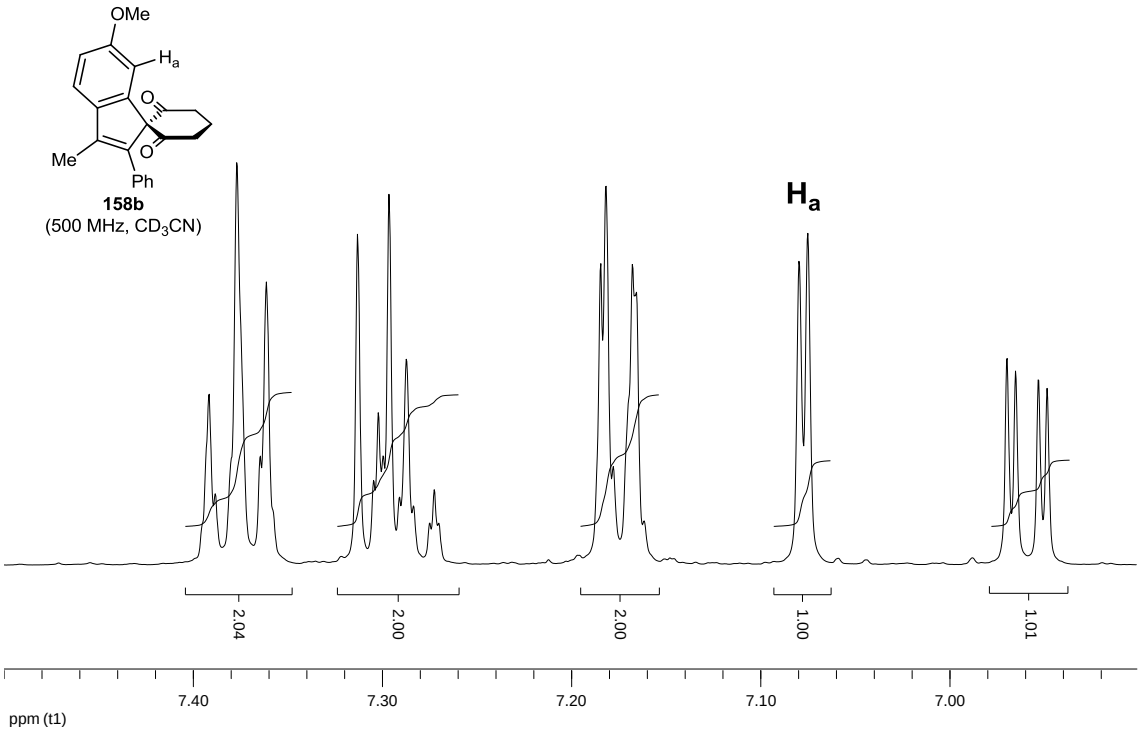
5.2.4.2. Oxidative Annulation of 149c in the Presence of D_2O

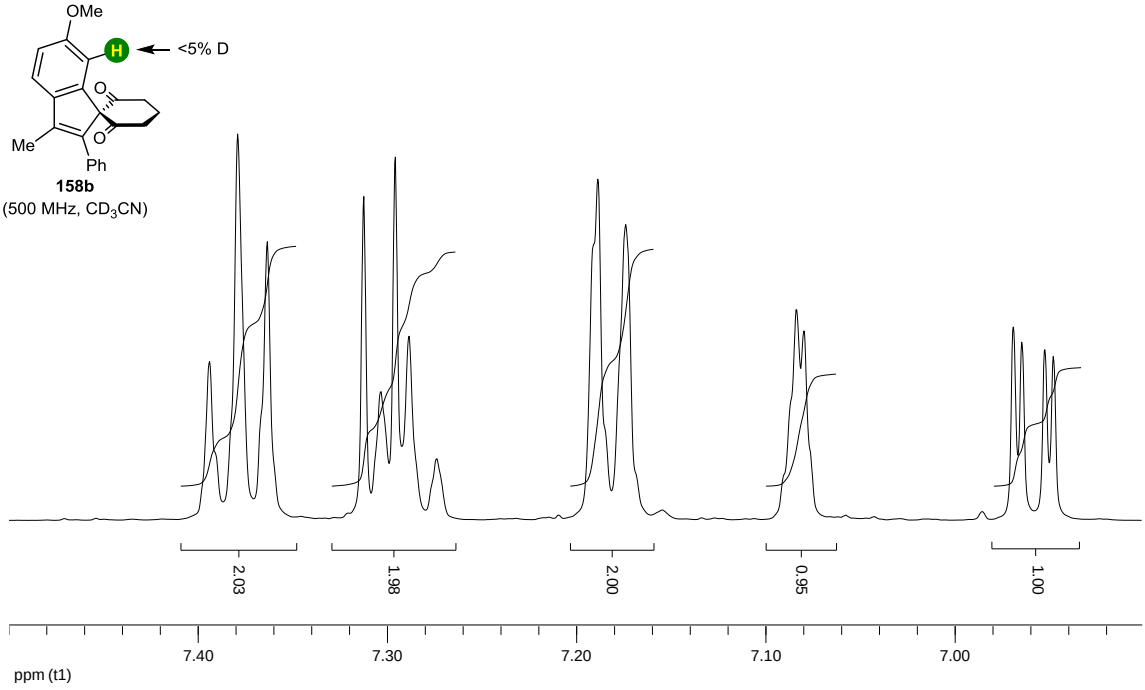


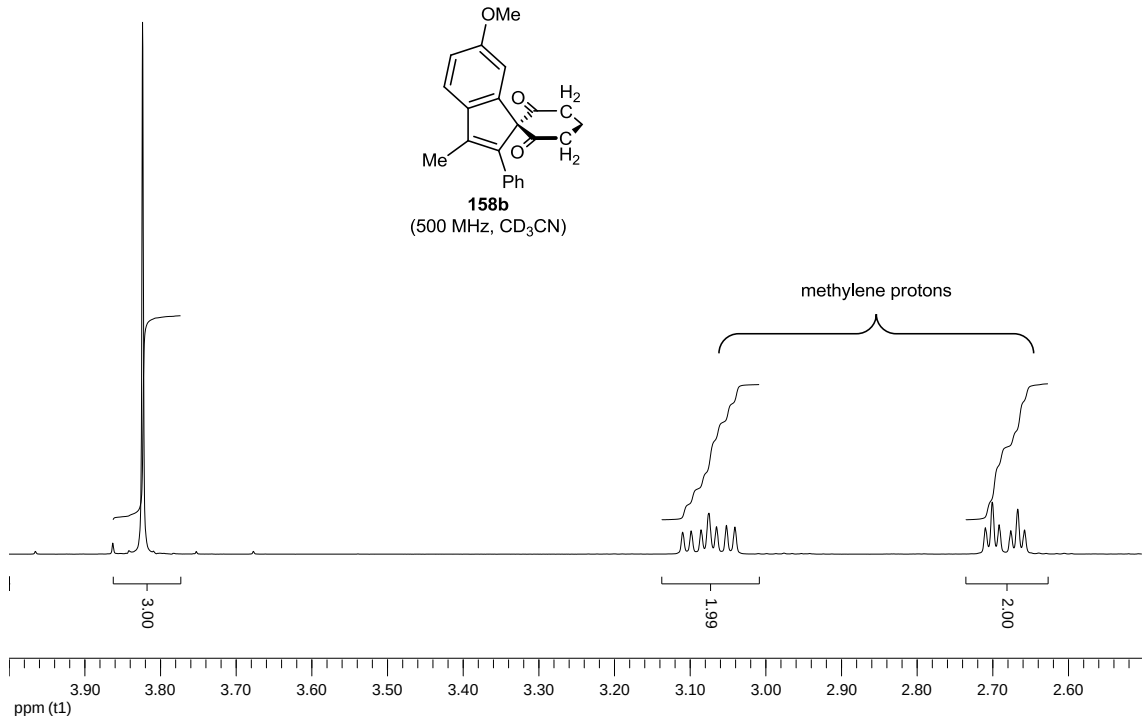
To a mixture of **149c** (109 mg, 0.50 mmol), $Cu(OAc)_2$ (200 mg, 1.10 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) in dioxane (1.0 mL) and D_2O (0.5 mL) was added alkyne **156a** (94 μL, 0.75 mmol), and the resulting mixture was stirred at 90 °C for 15 min. The reaction was filtered through a pad of silica gel eluting with Et_2O (100 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography (10% acetone/hexane) to give the spiroindene $[D]_n$-**158b** as a white solid (76 mg, 45%) followed by $[D]_n$-**149c** (11 mg, 10%) as a white solid.

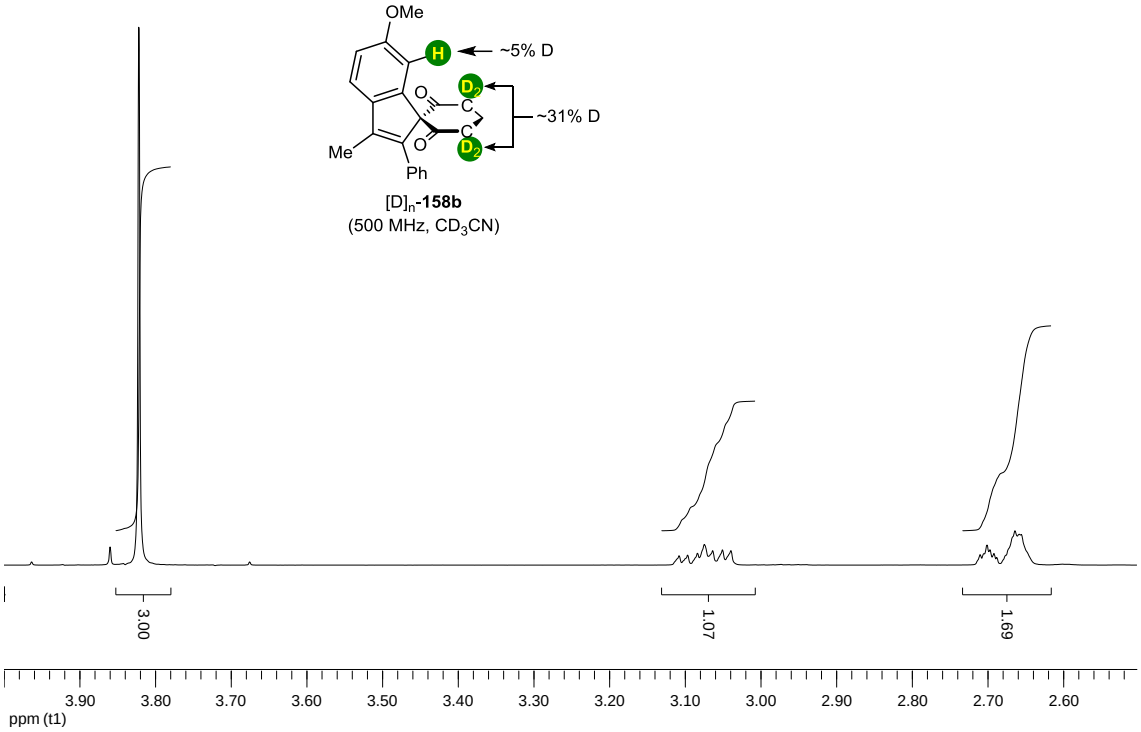


(For an expanded NMR spectrum of undeuterated **149c** for comparison, see page 163)

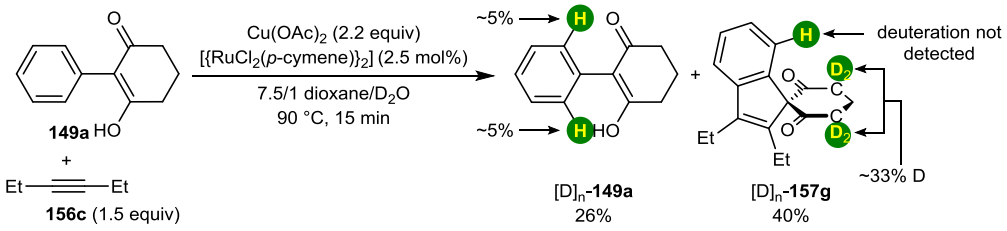



OMe
H
<5% D
O
O
Me
Ph
158b
(500 MHz, CD3CN)
2.03
1.98
2.00
0.95
1.00
7.40
7.30
7.20
7.10
7.00
ppm (t1)

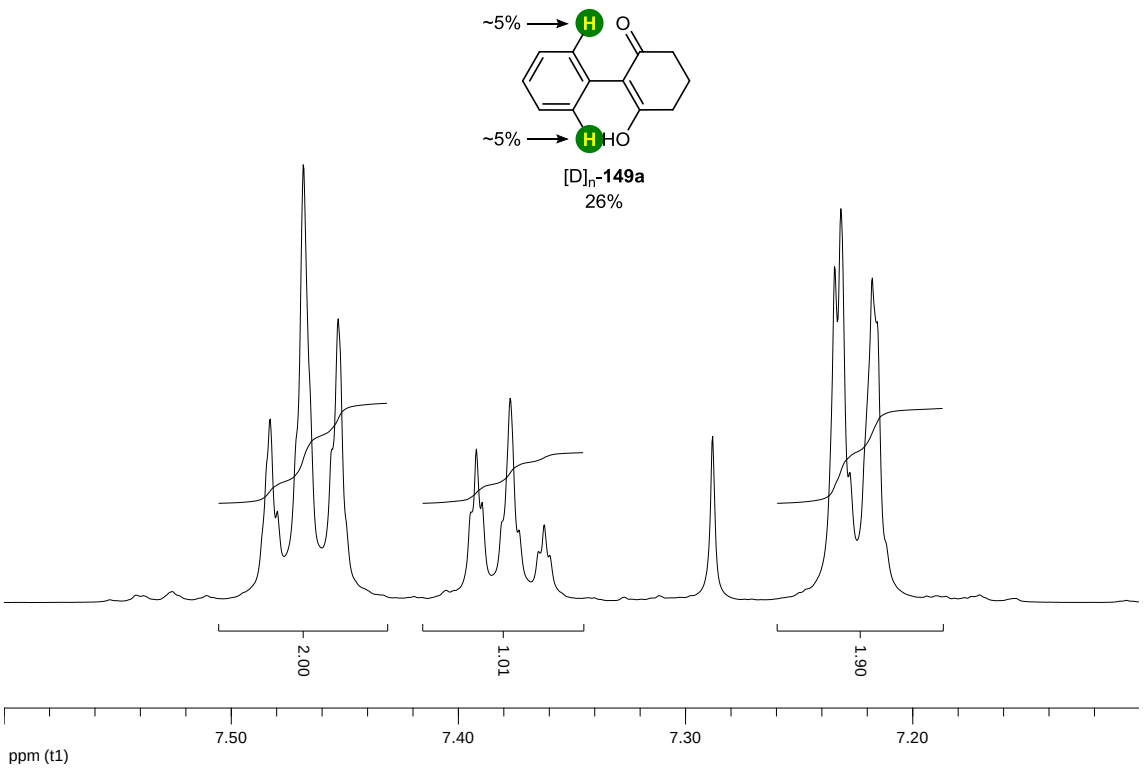

OMe
O
H2
C
C
H2
Me
O
Ph
158b
(500 MHz, CD3CN)
methylene protons
3.00
1.99
2.00
3.90
3.80
3.70
3.60
3.50
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
ppm (t1)



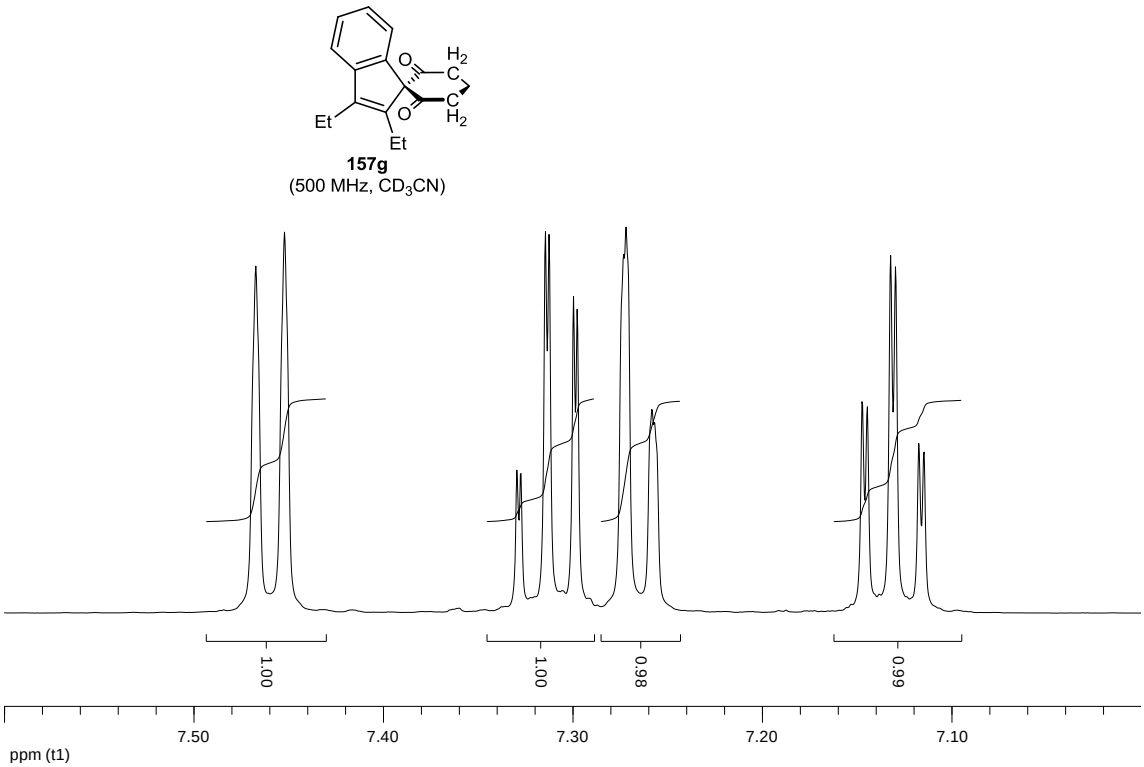
5.2.4.3. Oxidative Annulation of 149a in the Presence of D_2O



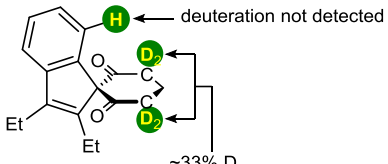
To a mixture of **149a** (94 mg, 0.50 mmol), $Cu(OAc)_2$ (200 mg, 1.10 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) in dioxane (1.0 mL) and D_2O (0.2 mL) was added alkyne **156c** (61 μL, 0.75 mmol), and the resulting mixture was stirred at 90 °C for 15 min. The reaction was filtered through a pad of silica gel eluting with Et_2O (100 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography (5% acetone/hexane) to give the spiroindene $[D]_n$-**157g** as a white solid (54 mg, 40%) followed by $[D]_n$-**149a** as a pale yellow solid (25 mg, 26%).



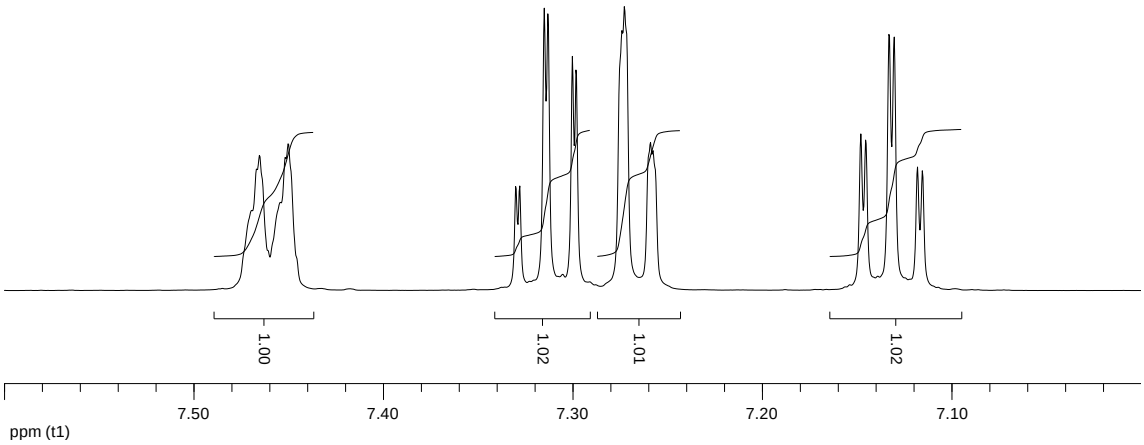
$[D]_n$-**149a**
26%

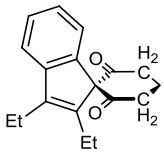


157g
(500 MHz, CD_3CN)

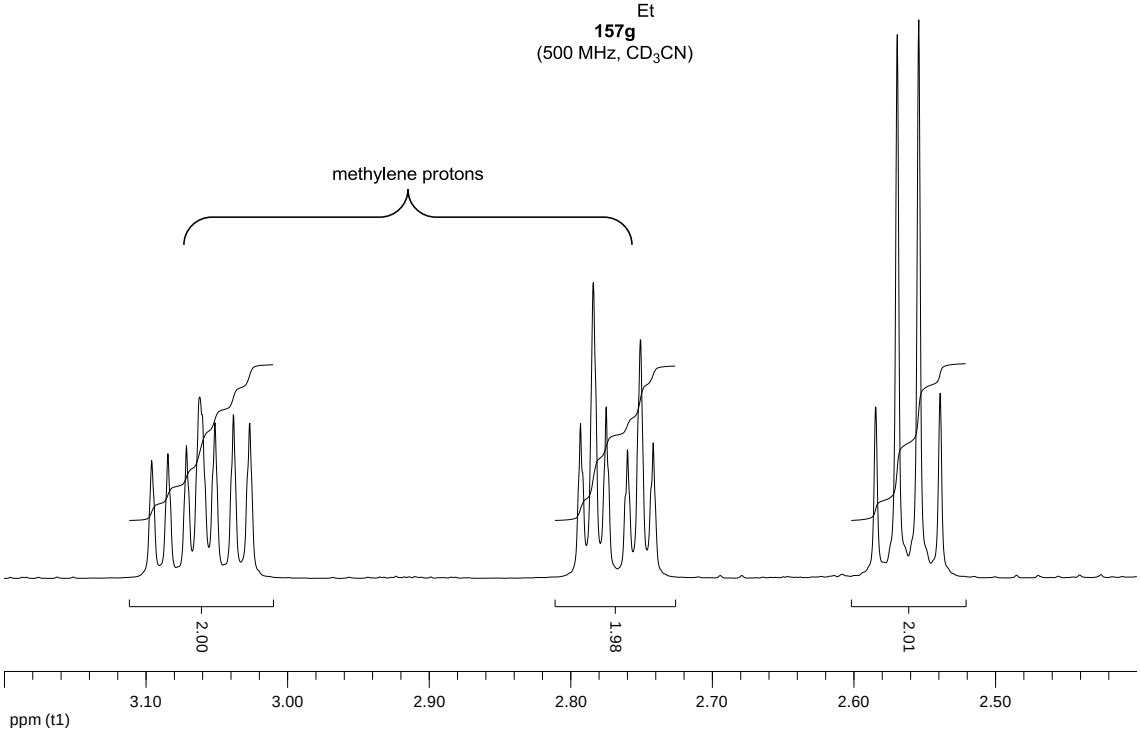


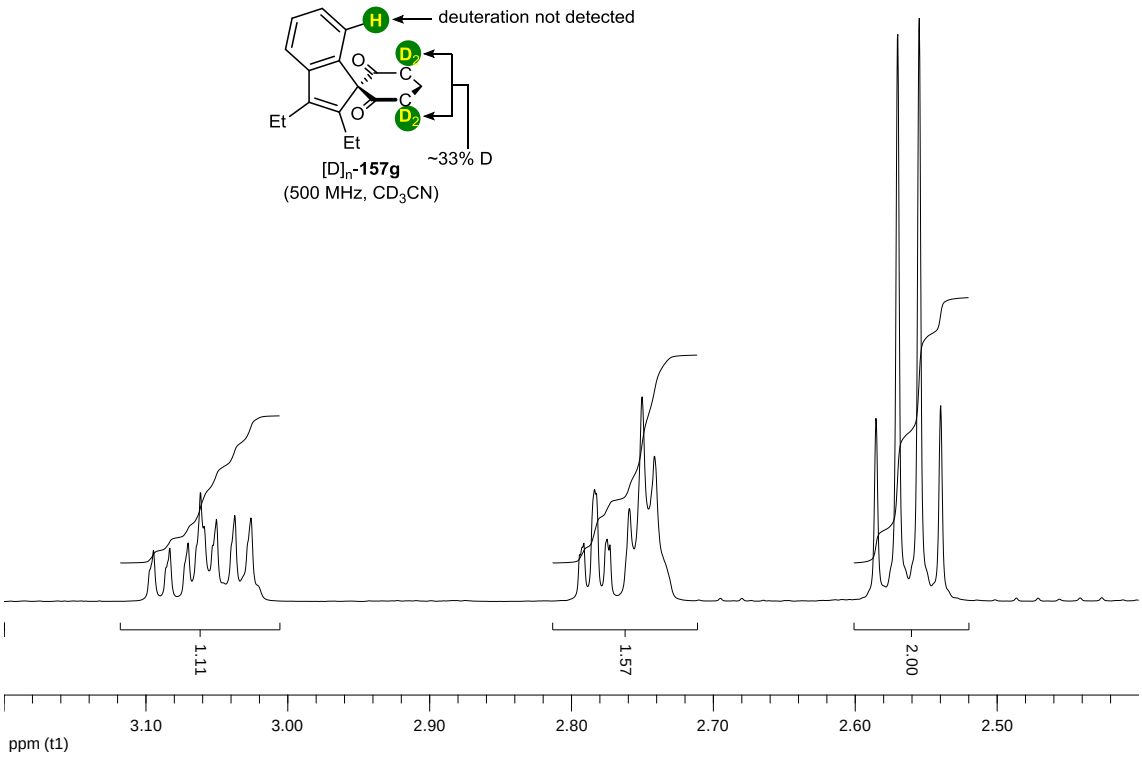
$[D]_n$-**157g**
(500 MHz, CD_3CN)



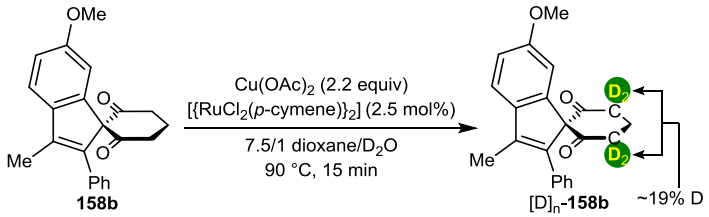


157g
(500 MHz, CD_3CN)

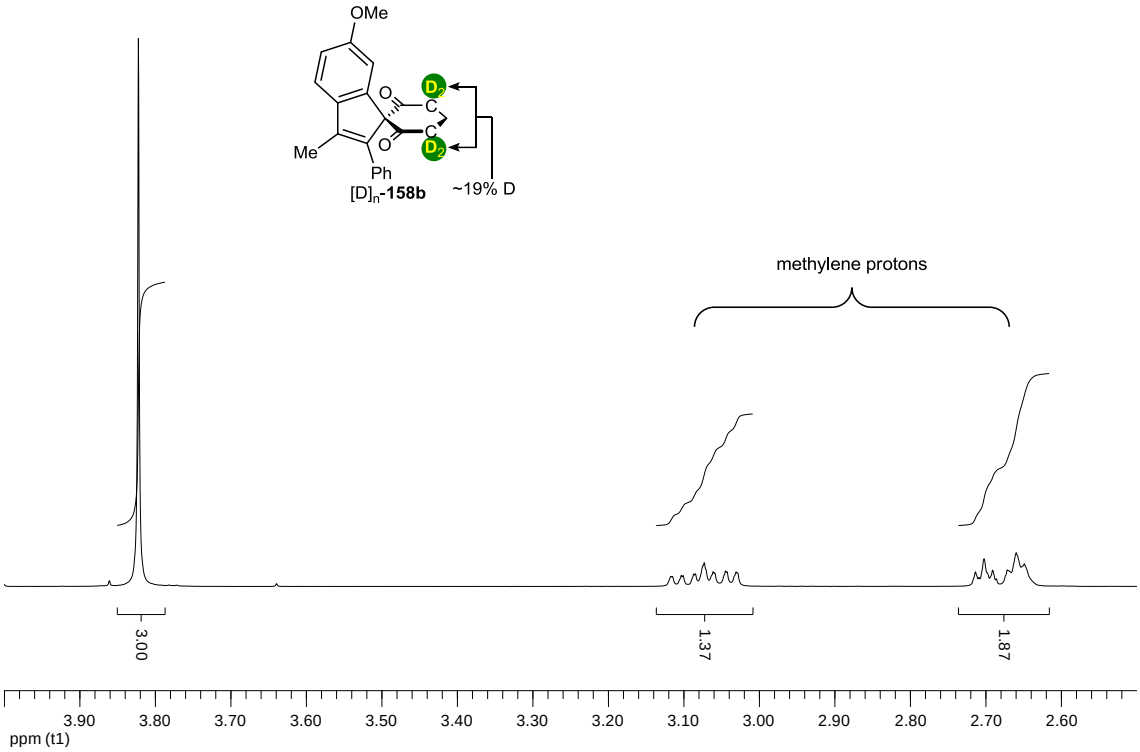




5.2.4.4. H/D Scrambling of 158b



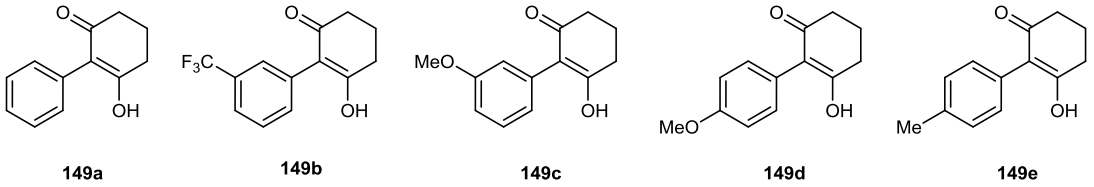
A mixture of **158b** (50 mg, 0.15 mmol), $Cu(OAc)_2$ (60 mg, 0.33 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (2.3 mg, 3.75 μmol) in dioxane (0.45 mL) and D_2O (60 μL) was stirred at 90 °C for 15 min. The reaction was filtered through a pad of silica gel eluting with Et_2O (50 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography (10% acetone/hexane) to give $[D]_n$-**158b** as a white solid (40 mg, 80%).



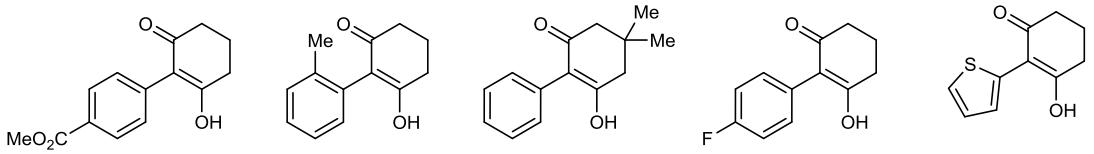
(For an expanded NMR spectrum of undeuterated **158b** for comparison, see page 165)

5.3. Synthesis of Benzopyrans by Pd(II)- or Ru(II)-Catalyzed C–H Alkenylation of 2-Aryl-3-hydroxy-2-cyclohexenones

5.3.1. Preparation of 2-Aryl-1,3-dicarbonyl Compounds



149a **149b** **149c** **149d** **149e**

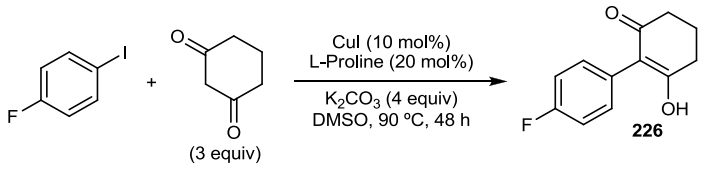


149f **149g** **149h** **226** **227**[a]

[a]Experiment performed by Martin D. Wieczysty

Substrates **149a-h**, and **227** were prepared as described previously.[152]

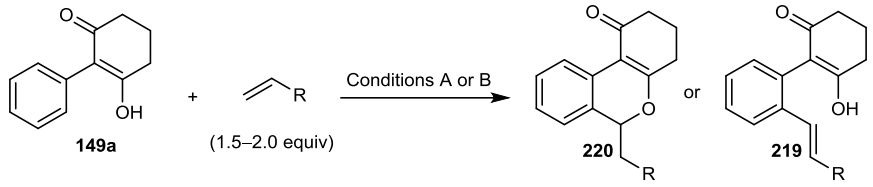
5.3.1.1. Preparation of 2-(4-Fluorophenyl)-3-hydroxycyclohex-2-en-1-one (226)



4-Fluoroiodobenzene (1.00 g, 4.50 mmol) was added to a stirred solution of CuI (86 mg, 0.45 mmol), L-proline (104 mg, 0.90 mmol) K_2CO_3 (2.49 g, 18.0 mmol), and cyclohexane-1,3-dione (1.50 g, 13.5 mmol) in anhydrous DMSO (18 mL), and the reaction mixture was then stirred at 90 °C for 48 h. The reaction was cooled to 0 °C and acidified with 2 *N* HCl to pH 3–4 and the aqueous layer was separated and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. Purification of the residue by column chromatography (40% EtOAc/hexane) gave **226** as a white solid (300 mg, 32%). R_f = 0.30 (50% EtOAc/hexane); m.p. 200-202 °C (EtOAc/hexane); IR 2949, 2918, 1610 (C=O), 1587, 1573, 1504, 1363, 1300, 1213, 1170, 1128, 831, 709 cm^{-1}; ^1H NMR (500 MHz, d^6-DMSO) δ 10.70 (1H, br s, O**H**), 7.15-7.11 (2H, m, Ar**H**), 7.10-7.05 (2H, m, Ar**H**), 2.40 (4H, br s, 2 × C$\mathbf{H}_2$C=O), 1.92

(2H, app quin, J = 6.4 Hz, $CH_2C\mathbf{H}_2CH_2$); ^{13}C NMR (125.8 MHz, d^6-DMSO) δ 160.6 (CF, d, J = 241.8 Hz), 132.7 (CH, d, J = 7.8 Hz, 2 × CH), 130.3 (C, d, J = 3.2 Hz), 115.4 (C), 113.9 (CH, d, J = 20.9 Hz, 2 × CH), 20.3 (CH_2), some signals not observed due to keto–enol tautomerism; HRMS (ESI) Exact mass calcd for $C_{12}H_{12}O_2F$ $[M+H]^+$: 207.0816, found: 207.0816.

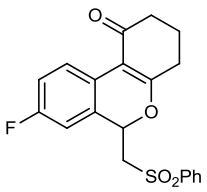
5.3.2. Palladium or Ruthenium-Catalyzed C–H Alkenylation



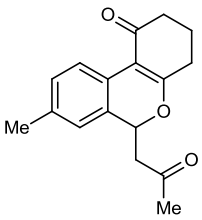
Conditions A: $Pd(OAc)_2$ (5 mol %)
$Cu(OAc)_2$ (2.1 equiv), DMF, 120 °C, 2–24 h
Conditions B: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2$ (2.1 equiv)
K_2CO_3 (2.0 equiv), *t*-AmOH, 90 °C, 2–24 h

Procedure A: To a mixture of the appropriate 2-aryl-3-hydroxy-2-cyclohexenone (0.50 mmol), $Cu(OAc)_2$ (191 mg, 1.05 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in DMF (1.0 mL) was added the appropriate alkene (0.75 or 1.00 mmol) in DMF (0.5 mL), and the resulting mixture was stirred at 120 °C for the indicated reaction time. The reaction was cooled to room temperature and filtered through a pad of silica gel eluting with Et_2O (2 × 100 mL). The filtrate was washed with H_2O (2 × 50 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography gave the benzopyran.

Procedure B: To a mixture of the appropriate 2-aryl-3-hydroxy-2-cyclohexenone (0.50 mmol), $Cu(OAc)_2$ (191 mg, 1.05 mmol), K_2CO_3 (138 mg, 1.00 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) in *t*-AmOH (1.5 mL) was added the appropriate alkene (0.75 or 1.00 mmol) in *t*-AmOH (0.5 mL), and the resulting mixture was stirred at 90 °°C for the indicated reaction time. The reaction was cooled to room temperature and filtered through a pad of silica gel eluting with Et_2O (2 × 100 mL). The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification of the residue by column chromatography gave the benzopyran.

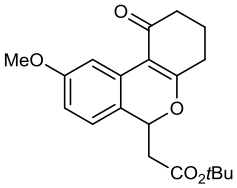


6-[(Benzenesulfonyl)methyl]-8-fluoro-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-1-one (220b). The title compound was prepared according to General Procedure A from cyclohexenone **226** (103 mg, 0.50 mmol) and phenyl vinyl sulfone (126 mg, 0.75 mmol) for a reaction time of 5 h and purified by column chromatography (15% EtOAc/hexane) to give an off-white solid (93 mg, 50%); R_f = 0.60 (50% EtOAc/hexane); m.p. 192-194 °C; IR 2926, 2854, 1718 (C), 1652 (C=O), 1582, 1500, 1382, 1300, 1255, 1136, 1000, 800, 682, 605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, dd, J = 8.8, 5.6 Hz, Ar**H**), 7.97 (2H, d, J = 7.4 Hz, Ar**H**), 7.70 (1H, t, J = 7.4 Hz, Ar**H**), 7.64-7.53 (2H, m, Ar**H**), 7.02 (1H, td, J = 8.7, 2.6 Hz, Ar**H**), 6.73 (1H, dd, J = 8.3, 2.7 Hz, Ar**H**) 5.90 (1H, dd, J = 10.4, 2.4 Hz, C**H**CH_2), 3.81 (1H, dd, J = 14.9, 10.4 Hz, C$\mathbf{H}_2$S), 3.13 (1H, dd, J = 14.9, 2.5 Hz, C$\mathbf{H}_2$S), 2.54 (1H, dt, J = 16.5, 4.5 Hz, CH_2C$\mathbf{H}_2$), 2.53-2.39 (1H, m, CH_2C$\mathbf{H}_2$), 2.33 (1H, dt, J = 18.5, 4.8 Hz, CH_2C$\mathbf{H}_2$), 2.17-2.08 (1H, m, CH_2C$\mathbf{H}_2$), 1.97-1.85 (2H, m, CH_2C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.1 (C=O), 170.2 (C), 161.6 (C, d, J = 248.4 Hz), 139.8 (C), 134.1 (CH), 129.5 (2 × CH), 128.8 (C, d, J = 7.0 Hz), 128.2 (2 × CH), 127.6 (CH, d, J = 7.7 Hz), 122.7 (C, d, J = 3.2 Hz), 116.0 (CH, d, J = 20.6 Hz), 110.7 (CH, d, J = 23.0 Hz), 72.8 (CH, d, J = 1.9 Hz), 59.1 (CH_2), 38.2 (CH_2), 28.3 (CH_2), 19.8 (CH_2), one C not observed, possibly due to overlapping signals; ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.0 (1F, s); HRMS (EI) Exact mass calcd for $C_{20}H_{17}O_4FS$ $[M]^+$: 372.0821, found: 372.0826.

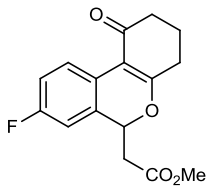


9-Methoxy-6-(2-oxopropyl)-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-1-one (220e). The title compound was prepared according to General Procedure A from cyclohexenone **149e** (109 mg, 0.50 mmol) and methyl vinyl ketone (83 μL, 1.00 mmol) for a reaction time of 2 h and purified by column chromatography (10% acetone/hexane) to give a colorless viscous oil (100 mg, 73%). R_f = 0.10 (20% EtOAc/hexane); IR 2949, 2927, 1714 (C=O), 1651 (C=O), 1595 (C=C), 1492, 1390, 1371, 1282, 1234, 1184, 1163, 1033, 1002, 860, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (1H, d, J = 2.6 Hz, Ar**H**), 6.93 (1H, d, J = 8.4 Hz, Ar**H**), 6.76 (1H, dd, J = 8.4, 2.6 Hz, Ar**H**), 5.72 (1H, dd, J = 8.2, 5.1 Hz, C**H**CH_2), 3.83 (3H, s, OC$\mathbf{H}_3$), 3.06 (1H, dd, J = 16.2, 8.2 Hz, C$\mathbf{H}_2$COMe), 2.82 (1H, dd, J = 16.2, 5.1 Hz, C$\mathbf{H}_2$COMe), 2.61-2.44 (4H, m, 2 × C$\mathbf{H}_2$C=O), 2.18 (3H, s, C$\mathbf{H}_3$C=O), 2.06-1.94 (2H, m, CH_2C$\mathbf{H}_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.9 (C), 196.3 (C=O), 172.2 (C),

159.6 (C), 127.8 (C), 124.5 (CH), 121.5 (C), 113.3 (CH), 112.0 (C), 110.0 (CH), 74.8 (CH), 55.3 (CH_3), 48.2 (CH_2), 38.3 (CH_2), 30.8 (CH_3), 29.2 (CH_2), 19.9 (CH_2); HRMS (EI) Exact mass calcd for $C_{17}H_{18}O_4$ $[M]^+$: 286.1198, found: 286.1199.

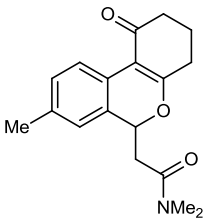


***tert*-Butyl 2-{9-methoxy-1-oxo-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-6-yl}acetate (220g)**. The title compound was prepared according to General Procedure A from cyclohexenone **149c** (109 mg, 0.50 mmol) and *tert*-butyl vinyl ketone (146 μL, 1.00 mmol) for a reaction time of 2 h and purified by column chromatography (10% EtOAc/hexane) to give a colorless viscous oil (80 mg, 47%). R_f = 0.80 (50% EtOAc/hexane); IR 2980, 2945, 2831, 1732 (C=O), 1716 (C=O), 1651, 1597, 1496, 1392, 1236, 1149, 1012, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (1H, d, J = 2.6 Hz, Ar**H**), 6.94 (1H, d, J = 8.4 Hz, Ar**H**), 6.76 (1H, dd, J = 8.4, 2.6 Hz, Ar**H**), 5.63 (1H, dd, J = 9.3, 4.9 Hz, C**H**CH_2), 3.83 (3H, s, OC**H**$_3$), 2.80 (1H, dd, J = 14.8, 9.3 Hz, C**H**$_2CO_2{}^t$Bu), 2.60-2.47 (5H, m, C**H**$_2CO_2{}^t$Bu and C**H**$_2$C**H**$_2$C=O), 2.06-1.93 (2H, m, CH_2C**H**$_2CH_2$), 1.47 (9H, s, 3 × C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.3 (C), 172.1 (C), 168.9 (C), 159.7 (C), 127.8 (C), 124.5 (CH), 121.4 (C), 113.3 (CH), 111.9 (C), 109.9 (CH), 81.2 (C), 75.9 (CH), 55.3 (CH_3), 41.5 (CH_2), 38.4 (CH_2), 29.2 (CH_2), 28.0 (CH_3), 19.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{20}H_{25}O_5$ $[M+H]^+$: 345.1697, found: 345.1698.

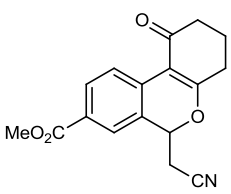


Methyl 2-{8-fluoro-1-oxo-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-6-yl}acetate (220k). The title compound was prepared according to General Procedure B from cyclohexenone **226** (103 mg, 0.50 mmol) and methyl acrylate (91 μL, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane) to give a colorless viscous oil (83 mg, 57%). R_f = 0.40 (50% EtOAc/hexane); IR 2953, 1737 (C=O), 1651 (C=O), 1600 (C=C), 1581, 1496, 1435, 1381, 1253, 1166, 1020, 997, 866, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, dd, J = 8.8, 5.7 Hz, Ar**H**), 7.02 (1H, td, J = 8.7, 2.7 Hz, Ar**H**), 6.77 (1H, dd, J = 8.6, 2.7 Hz, Ar**H**), 5.67 (1H, dd, J = 9.2, 4.7 Hz, C**H**CH_2), 3.75 (3H, s, OC**H**$_3$), 2.95 (1H, dd, J = 15.2, 9.2 Hz, C**H**$_2CO_2$Me), 2.67 (1H, dd, J = 15.2, 4.8 Hz, C**H**$_2CO_2$Me), 2.61-2.47 (4H, m, 2 × C**H**$_2$), 2.07-1.93 (2H, m, CH_2C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.2 (C), 170.9 (C), 169.8 (C), 161.5 (C, d, J = 247.3 Hz), 131.0 (C, d, J = 7.1 Hz), 127.4 (CH, d, J =

7.7 Hz), 122.7 (C, d, J = 3.2 Hz), 115.3 (CH, d, J = 20.6 Hz), 111.7 (C), 110.7 (CH, d, J = 22.9 Hz), 75.0 (CH), 52.1 (CH_3), 39.6 (CH_2), 38.2 (CH_2), 29.0 (CH_2), 19.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.9 (1F, s); HRMS (EI) Exact mass calcd for $C_{16}H_{15}O_4F$ $[M]^+$: 290.0949, found: 290.0948.

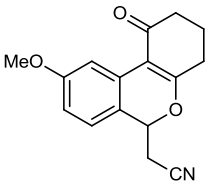


***N*,*N*-Dimethyl-2-{8-methyl-1-oxo-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-6-yl}acetamide (220m)**. The title compound was prepared according to General Procedure B from cyclohexenone **149e** (101 mg, 0.50 mmol) and *N*,*N*-dimethyl acrylamide (103 μL, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (20% acetone/hexane) to give a colorless viscous oil (67 mg, 45%). R_f = 0.50 (40% acetone/hexane); IR 2943, 2831, 1635 (C=O), 1616 (C=C), 1587, 1481, 1388, 1330, 1284, 1124, 1101, 952, 808, 785 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (1H, d, J = 8.1 Hz, Ar**H**), 7.12 (1H, dd, J = 8.1, 1.2 Hz, Ar**H**), 6.87 (1H, s, Ar**H**), 5.82 (1H, dd, J = 7.8, 5.3 Hz, C**H**CH_2), 2.99-2.93 (1H, m, C**H**$_2$CONMe$_2$), 2.95 (*N*C**H**$_3$), 2.83 (3H, s, *N*C**H**$_3$), 2.69 (1H, dd, J = 15.1, 5.3 Hz, C**H**$_2$CONMe$_2$), 2.61-2.53 (2H, m, CH_2C**H**$_2$), 2.53-2.44 (2H, m, CH_2C**H**$_2$), 2.31 (3H, s, ArC**H**$_3$), 2.03-1.93 (2H, m, CH_2C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.4 (C), 171.3 (C), 168.9 (C), 136.9 (C), 129.6 (C), 129.1 (CH), 124.9 (CH), 124.4 (CH), 123.7 (C), 111.9 (C), 76.1 (CH), 38.4 (CH_2), 38.3 (CH_3), 37.3 (CH_3), 35.5 (CH_2), 29.3 (CH_2), 21.1 (CH_3), 20.0 (CH_2); HRMS (ESI) Exact mass calcd for $C_{18}H_{22}O_3N$ $[M+H]^+$: 300.1598, found: 300.1594.



Methyl 6-(cyanomethyl)-1-oxo-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromene-8-carboxylate (220o). The title compound was prepared according to a slight modification of General Procedure B (in that K_2CO_3 was not employed) from cyclohexenone **149f** (123 mg, 0.50 mmol) and acrylonitrile (66 μL, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/hexane) to give an off-white solid (110 mg, 74%). R_f = 0.40 (50% EtOAc/hexane); m.p. 122-124 °C (EtOAc/hexane); IR 2951, 2922, 2856, 2254 (C≡N), 1714 (C=O), 1654 (C=O), 1597 (C=C), 1558, 1462, 1436, 1379, 1292, 1226, 1195, 997, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (1H, d, J = 8.4 Hz, Ar**H**), 8.03 (1H, dd, J = 8.4, 1.8 Hz, Ar**H**), 7.74 (1H, d, J = 1.7 Hz, Ar**H**), 5.60 (1H, dd, J = 8.3, 4.6 Hz, C**H**CH_2), 3.91

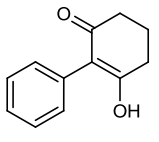
(3H, s, C**H**$_3$), 3.02 (1H, dd, *J* = 17.0, 8.4 Hz, C**H**$_2$CN), 2.84 (1H, dd, *J* = 17.0, 4.6 Hz, C**H**$_2$CN), 2.69-2.65 (2H, m, CH$_2$C**H**$_2$), 2.64-2.51 (2H, m, CH$_2$C**H**$_2$), 2.12-1.98 (2H, m, CH$_2$C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 195.8 (C), 172.3 (C), 166.2 (C), 130.7 (CH and C), 128.9 (C), 126.9 (C), 125.5 (CH), 124.9 (CH), 115.5 (C), 111.8 (C), 73.8 (CH), 52.2 (CH_3), 38.2 (CH_2), 29.2 (CH_2), 23.6 (CH_2), 19.7 (CH_2); HRMS (ESI) Exact mass calcd for $C_{17}H_{16}O_4N$ $[M+H]^+$: 298.1074, found: 298.1079.



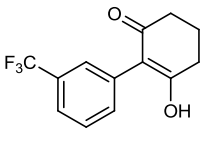
2-{9-Methoxy-1-oxo-1*H*,2*H*,3*H*,4*H*,6*H*-benzo[*c*]chromen-6-yl}acetonitrile (220p). The title compound was prepared according to General Procedure B from cyclohexenone **149c** (109 mg, 0.50 mmol) and acrylonitrile (66 μL, 1.00 mmol) for a reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane) to give a colorless viscous oil (40 mg, 30%). R_f = 0.46 (50% EtOAc/hexane); IR 2951, 2935, 2846, 2253 (C≡N), 1712 (C=O), 1658 (C=O), 1597, 1559, 1462, 1367, 1280, 997, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (1H, d, *J* = 2.6 Hz, Ar**H**), 6.98 (1H, d, *J* = 8.4, Hz, Ar**H**), 6.81 (1H, dd, *J* = 8.4, 2.6 Hz, Ar**H**), 5.51 (1H, dd, *J* = 8.0, 5.0 Hz, C**H**CH$_2$), 3.84 (3H, s, OC**H**$_3$), 2.93 (1H, dd, *J* = 16.9, 8.0 Hz, C**H**$_2$CN), 2.73 (1H, dd, *J* = 16.9, 5.0 Hz, C**H**$_2$CN), 2.66-2.60 (2H, m, CH$_2$C**H**$_2$), 2.60-2.49 (2H, m, CH$_2$C**H**$_2$), 2.11-1.96 (2H, m, CH$_2$C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.2 (C=O), 170.9 (C), 160.3 (C), 127.5 (C), 124.8 (CH), 119.2 (C), 115.9 (C), 113.7 (CH), 111.9 (C), 110.4 (CH), 73.8 (CH), 55.3 (CH_3), 38.3 (CH_2), 29.1 (CH_2), 23.8 (CH_2), 19.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{16}H_{16}O_3N$ $[M+H]^+$: 270.1130, found: 270.1128.

5.4. Synthesis of Spiroindanes by Palladium-Catalyzed Oxidative Annulations of 1,3-Dienes Involving C–H Functionalization

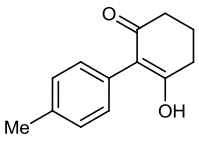
5.4.1. Preparation of 2-Aryl-1,3-dicarbonyl Substrates



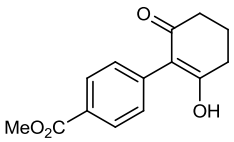
149a



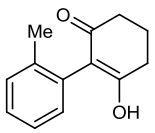
149b



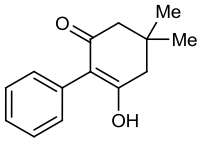
149e



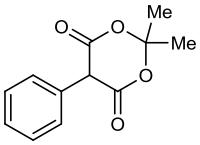
149f



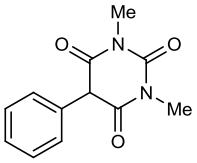
149g



149h



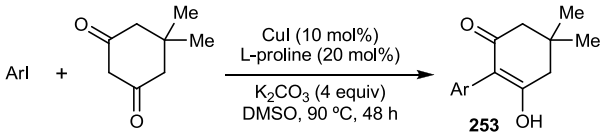
151a



153a

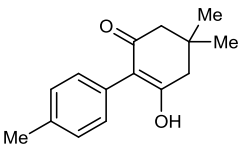
Substrates **149a**, **149b**, **149e-h**, **151a**, and **153a** were prepared as described previously.[122]

5.4.1.1. Preparation of Dimedone-derived 2-Aryl-1,3-dicarbonyl Substrates: General Procedure A

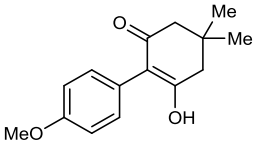


253

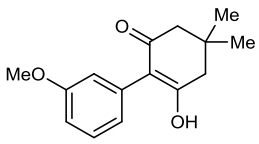
The appropriate aryl iodide (1.0 equiv) was added to a stirred solution of CuI (10 mol%), *L*-proline (20 mol%), K_2CO_3 (4.0 equiv), and the appropriate 1,3-dicarbonyl compound (3.0 equiv) in anhydrous DMSO (4 mL/mmol), and the reaction mixture was then stirred at 90 °C for 48 h. The reaction was cooled to 0 °C and acidified with 2 *N* HCl to pH 3–4 and the aqueous layer was separated and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. Purification of the residue by column chromatography (40% EtOAc/hexane) gave the 2-aryl-1,3-dicarbonyl compound.



3-Hydroxy-5,5-dimethyl-2-(4-methylphenyl)cyclohex-2-en-1-one (253a). The title compound was prepared according to General Procedure A from 4-iodotoluene (5.45 g, 25.0 mmol) and dimedone (10.51 g, 75.0 mmol), and purified by column chromatography (40% EtOAc/hexane) to give an off-white solid (3.66 g, 64%). R_f = 0.40 (40% EtOAc/hexane); m.p. 202-204 °C (EtOAc/petrol); IR 1718 (C=O), 1575, 1514, 1406, 1336, 1300, 1273, 1254, 1144, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 7.9 Hz, Ar**H**), 7.09 (2H, d, J = 7.9 Hz, Ar**H**), 6.33 (1H, br s, O**H**) 2.40 (4H, br s, C**H**$_2$C(CH$_3$)$_2$C**H**$_2$), 2.37 (3H, s, ArC**H**$_3$), 1.16 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9 (C), 130.4 (2 × CH), 130.0 (2 × CH), 127.6 (C), 116.7 (C), 31.7 (CH_2), 28.3 (2 × CH_3), 21.2 (CH_3), some signals not observed due to keto–enol tautomerism; HRMS (ESI) Exact mass calcd for $C_{15}H_{18}O_2Na$ $[M+Na]^+$: 253.1199, found: 253.1190.



3-Hydroxy-2-(4-methoxyphenyl)-5,5-dimethylcyclohex-2-en-1-one (253b). The title compound was prepared according to General Procedure A from 4-iodoanisole (4.68 g, 20.0 mmol) and dimedone (8.41 g, 60.0 mmol), and purified by column chromatography (40% EtOAc/hexane) to give an off-white solid (2.45 g, 50%). R_f = 0.43 (60% EtOAc/hexane); m.p. 150-152 °C (EtOAc/petrol); IR 2953, 1611 (C=O), 1568, 1512, 1465, 1361, 1331, 1282, 1248, 1174, 1025, 885, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (2H, d, J = 8.5 Hz, Ar**H**), 6.97 (2H, d, J = 8.5 Hz, Ar**H**), 6.19 (1H, br s, O**H**), 3.82 (3H, s, OC**H**$_3$), 2.47 (2H, br s, C**H**$_2$C(CH$_3$)$_2$), 2.38 (2H, br s, C**H**$_2$C(CH$_3$)$_2$), 1.16 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.4 (C), 131.8 (2 × CH), 122.5 (C), 116.4 (C), 114.8 (2 × CH), 55.3 (CH_3), 50.8 (C), 31.7 (CH_2), 28.3 (2 × CH_3), some signals not observed due to keto–enol tautomerism; HRMS (ESI) Exact mass calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found: 247.1314.

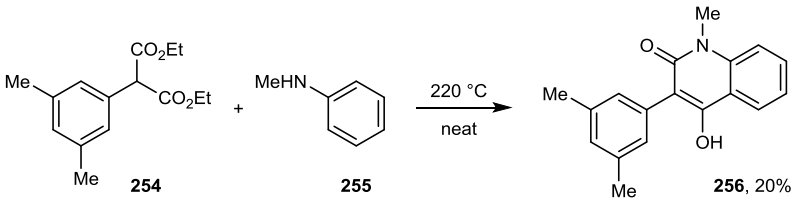


3-Hydroxy-2-(3-methoxyphenyl)-5,5-dimethylcyclohex-2-en-1-one (253c). The title compound was prepared according to General Procedure A from 3-iodoanisole (4.68 g, 20.0 mmol) and dimedone (8.41 g, 60.0 mmol), and purified by column chromatography (40% EtOAc/hexane) to give an off-white solid (3.20 g, 65%). R_f = 0.42 (60% EtOAc/hexane); m.p. 122-124 °C (EtOAc/petrol); IR 2959, 1606 (C=O), 1575, 1488,

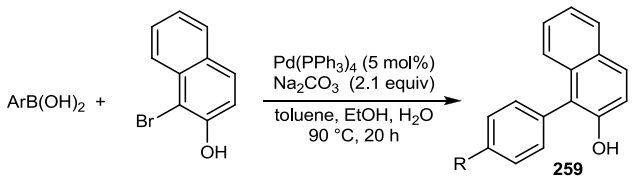
1339, 1309, 1282, 1252, 1029, 835, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (1H, m, Ar**H**), 6.87 (1H, ddd, J = 8.3, 2.6, 0.8 Hz, Ar**H**), 6.79-6.74 (1H, m, Ar**H**), 6.72 (1H, dd, J = 2.4, 1.5 Hz, Ar**H**), 6.64 (1H, br s, O**H**), 3.79 (3H, s, OC**H**$_3$), 2.40 (4H, br s, C**H**$_2$C(CH$_3$)$_2$C**H**$_2$), 1.15 (6H, C(C**H**$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.1 (C), 132.3 (C), 130.2 (CH), 122.6 (CH), 116.7 (C), 116.0 (CH), 113.9 (CH), 55.2 (CH_3), 31.7 (CH_2), 28.3 (2 × CH_3), some signals not observed due to keto–enol tautomerism; HRMS (ESI) Exact mass calcd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found: 247.1323.

5.4.1.2. Preparation of Unsymmetrical 1,3-Dicarbonyl Substrate

The unsymmetrical 1,3-dicarbonyl compound **256** was synthesized from diethyl 2-(3,5-dimethylphenyl)malonate **254** (1.0 equiv) and *N*-methylaniline **255** (1.0 equiv) by heating at 220 °C (Scheme 3.7).[157]

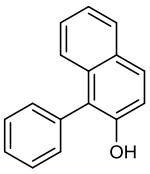


5.4.2. Preparation of 1-Aryl-2-naphthols: General Procedure B

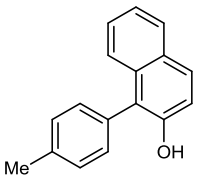


A 100 mL oven-dried round bottom flask with a stir bar was fitted with a rubber septum, and the flask was purged with nitrogen and charged with $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (2.1 equiv), 1-bromonaphthalen-2-ol (1 equiv), arylboronic acid (2 equiv), in a mixture of solvent (toluene: EtOH:deoxygenated H_2O (5:1:1.1). The mixture was heated at 90 °C for 20 h and cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

Purification of the residue by column chromatography gave 1-aryl-2-naphthols (**259**) as an off-white solid that displayed spectroscopic data consistent with those reported previously.[158]

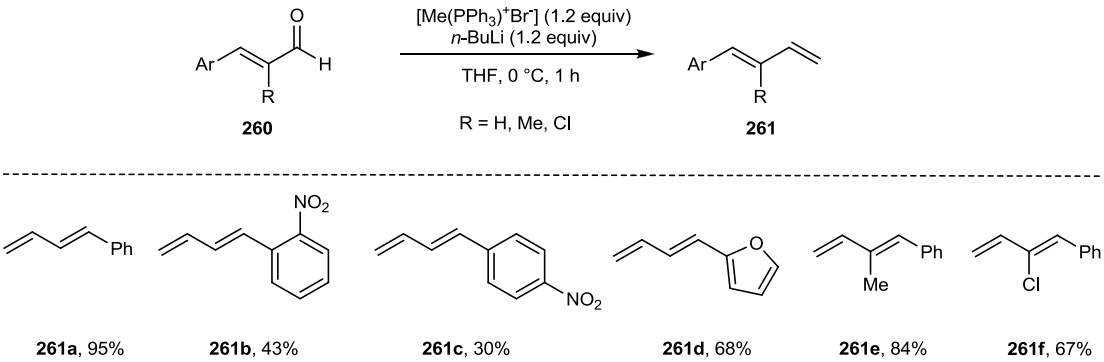


1-Phenyl-2-naphthol (259a). The title compound was prepared according to General Procedure B from phenylboronic acid (1.09 g, 8.96 mmol), 1-bromonaphthalen-2-ol (1.00 g, 4.48 mmol), $Pd(PPh_3)_4$ (260 mg, 0.22 mmol), Na_2CO_3 (997 mg, 9.41 mmol), and purified by column chromatography (3% EtOAc/petrol) to give 1-phenyl-2-naphthol (**259a**) as an off-white solid (1.67 g, 85%).



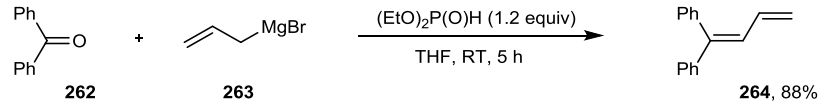
1-*p*-Tolyl-2-naphthol (259b). The title compound was prepared according to General Procedure B from *p*-tolylboronic acid (364 mg, 2.68 mmol), 1-bromonaphthalen-2-ol (300 mg, 1.34 mmol), $Pd(PPh_3)_4$ (77 mg, 0.07 mmol), Na_2CO_3 (298 mg, 2.8 mmol), and purified by column chromatography (2% EtOAc/petrol) to give 1-*p*-tolyl-2-naphthol (**259b**) as an off-white solid (202 mg, 64%).

5.4.3. Preparation of 1,3-Dienes



1,3-Dienes including **261a**,[159] **261b**,[160] **261c**,[160] **261d**,[160] **261e**,[161] and **261f**,[162] were prepared according to previously reported procedures.

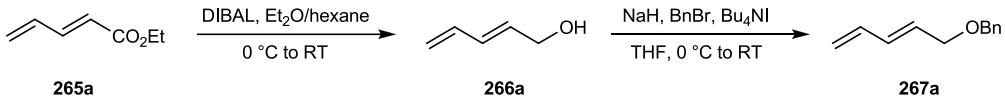
5.4.3.1. Preparation of Buta-1,3-diene-1,1-diyldibenzene (264)



262 **263** **264**, 88%

The diene **264** was prepared by the olefination of benzophenone **262** with allyl magnesium bromide **263** in the presence of diethyl phosphite.[163]

5.4.3.2. Preparation of {[(2*E*)-penta-2,4-dien-1-yloxy]methyl}benzene (267a)

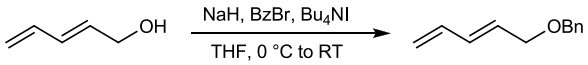


265a **266a** **267a**

To a solution of the ester **265a**[192] (5.67 g, 45.0 mmol) in Et_2O (100 mL) at 0 °C was added DIBAL (1.0 M in hexane, 90 mL, 90 mmol) over *ca.* 5 min and the mixture was stirred at this temperature for 20 min, and at room temperature for 4 h. The reaction was cooled to 0 °C and quenched carefully with 1 *N* aqueous HCl solution until the pH of the mixture was 5-6. The aqueous layer was separated and extracted with Et_2O (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave (*E*)-penta-2,4-dien-1-ol (**266a**) (3.29 g, 87% crude yield) as a colorless oil which was taken onto the next step without purification.

To a suspension of NaH (60% in mineral oil, 457 mg, 11.9 mmol) in THF (10 mL) at 0 °C was added a solution of **266a** (500 mg, 5.9 mmol) in THF (5 mL), and the mixture was stirred for 30 min. To this mixture was added Bu_4NI (219 mg, 0.59 mmol) in one portion followed by BnBr (0.85 mL, 7.16 mmol) dropwise and the mixture was stirred at room temperature for 12 h. The reaction was quenched carefully with H_2O (10 mL) and the aqueous layer was separated and washed with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane) gave the benzyl ether **267a** as a colorless oil (450 mg, 44%) that displayed spectroscopic data consistent with those reported previously.[193]

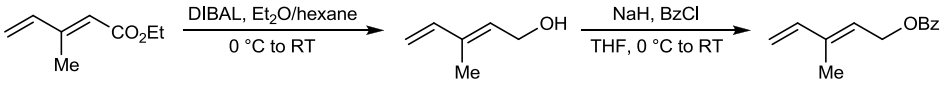
5.4.3.3. Preparation of (*E*)-penta-2,4-dien-1-yl benzoate (267b)



266a **267b**

To a suspension of NaH (60% in mineral oil, 457 mg, 11.9 mmol) in THF (10 mL) at 0 °C was added a solution of crude **266a** (500 mg, 5.94 mmol, prepared as described above) in THF (5 mL), and the mixture was stirred at this temperature for 30 min. Benzoyl chloride (0.83 mL, 7.1 mmol) was added dropwise over *ca*. 1 min and the mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O (10 mL), and the aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane) gave the benzoyl ether **267b** as a colorless oil (780 mg, 70%). This material contained a small quantity (~5%) of an isomeric impurity. R_f = 0.58 (10% EtOAc/hexane); IR 1718 (C=O), 1602, 1451, 1368, 1314, 1267, 1176, 1109, 1070, 1026, 953, 835, 709, 644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12-8.05 (2H, m, Ar**H**), 7.58 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.47 (2H, t, *J* = 7.7 Hz, Ar**H**), 6.46-6.33 (2H, m, C**H**=C**H**CH_2), 5.99-5.85 (1H, m, CH_2=C**H**), 5.36-5.25 (1H, m, C**H**$_2$=CH), 5.23-5.14 (1H, m, C**H**$_2$=CH), 4.88 (2H, d, *J* = 6.0 Hz, OC**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.2 (C), 135.9 (CH), 134.6 (CH), 132.9 (CH), 130.1 (C), 129.6 (2 × CH), 128.3 (2 × CH), 127.1 (CH), 118.6 (CH_2), 64.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{12}H_{12}O_2Na$ $[M+Na]^+$: 211.0730, found: 211.0722.

5.4.3.4. Preparation of (*E*)-3-methylpenta-2,4-dien-1-yl benzoate (267c)



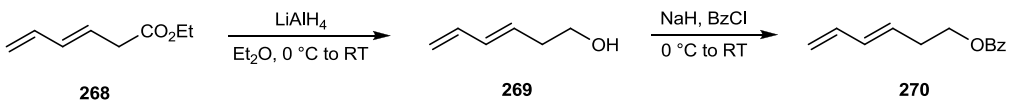
265b **266b** **267c**

To a solution of the ester **265b**,[194] (2.80 g, 20.0 mmol) in Et_2O (50 mL) at 0 °C was added DIBAL (1.0 M in hexane, 40.0 mL, 40 mmol) over *ca.* 5 min and the mixture was stirred at this temperature for 20 min, and at room temperature for 4 h. The reaction was cooled to 0 °C, and slowly quenched with 1 *N* aqueous HCl solution until the pH of the mixture was 5-6. The aqueous layer was separated and extracted with Et_2O (2 × 60 mL) and the combined organic layers were washed with brine (50

mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave (*E*)-3-methylpenta-2,4-dien-1-ol (**266b**) (1.92 g, 98% crude yield) as a colorless oil which was taken onto the next step without purification.

To a suspension of NaH (60% in mineral oil, 392 mg, 10.2 mmol) in THF (10 mL) at 0 °C was added a solution of **266b** (500 mg, 5.09 mmol) in THF (5 mL) and the mixture was stirred at this temperature for 30 min. Benzoyl chloride (0.71 mL, 6.12 mmol) was added dropwise over *ca.* 1 min and the mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (2% EtOAc/petrol) gave the *benzoyl ester* **267c** as a colorless oil (585 mg, 57%). R_f = 0.71 (20% EtOAc/hexane); IR 1717 (C=O), 1608, 1451, 1339, 1314, 1268, 1176, 1109, 1069, 1026, 991, 904, 709, 644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09-8.04 (2H, m, Ar**H**), 7.53 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.47-7.42 (2H, m, Ar**H)**, 6.43 (1H, dd, *J* = 17.4, 10.7 Hz, CH_2=C**H**), 5.75 (1H, t, *J* = 7.0 Hz, =C**H**CH_2), 5.29 (1H, d, *J* = 17.4 Hz, C**H**$_2$=CH), 5.13 (1H, d, *J* = 10.7 Hz, C**H**$_2$=CH), 4.98 (2H, d, *J* = 7.0 Hz, C**H**$_2$O), 1.90 (3H, m, =CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.5 (C), 140.3 (CH), 138.7 (C), 132.9 (CH), 130.2 (C), 129.6 (2 × CH), 128.3 (2 × CH), 125.2 (CH), 113.9 (CH_2), 61.6 (CH_2), 12.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{13}H_{14}O_2Na$ $[M+Na]^+$: 225.0886, found: 225.0882.

5.4.3.5. Preparation of (*E*)-hexa-3,5-dien-1-yl benzoate (270)



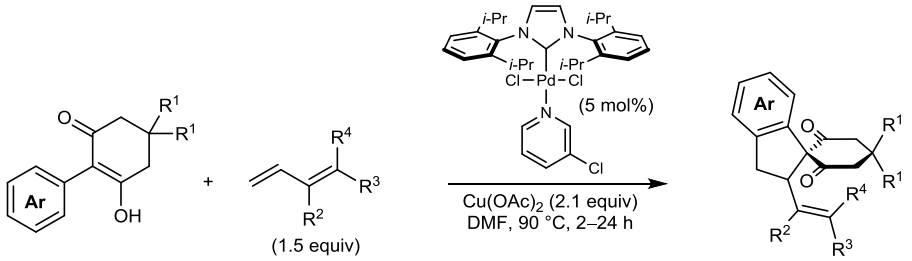
268 **269** **270**

To a solution of the ester **268** (1.50 g, 10.7 mmol) in Et_2O (30 mL) at 0 °C, was added $LiAlH_4$ (2.4 M in Et_2O, 7.0 mL, 16.8 mmol) over *ca.* 2 min, and the mixture was stirred at this temperature for 20 min and at room temperature for 4 h. The reaction was cooled to 0 °C, and quenched carefully with 1 *N* aqueous HCl solution until the pH of the mixture was 5-6. The aqueous layer was separated and extracted with Et_2O (2 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave (*E*)-hexa-3,5-dien-1-ol (**269**)

(886 mg, 9.04 mmol, 82% crude yield) as a colorless oil which was taken onto the next step without purification.

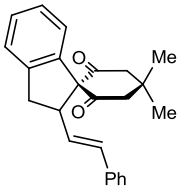
To a suspension of NaH (60% in mineral oil, 700 mg, 18.1 mmol) in THF (20 mL) at 0 °C was added a solution of **269** (886 mg, 9.04 mmol) in THF (5 mL) and the mixture was stirred at this temperature for 30 min. Benzoyl chloride (1.6 mL, 13.6 mmol) was added dropwise over *ca.* 1 min and the mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (2% EtOAc/petrol) gave the *benzoyl ester* **270** as a colorless oil (1.43 g, 78%, *ca.* 95% purity). R_f = 0.51 (30% EtOAc/hexane); IR 1718 (C=O), 1602, 1451, 1368, 1314, 1267, 1176, 1109, 1070, 1026, 953, 835, 709, 644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-8.03 (2H, m, Ar**H**), 7.59-7.52 (1H, m, Ar**H**), 7.48-7.41 (2H, m, Ar**H**), 6.35 (1H, dt, *J* = 16.8, 10.2 Hz, =C**H**CH_2), 6.20 (1H, app dd, *J* = 15.2, 10.4 Hz, CH_2=C**H**), 5.82-5.70 (1H, m, C**H**=$CHCH_2$), 5.16 (1H, d, *J* = 16.6 Hz, C**H**$_2$=CH), 5.04 (1H, d, *J* = 9.9 Hz, C**H**$_2$=CH), 4.38 (2H, t, *J* = 6.8 Hz, C**H**$_2$O), 2.57 (2H, q, *J* = 6.8 Hz, C**H**$_2$$CH_2O$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.5 (C), 136.7 (CH), 133.5 (CH), 132.8 (CH), 130.3 (C), 129.6 (CH), 129.5 (2 × CH), 128.3 (2 × CH), 116.1 (CH_2), 64.0 (CH_2), 31.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{13}H_{14}O_2Na$ $[M+Na]^+$: 225.0886, found: 225.0891.

5.4.4. PEPPSI-IPr-Catalyzed Oxidative Annulations: General Procedure C

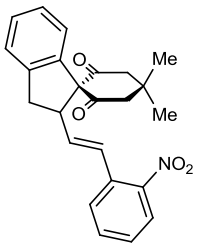


To a mixture of the appropriate 2-aryl-1,3-dicarbonyl compound (0.50 mmol), $Cu(OAc)_2$ (191 mg, 1.05 mmol), and PEPPSI-IPr (17.0 mg, 0.025 mmol) in degassed DMF (1 mL) was added the appropriate diene (0.75 mmol) in degassed DMF (0.5 mL), and the resulting mixture was stirred at 90 °C for 4–24 h. The reaction was filtered through a pad of silica gel eluting with Et_2O (100 mL), washed with H_2O (50

mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the spiroindane.

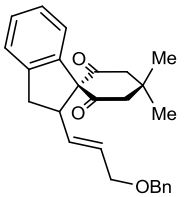


4,4-Dimethyl-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271a). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (6% EtOAc/hexane) to give an off-white solid (114 mg, 66%). R_f = 0.55 (30% EtOAc/hexane); m.p. 140-142 °C (EtOAc/petrol); IR 2960, 1721 (C=O), 1688 (C=O), 1495, 1457, 1369, 1328, 1250, 1206, 1099, 982, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (6H, m, Ar**H**), 7.28-7.22 (2H, m, Ar**H**), 7.07 (1H, d, *J* = 7.4 Hz, Ar**H**), 6.61 (1H, d, *J* = 15.8 Hz, =C**H**Ph), 6.28 (1H, dd, *J* = 15.8, 9.8 Hz, C**H**=CHPh), 3.83-3.75 (1H, m, CH_2C**H**), 3.23-3.14 (2H, m, C**H**$_2$CH), 2.83 (1H, d, *J* = 15.3 Hz, C**H**$_2$C=O), 2.76-2.67 (2H, m, C**H**$_2$C=O), 2.52 (1H, d, *J* = 15.1 Hz, C**H**$_2$C=O), 1.11 (3H, s, CC**H**$_3$), 1.05 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 207.8 (C), 206.6 (C), 144.0 (C), 140.3 (C), 136.4 (C), 133.2 (CH), 128.7 (CH), 128.6 (2 × CH), 128.3 (CH), 127.8 (CH), 126.7 (CH), 126.4 (2 × CH), 125.0 (CH), 124.8 (CH), 80.1 (C), 53.7 (CH_2), 53.58 (CH), 53.56 (CH_2), 38.3 (CH_2), 30.5 (C), 29.3 (CH_3), 28.4 (CH_3); HRMS (ESI) Exact mass calcd for $C_{24}H_{24}O_2Na$ $[M+Na]^+$: 367.1669, found: 367.1654.

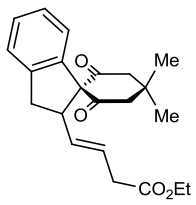


4,4-Dimethyl-2'-[(*E*)-2-(2-nitrophenyl)ethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271b). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **261b** (131 mg, 0.75 mmol), and purified by column chromatography (8% EtOAc/hexane) to give an off-white solid (128 mg, 66%). R_f = 0.39 (30% EtOAc/hexane); m.p. 148-150 °C (EtOAc/petrol); IR 2957, 1721 (C=O), 1689 (C=O), 1517, 1480, 1346, 1330, 1205, 1097, 1066, 967, 862, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 7.52 (1H, td, *J* = 7.8, 1.2 Hz, Ar**H**), 7.46 (1H, dd, *J* = 7.8, 1.3 Hz, Ar**H**), 7.41-7.36 (1H, m, Ar**H**), 7.32-7.22 (3H, m, Ar**H**), 7.10 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.06 (1H, d, *J* = 15.6 Hz, =C**H**Ar), 6.18 (1H, dd, *J* =

15.6, 9.8 Hz, C**H**=CHAr), 3.85 (1H, dt, *J* = 9.8, 7.0 Hz, CH_2C**H**), 3.26 (1H, dd, *J* = 15.5, 7.6 Hz, C**H**$_2$CH), 3.12 (1H, dd, *J* = 15.5, 6.6 Hz, C**H**$_2$CH), 2.98 (1H, d, *J* = 15.3 Hz, C**H**$_2$C=O), 2.77-2.67 (2H, m, C**H**$_2$C=O), 2.57 (1H, d, *J* = 14.9 Hz, C**H**$_2$C=O), 1.10 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 206.7 (C), 206.5 (C), 147.5 (C), 143.5 (C), 139.6 (C), 134.2 (CH), 133.2 (CH), 132.4 (C), 129.0 (CH), 128.42 (CH), 128.36 (CH), 128.2 (CH), 126.8 (CH), 125.1 (CH), 125.0 (CH), 124.5 (CH), 80.4 (C), 53.5 (CH_2), 53.0 (CH_2), 52.2 (CH), 37.9 (CH_2), 30.5 (C), 29.2 (CH_3), 28.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{24}H_{23}NO_4Na$ $[M+Na]^+$: 412.1519, found 412.1520.

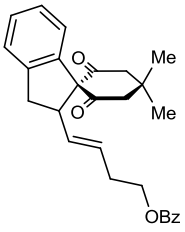


2'-[(*E*)-3-(Benzyloxy)prop-1-en-1-yl]-4,4-dimethyl-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271c). The title compound was prepared according to General Procedure C from dione **149h** (109 mg, 0.50 mmol) and 1,3-diene **267a** (131mg, 0.75 mmol), and purified by column chromatography (8% EtOAc/petrol) to give a light yellow viscous liquid (144 mg, 74%). R_f = 0.54 (30% EtOAc/petrol); IR 2965, 2915, 1720 (C=O), 1690 (C=O), 1602, 1550, 1512, 1454, 1370, 1227, 1203, 1062, 828, 793 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.20 (8H, m, Ar**H**), 7.06 (1H, d, *J* = 7.5 Hz, Ar**H**), 5.89-5.77 (2H, m, C**H**=C**H**), 4.51 (2H, s, C**H**$_2$Ph), 4.04-3.95 (2H, m, C**H**$_2$OBn), 3.63 (1H, dd, *J* = 16.2, 7.8 Hz, C**H**CH=CH), 3.13 (1H, dd, *J* = 15.4, 7.6 Hz, C**H**$_2$CHCH=), 3.07 (1H, dd, *J* = 15.4, 7.8 Hz, C**H**$_2$CHCH=), 2.82 (1H, d, *J* = 15.3 Hz, C**H**$_2$C=O), 2.71 (1H, dd, *J* = 10.3, 1.7 Hz, C**H**$_2$C=O), 2.68 (1H, dd, *J* = 10.3, 1.7 Hz, C**H**$_2$C=O), 2.55 (1H, d, *J* = 15.3 Hz, C**H**$_2$C=O), 1.11 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 207.4 (C), 206.3 (C), 143.8 (C), 140.1 (C), 138.1 (C), 132.3 (CH), 130.3 (CH), 128.3 (2 × CH), 128.2 (CH), 127.6 (2 × CH), 127.5 (CH), 126.6 (CH), 124.8 (2 × CH), 79.9 (C), 72.1 (CH_2), 69.9 (CH_2), 53.5 (CH_2), 53.4 (CH_2), 52.7 (CH), 37.8 (CH_2), 30.4 (C), 29.3 (CH_3), 28.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{29}O_3$ $[M+H]^+$: 389.2111, found: 389.2115.



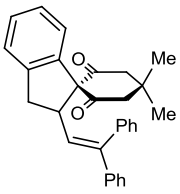
Ethyl (*E*)-4-{4,4-dimethyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}but-3-enoate (271d). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **268** (105 mg,

0.75 mmol), and purified by column chromatography (8% EtOAc/petrol) to give a light yellow viscous liquid (111 mg, 63%). R_f = 0.50 (30% EtOAc/petrol); IR 2956, 1734 (C=O), 1688 (C=O), 1478, 1367, 1315, 1208, 1177, 1142, 983, 893, 759, 644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.17 (3H, m, Ar**H**), 7.00 (1H, d, *J* = 7.4 Hz, Ar**H**), 5.84-5.73 (1H, m, =C**H**CH_2), 5.59 (1H, ddt, *J* = 15.3, 9.8, 1.2 Hz, C**H**=$CHCH_2$), 4.14 (2H, q, *J* = 7.1 Hz, OC$\mathbf{H}_2$), 3.53 (1H, dt, *J* = 9.6, 7.7 Hz, C**H**CH=CH), 3.15-2.96 (4H, m, C$\mathbf{H}_2$CHCH=CHC$\mathbf{H}_2$C=O), 2.87 (1H, d, *J* = 15.3 Hz, $(CH_3)_2$CC$\mathbf{H}_2$C=O), 2.71-2.61 (2H, m, $(CH_3)_2$CC$\mathbf{H}_2$C=O), 2.57 (1H, d, *J* = 15.3 Hz, $(CH_3)_2$CC$\mathbf{H}_2$C=O), 1.27 (3H, t, *J* = 7.1 Hz, CH_2C$\mathbf{H}_3$), 1.12 (3H, s, CC$\mathbf{H}_3$), 1.08 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.0 (C), 206.7 (C), 171.3 (C), 143.9 (C), 140.1 (C), 133.2 (CH), 128.2 (CH), 126.7 (CH), 126.1 (CH), 125.0 (CH), 124.7 (CH), 79.9 (C), 60.7 (CH_2), 53.7 (CH_2), 53.6 (CH), 53.4 (CH_2), 37.9 (CH_2), 37.6 (CH_2), 30.5 (C), 29.5 (CH_3), 28.2 (CH_3), 14.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{27}O_4$ $[M+H]^+$: 355.1904, found: 355.1907.

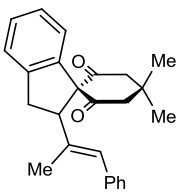


(*E*)-4-{4,4-Dimethyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}but-3-en-1-yl benzoate (271e). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **270** (151 mg, 0.75 mmol), and purified by column chromatography (6% EtOAc/petrol) to give a light yellow viscous liquid (153 mg, 73%). R_f = 0.58 (30% EtOAc/petrol); IR 2951, 2928, 1718 (C=O), 1692 (C=O), 1602, 1451, 1371, 1272, 1227, 1114, 1070, 978, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-8.01 (2H, m, Ar**H**), 7.61-7.40 (1H, m, Ar**H**), 7.49-7.42 (2H, m, Ar**H**), 7.29-7.18 (3H, m, Ar**H**), 7.03 (1H, d, *J* = 7.4 Hz, Ar**H**), 5.78-5.60 (2H, m, C**H**=C**H**), 4.34 (2H, t, *J* = 6.6 Hz, C$\mathbf{H}_2$O), 3.56 (1H, dt, *J* = 9.2, 7.5 Hz, C**H**CH=), 3.09 (1H, dd, *J* = 15.4, 7.6 Hz, C$\mathbf{H}_2$CHCH=), 2.98 (1H, dd, *J* = 15.4, 7.5 Hz, C$\mathbf{H}_2$CHCH=), 2.78 (1H, d, *J* = 15.2 Hz, C$\mathbf{H}_2$C=O), 2.66 (1H, dd, *J* = 15.2, 1.8 Hz, C$\mathbf{H}_2$C=O), 2.60 (1H, dd, *J* = 15.0, 1.8 Hz, C$\mathbf{H}_2$C=O), 2.56-2.41 (3H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_2$$CH_2$O), 1.06 (3H, s, CC$\mathbf{H}_3$), 1.04 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.5 (C), 206.3 (C), 166.4 (C), 143.9 (C), 140.0 (C), 132.9 (CH), 132.1 (CH), 130.1 (C), 129.58 (CH), 129.55 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 126.6 (CH), 124.9 (CH), 124.8 (CH), 80.0 (C), 64.0 (CH_2), 53.6 (CH_2), 53.4 (CH_2),

53.1 (CH), 38.1 (CH_2), 31.8 (CH_2), 30.4 (C), 29.4 (CH_3), 28.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{28}O_4Na$ $[M+Na]^+$: 439.1880, found: 439.1890.

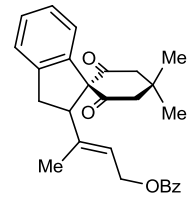


2'-(2,2-Diphenylethenyl)-4,4-dimethyl-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271f). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **264** (154 mg, 0.75 mmol), and purified by column chromatography (5% EtOAc/petrol) to give a yellow solid (154 mg, 73%). R_f = 0.66 (30% EtOAc/petrol); m.p. 152-154 °C (EtOAc/petrol); IR 2957, 1723 (C=O), 1694 (C=O), 1558, 1457, 1372, 1203, 1065, 835, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.38 (3H, m, Ar**H**), 7.35-7.15 (10H, m, Ar**H**), 7.12-7.05 (1H, m, Ar**H**), 6.04 (1H, d, *J* = 11.2 Hz, C**H**=), 3.78 (1H, ddd, *J* = 11.4, 7.5, 4.0 Hz, CH_2C**H**), 3.27 (1H, dd, *J* = 15.5, 7.5 Hz, C**H**$_2$CH), 3.06 (1H, dd, *J* = 15.5, 4.0 Hz, C**H**$_2$CH), 2.68-2.56 (2H, m, C**H**$_2$C=O), 2.48 (1H, d, *J* = 14.8 Hz, C**H**$_2$C=O), 2.41 (1H, dd, *J* = 14.8, 1.3 Hz, C**H**$_2$C=O), 1.06 (3H, s, CC**H**$_3$), 1.01 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 206.6 (C), 206.5 (C), 143.8 (C), 143.5 (C), 141.4 (C), 139.0 (C), 138.5 (C), 129.8 (2 × CH), 128.5 (2 × C), 128.3 (CH), 128.2 (2 × CH), 127.79 (CH), 127.75 (CH), 127.4 (2 × CH), 127.3 (CH), 126.7 (CH), 126.4 (CH), 124.7 (CH), 80.8 (C), 53.8 (CH_2), 52.2 (CH_2), 49.0 (CH), 38.4 (CH_2), 30.2 (C), 30.1 (CH_3), 27.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{30}H_{28}O_2Na$ $[M+Na]^+$: 443.1982, found: 443.1983.

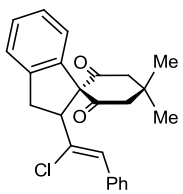


4,4-Dimethyl-2'-[(*E*)-1-phenylprop-1-en-2-yl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271g). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **261e** (108 mg, 0.75 mmol), and purified by column chromatography (6% EtOAc/hexane) to give a white solid (125 mg, 70%). R_f = 0.54 (30% EtOAc/hexane); m.p. 158-160 °C (EtOAc/petrol); IR 2947, 1717 (C=O), 1689 (C=O), 1481, 1457, 1368, 1242, 1194, 1079, 868, 788, 759, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (8H, m, Ar**H**), 7.01 (1H, d, *J* = 7.2 Hz, Ar**H**), 6.57 (1H, s, =C**H**Ph), 3.68 (1H, dd, *J* = 7.4, 5.3 Hz, CH_2C**H**), 3.22 (1H, dd, *J* = 15.8, 7.5 Hz, C**H**$_2$CH), 3.13 (1H, dd, *J* = 15.8, 5.3 Hz, C**H**$_2$CH), 3.00 (1H, d, *J* = 15.2 Hz, C**H**$_2$C=O), 2.81 (1H, d, *J* = 14.3 Hz, C**H**$_2$C=O),

2.67 (1H, dd, *J* = 15.2, 2.8 Hz, C**H**$_2$C=O), 2.60 (1H, dd, *J* = 14.3, 2.8 Hz, C**H**$_2$C=O), 1.60 (3H, d, *J* = 1.6 Hz, =CC**H**$_3$), 1.19 (3H, s, CC**H**$_3$), 1.04 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.0 (C), 206.5 (C), 144.2 (C), 139.5 (C), 137.4 (C), 136.9 (C), 130.6 (CH), 128.9 (2 × CH), 128.24 (2 × CH), 128.21 (CH), 126.8 (CH), 126.6 (CH), 125.9 (CH), 124.0 (CH), 81.1 (C), 61.2 (CH), 54.4 (CH_2), 52.9 (CH_2), 35.8 (CH_2), 30.7 (C), 30.4 (CH_3), 27.1 (CH_3), 15.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{25}H_{26}O_2Na$ $[M+Na]^+$: 381.1825, found: 381.1820.

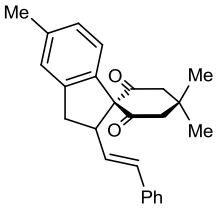


(*E*)-3-{4,4-Dimethyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}but-2-en-1-yl benzoate (271h). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **267c** (151 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a yellow viscous liquid (125 mg, 60%). R_f = 0.45 (30% EtOAc/hexane); IR 2957, 1718 (C=O), 1689 (C=O), 1517, 1456, 1347, 1265, 1097, 1066, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.02 (2H, m, Ar**H**), 7.61-7.56 (1H, m, Ar**H**), 7.49-7.43 (2H, m, Ar**H**), 7.31-7.21 (3H, m, Ar**H**), 6.96 (1H, d, *J* = 7.5 Hz, Ar**H**), 5.76 (1H, t, *J* = 6.7 Hz, =C**H**), 4.89 (1H, dd, *J* = 12.8, 7.0 Hz, C**H**$_2$O), 4.81 (1H, dd, *J* = 12.8, 6.5 Hz, C**H**$_2$O), 3.55 (1H, dd, *J* = 7.3, 6.0 Hz, ArCH$_2$C**H**), 3.17-3.03 (2H, m, ArC**H**$_2$), 2.87 (1H, d, *J* = 15.3 Hz, C**H**$_2$C=O), 2.72 (1H, d, *J* = 14.4 Hz, C**H**$_2$C=O), 2.60 (1H, dd, *J* = 15.2, 2.7 Hz, C**H**$_2$C=O), 2.54 (1H, dd, *J* = 14.4, 2.7 Hz, C**H**$_2$C=O), 1.55 (3H, s, =CC**H**$_3$), 1.12 (3H, s, CC**H**$_3$), 1.01 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.1 (C), 206.6 (C), 166.4 (C), 144.0 (C), 140.7 (C), 139.6 (C), 133.0 (CH), 130.0 (C), 129.5 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 126.7 (CH), 125.7 (CH), 124.8 (CH), 124.1 (CH), 80.7 (C), 61.0 (CH_2), 60.0 (CH), 54.2 (CH_2), 52.9 (CH_2), 35.5 (CH_2), 30.3 (C and CH_3), 27.2 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{28}O_4Na$ $[M+Na]^+$: 439.1880, found: 439.1891.

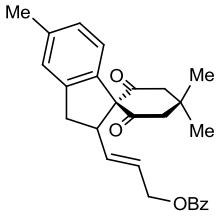


2'-[(*Z*)-1-Chloro-2-phenylethenyl]-4,4-dimethyl-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (271i). The title compound was prepared according to General Procedure C from dione **149h** (108 mg, 0.50 mmol) and 1,3-diene **261f** (123 mg, 0.75 mmol), and purified by column chromatography (5% EtOAc/hexane) to give an off-

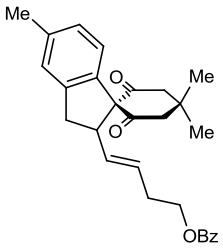
white solid (127 mg, 67%). R_f = 0.55 (30% EtOAc/hexane); m.p. 144-146 °C (EtOAc/petrol); IR 2953, 1724 (C=O), 1693 (C=O), 1558, 1482, 1369, 1322, 1211, 1193, 1066, 932, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.56 (2H, m, Ar**H**), 7.44-7.22 (6H, m, Ar**H**), 6.97 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.79 (1H, s, =C**H**Ph), 4.06 (1H, dd, *J* = 9.8, 7.6 Hz, CH_2C**H**), 3.60 (1H, dd, *J* = 15.3, 10.0 Hz, C**H**$_2$CH), 3.20 (1H, dd, *J* = 15.3, 7.5 Hz, C**H**$_2$CH), 2.93 (1H, d, *J* = 16.3 Hz, C**H**$_2$C=O), 2.79 (1H, d, *J* = 16.3 Hz, C**H**$_2$C=O), 2.71 (2H, s, C**H**$_2$C=O), 1.17 (3H, s, CC**H**$_3$), 1.13 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.5 (C), 205.8 (C), 143.1 (C), 140.7 (C), 134.1 (C), 131.5 (C), 129.2 (2 × CH), 128.8 (CH), 128.34 (CH), 128.30 (2 × CH), 128.28 (CH), 127.0 (CH), 124.6 (CH), 124.5 (CH), 78.5 (C), 60.9 (CH), 54.0 (CH_2), 53.9 (CH_2), 36.3 (CH_2), 30.3 (C), 30.1 (CH_3), 28.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{24}H_{23}ClO_2Na$ $[M+Na]^+$: 401.1279, found: 401.1272.



4,4,5'-Trimethyl-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272a). The title compound was prepared according to General Procedure C from dione **253a** (115 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (7% EtOAc/hexane) to give a light yellow viscous liquid (145 mg, 81%). R_f = 0.59 (30% EtOAc/hexane); IR 2960, 1728 (C=O), 1690 (C=O), 1495, 1371, 1324, 1223, 1074, 973, 909, 751, 733, 692, 632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.32 (4H, m, Ar**H**), 7.31-7.25 (1H, m, Ar**H**), 7.15 (1H, s, Ar**H**), 7.09 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.99 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.63 (1H, d, *J* = 15.8 Hz, =C**H**Ph), 6.31 (1H, dd, *J* = 15.8, 9.8 Hz, C**H**=CHPh), 3.81 (1H, dd, *J* = 17.6, 7.9 Hz, CH_2C**H**), 3.17 (2H, d, *J* = 7.9 Hz, C**H**$_2$CH), 2.84 (1H, d, *J* = 15.4 Hz, C**H**$_2$C=O), 2.79-2.69 (2H, m, C**H**$_2$C=O), 2.54 (1H, d, *J* = 15.2 Hz, C**H**$_2$C=O), 2.39 (3H, s, ArC**H**$_3$), 1.13 (3H, s, CC**H**$_3$), 1.07 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 207.8 (C), 206.8 (C), 144.1 (C), 138.2 (C), 137.4 (C), 136.5 (C), 133.1 (CH), 128.8 (CH), 128.6 (2 × CH), 127.7 (CH), 127.6 (CH), 126.3 (2 × CH), 125.7 (CH), 124.4 (CH), 79.8 (C), 53.6 (CH_2), 53.6 (CH), 53.5 (CH_2), 38.1 (CH_2), 30.5 (C), 29.2 (CH_3), 28.4 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{25}H_{26}O_2Na$ $[M+Na]^+$: 381.1825, found: 381.1819.

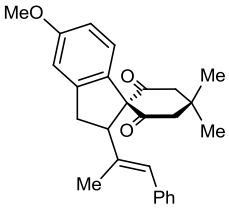


(*E*)-3-{4,4,5'-Trimethyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}prop-2-en-1-yl benzoate (272b). The title compound was prepared according to General Procedure C from dione **253a** (115 mg, 0.50 mmol) and 1,3-diene **267b** (141 mg, 0.75 mmol), and purified by column chromatography (7% EtOAc/hexane) to give an off-white solid (154 mg, 74%). R_f = 0.56 (30% EtOAc/hexane); m.p. 108-110 °C (EtOAc/petrol); IR 2962, 1710 (C=O), 1694 (C=O), 1274, 1262, 1227, 1118, 978, 808, 714, 638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (2H, dt, *J* = 8.4, 1.5 Hz, Ar**H**), 7.60-7.55 (1H, m, Ar**H**), 7.48-7.42 (2H, m, Ar**H**), 7.09 (1H, s, Ar**H**), 7.02 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.92 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.01-5.87 (2H, m, C**H**=C**H**), 4.78 (2H, d, *J* = 5.4 Hz, C$\mathbf{H}_2$O), 3.69 (1H, q, *J* = 8.6 Hz, ArCH_2C**H**), 3.13-3.04 (2H, m, ArC$\mathbf{H}_2$), 2.78-2.65 (3H, m, 2 × C$\mathbf{H}_2$C=O), 2.50 (1H, d, *J* = 15.3 Hz, C$\mathbf{H}_2$C=O), 2.33 (3H, s, ArC$\mathbf{H}_3$), 1.09 (3H, s, CC$\mathbf{H}_3$), 1.04 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 207.8 (C), 206.7 (C), 166.2 (C), 144.0 (C), 138.3 (C), 137.7 (C), 134.3 (CH), 133.0 (CH), 130.0 (C), 129.6 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 127.6 (CH), 125.8 (CH), 124.1 (CH), 79.4 (C), 64.7 (CH_2), 53.8 (CH_2), 53.3 (CH_2), 52.4 (CH), 37.7 (CH_2), 30.6 (C), 28.9 (CH_3), 28.7 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{28}O_4Na$ $[M+Na]^+$: 439.1880, found: 439.1882.

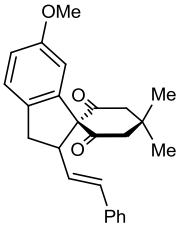


(*E*)-4-{4,4,5'-Trimethyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}but-3-en-1-yl benzoate (272c). The title compound was prepared according to General Procedure C from dione **253a** (115 mg, 0.50 mmol) and 1,3-diene **270** (151 mg, 0.75 mmol), and purified by column chromatography (6% EtOAc/petrol) to give a light yellow viscous liquid (169 mg, 79%). R_f = 0.60 (30% EtOAc/petrol); IR 2989, 2923, 1712 (C=O), 1694 (C=O), 1678 (C=O), 1585, 1560, 1545, 1469, 1370, 1276, 1193, 1123, 1069, 968, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-8.02 (2H, m, Ar**H**), 7.61-7.55 (1H, m, Ar**H**), 7.49-7.43 (2H, m, Ar**H**), 7.06 (1H, s, Ar**H**), 7.03 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.91 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.79-5.61 (2H, m, C**H**=C**H**), 4.34 (2H, t, *J* = 6.6 Hz, C$\mathbf{H}_2$O), 3.55 (1H, dt, *J* = 9.0, 7.6 Hz, ArCH_2C**H**), 3.05 (1H, dd, *J* = 15.4, 7.6 Hz, ArC$\mathbf{H}_2$), 2.94 (1H, dd, *J* = 15.4, 7.5 Hz, ArC$\mathbf{H}_2$), 2.77 (1H, d, *J* = 15.2 Hz, C$\mathbf{H}_2$C=O),

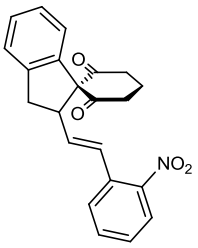
2.66 (1H, dd, *J* = 15.2, 1.8 Hz, C**H**$_2$C=O), 2.60 (1H, dd, *J* = 15.0, 1.8 Hz, C**H**$_2$C=O), 2.55-2.43 (3H, m, C**H**$_2$C=O and C**H**$_2$CH$_2$O), 2.33 (3H, s, ArC**H**$_3$), 1.05 (3H, s, CC**H**$_3$), 1.03 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.7 (C), 206.5 (C), 164.4 (C), 143.9 (C), 138.0 (C), 137.1 (C), 132.9 (CH), 132.2 (CH), 130.1 (C), 129.5 (2 × CH), 129.4 (CH), 128.3 (2 × CH), 127.5 (CH), 125.5 (CH), 124.5 (CH), 79.7 (C), 64.0 (CH_2), 53.6 (CH_2), 53.4 (CH_2), 53.2 (CH), 38.0 (CH_2), 31.8 (CH_2), 30.4 (C), 29.3 (CH_3), 28.2 (CH_3), 21.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{28}H_{31}O_4$ $[M+H]^+$: 431.2217, found: 431.2227.



5'-Methoxy-4,4-dimethyl-2'-[(*E*)-1-phenylprop-1-en-2-yl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272d). The title compound was prepared according to General Procedure C from dione **253b** (123 mg, 0.50 mmol) and 1,3-diene **261e** (108 mg, 0.75 mmol), and purified by column chromatography (7% EtOAc/petrol) to give a light yellow solid (109 mg, 56%). R_f = 0.60 (30% EtOAc/petrol); m.p. 118-120 °C (EtOAc/petrol); IR 2957, 1699 (C=O), 1687 (C=O), 1616, 1493, 1463, 1318, 1257, 1220, 1196, 1082, 1032, 855, 820 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (2H, m, Ar**H**), 7.29-7.20 (3H, m, Ar**H**), 6.92 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.86-6.80 (2H, m, Ar**H**), 6.56 (1H, s, =C**H**Ph), 3.84 (3H, s, OC**H**$_3$), 3.68 (1H, dd, *J* = 7.5, 5.0 Hz, CH_2C**H**), 3.19 (1H, dd, *J* = 15.9, 7.6 Hz, C**H**$_2$CH), 3.07 (1H, dd, *J* = 15.9, 5.1 Hz, C**H**$_2$CH), 3.00 (1H, d, *J* = 15.1 Hz, C**H**$_2$C=O), 2.81 (1H, d, *J* = 14.3 Hz, C**H**$_2$C=O), 2.65 (1H, dd, *J* = 15.1, 2.8 Hz, C**H**$_2$C=O), 2.59 (1H, dd, *J* = 14.2, 2.8 Hz, C**H**$_2$C=O), 1.61 (3H, d, *J* = 1.2 Hz, =CC**H**$_3$), 1.18 (3H, s, CC**H**$_3$), 1.03 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.1 (C), 206.7 (C), 159.8 (C), 145.7 (C), 137.5 (C), 136.9 (C), 131.5 (C), 130.5 (CH), 128.9 (2 × CH), 128.2 (2 × CH), 126.8 (CH), 126.5 (CH), 112.8 (CH), 109.2 (CH), 80.5 (C), 61.4 (CH), 55.2 (CH_3), 54.3 (CH_2), 52.8 (CH_2), 35.9 (CH_2), 30.6 (C), 30.5 (CH_3), 27.0 (CH_3), 14.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{28}O_3Na$ $[M+Na]^+$: 411.1931, found: 411.1936.

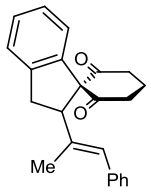


6'-Methoxy-4,4-dimethyl-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272e). The title compound was prepared according to General Procedure C from dione **253c** (125 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (5% EtOAc/petrol) to give an off-white solid (87 mg, 46%). R_f = 0.63 (30% EtOAc/petrol); m.p. 178-180 °C (EtOAc/petrol); IR 2958, 1688 (C=O), 1600, 1487, 1465, 1330, 1220, 1025, 970, 829, 752, 643, 639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (5H, m, Ar**H**), 7.20 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.85 (1H, dd, *J* = 8.3, 2.4 Hz, Ar**H**), 6.62-6.55 (2H, m, Ar**H** and =C**H**Ph), 6.25 (1H, dd, *J* = 15.8, 9.8 Hz, C**H**=CHPh), 3.86-3.72 (1H, m, CH_2C**H**), 3.81 (3H, s, OC**H**$_3$), 3.23-3.01 (2H, m, C**H**$_2$CH), 2.82 (1H, d, *J* = 15.4 Hz, C**H**$_2$C=O), 2.74-2.65 (2H, m, C**H**$_2$C=O), 2.52 (1H, d, *J* = 15.2 Hz, C**H**$_2$C=O), 1.09 (3H, s, CC**H**$_3$), 1.05 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.6 (C), 206.5 (C), 158.6 (C), 141.4 (C), 136.4 (C), 136.0 (C), 133.1 (CH), 128.7 (CH), 128.6 (2 × CH), 127.8 (CH), 126.4 (2 × CH), 125.4 (CH), 113.7 (CH), 111.0 (CH), 80.2 (C), 55.4 (CH_3), 54.2 (CH), 53.7 (CH_2), 53.6 (CH_2), 37.4 (CH_2), 30.5 (C), 29.4 (CH_3), 28.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{25}H_{26}O_3Na$ $[M+Na]^+$: 397.1774, found: 397.1779.

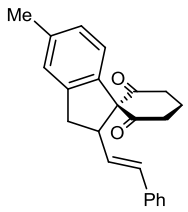


2'-[(*E*)-2-(2-Nitrophenyl)ethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272g). The title compound was prepared according to General Procedure C from dione **149a** (94 mg, 0.50 mmol) and 1,3-diene **261b** (131 mg, 0.75 mmol), and purified by column chromatography (10% EtOAc/hexane) to give a yellow viscous liquid (110 mg, 61%). R_f = 0.26 (30% EtOAc/hexane); IR 2970, 1722 (C=O), 1694 (C=O), 1606, 1520, 1457, 1344, 1313, 1264, 1204, 1044, 970, 909, 861, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (1H, dd, *J* = 8.2, 1.1 Hz, Ar**H**), 7.56-7.45 (2H, m, Ar**H**), 7.39 (1H, ddd, *J* = 8.6, 7.2, 1.6 Hz, Ar**H**), 7.33-7.21 (3H, m, Ar**H**), 7.07 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.02 (1H, d, *J* = 15.6 Hz, =C**H**Ph), 6.15 (1H, dd, *J* = 15.6, 9.6 Hz, C**H**=CHPh), 3.93-3.84 (1H, m, ArCH$_2$C**H**), 3.29 (1H, dd, *J* = 15.5, 7.6 Hz, ArC**H**$_2$), 3.14 (1H, dd, *J* = 15.5, 6.3 Hz, ArC**H**$_2$), 3.06-2.95 (1H, m, C**H**$_2$C=O), 2.90-2.72 (2H, m, C**H**$_2$C=O), 2.70-2.59 (1H, m, C**H**$_2$C=O), 2.27-2.14 (1H, m, CH_2C**H**$_2$CH$_2$), 2.13-1.98 (1H, m, CH_2C**H**$_2$CH$_2$); ^{13}C

NMR (125.8 MHz, $CDCl_3$) δ 207.4 (C), 206.8 (C), 147.5 (C), 143.5 (C), 140.1 (C), 134.2 (CH), 133.2 (CH), 132.5 (C), 129.1 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.9 (CH), 125.2 (CH), 125.0 (CH), 124.5 (CH), 81.7 (C), 52.5 (CH), 39.8 (CH_2), 39.3 (CH_2), 38.1 (CH_2), 17.0 (CH_2); HRMS (ESI) Exact mass calcd for $C_{22}H_{19}NO_4Na$ $[M+Na]^+$: 384.1206, found: 384.1203.

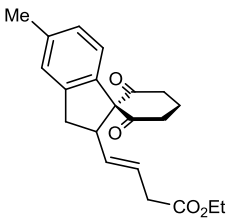


2'-[(*E*)-1-Phenylprop-1-en-2-yl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272h). The title compound was prepared according to General Procedure C from dione **149a** (94 mg, 0.50 mmol) and 1,3-diene **261e** (108 mg, 0.75 mmol), and purified by column chromatography (8% EtOAc/hexane) to give an off-white solid (78 mg, 47%). R_f = 0.40 (30% EtOAc/hexane); m.p. 143-145 °C (EtOAc/petrol); IR 2988, 1717 (C=O), 1689 (C=O), 1653, 1558, 1457, 1394, 1189, 1160, 1077, 917, 749, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (8H, m, Ar**H**), 7.03 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.55 (1H, s, =C**H**Ph), 3.91 (1H, dd, *J* = 10.0, 3.7 Hz, $ArCH_2C$**H**), 3.25 (2H, d, *J* = 6.9 Hz, ArC**H**$_2$), 3.03-2.95 (1H, m, C**H**$_2$C=O), 2.86-2.71 (3H, m, 2 × C**H**$_2$C=O), 2.29-2.19 (1H, m, CH_2C**H**$_2CH_2$), 2.09-1.98 (1H, m, CH_2C**H**$_2CH_2$), 1.62 (3H, d, *J* = 1.2 Hz, =CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.2 (C), 206.6 (C), 144.2 (C), 140.4 (C), 137.15 (C), 137.14 (C), 129.3 (CH), 129.0 (2 × CH), 128.2 (CH), 128.2 (2 × CH), 126.65 (CH), 126.62 (CH), 125.1 (CH), 124.3 (CH), 81.4 (C), 59.4 (CH), 39.8 (CH_2), 39.4 (CH_2), 36.0 (CH_2), 17.3 (CH_2), 15.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}O_2Na$ $[M+Na]^+$: 353.1512, found: 353.1513.

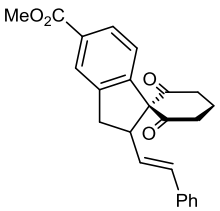


5'-Methyl-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (270i). The title compound was prepared according to General Procedure C from dione **149e** (101 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (9% EtOAc/hexane) to give an off-white solid (120 mg, 73%). R_f = 0.51 (30% EtOAc/hexane); m.p. 142-144 °C (EtOAc/petrol); IR 2929, 1718 (C=O), 1690 (C=O), 1493, 1449, 1413, 1317, 1269, 1223, 1186, 1097, 1075, 815, 753, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (4H, m, Ar**H**), 7.28-7.23 (1H, m, Ar**H**), 7.12 (1H, s, Ar**H**), 7.05 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.90 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.58 (1H, d, *J* = 15.8 Hz, =C**H**Ph), 6.24

(1H, dd, *J* = 15.8, 9.8 Hz, C**H**=CHPh), 3.82-3.73 (1H, m, C**H**CH=CH), 3.21-3.10 (2H, m, C**H**$_2$CH), 2.89-2.70 (3H, m, C**H**$_2$C=O), 2.63-2.54 (1H, m, C**H**$_2$C=O), 2.36 (3H, s, ArC**H**$_3$), 2.17-2.07 (1H, m, CH$_2$C**H**$_2$CH$_2$), 2.06-1.97 (1H, m, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.7 (C), 207.2 (C), 144.1 (C), 138.2 (C), 138.0 (C), 136.4 (C), 132.9 (CH), 128.6 (2 × CH), 128.6 (CH), 127.8 (CH), 127.7 (CH), 126.4 (2 × CH), 125.6 (CH), 124.5 (CH), 80.9 (C), 54.5 (CH), 40.0 (CH$_2$), 39.9 (CH$_2$), 38.3 (CH$_2$), 21.4 (CH$_3$), 17.1 (CH$_2$); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}O_2Na$ $[M+Na]^+$: 353.1512, found: 353.1510.

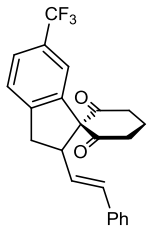


Ethyl (*E*)-4-{5'-methyl-2,6-dioxo-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2'-yl}but-3-enoate (272j). The title compound was prepared according to General Procedure C from dione **149e** (101 mg, 0.50 mmol) and 1,3-diene **268** (105 mg, 0.75 mmol), and purified by column chromatography (15% EtOAc/petrol) to give a yellow viscous liquid (100 mg, 59%). R_f = 0.34 (30% EtOAc/petrol); IR 2973, 1732 (C=O), 1718 (C=O), 1693 (C=O), 1496, 1323, 1177, 1022, 990, 823, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, s, Ar**H**), 7.02 (1H, dd, *J* = 7.8, 0.7 Hz, Ar**H**), 6.86 (1H, d, *J* = 7.8 Hz, Ar**H**), 5.81-5.72 (1H, m, =C**H**CH$_2$), 5.57 (1H, ddt, *J* = 15.3, 9.6, 1.2 Hz, C**H**=CHCH$_2$), 4.14 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.58 (1H, dt, *J* = 9.4, 7.5 Hz, ArCH$_2$C**H**), 3.14-2.94 (4H, m, ArC**H**$_2$ and =CHC**H**$_2$), 2.92-2.58 (4H, m, 2 × C**H**$_2$C=O), 2.33 (3H, s, ArC**H**$_3$), 2.22-2.10 (1H, m, CH$_2$C**H**$_2$CH$_2$), 2.06-1.93 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.27 (3H, t, *J* = 7.1 Hz, C**H**$_2$CH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.6 (C), 207.2 (C), 171.3 (C), 143.9 (C), 138.1 (C), 137.7 (C), 133.2 (CH), 127.6 (CH), 125.6 (CH), 125.5 (CH), 124.6 (CH), 80.8 (C), 60.7 (CH$_2$), 53.8 (CH), 40.0 (CH$_2$), 39.7 (CH$_2$), 38.0 (CH$_2$), 37.6 (CH$_2$), 21.3 (CH$_3$), 17.1 (CH$_2$), 14.1 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{21}H_{25}O_4$ $[M+H]^+$: 341.1747, found: 341.1744.

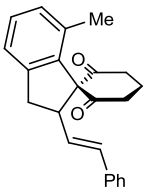


Methyl 2,6-dioxo-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-5'-carboxylate (272k). The title compound was prepared according to General Procedure C from dione **149f** (123 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (12%

EtOAc/hexane) to give an off-white solid (101 mg, 54%). R_f = 0.30 (30% EtOAc/hexane); m.p. 138-140 °C (EtOAc/petrol); IR 2989, 1721 (C=O), 1684 (C=O), 1653, 1558, 1506, 1436, 1294, 1198, 986, 765, 751, 656, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, s, Ar**H**), 7.94 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.37-7.23 (5H, m, Ar**H**), 7.07 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.61 (1H, d, *J* = 15.7 Hz, =C**H**Ph), 6.16 (1H, dd, *J* = 15.7, 9.9 Hz, C**H**=CHPh), 3.92 (3H, s, OC**H**$_3$), 3.76 (1H, dt, *J* = 9.7, 7.4 Hz, ArCH$_2$C**H**), 3.25 (1H, dd, *J* = 15.6, 7.5 Hz, ArC**H**$_2$), 3.14 (1H, dd, *J* = 15.6, 7.3 Hz, ArC**H**$_2$), 2.92-2.68 (3H, m, 2 × C**H**$_2$C=O), 2.66-2.56 (1H, m, C**H**$_2$C=O), 2.23-2.10 (1H, m, CH$_2$C**H**$_2$CH$_2$), 2.08-1.93 (1H, m, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.7 (C), 206.2 (C), 166.8 (C), 145.6 (C), 144.4 (C), 136.0 (C), 133.4 (CH), 130.2 (C), 128.6 (2 × CH), 128.4 (CH), 128.0 (CH), 127.6 (CH), 126.4 (2 × CH), 125.9 (CH), 125.3 (CH), 81.2 (C), 55.0 (CH), 52.1 (CH_3), 40.1 (CH_2), 39.6 (CH_2), 38.1 (CH_2), 17.1 (CH_2); HRMS (ESI) Exact mass calcd for $C_{24}H_{22}O_4Na$ $[M+Na]^+$: 397.1410, found: 397.1415.

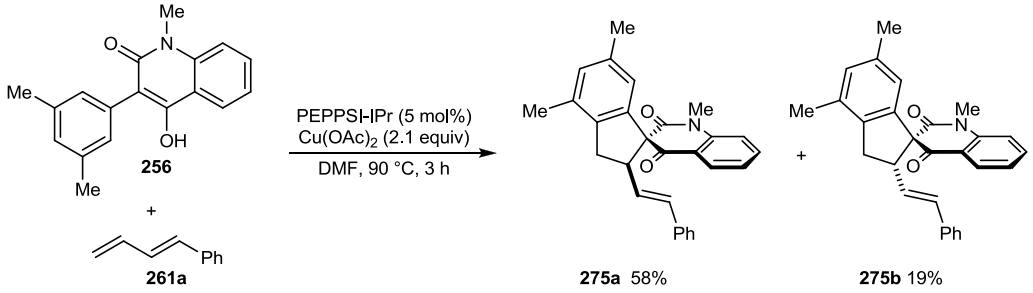


2'-[(*E*)-2-phenylethenyl]-6'-(trifluoromethyl)-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272l). The title compound was prepared according to General Procedure C from dione **149b** (128 mg, 0.50 mmol) and diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (5% EtOAc/pet.ether) to give a yellow solid (65 mg, 34%). R_f = 0.60 (30% EtOAc/pet.ether); m.p. 160-162 °C; IR (film) 1688 (C=O), 1423, 1332, 1322, 1153, 1120, 982, 892, 827, 745, 639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.40 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.38-7.22 (6H, m, Ar**H**), 6.62 (1H, d, *J* = 15.7 Hz, =C**H**Ph), 6.13 (1H, dd, *J* = 10.0, 15.7 Hz, C**H**=CHPh), 3.74 (1H, dt, *J* = 7.2, 9.8 Hz, ArCH$_2$C**H**), 3.26 (1H, dd, *J* = 7.5, 16.0 Hz, ArC**H**$_2$CH), 3.13 (1H, dd, *J* = 7.0, 16.0 Hz, ArC**H**$_2$CH), 2.94-2.70 (3H, m, C**H**C=O, C**H**$_2$C=O), 2.67-2.57 (1H, m, C**H**C=O), 2.25-2.13 (1H, m, CH$_2$C**H**CH$_2$), 2.07-1.94 (1H, m, CH$_2$C**H**CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (C), 206.3 (C), 148.1 (C), 141.1 (C), 135.6 (C), 133.6 (CH), 129.5 (CH), 129.2 (CH), 128.7 (2 × CH), 128.2 (CH), 127.3 (CH), 126.4 (2 × CH), 125.0 (CH), 122.5 (C), 81.0 (C), 55.1 (CH), 40.1 (CH_2), 39.6 (CH_2), 38.2 (CH_2), 17.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.8 (3F, s, CF_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{19}F_3O_2Na$ $[M+Na]^+$: 407.1229, found: 407.1235.



7'-Methyl-2'-[(*E*)-2-phenylethenyl]-2',3'-dihydrospiro[cyclohexane-1,1'-indene]-2,6-dione (272m). The title compound was prepared according to General Procedure C from dione **149g** (101 mg, 0.50 mmol) and 1,3-diene **261a** (98 mg, 0.75 mmol), and purified by column chromatography (7% EtOAc/petrol) to give an off-white solid (99 mg, 60%). R_f = 0.67 (30% EtOAc/petrol); m.p. 156-158 °C (EtOAc/petrol); IR 2988, 1717 (C=O), 1689 (C=O), 1558, 1506, 1394, 1319, 1260, 1231, 1074, 867, 754, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.27 (5H, m, Ar**H**), 7.23 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.14 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.05 (1H, d, *J* = 7.4 Hz, Ar**H**), 6.62 (1H, d, *J* = 15.7 Hz, =C**H**Ph), 6.17 (1H, dd, *J* = 15.7, 10.3 Hz, C**H**=CHPh), 3.58-3.47 (1H, m, $ArCH_2C$**H**), 3.24 (1H, dd, *J* = 15.6, 7.8 Hz, ArC**H**$_2$), 3.08 (1H, dd, *J* = 15.6, 8.3 Hz, ArC**H**$_2$), 2.93-2.72 (3H, m, 2 × C**H**$_2$C=O), 2.63 (1H, ddd, *J* = 16.9, 11.5, 5.6 Hz, C**H**$_2$C=O), 2.28-2.12 (1H, m, CH_2C**H**$_2CH_2$), 2.06-1.92 (1H, m, CH_2C**H**$_2CH_2$), 1.97 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.5 (C), 207.6 (C), 144.3 (C), 140.4 (C), 136.0 (C), 133.6 (C), 133.4 (CH), 128.7 (2 × CH), 128.62 (CH), 128.57 (CH), 128.47 (CH), 128.1 (CH), 126.4 (2 × CH), 121.7 (CH), 80.9 (C), 56.9 (CH), 40.8 (CH_2), 39.9 (CH_2), 39.0 (CH_2), 20.6 (CH_3), 17.4 (CH_2); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}O_2Na$ $[M+Na]^+$: 353.1512, found: 353.1513.

(±)-(1*R*,2*R*)-1',4,6-Trimethyl-2-[(*E*)-2-phenylethenyl]-2,2',3,4'-tetrahydro-1'*H*-spiro[indene-1,3'-quinoline]-2',4'-dione (275a) and (±)-(1*R*,2*S*)-1',4,6-trimethyl-2-[(*E*)-2-phenylethenyl]-2,2',3,4'-tetrahydro-1'*H*-spiro[indene-1,3'-quinoline]-2',4'-dione (275b)



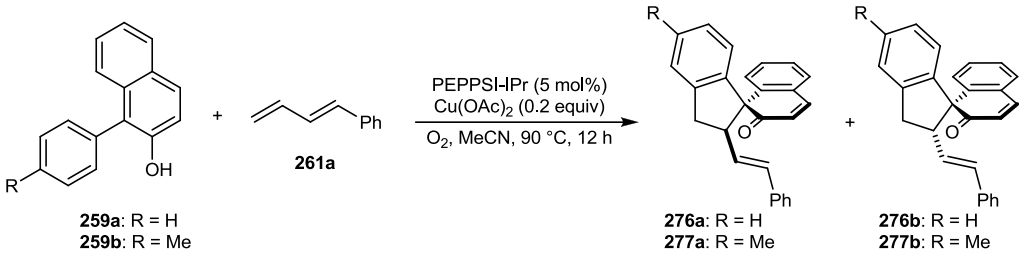
To a mixture of the ketoamide **256** (140 mg, 0.50 mmol), $Cu(OAc)_2$ (191 mg, 1.05 mmol), and PEPPSI-IPr (17.0 mg, 0.025 mmol) in degassed DMF (1 mL) was added the diene **261a** (98 mg, 0.75 mmol) in degassed DMF (0.5 mL), and the resulting mixture was stirred at 90 °C for 3 h. The reaction was filtered through a pad of silica

gel eluting with Et_2O (100 mL), the diethyl ether solvent was washed with H_2O (50 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/petrol) gave the *spiroindane* **275b** (38 mg, 19%) as a pale yellow amorphous solid followed by the *spiroindane* **275a** (118 mg, 58%) as an off-white solid.

Data for **275a**: R_f = 0.20 (10% EtOAc/petrol); m.p. 170-172 °C (EtOAc/petrol); IR 1691 (C=O), 1658, 1599, 1468, 1349, 1302, 1173, 983, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, dd, *J* = 7.7, 1.6 Hz, Ar**H**), 7.63 (1H, ddd, *J* = 8.7, 7.4, 1.7 Hz, Ar**H**), 7.26-7.13 (7H, m, Ar**H**), 6.91 (1H, s, Ar**H**), 6.58 (1H, d, *J* = 15.8 Hz, =C**H**Ph), 6.53 (1H, s, Ar**H**), 6.45 (1H, dd, *J* = 15.8, 9.0 Hz, C**H**=CHPh), 4.33-4.26 (1H, m, CH_2C**H**), 3.59 (3H, s, *N*C$\mathbf{H}_3$), 3.35 (1H, dd, *J* = 15.2, 10.5 Hz, C$\mathbf{H}_2$CH), 3.17 (1H, dd, *J* = 15.2, 8.1 Hz, C$\mathbf{H}_2$CH), 2.30 (3H, s, ArC$\mathbf{H}_3$), 2.21 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.4 (C), 172.0 (C), 143.5 (C), 142.1 (C), 140.2 (C), 136.9 (C), 136.7 (C), 136.1 (CH), 134.5 (C), 132.6 (CH), 130.5 (CH), 128.5 (CH), 128.4 (2 × CH), 128.2 (CH), 127.3 (CH), 126.3 (2 × CH), 123.2 (CH), 121.0 (CH), 120.7 (C), 114.8 (CH), 73.5 (C), 54.6 (CH), 36.6 (CH_2), 30.3 (CH_3), 21.2 (CH_3), 19.2 (CH_3); HRMS (ESI) Exact mass calcd for $C_{28}H_{26}NO_2$ $[M+H]^+$: 408.1958, found: 408.1966.

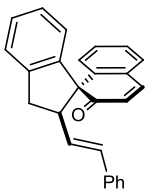
Data for **275b**: R_f = 0.21 (10% EtOAc/petrol); IR 3021, 1692 (C=O), 1658, 1599, 1470, 1348, 970, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, dd, *J* = 7.7, 1.6 Hz, Ar**H**), 7.64 (1H, ddd, *J* = 8.8, 7.4, 1.7 Hz, Ar**H**), 7.27-7.16 (6H, m, Ar**H** and C**H**=C**H**Ph), 7.12 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.93 (1H, s, Ar**H**), 6.50 (1H, s, Ar**H**), 6.43 (1H, d, *J* = 2.4 Hz, Ar**H**), 6.42 (1H, s, Ar**H**), 4.15-4.05 (1H, m, CH_2C**H**), 3.43-3.31 (1H, m, C$\mathbf{H}_2$CH), 3.39 (3H, s, *N*C$\mathbf{H}_3$), 3.17 (1H, dd, *J* = 15.1, 8.1 Hz, C$\mathbf{H}_2$CH), 2.30 (3H, s, ArC$\mathbf{H}_3$), 2.22 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.7 (C), 170.3 (C), 143.8 (C), 142.5 (C), 140.4 (C), 136.9 (C), 136.8 (C), 136.3 (CH), 134.1 (C), 132.9 (CH), 130.5 (CH), 128.4 (2 × CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 126.2 (2 × CH), 123.0 (CH), 121.5 (CH), 121.2 (C), 114.8 (CH), 73.5 (C), 54.3 (CH), 36.8 (CH_2), 29.5 (CH_3), 21.2 (CH_3), 19.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{28}H_{26}NO_2$ $[M+H]^+$: 408.1958, found: 408.1969.

5.4.5. Dearomatized Oxidative Annulation: General Procedure D

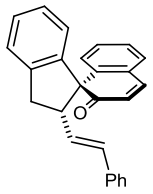


To a mixture of the 1-aryl-2-naphthol (**259**) (0.50 mmol), $Cu(OAc)_2$ (18.2 mg, 0.10 mmol), and PEPPSI-IPr (17.0 mg, 0.025 mmol) in MeCN (2.0 mL) at room temperature was added a solution of 1,3-diene **261a** (97.5 mg, 0.75 mmol) in MeCN (0.5 mL), and the resulting mixture was stirred at 90 °C for 12 h under an O_2 atmosphere (balloon). The reaction was filtered through a pad of silica gel eluting with Et_2O (100 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (3% acetone/petrol) gave the *spiroindane* **276** and **277** as a solid.

The title compound was prepared according to General Procedure D from 1-phenyl-2-naphthol **259a** (110 mg, 0.50 mmol), affording the *spiroindane* **276a** (113 mg, 65%) as a pale yellow solid followed by the *spiroindane* **276b** (33 mg, 19%) as an amorphous pale yellow solid.

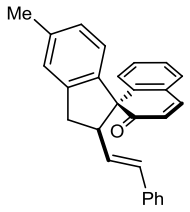


(±)-(1*S*,2*R*)-2-[(*E*)-2-Phenylethenyl]-2,3-dihydro-2'*H*-spiro[indene-1,1'-naphthalene]-2'-one (276a). R_f = 0.40 (10% acetone/petrol); m.p. 108-110 °C (EtOAc/petrol); IR 1697 (C=O), 1650, 1617, 1560, 1545, 1481, 1430, 1394, 816, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.17 (13H, m, Ar**H** and C**H**=CHC=O), 6.80 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.24-6.10 (3H, m, CH=C**H**C=O and C**H**=C**H**Ph), 3.60-3.45 (2H, m, C**H**$_2$C**H**), 3.15 (1H, dd, *J* = 14.0, 6.3 Hz, CHC**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.3 (C), 146.0 (C), 145.4 (C), 145.3 (CH), 145.1 (C), 136.9 (C), 131.4 (CH), 130.9 (C), 130.0 (CH), 128.9 (CH), 128.8 (CH), 128.4 (2 × CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 126.3 (2 × CH), 125.2 (CH), 124.9 (CH), 124.4 (CH), 69.4 (C), 64.2 (CH), 36.3 (CH_2); HRMS (ESI) Exact mass calcd for $C_{26}H_{20}ONa$ $[M+Na]^+$: 371.1406, found: 371.1388.

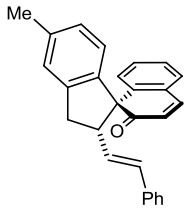


(±)-(1*S*,2*S*)-2-[(*E*)-2-phenylethenyl]-2,3-dihydro-2'*H*-spiro[indene-1,1'-naphthalene]-2'-one (276b). R_f = 0.38 (10% acetone/petrol); IR 2900, 1698 (C=O), 1658, 1565, 1479, 1448, 1395, 1248, 1204, 966, 909, 759, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 9.8 Hz, C**H**=CHC=O), 7.42 (1H, d, J = 7.4 Hz, Ar**H**), 7.39-7.16 (8H, m, Ar**H**), 7.07-7.01 (2H, m, Ar**H**), 6.98 (1H, d, J = 7.5 Hz, Ar**H**), 6.68-6.62 (1H, m, Ar**H**), 6.35 (1H, d, J = 15.8 Hz, =C**H**Ph), 6.34 (1H, d, J = 9.8 Hz, =C**H**C=O), 5.48 (1H, dd, J = 15.8, 9.1 Hz, C**H**=CHPh), 3.70-3.60 (1H, m, CH_2C**H**), 3.28 (1H, dd, J = 15.8, 7.8 Hz, CHC**H**$_2$), 3.15 (1H, dd, J = 15.8, 10.2 Hz, CHC**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.1 (C), 145.8 (CH), 144.8 (C), 144.0 (C), 141.7 (C), 136.8 (C), 132.4 (CH), 130.1 (C), 129.5 (CH), 129.4 (CH), 128.4 (2 × CH), 128.3 (C), 128.0 (CH), 127.70 (CH), 127.65 (CH), 127.3 (CH), 127.2 (CH), 126.1 (2 × CH), 125.8 (CH), 125.6 (CH), 124.3 (CH), 70.3 (C), 59.8 (CH), 37.6 (CH_2); HRMS (ESI) Exact mass calcd for $C_{26}H_{20}ONa$ $[M+Na]^+$: 371.1406, found: 371.1399.

The title compound was prepared according to General Procedure D from 1-*p*-tolyl-2-naphthol **259b** (117 mg, 0.50 mmol), affording the *spiroindane* **277a** (96 mg, 53%) as an off-white solid followed by the *spiroindane* **277b** (27 mg, 15%) as an amorphous pale yellow solid.



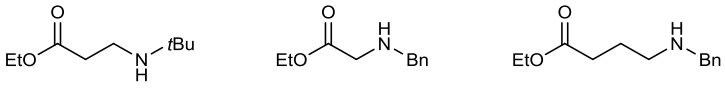
(±)-(1*S*,2*R*)-2-[(*E*)-2-*p*-tolylethenyl]-2,3-dihydro-2'*H*-spiro[indene-1,1'-naphthalene]-2'-one (277a). R_f = 0.40 (10% acetone/petrol); m.p. 117-119 °C (EtOAc/petrol); IR 2905, 1700 (C=O), 1652, 1617, 1565, 1492, 1448, 1396, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, J = 9.8 Hz, Ar**H** and C**H**=CHC=O), 7.40-7.36 (1H, m, Ar**H**), 7.35-7.31 (2H, m, Ar**H**), 7.30-7.17 (7H, m, Ar**H**), 7.01 (1H, d, J = 7.7 Hz, Ar**H**), 6.67 (1H, d, J = 7.7 Hz, Ar**H**), 6.21-6.08 (3H, m, C**H**=CHC=O & C**H**=C**H**Ph), 3.56-3.37 (2H, m, ArC**H**$_2$C**H**), 3.09 (1H, dd, J = 14.5, 6.8 Hz, ArC**H**$_2$CH), 2.41 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.6 (C), 145.5 (C), 145.3 (CH), 143.0 (C), 137.6 (C), 136.9 (C), 131.3 (CH), 130.9 (C), 130.0 (CH), 128.8 (CH), 128.7 (CH), 128.4 (2 × CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 126.3 (2 × CH), 125.21 (CH), 125.20 (CH), 124.6 (CH), 69.1 (CH), 64.5 (C), 36.2 (CH_2), 21.4 (CH_3). HRMS (ESI) Exact mass calcd for $C_{27}H_{23}O$ $[M+H]^+$: 363.1743, found: 363.1741.



(±)-(1*S*,2*S*)-2-[(*E*)-2-*p*-tolylethenyl]-2,3-dihydro-2'*H*-spiro[indene-1,1'-naphthalene]-2'-one (277b). R_f = 0.40 (10% acetone/petrol); IR 2924, 1700 (C=O), 1659, 1617, 1563, 1493, 1448, 1395, 1240, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 9.8 Hz, C**H**=CHCO), 7.34 (1H, dd, *J* = 7.3, 1.7 Hz, Ar**H**), 7.31 (1H, dd, *J* = 7.2, 1.4 Hz, Ar**H**), 7.29-7.15 (5H, m, Ar**H**), 7.10 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.04-6.99 (2H, m, Ar**H**), 6.85 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.68-6.63 (1H, m, Ar**H**), 6.35-6.28 (2H, m, CH=C**H**Ph and =C**H**C=O), 5.45 (1H, dd, *J* = 15.7, 9.2 Hz, C**H**=CHPh), 3.67-3.56 (1H, m, $ArCH_2C$**H**), 3.22 (1H, dd, *J* = 15.8, 7.8 Hz, ArC**H**$_2CH$), 3.10 (1H, dd, *J* = 15.8, 10.2 Hz, ArC**H**$_2CH$), 2.42 (3H, s, ArC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.4 (C=O), 145.8 (CH), 144.1 (C), 142.0 (C), 141.8 (C), 137.8 (C), 136.9 (C), 132.3 (CH), 130.1 (C), 129.5 (CH), 129.4 (CH), 128.6 (CH), 128.4 (CH), 128.6 (CH), 128.4 (2 × CH), 128.3 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 126.1(2 × CH), 125.7 (CH), 125.5 (CH), 124.9 (CH), 70.0 (C), 60.0 (CH), 37.5 (CH_2), 21.4 (CH_3). HRMS (ESI) Exact mass calcd for $C_{27}H_{23}O$ $[M+H]^+$: 363.1743, found: 363.1734.

5.5. Enantioselective Spiroindene Formation *via* C–H Functionalization Using Chiral Cyclopentadienyl Rhodium Catalysts

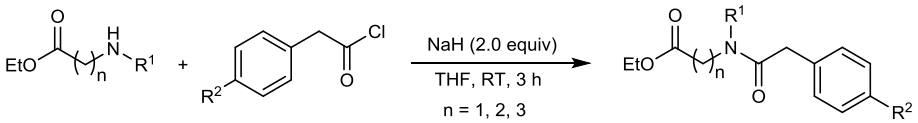
5.5.1. Preparation of aminoester derivatives



311a **311b** **311c**

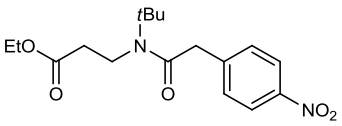
The substrates **311a**,[186] **311b**,[187] **311c**,[188] were synthesized according to the literature reported procedures.

5.5.2. Preparation of Amide Intermediates: General Procedure A



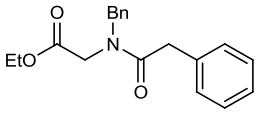
311 **312** **313**

To a suspension of NaH (60% in mineral oil, 2.0 equiv) in THF (50 mL) at 0 °C was added a solution of **311** (1.0 equiv) in THF (25 mL), and the mixture was stirred for 30 min. To this mixture was added appropriate phenylacetyl chloride (1.0 equiv) slowly and the mixture was stirred at room temperature for 3 h. The reaction was quenched carefully with HCl (10%) and the aqueous layer was separated and washed with DCM (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the corresponding amide **313**.



Ethyl 3-[*N*-*tert*-butyl-2-(4-nitrophenyl)acetamido]propanoate (313a). The title compound was prepared according to General Procedure A from **311a** (5.19 g, 30.0 mmol) and 4-nitrophenylacetyl chloride (5.97 g, 30.0 mmol), and NaH (2.30 g, 60.0 mmol) and purified by column chromatography (10% acetone/petrol) to give a yellow viscous liquid (6.25 g, 62%). R_f = 0.44 (30% acetone/petrol); IR 1730 (C=O), 1643 (C=O), 1606, 1510, 1397, 1343, 1211, 1225, 1053, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21-8.16 (2H, m, Ar**H**), 7.44-7.42 (2H, m, Ar**H**), 4.17 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 3.83 (2H, s, C**H**$_2$C=O), 3.68-3.61

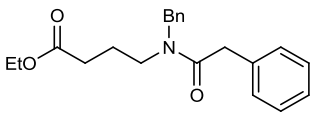
(2H, m, *N*C**H**$_2$CH$_2$), 2.60-2.54 (2H, m, CH$_2$C**H**$_2$C=O), 1.45 (9H, s, C(C**H**$_3$)$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.7 (C), 170.1 (C), 146.9 (C), 143.3 (C), 130.0 (2 × CH), 123.7 (2 × CH), 61.0 (CH$_2$), 57.7 (C), 43.1 (CH$_2$), 41.2 (CH$_2$), 36.7 (CH$_2$), 28.8 (3 × CH$_3$), 14.1 (CH$_3$); HRMS (ESI) Exact mass calcd for $C_{17}H_{24}N_2O_5Na$ [M+Na]$^+$: 359.1577, found: 359.1579.



Ethyl 2-(*N*-benzyl-2-phenylacetamido)acetate (313b). The title compound was prepared according to General Procedure A from **311b** (5.02 g, 26.0 mmol) and phenylacetyl chloride (3.44 mL, 26.0 mmol), and NaH (1.99 g, 52.0 mmol) and purified by column chromatography (10% acetone/petrol) to give a mixture of rotamers as a colorless viscous liquid (5.50 g, 68%). R_f = 0.53 (30% acetone/petrol); IR 1744 (C=O), 1651 (C=O), 1602, 1496, 1374, 1196, 1028, 732 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{19}H_{21}NO_3Na$ [M+Na]$^+$: 334.1414, found: 334.1414.

Major rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.20 (8H, m, Ar**H**), 7.11 (2H, d, *J* = 6.6 Hz, Ar**H**), 4.62 (2H, s, *N*C**H**$_2$Ph), 4.19 (2H, q, *J* = 7.2 Hz, OC**H**$_2$CH$_3$), 4.07 (2H, s, C**H**$_2$Ph), 3.85 (2H, s, *N*C**H**$_2$C=O), 1.29-1.19 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 171.8 (C), 169.1 (C), 135.8 (C), 134.5 (C), 128.9 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 127.8 (CH), 126.8 (CH), 126.7 (2 × CH), 61.1 (CH$_2$), 52.4 (CH$_2$), 47.1 (CH$_2$), 40.5 (CH$_2$), 14.0 (CH$_3$).

Minor rotamer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.20 (10H, m, Ar**H**), 4.70 (2H, s, *N*C**H**$_2$Ph), 4.12 (2H, q, *J* = 7.2 Hz, OC**H**$_2$CH$_3$), 3.93 (2H, s, C**H**$_2$Ph), 3.75 (2H, s, *N*C**H**$_2$C=O), 1.29-1.19 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 171.4 (C), 168.9 (C), 136.6 (C), 134.4 (C), 128.8 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.5 (CH), 126.9 (CH), 109.9 (CH), 61.5 (CH$_2$), 49.7 (CH$_2$), 48.6 (CH$_2$), 41.0 (CH$_2$), 14.0 (CH$_3$).



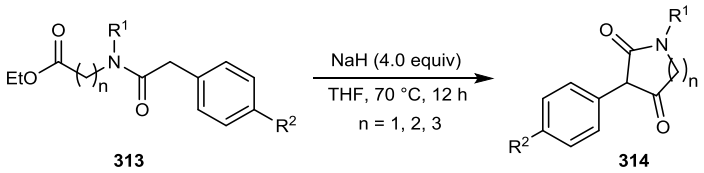
Ethyl 4-(*N*-benzyl-2-phenylacetamido)butanoate (313c). The title compound was prepared according to General Procedure A from **311c** (5.52 g, 25.0 mmol) and phenylacetyl chloride (3.30 mL, 25.0 mmol), and NaH (1.92 g, 50.0 mmol) and purified by column chromatography (8% acetone/petrol) to give a mixture of rotamers

as a colorless viscous liquid (4.60 g, 54%). R_f = 0.50 (30% acetone/petrol); IR 1728 (C=O), 1644 (C=O), 1601, 1496, 1453, 1373, 1150, 1030, 731 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{21}H_{25}NO_3Na$ $[M+Na]^+$: 362.1727, found: 362.1729.

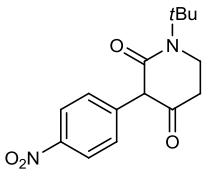
Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.20 (8H, m, Ar**H**), 7.14 (2H, d, J = 6.9 Hz, Ar**H**), 4.55 (2H, s, *N*C**H**$_2$Ph), 4.20-4.08 (2H, m, OC**H**$_2$CH$_3$), 3.74 (2H, s, C**H**$_2$Ph), 3.48-3.40 (2H, m, *N*C**H**$_2$CH$_2$), 2.31 (2H, t, J = 7.4 Hz, CH$_2$C**H**$_2$CO), 1.94-1.86 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.30-1.22 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C), 171.8 (C), 137.1 (C), 134.8 (C), 129.1 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 127.7 (CH), 126.7 (CH), 126.1 (2 × CH), 60.4 (CH$_2$), 51.1 (CH$_2$), 46.2 (CH$_2$), 40.7 (CH$_2$), 31.2 (CH$_2$), 22.3 (CH$_2$), 13.9 (CH$_3$).

Minor rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.20 (10H, m, Ar**H**), 4.66 (2H, s, *N*C**H**$_2$Ph), 4.20-4.08 (2H, m, OC**H**$_2$CH$_3$), 3.86 (2H, s, C**H**$_2$Ph), 3.29-3.22 (2H, m, *N*C**H**$_2$CH$_2$), 2.25 (2H, t, J = 6.9 Hz, CH$_2$C**H**$_2$CO), 1.86-1.78 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.30-1.22 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 171.4 (C), 134.8 (C), 133.8 (C), 128.7 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 127.4 (CH), 127.1 (CH), 126.6 (2 × CH), 60.1 (CH$_2$), 47.9 (CH$_2$), 45.2 (CH$_2$), 40.3 (CH$_2$), 30.4 (CH$_2$), 23.1 (CH$_2$), 13.9 (CH$_3$).

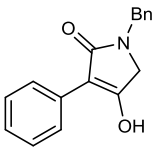
5.5.3. Preparation of 2-Aryl 1,3-dicarbonyl Substrates: General Procedure B



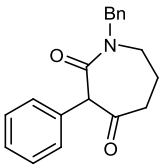
To a suspension of NaH (60% in mineral oil, 4.0 equiv) in THF (20 mL) at 0 °C was added a solution of **313** (1.0 equiv) in THF (10 mL), and the mixture was stirred for 10 min and then heated at 70 °C for 12 h. The reaction was quenched carefully with HCl (10%) and the aqueous layer was separated and washed with DCM (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the corresponding 1,3-dicarbonyl compound **314**.



1-*tert*-Butyl-3-(4-nitrophenyl)piperidine-2,4-dione (314a). The title compound was prepared according to General Procedure B from **313a** (2.60 g, 7.7 mmol) and NaH (1.19 g, 31.0 mmol) and purified by column chromatography (10% acetone/petrol) to give a yellow solid (1.15 g, 51%). R_f = 0.43 (30% acetone/petrol); m.p. 159-160 °C; IR 1719 (C=O), 1648 (C=O), 1522, 1412, 1346, 1298, 1010, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.20 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 4.74 (1H, s, C**H**C=O), 3.89-3.70 (2H, m, *N*C**H**$_2$CH$_2$), 2.81-2.58 (2H, m, CH$_2$C**H**$_2$C=O), 1.51 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.6 (C), 166.0 (C), 147.4 (C), 139.7 (C), 131.1 (2 × CH), 123.4 (2 × CH), 66.4 (CH), 58.7 (C), 39.2 (CH$_2$), 38.6 (CH$_2$), 28.7 (3 × CH$_3$); HRMS (ESI) Exact mass calcd for $C_{15}H_{19}N_2O_4$ $[M+H]^+$: 291.1339, found: 291.1338.



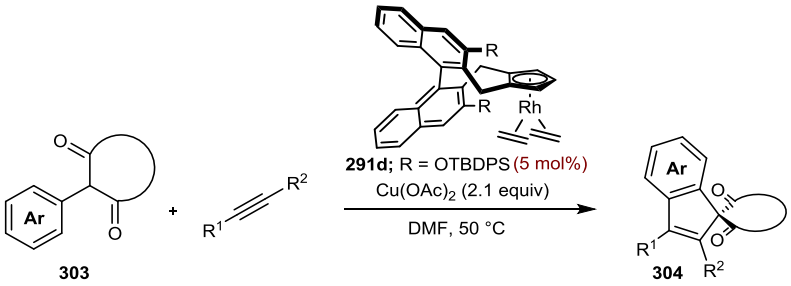
1-Benzyl-3-phenylpyrrolidine-2,4-dione (314b). The title compound was prepared according to General Procedure B from **313b** (2.80 g, 9.0 mmol) and NaH (1.38 g, 36.0 mmol) and purified by column chromatography (10% acetone/petrol) to give a white solid (1.93 g, 81%). R_f = 0.23 (30% acetone/petrol); m.p. 205-206 °C; IR 1665 (C=O), 1579 (C=O), 1450, 1385, 1313, 1218, 974, 782 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.02 (2H, d, J = 7.4 Hz, Ar**H**), 7.40-7.30 (4H, m, Ar**H**), 7.29-7.20 (3H, m, Ar**H**), 7.17 (1H, t, J = 7.4 Hz, Ar**H**), 4.56 (2H, s, *N*C**H**$_2$Ph), 3.85 (2H, s, *N*C**H**$_2$C=O); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.0 (C), 167.0 (C), 138.1 (C), 132.3 (C), 128.6 (2 × CH), 127.7 (2 × CH), 127.5 (2 × CH), 127.1 (CH), 126.7 (2 × CH), 125.6 (C), 102.8 (CH), 48.7 (CH$_2$), 44.5 (CH$_2$); HRMS (ESI) Exact mass calcd for $C_{17}H_{15}NO_2Na$ $[M+Na]^+$: 288.0995, found: 288.0995.



1-Benzyl-3-phenylazepane-2,4-dione (314c). The title compound was prepared according to General Procedure B from **313c** (2.37 g, 7.0 mmol) and NaH (1.25 g, 28.0 mmol) and purified by column chromatography (10% acetone/petrol) to give an off-white solid (1.40 g, 68%). R_f = 0.48 (30% acetone/petrol); m.p. 142-143 °C; IR 1718, 1636 (C=O), 1605, 1478, 1249, 951, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.50-7.15 (10H, m, Ar**H**), 5.62 (1H, s, C**H**C=O), 4.70 (1H, d, J = 14.6 Hz, *N*C**H**$_2$Ph), 4.50 (1H, d, J = 14.6 Hz, *N*C**H**$_2$Ph), 4.32-4.04 (1H, m, *N*C**H**$_2$CH$_2$), 3.43 (1H, d, J = 15.0 Hz,

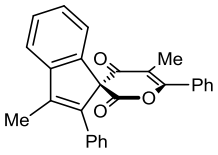
*N*C**H**$_2$CH$_2$), 2.86 (1H, dd, *J* = 17.9, 10.5 Hz, CH$_2$C**H**$_2$C=O), 2.03 (1H, br s, CH$_2$C**H**$_2$C=O), 1.76 (1H, br s, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (100.6 MHz, DMSO-d$_6$) δ 204.1 (C), 166.9 (C), 138.0 (C), 134.4 (C), 130.9 (2 × CH), 128.5 (2 × CH), 127.9 (2 × CH), 127.3 (CH), 127.2 (2 × CH), 126.9 (CH), 62.2 (CH), 50.5 (CH$_2$), 46.2 (CH$_2$), 43.0 (CH$_2$), 27.1 (CH$_2$); HRMS (ESI) Exact mass calcd for $C_{19}H_{19}NO_2Na$ $[M+Na]^+$: 316.1308, found: 316.1298.

5.5.4. Asymmetric Cp^{x}Rh-Catalyzed Oxidative Annulation Reactions: General Procedure C



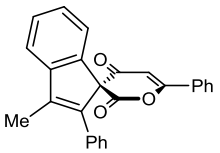
303 304

To a mixture of the appropriate 2-aryl-1,3-dicarbonyl compound (0.20 mmol), Cu(OAc)$_2$ (76.0 mg, 0.42 mmol), and Cp^{x}Rh **291d** (10.1 mg, 0.010 mmol) in DMF (1.5 mL) was added the appropriate alkyne (0.30 mmol) in DMF (0.5 mL), and the resulting mixture was stirred at 50 °C. The reaction mixture was quenched with brine (20 mL), extracted with EtOAc (20 mL) and dried (MgSO$_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give the spiroindene.

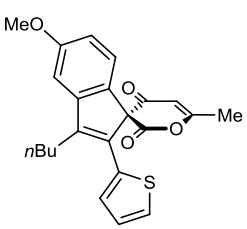


(*S*)-3,5'-Dimethyl-2,6'-diphenyl-2',4'-dihydrospiro[indene-1,3'-pyran]-2',4'-dione (304b). The title compound was prepared according to General Procedure C from dione **303e** (55.6 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give a light yellow amorphous solid (73.4 mg, 94%). R_f = 0.44 (30% acetone/petrol); $[\alpha]_D^{20}$ +5.8 (*c* 1.50, CHCl$_3$); m.p. 158-159 °C (acetone/petrol); IR 1774 (C=O), 1673 (C=O), 1626, 1493, 1343, 1099, 1010, 751 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66-7.61 (2H, m, Ar**H**), 7.55-7.48 (3H, m, Ar**H**), 7.46-7.43 (2H, m, Ar**H**), 7.42-7.31 (6H, m, Ar**H**), 7.26 (1H, ddd, *J* = 7.6, 5.7, 3.2 Hz, Ar**H**), 2.26 (3H, s, CC**H**$_3$), 2.00 (3H, s, =CC**H**$_3$); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 190.4 (C), 166.3 (C), 161.7 (C), 146.3 (C), 141.7 (C), 141.2 (C), 139.9 (C), 134.5 (C), 131.5 (C), 131.1 (CH), 129.3 (2 × CH), 129.2 (CH), 128.8 (2 × CH), 128.4 (4 × CH), 127.8 (CH), 126.5 (CH), 121.2 (CH), 121.0 (CH), 113.6 (C), 77.3 (C), 11.9 (CH_3), 11.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{20}O_3Na$ $[M+Na]^+$: 415.1305, found: 415.1313. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 *i*-hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 20.3 min, t_r (major) = 25.3 min; 95% ee.

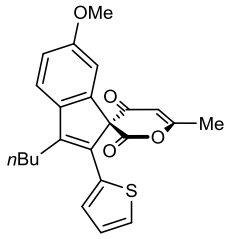


(*S*)-3-Methyl-2,6'-diphenyl-2',4'-dihydrospiro[indene-1,3'-pyran]-2',4'-dione (304c). The title compound was prepared according to General Procedure C from dione **303f** (52.8 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give a light yellow amorphous solid (56.0 mg, 74%). R_f = 0.39 (30% acetone/petrol); $[\alpha]_D^{20}$ +9.3 (*c* 1.00, $CHCl_3$); m.p. 186-187 °C (acetone/petrol); IR 1774 (C=O), 1676 (C=O), 1621, 1597, 1466, 1331, 1245, 1092, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.91 (2H, m, Ar**H**), 7.62 (1H, ddd, *J* = 7.3, 3.7, 1.1 Hz, Ar**H**), 7.58-7.51 (2H, m, Ar**H**), 7.45-7.35 (6H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 7.24-7.17 (1H, m, Ar**H**), 6.56 (1H, s, C**H**C=O), 2.32 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 189.4 (C), 166.1 (C), 164.8 (C), 146.3 (C), 142.0 (C), 141.4 (C), 139.7 (C), 134.4 (C), 133.0 (CH), 129.7 (C), 129.3 (CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.5 (2 × CH), 127.8 (CH), 126.8 (2 × CH), 126.4 (CH), 121.1 (CH), 120.9 (CH), 103.4 (CH), 75.0 (C), 12.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{18}O_3Na$ $[M+Na]^+$: 401.1148, found: 401.1150. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (98:2 *i*-hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 40.0 min, t_r (major) = 47.7 min; 94% ee.



(*S*)-3-Butyl-5-methoxy-6'-methyl-2-(thiophen-2-yl)-2',4'-dihydrospiro[indene-1,3'-pyran]-2',4'-dione (304d). The title compound was prepared according to General Procedure C from dione **303b** (46.4 mg, 0.20 mmol) and alkyne **156j** (49.2 mg, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give a light brown solid (67.0 mg, 85%). R_f = 0.45 (30% acetone/petrol); $[\alpha]_D^{20}$ +10.9 (*c* 1.20, $CHCl_3$); m.p. 184-185 °C (acetone/petrol); IR

1778 (C=O), 1672 (C=O), 1645, 1596, 1479, 1328, 1257, 1130, 989, 857, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, J = 5.1, 1.1 Hz, Ar**H**), 7.15 (1H, d, J = 8.3 Hz, Ar**H**), 7.02 (1H, dd, J = 5.1, 3.7 Hz, Ar**H**), 6.93 (1H, d, J = 2.4 Hz, Ar**H**), 6.81 (1H, dd, J = 3.7, 1.1 Hz, Ar**H**), 6.70 (1H, dd, J = 8.3, 2.4 Hz, Ar**H**), 5.92 (1H, q, J = 0.8 Hz, Ar**H**), 3.84 (3H, s, OC**H**$_3$), 2.93-2.84 (2H, m, C**H**$_2$CH$_2$ CH$_2$CH$_3$), 2.37 (3H, d, J = 0.8 Hz, =CC**H**$_3$), 1.79-1.67 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.59-1.49 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.99 (3H, t, J = 7.3 Hz, CH$_2$ CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 188.6 (C), 168.2 (C), 166.2 (C), 161.1 (C), 147.2 (C), 145.6 (C), 136.2 (C), 134.0 (C), 132.9 (C), 127.1 (CH), 126.4 (CH), 126.0 (CH), 121.5 (CH), 111.1 (CH), 107.7 (CH), 106.8 (CH), 73.5 (C), 55.6 (CH_3), 30.2 (CH_2), 26.5 (CH_2), 23.0 (CH_2), 20.6 (CH_3), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{22}O_4SNa$ $[M+Na]^+$: 417.1131, found: 417.1129. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *i*-hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 10.3 min, t_r (major) = 10.9 min; 95% ee.

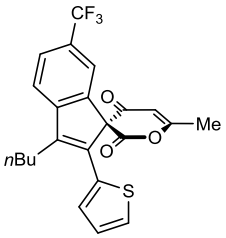


(*S*)-3-Butyl-6-methoxy-6'-methyl-2-(thiophen-2-yl)-2',4'-dihydrospiro[indene-1,3'-pyran]-2',4'-dione (304e). The title compound was prepared according to General Procedure C from dione **303c** (46.4 mg, 0.20 mmol) and alkyne **156j** (49.2 mg, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give a light brown solid (67.0 mg, 85%). R_f = 0.45 (30% acetone/petrol); $[\alpha]_D^{20}$ +11.5 (*c* 2.40, $CHCl_3$); m.p. 184-185 °C (acetone/petrol); IR 1778 (C=O), 1677 (C=O), 1649, 1604, 1482, 1384, 1324, 1222, 985, 817 cm^{-1}; HRMS (ESI) Exact mass calcd for $C_{23}H_{22}O_4SNa$ $[M+Na]^+$: 417.1131, found: 417.1129.

Major regioisomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, Ar**H**), 7.04-6.98 (1H, m, Ar**H**), 6.94-6.80 (2H, m, Ar**H**), 6.78 (1H, dd, J = 3.7, 1.1 Hz, Ar**H**), 5.92 (1H, q, J = 0.8 Hz, =CC**H**), 3.81 (3H, s, OC**H**$_3$), 2.95-2.80 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.36 (3H, d, J = 0.8 Hz, =CC**H**$_3$), 1.79-1.67 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.60-1.47 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.99 (3H, t, J = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 188.5 (C), 168.3 (C), 166.0 (C), 158.7 (C), 145.9 (C), 142.4 (C), 138.3 (C), 136.4 (C), 130.9 (C), 127.1 (CH), 125.9 (CH), 125.5 (CH), 121.8 (CH), 113.2 (CH), 109.1 (CH), 106.9 (CH), 73.9 (C), 55.7 (CH_3), 30.3 (CH_2), 26.6

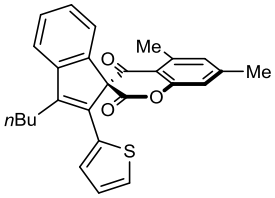
(CH_2), 23.0 (CH_2), 20.6 (CH_3), 14.0 (CH_3). Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (85:15 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 24.0 min, t_r (major) = 27.4 min; 94% ee.

Minor regioisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (1H, m, Ar**H**), 7.15 (1H, dd, *J* = 8.3, 7.6 Hz, Ar**H**), 7.04-6.98 (1H, m, Ar**H**), 6.94-6.80 (3H, m, Ar**H**), 5.91 (1H, d, *J* = 0.8 Hz, =CC**H**), 3.88 (3H, s, OC**H**$_3$), 3.08-2.97 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.34 (3H, d, *J* = 0.8 Hz, =CC**H**$_3$), 1.79-1.67 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.60-1.47 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.99 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 188.4 (C), 168.2 (C), 166.1 (C), 155.1 (C), 147.9 (C), 142.7 (C), 136.3 (C), 132.8 (C), 131.1 (C), 127.8 (CH), 127.0 (CH), 126.3 (CH), 125.6 (CH), 113.6 (CH), 112.4 (CH), 107.0 (CH), 74.3 (C), 55.4 (CH_3), 31.1 (CH_2), 28.5 (CH_2), 22.9 (CH_2), 20.6 (CH_3), 13.9 (CH_3). Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (85:15 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 13.7 min, t_r (minor) = 17.5 min; 96% ee.

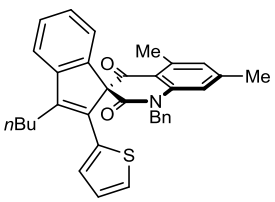


(*S*)-3-Butyl-6'-methyl-2-(thiophen-2-yl)-6-(trifluoromethyl)-2',4'-dihydrospiro[indene-1,3'-pyran]-2',4'-dione (304f). The title compound was prepared according to General Procedure C from dione **303d** (54.0 mg, 0.20 mmol) and alkyne **156j** (49.2 mg, 0.30 mmol), and purified by column chromatography (7% acetone/petrol) to give a light brown solid (58.0 mg, 67%). R_f = 0.54 (30% acetone/petrol); $[\alpha]_D^{20}$ +4.0 (*c* 1.30, $CHCl_3$); m.p. 177-178 °C (acetone/petrol); IR 1776 (C=O), 1677 (C=O), 1649, 1463, 1322, 1281, 1123, 987, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.65 (1H, m, Ar**H**), 7.49 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.43-7.40 (1H, m, Ar**H**), 7.38 (1H, dd, *J* = 5.1, 1.0 Hz, Ar**H**), 7.07-7.02 (1H, m, Ar**H**), 6.86 (1H, dd, *J* = 3.7, 1.1 Hz, Ar**H**), 5.99 (1H, q, *J* = 0.8 Hz, =CC**H**), 3.00-2.85 (2H, m, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.43 (3H, d, *J* = 0.8 Hz, =CC**H**$_3$), 1.79-1.66 (2H, m, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.61-1.47 (2H, m, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.99 (3H, t, *J* = 7.3 Hz, CH$_2$ CH$_2$CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 187.5 (C), 168.8 (C), 165.3 (C), 149.3 (C), 144.9 (C), 141.1 (C), 136.0 (C), 135.5 (C), 128.3 (C, q, *J* = 32.7 Hz), 127.4 (CH), 127.1 (CH), 127.0 (CH, q, *J* = 3.8 Hz), 126.9 (CH), 124.0 (C, q, *J* = 272.0 Hz), 121.2 (CH), 117.7 (CH, q, *J* = 3.8 Hz), 106.9 (CH), 73.8 (C), 30.1 (CH_2), 26.5 (CH_2),

22.9 (CH_2), 20.8 (CH_3), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.8 (3F, s, CF_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{19}F_3O_3NaS$ $[M+Na]^+$: 455.0899, found: 455.0913. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 *i*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 14.6 min, t_r (major) = 23.5 min; 96% ee.

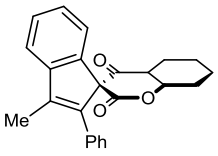


(*S*)-3'-Butyl-5,7-dimethyl-2'-(thiophen-2-yl)-2,4-dihydrospiro[1-benzopyran-3,1'-indene]-2,4-dione (304g). The title compound was prepared according to General Procedure C from dione **303h** (53.2 mg, 0.20 mmol) and alkyne **156j** (49.2 mg, 0.30 mmol), and purified by column chromatography (7% acetone/petrol) to give a yellow solid (57.0 mg, 66%). R_f = 0.53 (30% acetone/petrol); $[\alpha]_D^{20}$ +1.7 (*c* 1.40, $CHCl_3$); m.p. 150-151 °C (acetone/petrol); IR 1765 (C=O), 1683 (C=O), 1618, 1569, 1455, 1266, 1186, 1067, 761, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (1H, m, Ar**H**), 7.36 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.31 (1H, dd, *J* = 2.1, 1.1 Hz, Ar**H**), 7.10-7.03 (2H, m, Ar**H**), 7.00 (1H, dd, *J* = 5.1, 3.7 Hz, Ar**H**), 6.99-6.92 (2H, m, Ar**H**), 6.85 (1H, dd, *J* = 3.7, 1.0 Hz, Ar**H**), 3.02-2.89 (2H, m, C**H**$_2$$CH_2CH_2CH_3$), 2.54 (3H, s, ArC**H**$_3$), 2.48 (3H, s, ArC**H**$_3$), 1.84-1.72 (2H, m, CH_2C**H**$_2$$CH_2CH_3$), 1.64-1.51 (2H, m, CH_2CH_2C**H**$_2$$CH_3$), 1.01 (3H, t, *J* = 7.3 Hz, $CH_2CH_2CH_2$C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 187.7 (C), 165.5 (C), 156.1 (C), 147.8 (C), 145.6 (C), 145.3 (C), 143.1 (C), 140.6 (C), 136.6 (C), 133.4 (C), 129.5 (CH), 129.3 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 125.8 (CH), 121.2 (CH), 121.1 (CH), 116.0 (CH), 115.4 (C), 75.6 (C), 30.3 (CH_2), 26.6 (CH_2), 23.1 (CH_2), 21.93 (CH_3), 21.91 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{27}H_{24}O_3SNa$ $[M+Na]^+$: 451.1338, found: 451.1340. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 *i*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 11.4 min, t_r (major) = 22.7 min; 81% ee.



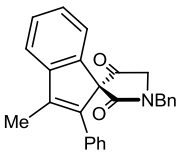
(*S*)-1'-Benzyl-3-butyl-5',7'-dimethyl-2-(thiophen-2-yl)-2',4'-dihydro-1'*H*-spiro[indene-1,3'-quinoline]-2',4'-dione (303h). The title compound was prepared according to General Procedure C from dione **303i** (71.0 mg, 0.20 mmol) and alkyne **156j** (49.2 mg, 0.30 mmol), and purified by column chromatography (6%

acetone/petrol) to give a yellow amorphous solid (87.0 mg, 84%). R_f = 0.35 (20% acetone/petrol); $[\alpha]_D^{20}$ +0.7 (*c* 1.30, $CHCl_3$); m.p. 137-138 °C (acetone/petrol); IR 1763 (C=O), 1661 (C=O), 1621, 1572, 1454, 1317, 1264, 1189, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.35 (1H, dd, *J* = 7.5, 1.0 Hz, Ar**H**), 7.34-7.31 (2H, m, Ar**H**), 7.30 (1H, s, Ar**H**), 7.29-7.23 (3H, m, Ar**H**), 7.07-7.03 (1H, m, Ar**H**), 7.03-7.00 (1H, m, Ar**H**), 6.99 (1H, s, Ar**H**), 6.94 (1H, d, *J* = 7.4 Hz, Ar**H**), 6.91 (1H, dd, *J* = 3.7, 1.0 Hz, Ar**H**), 6.83 (1H, br s, Ar**H**), 5.51 (1H, d, *J* = 15.9 Hz, *N*C**H**$_2$Ph), 5.16 (1H, d, *J* = 15.9 Hz, *N*C**H**$_2$Ph), 3.08-2.93 (2H, m, $CH_2C\mathbf{H}_2CH_2CH_3$), 2.50 (3H, s, ArC**H**$_3$), 2.34 (3H, s, ArC**H**$_3$), 1.88-1.76 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.68-1.54 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.03 (3H, t, *J* = 7.3 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 191.0 (C), 168.4 (C), 146.0 (C), 145.6 (C), 144.3 (C), 143.9 (C), 143.3 (C), 141.7 (C), 137.5 (C), 136.4 (C), 134.9 (C), 128.8 (3 × CH), 128.1 (CH), 127.3 (CH), 126.9 (CH), 126.65 (2 × CH), 126.64 (CH), 125.7 (CH), 125.4 (CH), 121.1 (CH), 120.9 (CH), 118.2 (C), 114.8 (CH), 77.2 (C), 47.1 (CH_2), 30.4 (CH_2), 26.6 (CH_2), 23.1 (CH_2), 22.6 (CH_3), 22.2 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{34}H_{31}NO_2NaS$ $[M+Na]^+$: 540.1968, found: 540.1960. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 *i*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 18.9 min, t_r (minor) = 24.4 min; 68% ee.

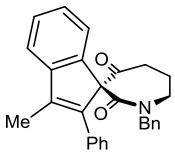


(*S*)-3'-Methyl-2'-phenyl-2,4,5,6,7,8-hexahydrospiro[1-benzopyran-3,1'-indene]-2,4-dione (304i). The title compound was prepared according to General Procedure C from dione **303g** (48.4 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (7% acetone/petrol) to give an off-white amorphous solid (58.0 mg, 82%). R_f = 0.56 (30% acetone/petrol); $[\alpha]_D^{20}$ +3.5 (*c* 1.00, $CHCl_3$); m.p. 199-200 °C (acetone/petrol); IR 1770 (C=O), 1674 (C=O), 1641, 1379, 1259, 1127, 1035, 945, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.36 (4H, m, Ar**H**), 7.35-7.29 (3H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 2.54 (1H, dt, *J* = 12.4, 5.5 Hz, $CH_2C\mathbf{H}_2$), 2.44-7.25 (3H, m, $CH_2C\mathbf{H}_2C\mathbf{H}_2$), 7.22 (3H, s, CC**H**$_3$), 1.92-1.58 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 188.9 (C), 166.6 (C), 165.5 (C), 146.3 (C), 141.5 (C), 141.3 (C), 139.9 (C), 134.5 (C), 129.2 (2 × CH), 129.1 (CH), 128.4 (2 × CH), 127.8 (CH), 126.4 (CH), 121.1 (CH), 120.98 (CH), 114.9 (C), 75.5 (C), 27.6 (CH_2), 21.7 (CH_2),

21.3 (CH_2), 20.9 (CH_2), 11.9 (CH_3). HRMS (ESI) Exact mass calcd for $C_{24}H_{20}O_3Na$ $[M+Na]^+$: 379.1305, found: 379.1308. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99:1 *i*-hexane:EtOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 16.3 min, t_r (minor) = 18.4 min; 94% ee.

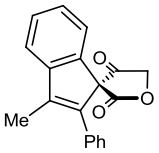


(*S*)-1'-Benzyl-3-methyl-2-phenylspiro[indene-1,3'-pyrrolidine]-2',4'-dione (304j). The title compound was prepared according to General Procedure C from dione **314b** (53.0 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give an off-white solid (60.6 mg, 80%). R_f = 0.45 (30% acetone/petrol); $[\alpha]_D^{20}$ –7.5 (*c* 1.70, $CHCl_3$); m.p. 154-155 °C (acetone/petrol); IR 1753 (C=O), 1689 (C=O), 1470, 1255, 1049, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (2H, m, Ar**H**), 7.38-7.30 (6H, m, Ar**H**), 7.30-7.25 (2H, m, Ar**H**), 7.22 (1H, ddd, *J* = 7.5, 4.9, 3.7 Hz, Ar**H**), 7.15-7.07 (3H, m, Ar**H**), 4.87 (1H, d, *J* = 14.6 Hz, *N*C**H**$_2$Ph), 4.61 (1H, d, *J* = 14.6 Hz, *N*C**H**$_2$Ph), 3.95 (1H, d, *J* = 17.8 Hz, *N*C**H**$_2$C=O), 3.64 (1H, d, *J* = 17.8 Hz, *N*C**H**$_2$C=O), 2.21 (s, 3H, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 205.2 (C), 170.6 (C), 147.1 (C), 141.9 (C), 141.8 (C), 139.1 (C), 134.8 (C), 134.5 (C), 128.9 (2 × CH), 128.8 (2 × CH), 128.6 (CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 127.9 (CH), 126.4 (CH), 121.2 (CH), 120.6 (CH), 72.3 (C), 55.9 (CH_2), 46.4 (CH_2), 11.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{21}NO_2Na$ $[M+Na]^+$: 402.1465, found: 402.1461. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 18.3 min, t_r (minor) = 27.0 min; 84% ee.

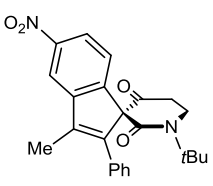


1-Benzyl-3'-methyl-2'-phenylspiro[azepane-3,1'-indene]-2,4-dione (304k). The title compound was prepared according to General Procedure C from dione **314c** (58.6 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give an off-white solid (59.4 mg, 73%). R_f = 0.51 (30% acetone/petrol); $[\alpha]_D^{20}$ –2.5 (*c* 1.30, $CHCl_3$); m.p. 178-179 °C (acetone/petrol); IR 1713 (C=O), 1627 (C=O), 1600, 1415, 1365, 1216, 1006, 934, 755, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.41-7.36 (2H, m, Ar**H**), 7.35-7.30 (5H, m, Ar**H**), 7.29-7.25 (2H, m, Ar**H**), 7.25-7.19 (4H, m, Ar**H**), 4.84 (1H, d, *J* = 14.2 Hz, *N*C**H**$_2$Ph),

4.52 (1H, d, *J* = 14.2 Hz, *N*C**H**$_2$Ph), 3.15 (1H, dt, *J* = 15.8, 4.9 Hz, *N*C**H**$_2$CH$_2$), 3.06-2.89 (2H, m, *N*C**H**$_2$CH$_2$ and C**H**$_2$C=O), 2.51 (ddd, 1H, *J* = 11.4, 8.3, 3.5 Hz, C**H**$_2$C=O), 2.00 (3H, s, CC**H**$_3$), 1.94-1.80 (1H, m, CH$_2$C**H**$_2$CH$_2$), 1.77-1.65 (1H, m, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 206.1 (C), 169.2 (C), 146.4 (C), 142.8 (C), 141.3 (C), 141.1 (C), 137.1 (C), 135.6 (C), 129.8 (2 × CH), 128.8 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 127.7 (CH), 127.7 (CH), 126.2 (CH), 122.2 (CH), 120.6 (CH), 80.2 (C), 51.6 (CH_2), 44.1 (CH_2), 38.3 (CH_2), 25.5 (CH_2), 11.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{28}H_{25}NO_2Na$ $[M+Na]^+$: 430.1778, found: 430.1773. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 *i*-hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 45.8 min, t_r (major) = 52.7 min; 94% ee.



(*S*)-3-Methyl-2-phenylspiro[indene-1,3'-oxolane]-2',4'-dione (304l). The title compound was prepared according to General Procedure C from dione **317** (35.2 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by column chromatography (10% acetone/petrol) to give an off-white amorphous solid (13.0 mg, 22%). R_f = 0.45 (30% acetone/petrol); $[\alpha]_D^{20}$ –9.8 (*c* 1.00, $CHCl_3$); m.p. 142-143 °C (acetone/petrol); IR 1753 (C=O), 1676 (C=O), 1621, 1598, 1470, 1330, 1255, 1049, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (2H, m, Ar**H**), 7.42-7.38 (2H, m, Ar**H**), 7.37-7.34 (1H, m, Ar**H**), 7.30-7.25 (3H, m, Ar**H**), 7.20 (1H, dt, *J* = 7.5, 0.9 Hz, Ar**H**), 4.90 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=O), 4.54 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=O), 2.21 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.3 (C), 172.3 (C), 146.9 (C), 143.0 (C), 140.3 (C), 137.8 (C), 133.6 (C), 129.3 (CH), 128.9 (2 × CH), 128.6 (2 × CH), 128.4 (CH), 126.9 (CH), 121.5 (CH), 121.0 (CH), 74.1 (CH_2), 68.7 (C), 11.7 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{14}O_3Na$ $[M+Na]^+$: 313.0835, found: 313.0822. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 *i*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 18.3 min, t_r (major) = 19.8 min; 90% ee.



(*S*)-1'-*tert*-Butyl-3-methyl-5-nitro-2-phenylspiro[indene-1,3'-piperidine]-2',4'-dione (304m). The title compound was prepared according to General Procedure C from dione **314a** (58.0 mg, 0.20 mmol) and alkyne **156a** (37.5 μL, 0.30 mmol), and purified by

column chromatography (10% acetone/petrol) to give a light yellow amorphous solid (64.5 mg, 80`%). R_f = 0.40 (30% acetone/petrol); $[\alpha]_D^{20}$ –9.4 (*c* 1.70, $CHCl_3$); m.p. 103-104 °C (acetone/petrol); IR 1731 (C=O), 1644 (C=O), 1522, 1463, 1339, 1196, 802, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, d, *J* = 1.7 Hz, Ar**H**), 8.12 (1H, dd, *J* = 8.1, 2.2 Hz, Ar**H**), 7.42-7.35 (3H, m, Ar**H**), 7.30-7.23 (3H, m, Ar**H**), 3.66 (1H, ddd, *J* = 12.7, 7.5, 4.9 Hz, *N*C**H**$_2$$CH_2$), 3.35 (1H, ddd, *J* = 13.0, 8.1, 4.7 Hz, *N*C**H**$_2$$CH_2$), 2.83 (1H, ddd, *J* = 15.0, 8.1, 4.9 Hz, *N*C**H**$_2$C=O), 2.65-2.54 (1H, m, CH_2C**H**$_2$C=O), 2.16 (3H, s, C**H**$_3$), 1.42 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.1 (C), 166.8 (C), 151.5 (C), 149.2 (C), 148.4 (C), 145.6 (C), 139.2 (C), 134.3 (C), 129.0 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 121.7 (CH), 121.5 (CH), 115.2 (CH), 78.1 (C), 59.1 (C), 41.3 (CH_2), 38.6 (CH_2), 28.0 (CH_3), 11.4 (CH_3). HRMS (ESI) Exact mass calcd for $C_{24}H_{24}N_2O_4Na$ $[M+Na]^+$: 427.1628, found: 428.1641. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 33.4 min, t_r (minor) = 36.7 min; 97% ee.

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83. The origin of this regioselectivity is not clear at the present time.
84. This process generates two equivalents of AcOH (see Figure 1.21), and some of the 2-aryl cyclic 1,3-dicarbonyl substrates are sensitive towards acid-catalyzed decomposition under the reaction conditions. Presumably, the presence of K_2CO_3 reduces the rate of this decomposition, leading to, in certain cases, higher yields.
85. The structures of spiroindenes **158a** and **158b** were confirmed by X-ray crystallography. CCDC 894550 (**158a**) and 897478 (**158b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via www.ccdc.cam.ac.uk/data_request/cif*.
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166. (a) In the work of Glorius and co-workers (see ref. 147), non- or weakly activated 1,3-dienes gave products different to those obtained from highly activated 1,3-dienes, as a result of over-oxidation; (b) Although iridium-catalyzed annulations of 1,3-dienes with cyclic ketimines (see ref. 145) occur with non-activated and highly activated 1,3-dienes, the mechanism of these reactions appears to be distinct from related processes in that the initially formed iridacycle reacts with the 1,3-diene in an oxidative cyclization rather than a migratory insertion; (c) Although a highly activated 4-nitrophenyl-substituted 1,3-diene was unsuitable in these reactions (none of **271j** could be isolated), reactions with a 2-nitrophenyl-substituted 1,3-diene, which might be expected to be electronically similar, were successful (**271b** and **272f**). Presumably, the 2-nitrophenyl group is twisted out of conjugation with the 1,3-diene to minimize unfavorable steric interactions with the 2-nitro group, thus reducing its electron-withdrawing ability.

167. We have found that dimedone-derived substrates are more stable toward acid-catalyzed decomposition than those derived from 1,3-cyclohexanedione.

168. Spiroindanes **274a** and **274b** were accompanied by additional inseparable, unidentified impurities, and therefore the yield was calculated by ^{1}H NMR analysis using an internal standard.

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Publications

1. Reddy Chidipudi, S.; **Khan, I**.; Lam, H. W. Functionalization of C(sp^3)–H and C(sp^2)–H Bonds: Synthesis of Spiroindenes by Enolate-Directed Ruthenium-Catalyzed Oxidative Annulation of Alkynes with 2-Aryl-1,3-dicarbonyl Compounds. *Angew. Chem., Int. Ed*. **2012**, *51*, 12115–12119.
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