Universität Rostock

Traditio et Innovatio

New Cycloadditions and Deconjugative Alkylations of α,β-Unsaturated Ketones Enabled by Transition Metal, Phosphine and Base Catalysis

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Declaration of Authorship

I hereby declare under oath that I have composed this dissertation independently and without unauthorized assistance. All external sources and materials used have been fully cited, and any borrowed ideas or text passages are clearly marked as such.

Rostock, [13.11.2025]

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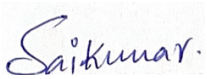

Dedication

"To my mother and mentors, whose unwavering support made this journey possible."

"उद्धरेदात्मनात्मानं नात्मानमवसादयेत्"

"Elevate yourself through the power of your mind, and not degrade yourself, for the mind can be the friend and also the enemy of the self."

— Bhagavad Gita, Chapter 6, Verse 5

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List of Abbreviations

Ac	Acetyl
AQ	Anthraquinone
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Cat.	Catalyst
CCDC	Cambridge Crystallographic Data Centre
CFL	Compact fluorescent lamp
CRTH2	Chemoattractant Receptor-Homologous Molecule
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-*N*,*N*-Dimethylaminopyridine
DCM	Dichloromethane
DMI	1,3-Dimethyl-2-imidazolidinone
e.r.	Enantiomeric ratio
EDG	Electron donating group
eq., equiv.	Molar equivalents
et al.	et alii (lat.)
EWG	Electron withdrawing group
FDA	U.S. Food and Drug Administration
HOMO	Highest occupied molecular orbital

LUMO	Lowest unoccupied molecular orbital
M	Molar mass
mL	Mililitre
mmol	Millimole
µMol	Micromole
mol	Mol
ODA	Oxa Diels-Alder
PC	Photocatalyst
RC	Rauhut-Currier
r.r.	Regioisomeric ratio
r.t.	Room temperature
Sens	Sensitizer
SAR	Structure Activity Relationship
Temp.	Temperature
THF	Tetrahydrofuran
UV	Ultraviolet

Abstract

This dissertation presents new catalytic methods for the functionalization of α,β-unsaturated ketones in cycloaddition and deconjugative alkylation reactions. The synthetic transformations explored and developed for these purposes are enabled by transition metal, organophosphine as well base catalysis.

First, a Lewis acid-catalyzed inverse electron demand oxa-Diels-Alder annulation of 1-oxadienes with vinylethers enabled the efficient synthesis of structurally elaborate azepane-fused pyrano[3,2-*b*]indoles, with a broad substrate scope and excellent *endo* diastereoselectivity. Second, phosphine organocatalysis was employed to induce divergent deconjugative Rauhut-Currier-type couplings or (3+2) annulations of alkylidene oxindoles with alkenes allenoates, opening viable accesses to polycyclic and spirocyclic oxindole molecular frameworks. Third, a Brønsted base-catalyzed deconjugative α-alkylation of enones was developed, offering direct access to functionalized carbonyl compounds under mild, metal-free conditions. These methodologies offer high chemoselectivity, scalability, and synthetic utility.

Mechanistic investigations, including NMR and crystallographic studies, offered valuable insights into reaction pathways and catalyst-dependent reaction control. Collectively, this work expands the synthetic toolbox for polycyclic heterocycle synthesis and holds promise for applications in medicinal chemistry and materials science.

Kurzfassung

Diese Dissertation stellt neue katalytische Methoden zur Funktionalisierung von α,β-ungesättigten Ketonen in Cycloadditionen und dekonjugierenden Alkylierungsreaktionen vor. Die hierfür untersuchten und entwickelten synthetischen Transformationen basieren auf Übergangsmetall-, Organophosphin- und Basenkatalyse.

Zunächst wurde eine Lewis-Säure-katalysierte Oxa-Diels-Alder-Reaktion mit inversem Elektronenbedarf entwickelt, die ausgehend von Enonen als 1-Oxadienen und Vinylethern die effiziente Synthese strukturell komplexer Azepan-kondensierter Pyrano[3,2-*b*]indole erlaubte, welche mit einem breiten Substratspektrum und exzellenter *endo*-Diastereoselektivität verlief. Zweitens wurde nucleophile Phosphin-Organokatalyse eingesetzt, um divergente dekonjugierende Rauhut-Currier-Kupplungen oder (3+2)-Anellierungen von Alkylidenoxindolen mit Alkenen sowie Allenoaten zu induzieren, wodurch ein praktikabler Zugang zu polycyclischen und spirocyclischen Oxindolgerüsten eröffnet wurde. Drittens wurde eine Brønsted-Base-katalysierte dekonjugierende α-Alkylierung von Enonen entwickelt, die einen direkten Zugang zu funktionalisierten Carbonylverbindungen unter milden, metallfreien Bedingungen ermöglicht. Diese Methoden zeichnen sich durch hohe Chemoselektivität, Skalierbarkeit und synthetischen Nutzen aus.

Mechanistische Untersuchungen, darunter NMR- und kristallographische Studien, lieferten wertvolle Einblicke in Reaktionswege und die katalysatorabhängige Reaktionskontrolle. Insgesamt erweitert diese Arbeit das Spektrum an synthetischen Methoden für die Synthese polycyclischer Heterocyclen, und die Ergebnisse sind vielversprechend für Anwendungen in der medizinischen Chemie und den Materialwissenschaften.

1. Introduction

1.1 Importance of Carbon-Carbon Bond Formation

The formation of carbon-carbon (C-C) bonds lies at the heart of organic synthesis and underpins the construction of virtually all molecular architectures. Because carbon is the central element in organic chemistry, the ability to selectively form C-C bonds enables the synthesis of a wide range of natural products, pharmaceuticals, agrochemicals, and functional materials.[1-3] Over the past century, numerous strategies have been developed to build molecular complexity from simple precursors, making C-C bond formation one of the most studied and continuously evolving areas in chemical research.[4-7]

Classical reactions such as the Aldol condensation, Michael addition, and Claisen rearrangement established the foundation of C-C bond construction in the early development of organic synthesis. These fundamental transformations provided chemists with essential tools for connecting carbon frameworks and exploring reactivity patterns. However, their broader application was often limited by harsh reaction conditions, low selectivity, and restricted functional group tolerance. These challenges inspired the development of milder, catalytic, and more versatile methodologies that could deliver similar or enhanced reactivity under controlled conditions.[8-10]

The development of transition-metal-catalyzed cross-coupling reactions such as the Suzuki–Miyaura, Heck, Negishi, Stille, and Sonogashira reactions has revolutionized modern organic synthesis, providing powerful and general strategies for C-C bond construction under mild and predictable conditions.[11-17]

These methods enable efficient coupling between prefunctionalized partners and have become indispensable in the synthesis of pharmaceuticals, agrochemicals, and advanced materials.[18-20] The broad impact of these transformations was recognized with the 2010 Nobel Prize in Chemistry, awarded to Heck, Negishi, and Suzuki for their pioneering contributions to palladium-catalyzed cross-coupling reactions.[21]

In total synthesis, C-C bond-forming reactions frequently define the efficiency and success of a synthetic route. The choice of methodology determines not only the number of steps required, but also the degree of control achievable over regioselectivity, stereoselectivity, and chemoselectivity. Consequently, the continued

development of new C-C bond-forming reactions with improved scope, functional group tolerance, and sustainability remains a major driving force in contemporary organic chemistry.[22]

1.2 Role of Catalysis

Catalysis represents a cornerstone of modern synthetic chemistry, enabling chemical transformations to proceed more rapidly, selectively, and efficiently than would otherwise be possible.[23-25] Catalysts lower activation barriers and increase reaction rates while simultaneously improving regio-, chemo-, and stereoselectivity, thereby making complex transformations feasible under mild conditions.[26-27] Beyond enhancing efficiency, catalysis contributes significantly to sustainable and environmentally responsible synthesis. By promoting reactions with greater atom economy and reduced waste generation, catalytic processes align directly with the principles of green chemistry, offering practical routes to efficient and resource-conscious chemical transformations.[28-33]

Transition-metal catalysts have had a transformative impact on C-C bond formation. [34] Their reactivity can be finely tuned through ligand design, allowing chemists to achieve high levels of control over selectivity and reactivity. Metal-based catalysis underlies many of the most powerful bond-forming methods developed in the past half century,[35] including palladium-catalyzed cross-couplings,[12-17] rhodium- and ruthenium-mediated cycloadditions, and nickel or copper-catalyzed reductive couplings.[36-37] In parallel, the field of organocatalysis has advanced dramatically as an attractive alternative to transition metal catalysis.[38-40]

Since the pioneering reports by List and MacMillan in 2000,[41-42] organocatalysis has evolved into one of the most dynamic areas in modern chemistry, advancing enantioselective synthesis and green catalysis. The development of chiral amines, phosphines, and *N*-heterocyclic carbenes has expanded the versatility of these systems, providing complementary reactivity to metal-based catalysts while maintaining operational simplicity and environmental compatibility.[43-44]

Organocatalysts are generally inexpensive, stable, environmentally benign, and exhibit high compatibility with sensitive functional groups They typically operate through hydrogen bonding, Brønsted acid/base activation mechanisms.[45-46] Within this field,

nucleophilic organocatalysis by tertiary phosphines has emerged as a particularly powerful approach. Phosphine catalysts activate electron-deficient substrates such as enones, acrylates, and allenoates via zwitterionic intermediates, enabling a wide range of synthetically valuable C-C bond-forming reactions.[47-50] Among these, the Rauhut-Currier (RC) reaction, (3+2) cycloadditions, and (4+2) annulations represent cornerstone transformations for constructing stereochemically rich, densely functionalized frameworks.[51-56] stand out as highly versatile tools for building stereochemically rich and densely functionalized scaffolds, making them indispensable in modern synthetic methodology.

Another important class of organocatalysts comprises strong, non-nucleophilic organic bases, notably 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). DBU acts as an efficient Brønsted base catalyst capable of generating enolates and vinylogous enolates under mild conditions. This property enables reactions such as deconjugative α-alkylation, Michael-type additions, and heterocyclic ring-forming processes. without the need for metals or stoichiometric bases. Owing to its high basicity and low nucleophilicity, DBU serves as a versatile and sustainable catalyst, achieving transformations typically associated with metal enolates but under far milder and greener conditions.[57-60]

Collectively, catalytic strategies both metal-based and organocatalytic play a decisive role in expanding the toolbox of C-C bond formation. They not only improve the efficiency of synthetic routes but also open access to molecular architectures that would be otherwise challenging to construct.

1.3 Representative Catalytic Strategies for Carbon-Carbon Bond Formation

Catalytic strategies for carbon-carbon bond formation are illustrated by several landmark transformations that continue to shape modern organic synthesis. Three areas of particular relevance to this thesis are Oxa-Diels-Alder reactions promoted by Lewis acids, Phosphine-Catalyzed Rauhut-Currier reaction and annulation processes, and DBU-mediated deconjugative α-alkylations reactions.

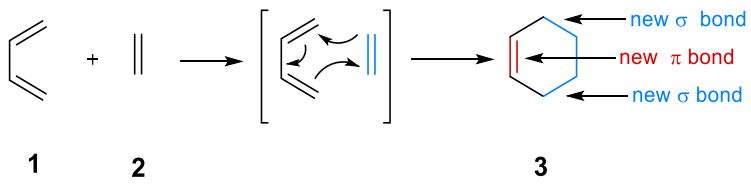
Together, these catalytic paradigms represent complementary strategies for C-C bond formation, highlighting how Lewis acid, nucleophilic, and Brønsted base activation can each be harnessed to achieve distinct reactivity and selectivity profiles.

1.3.1 The Diels-Alder Reaction and Its Variants

The Diels-Alder (DA) reaction, first reported in 1928 by Otto Diels and Kurt Alder, is one of the most celebrated and versatile pericyclic transformations in organic chemistry.[61] It involves a (4+2) cycloaddition between a conjugated 1,3-diene and an alkene or alkyne dienophile, forming a six-membered ring in a single, concerted step. This powerful transformation enables the simultaneous formation of multiple σ-bonds and stereocenters, often with excellent regio- and stereochemical control.[62-64]

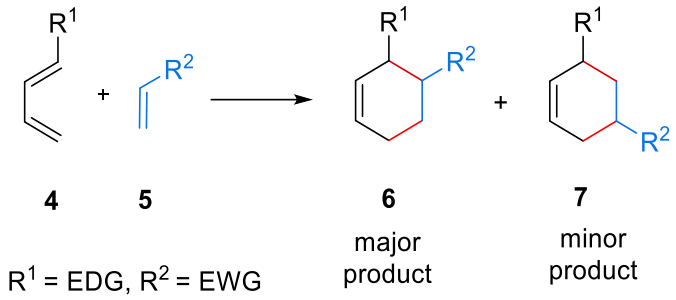
The Diels-Alder reaction has profoundly influenced the development of synthetic methodology, natural product total synthesis, and pharmaceutical chemistry,[65-67] owing to its unparalleled efficiency in constructing complex cyclic frameworks from simple precursors. In recognition of their pioneering work, Diels and Alder were awarded the 1950 Nobel Prize in Chemistry.[68]

The general course of the reaction is illustrated in Scheme 1, where a 1,3-diene **1** reacts with a dienophile **2** to yield a cyclohexene derivative **3** with two new σ-bonds and one new π-bond.



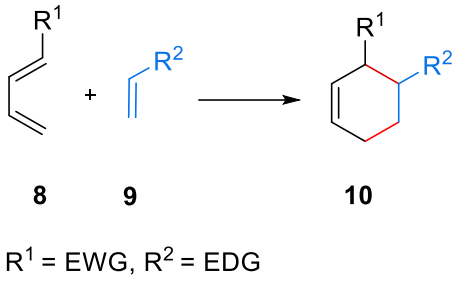
Scheme 1. General representation of Diels-Alder (4+2) cycloaddition.

In the normal electron-demand Diels-Alder reaction, the diene is electron-rich and activated by electron-donating groups (EDGs), while the dienophile is electron-deficient and activated by electron-withdrawing groups (EWGs). This is the most classical and widely used version of the reaction (Scheme 2).[69]



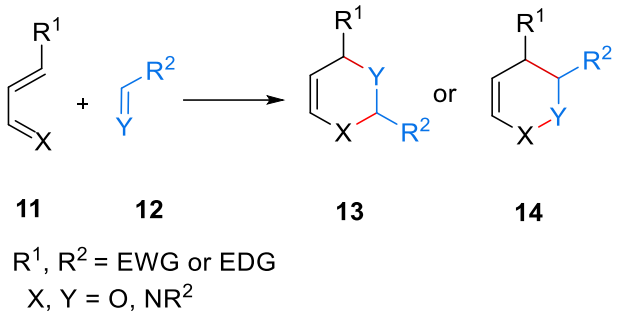
Scheme 2. Normal electron-demand Diels-Alder reaction between an EDG-substituted diene **4** and an EWG-substituted dienophile **5**.

In contrast, the inverse electron-demand Diels-Alder reaction involves an electron-deficient diene and an electron-rich dienophile. (Scheme 3). Depending on the nature of the reacting partners, the process can lead to either carbocyclic or heterocyclic products. This reactivity pattern is particularly valuable in the synthesis of heterocycles chemistry. Beyond these electronic variants, hetero-Diels-Alder reactions have emerged as powerful tool for the construction of oxygen- and nitrogen-containing six-membered heterocycles.



Scheme 3. Inverse electron-demand Diels-Alder reaction between an EWG-substituted diene **8** and an EDG-substituted dienophile **9**.

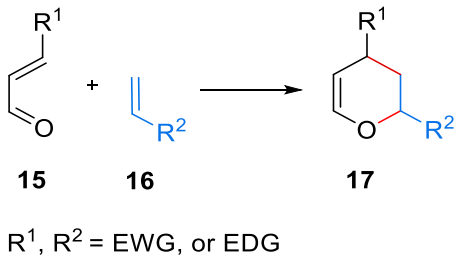
When one or more heteroatoms are incorporated in the diene or dienophile (e.g., X, Y = O, NR_2), the reaction proceeds as a Hetero-Diels-Alder (HDA) variant, furnishing oxygen- or nitrogen-containing heterocycles (Scheme 4). The substituents R^1 and R^2, bearing electron-withdrawing (EWG) or electron-donating (EDG) groups, influence both the regioselectivity and stereoselectivity of the cycloaddition, making the DA/HDA manifold a powerful and versatile tool for constructing diverse molecular architectures.[70-71]



Scheme 4. General Representation of Hetero-Diels-Alder Reactions.

The Oxa-Diels-Alder (ODA) reaction represents a hetero-Diels-Alder variant in which an oxygen atom participates in the cycloaddition, leading to the formation of oxygen-containing six-membered heterocycles such as pyran derivatives. In the normal electron-demand ODA reaction, an electron-rich diene reacts with an electron-deficient carbonyl or alkene dienophile to generate the corresponding Oxacyclic adduct (Scheme 5). Conversely, the inverse electron-demand ODA variant (Scheme 5) involves an electron-deficient diene and an electron-rich alkene or enol ether, affording complementary regio- and stereochemical outcomes.

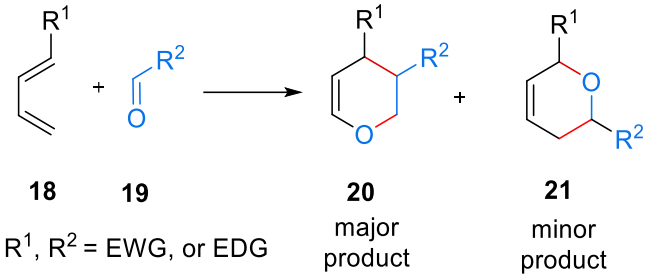
The substituents R¹ and R², which may be electron-donating (EDG) or electron-withdrawing (EWG) groups, strongly influence the reactivity and selectivity of both processes. These reactions provide efficient access to oxygenated heterocyclic frameworks that are commonly found in natural products, bioactive molecules, and pharmaceutical intermediates.



Scheme 5. General Representation of the Oxa-Diels-Alder (ODA) Reaction and Its Variants.

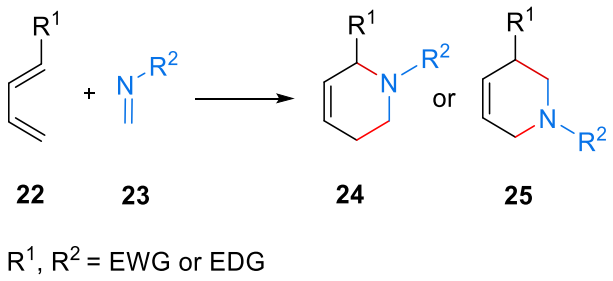
In this transformation (Scheme 6), the oxygen atom of the carbonyl group participates as a heteroatom component, giving rise to new C-C and C-O bonds in a single step.

Depending on the electronic nature of substituents R^1 and R^2 whether electron-withdrawing (EWG) or electron-donating (EDG), the reaction can proceed under thermal or catalytic conditions with high regio- and stereoselectivity.

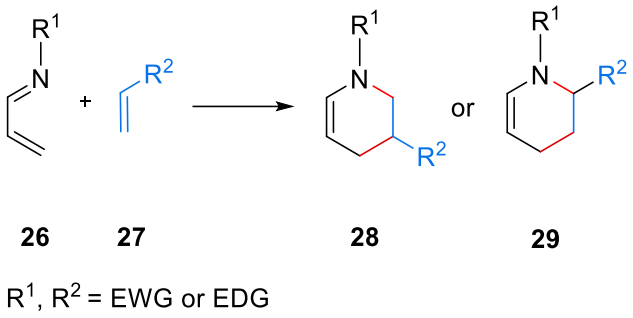


Scheme 6. Regioselectivity in the Oxa-Diels-Alder Reaction between Dienes Involving a Carbonyl Dienophile **18**.

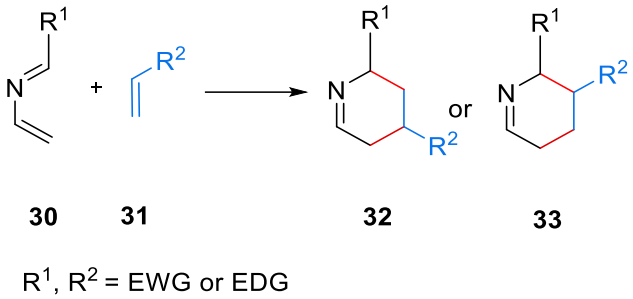
The Aza-Diels-Alder (ADA) reaction is a (4+2) cycloaddition that enables the construction of nitrogen-containing six-membered heterocycles, including piperidines, dihydropyridines, and related aza-heterocycles. This transformation provides an atom-economical route to complex nitrogen frameworks frequently encountered in alkaloids, natural products, and pharmaceuticals. Depending on the electronic nature of the reacting partners, three general mechanistic variants have been established (Scheme 7). In the imino dienophile variant, an imine ($C=NR^2$) functions as the dienophile, reacting with an electron-rich diene to afford dihydropyridine-type products. (Scheme 8). In the 1-aza-1,3-butadiene variant, the nitrogen atom forms part of the conjugated diene, engaging with an electron-deficient alkene or enone dienophile (Scheme 9). In the 2-aza-1,3-butadiene variant, nitrogen occupies the second position within the 1,3-diene system, leading to distinct regioselectivity and stereochemical outcomes.[72-73]



Scheme 7. Aza-Diels-Alder (ADA) Reaction Involving an Imino Dienophile **23.**



Scheme 8. Aza-Diels-Alder (ADA) Reaction Involving a 1-Aza-1,3-Butadiene **26**.



Scheme 9. Aza-Diels-Alder (ADA) Reaction Involving a 2-Aza-1,3-Butadiene **30.**

The substituents R¹ and R², whether electron-donating (EDG) or electron-withdrawing (EWG), strongly influence the rate, regioselectivity, and product distribution of the reaction. Collectively, these variants highlight the versatility of the ADA reaction as a key method for constructing nitrogen heterocycles with high structural diversity and stereochemical control.

Taken together, these variants highlight the breadth and adaptability of the Diels-Alder reaction. Its ability to accommodate different electronic demands and heteroatom participation underscores its central role in modern synthetic organic chemistry.

Catalytic variants including Lewis acid catalysis (e.g., $Sc(OTf)_3$, $Yb(fod)_3$, $Eu(fod)_3$), Brønsted acid catalysis, and Organocatalysis serve to improve reaction rates, regioselectivity, and stereocontrol.[74-75]

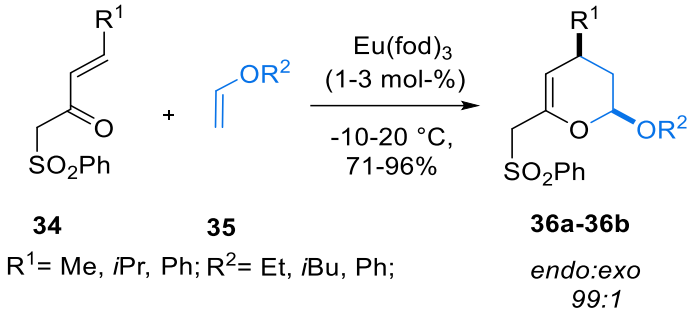
The Oxa-Diels-Alder reaction has attracted particular attention because it provides efficient access to oxygen-containing heterocycles such as pyrans, pyranoindoles, and fused oxindoles, which are commonly found in natural products and medicinally active compounds.[76-80]

Lewis Acid-Catalyzed Oxa-Diels-Alder Reactions

Lewis acid catalysis has emerged as a powerful strategy to enhance both the reactivity and selectivity of Diels-Alder and Oxa-Diels-Alder reactions.[81] Over the years, a wide variety of Lewis acids including boron, aluminum, titanium, lanthanide, and transition-metal complexes have been applied to expand the scope of these cycloadditions.[82]

Representative examples are outlined below.

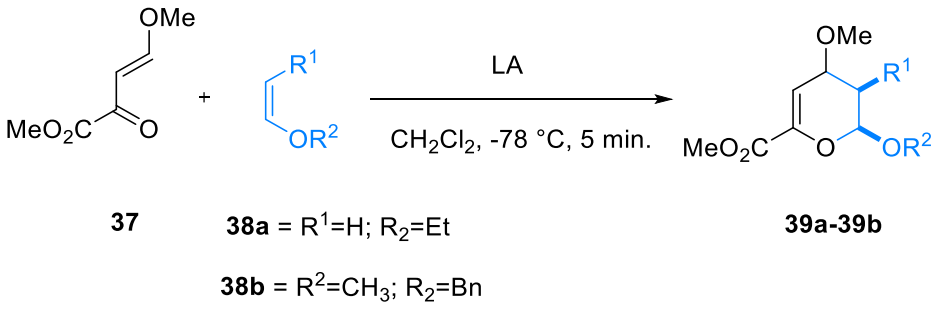
In 1994, Wada and co-workers (Scheme 10) reported that methylenesulfone-substituted enones **34** undergo efficient Oxa-Diels-Alder reactions with enol ethers **35** in the presence of $Eu(fod)_3$ (1-3 mol%) as the Lewis acid catalyst Europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate),[83] the reactions proceeded at low temperatures (-10 °C to -20 °C) to give the corresponding tetrahydropyran adducts in high yields (71-96%) and with excellent *endo*-selectivity (*endo:exo* = *99:1*). The method was applicable to a range of enone substrates bearing alkyl or aryl substituents (R^1 = Me, *i*Pr, Ph) which reacted smoothly with various enol ethers (R^2 = Et, *i*Bu, Ph), demonstrating broad functional group tolerance.



Scheme 10. $Eu(fod)_3$-catalyzed Oxa-Diels-Alder reaction of vinyl sulfones (**34**) with enol ethers, affording adducts **36a-36b**.[83]

In 1988 Boger and co-workers (Scheme 11) demonstrated that Lewis acids strongly influence both reactivity and stereoselectivity in the Oxa-Diels-Alder reaction of methyl vinyl ketone derivatives with enol ethers.[84] When $EtAlCl_2$ was used, the reaction proceeded rapidly at –78 °C in CH_2Cl_2 to give cyclic adduct **39a** in 75% yield, though with modest stereoselectivity (*endo*:*exo* = 0.8:1). Substitution and choice of Lewis acid proved critical and with $TiCl_4$, adduct **39a** was obtained in 61% yield with improved

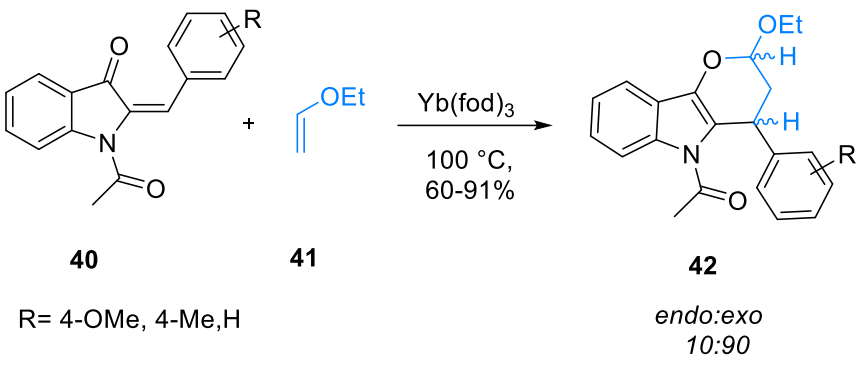
endo-selectivity (*endo:exo* = 1.3:4), whereas $EtAlCl_2$ with a substituted enol ether **39b** afforded the adduct in 46% yield and good *endo*-selectivity (*endo:exo* = 6:1).



Scheme 11. Lewis acid (LA)-Catalyzed Oxa-Diels-Alder reaction furnishing cyclic adducts **39a-39b**.[84]

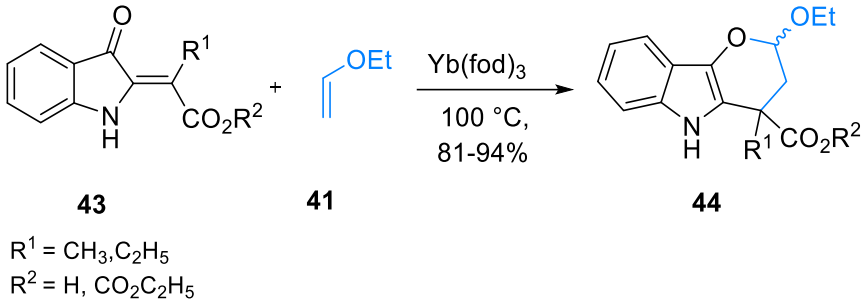
Enty	LA	*endo:exo*	Yield (%)
38a	$EtAlCl_2$	0.8:1	75
38a	$TiCl_4$	1:3.4	61
38b	$EtAlCl_2$	6:1	46

Mérou and Mérou reported (Scheme 12) in 1994 that indoxyl derivatives undergo efficient Oxa-Diels-Alder reactions with enol ethers in the presence of ytterbium(III) tris(2,2,6,6-tetramethyl-3,5-heptanedionate) [$Yb(fod)_3$] as a Lewis acid catalyst.[85] The reactions proceeded smoothly at 100 °C, delivering pyrano[3,2-*b*]indoles in good to excellent yields (60-91%). The method tolerated substituents such as methoxy, methyl, and hydrogen on the aromatic ring (R = 4-OMe, 4-Me, H), highlighting its substrate versatility.



Scheme 12. $Yb(fod)_3$-Catalyzed Oxa-Diels-Alder reaction of Indoxyls **40** to Form Pyrano[3,2-*b*] indoles **42.**[85]

In a subsequent study, Mérou and co-workers (Scheme 13) 1996 extended this approach to 3-ylideneoxindoles **43**, which reacted smoothly with enol ethers **41** under $Yb(fod)_3$ catalysis at 100 °C.[86] The reactions afforded fused pyrano[3,2-*b*]indole derivatives in 81-94% yields, further highlighting the versatility of $Yb(fod)_3$ as a Lewis acid catalyst for the synthesis of fused heterocycles.



43 **41** **44**

$R^1 = CH_3, C_2H_5$
$R^2 = H, CO_2C_2H_5$

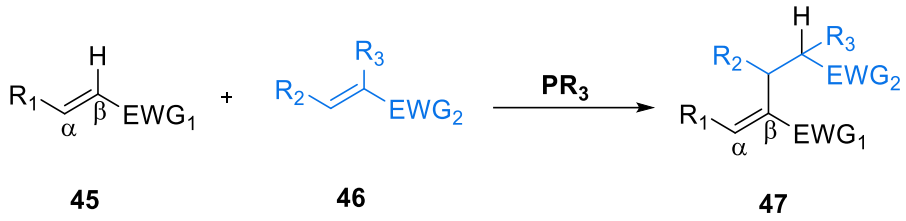
Scheme 13. $Yb(fod)_3$-Catalyzed Oxa-Diels-Alder reaction of 3-ylideneoxindoles **43** with enol ethers **41** to afford fused pyrano[3,2-*b*]indole derivatives **44**.[86]

This transformation (Scheme 12-13) represents an early and efficient example of lanthanide-catalyzed Oxa-Diels-Alder reactions, expanding the synthetic toolbox for constructing fused heteroaromatic scaffolds.

Taken together, these studies clearly demonstrate the pivotal role of Lewis acid catalysis in tuning both the efficiency and stereoselectivity of Oxa-Diels-Alder reactions. The early work of Boger (1988)[84] established the feasibility of using simple Lewis acids such as $EtAlCl_2$ and $TiCl_4$ to promote reactions of activated enones with enol ethers, though stereoselectivity was highly dependent on the choice of Lewis acid. Subsequent advances introduced lanthanide complexes such as $Eu(fod)_3$ and $Yb(fod)_3$, which significantly expanded the scope and improved the performance of these transformations. Wada's $Eu(fod)_3$ system (1994, 1996)[83] achieved excellent yields with nearly complete *endo*-selectivity, while Mérou's $Yb(fod)_3$ systems (1994, 1996)[85-86] enabled efficient construction of fused pyranoindole scaffolds with broad substrate tolerance. Thus, the progression from conventional Lewis acids to lanthanide-based catalysts represents a major advance, providing chemists with powerful tools to construct oxygen and nitrogen-containing heterocycles with high selectivity and synthetic utility.

1.3.2. Phosphine-Catalyzed Rauhut-Currier and (3+2) Annulation Reactions

The Rauhut-Currier reaction represents a powerful strategy for C-C bond construction, encompassing intermolecular, intramolecular, and asymmetric variants. a phosphine-catalyzed carbon-carbon bond-forming process between two electron-deficient alkenes, typically acrylates, acrylonitriles, or enones.

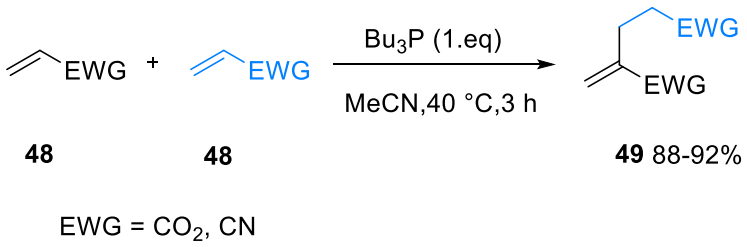


45 **46** **47**

Scheme 14. General Representation of the Phosphine-Catalyzed Rauhut-Currier Reaction between electron-deficient alkenes to give the coupled product **47**.

In this transformation (Scheme 14), the tertiary phosphine (PR_3) first acts as a nucleophile, attacking one of the activated alkenes (**45**) to form a zwitterionic phosphonium enolate intermediate. This intermediate subsequently adds to a second electron-poor alkene (**46**), producing a new C-C bond through a conjugate addition pathway. Following proton transfer and elimination of the phosphine catalyst, the α,β-unsaturated adduct (**47**) is generated.

Representative examples are outlined below.

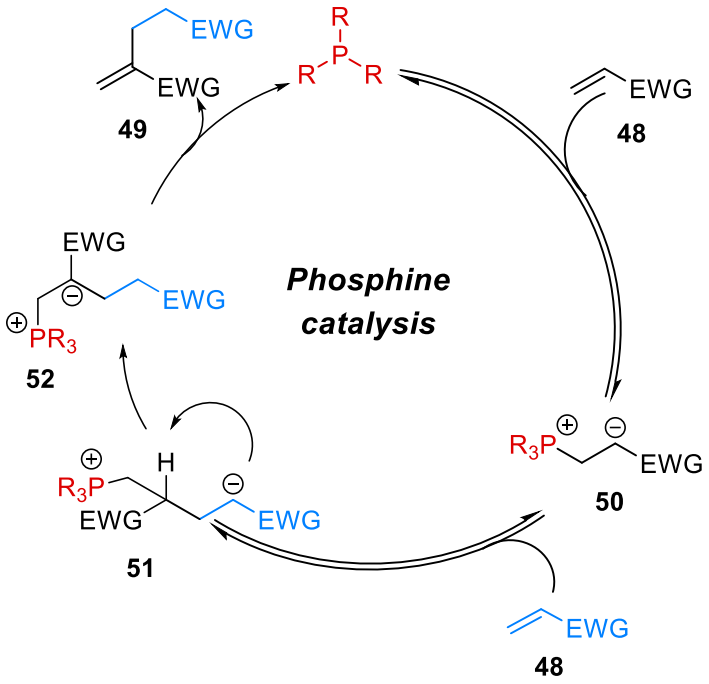


Scheme 15. Dimerization of Electron-Deficient Alkenes **48** in the Presence of Tributylphosphine (Bu_3P) to Give the Corresponding Coupled Product **49**.[87-88]

In 1963, Rauhut and Currier reported the first example of the phosphine-catalyzed dimerization of electron-deficient alkenes, such as acrylonitrile and ethyl acrylate, to

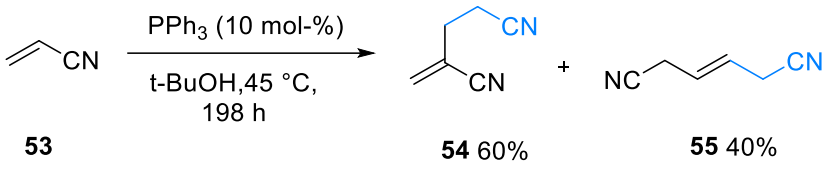
give highly functionalized diene products (Scheme 15).[87-88] This transformation, now known as the Rauhut-Currier (RC) reaction, represents one of the earliest and most influential applications of nucleophilic phosphine catalysis.

Mechanistically, the RC reaction proceeds via nucleophilic addition of the phosphine to an activated alkene, generating a zwitterionic phosphonium-enolate intermediate. This intermediate then undergoes conjugate addition to a second electron-deficient alkene, leading to C-C bond formation. Subsequent proton transfer regenerates the free phosphine catalyst and delivers the RC product. The overall catalytic cycle is illustrated in Scheme 16.



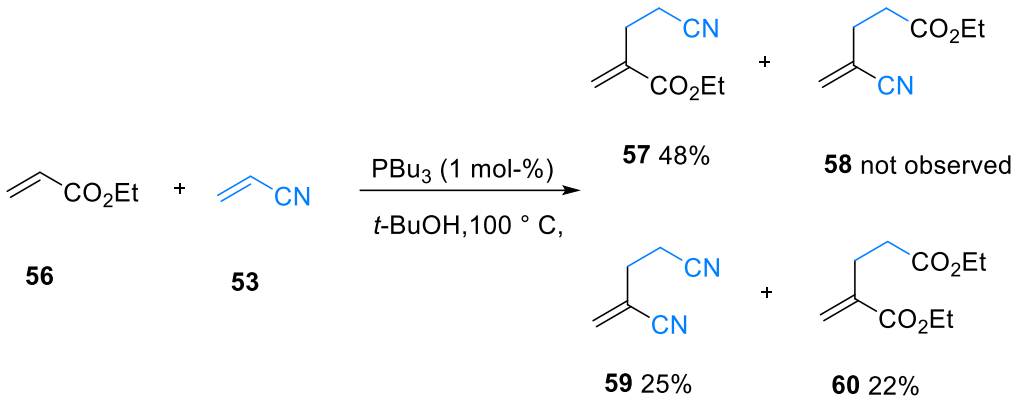
Scheme 16. Proposed Mechanism of the Phosphine-Catalyzed Rauhut-Currier Reaction.[87-88]

In 1965, Baizer and Anderson extended the scope of the RC reaction by reporting the triphenylphosphine (PPh_3)-catalyzed dimerization of acrylonitrile (Scheme 17).[89] Under these conditions, a mixture of linear and branched dimers was obtained in 60% and 40% yields, respectively. This study demonstrated that phosphine catalysis could effectively activate nitrile-substituted alkenes, expanding the utility of the RC reaction.



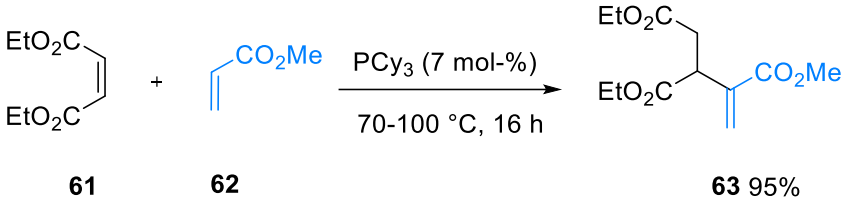
Scheme 17. Phosphine-Catalyzed Rauhut-Currier-type Dimerization of Acrylonitrile (**53**) Using Triphenylphosphine (PPh_3), Affording Dimeric Adducts **54**.[89]

In the same year, McClure disclosed in a patent the intermolecular RC reaction of acrylates with acrylonitriles using tributylphosphine (PBu_3) (Scheme 18).[90] This process furnished γ-coupled adducts in moderate yields with diverse product distributions. This was among the first examples of intermolecular cross-RC reactions between different activated alkenes.



Scheme 18. Phosphine-Catalyzed Intermolecular Rauhut-Currier Reaction of Acrylates **56** with Acrylonitriles (**53**) Using Tributylphosphine (PBu_3), Affording γ-Coupled Adducts **57**.[90]

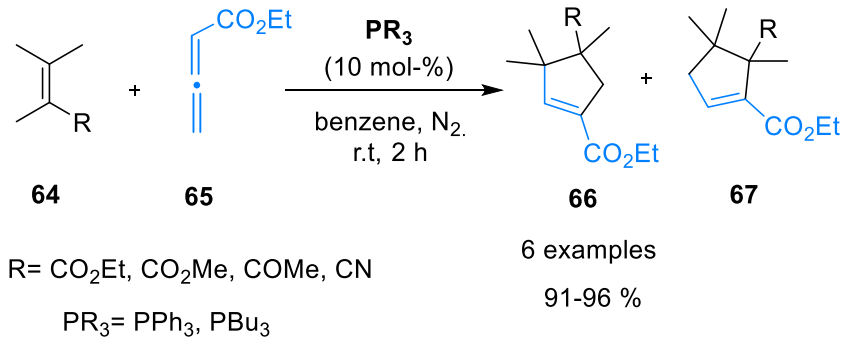
In 1969 Morita and Kobayashi further advanced the field by demonstrating the PCy_3-catalyzed intermolecular RC reaction between diesters and acrylates (Scheme 19).[91]



Scheme 19. Intermolecular Rauhut-Currier Reaction between an Activated Diester **61** and Methyl Acrylate (**62**) Catalyzed by Tricyclohexylphosphine (PCy_3).[91]

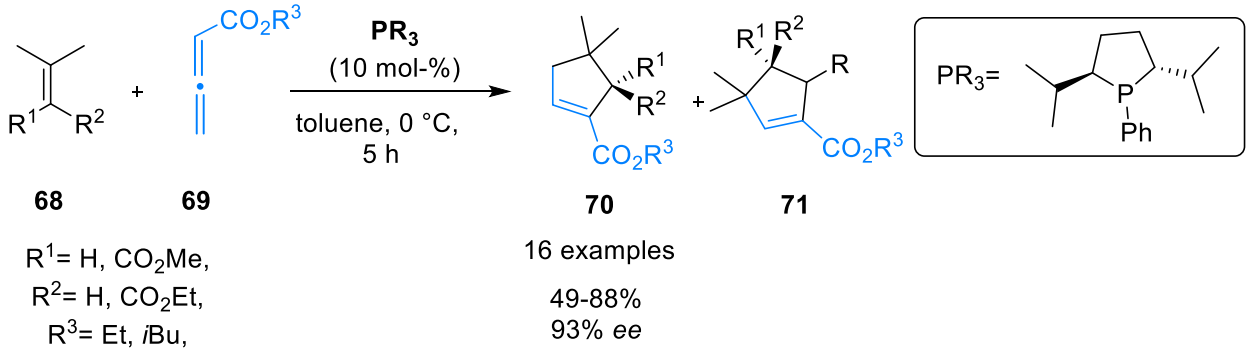
(3+2) Annulation

In 1995, Zhang and Lu reported the first example of a phosphine-catalyzed (3+2) annulation, involving 2,3-butadienoates (**65**) and electron-deficient olefins **64** (Scheme 20).[92] This reaction provided highly substituted cyclopentenes in good yields. Importantly, this discovery represented a significant departure from the traditional RC reaction, as the zwitterionic phosphonium enolate intermediate, when generated from allene carboxylate **65**, underwent intramolecular cyclization rather than simple coupling.



Scheme 20. Phosphine-Catalyzed (3+2) Cycloaddition of 2,3-Butadienoates (**65**) with Electron-Deficient Olefins **64**.[92]

In 1997, Zhang and co-workers reported (Scheme 21) the first asymmetric phosphine-catalyzed (3+2) annulation reaction, marking a milestone in the development of nucleophilic phosphine organocatalysis.[93]

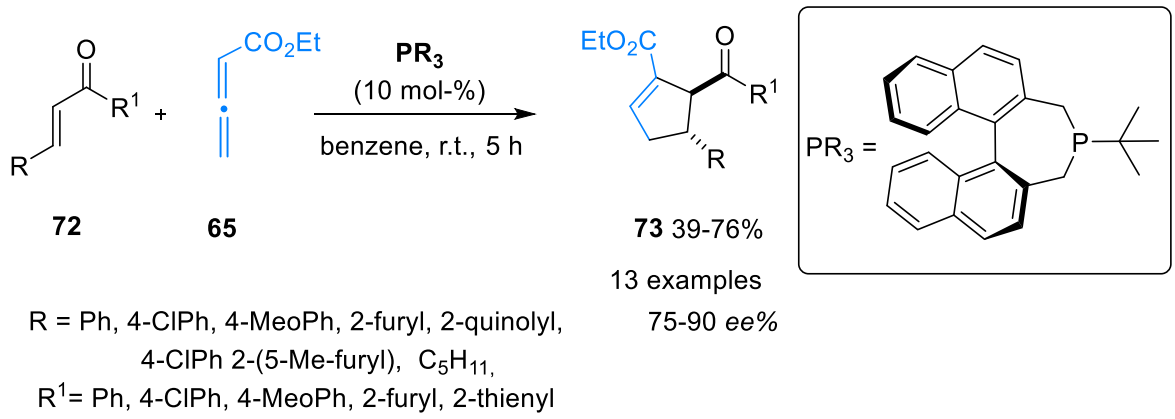


Scheme 21. Phosphine-Catalyzed (3+2) Cycloaddition of 2,3-Butadienoates (**69**) with Electron-Deficient Olefins **68**.[93]

Using a chiral phospholane catalyst, the group achieved an enantioselective (3+2) annulation between allenoates **69** and activated alkenes **68**, affording highly enantioenriched cyclopentenes in good yields (49-88%) and excellent enantioselectivities (up to 93% *ee*).

The reaction proceeds via phosphine activation of the allenoate to generate a zwitterionic phosphonium enolate intermediate, which undergoes cycloaddition with the alkene. This pioneering study demonstrated, for the first time, that chiral phosphines could efficiently mediate both reactivity and stereocontrol, thus establishing the foundation for a rapidly expanding field of asymmetric phosphine organocatalysis.

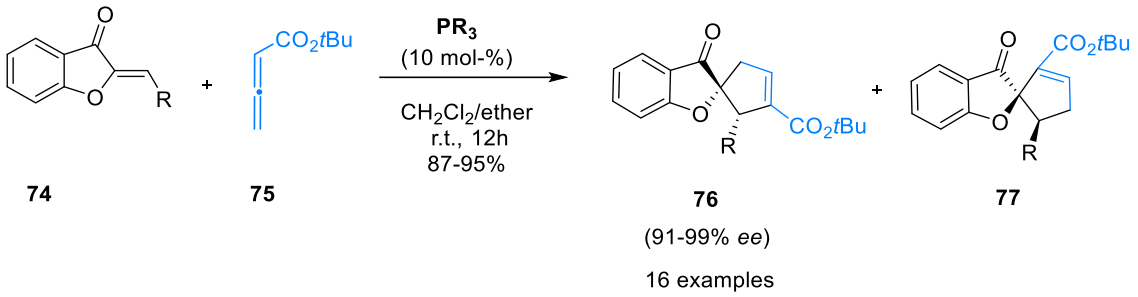
Building on these findings, Fu and co-workers reported in 2006 the asymmetric (3+2) cycloaddition of allenes **65** with enones **72** using a chiral binaphthyl-derived phosphine (Scheme 22)[94] This method enabled the enantioselective synthesis of cyclopentene derivatives in good yields and enantioselectivities. The use of amino acid-derived chiral phosphines established the feasibility of stereocontrol in (3+2) annulations, providing a new strategy for asymmetric construction of complex carbocycles.



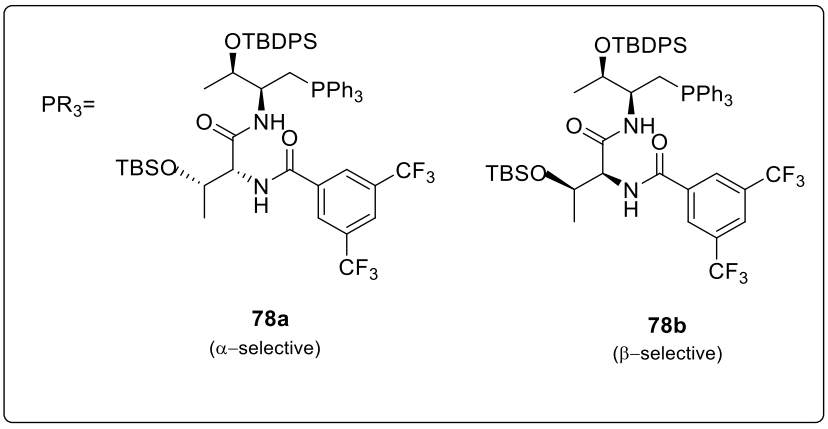
Scheme 22. Catalytic Asymmetric (3+2) Cycloaddition of Allenes **65** with Enones **71** to Form Cyclopentenes **73**.[94]

In 2017, Lu and co-workers reported a highly enantioselective phosphine-catalyzed (3+2) annulation of activated allenes **75** with alkylidene benzofuran-3(2*H*)-one **74**, providing access to spirocyclopentanes (Scheme 23),[95] an important class of bioactive heterocycles. The reaction employed a valine-derived chiral tertiary

phosphine catalyst, which was designed to combine both nucleophilic activation (through the phosphorus lone pair) and chiral induction (through the bulky amino acid-derived framework). The sterically demanding and conformationally rigid valine scaffold effectively controlled the approach of the allene to the benzofuran-derived intermediate, ensuring high diastereoselectivity and enantioselectivity. Across a broad range of benzofuran derivatives (R = Ph, 4-OMePh, 4-ClPh, 3-MePh, 2-thienyl, etc.), the reaction consistently delivered the desired spiro-oxindole cyclopentanes **76** in 91–99% *ee* and excellent yields.



R= Ph, 4-OCH_3Ph,4-CH_3Ph, 4-FPh, 4-ClPh, 4-BrPh, 3-ClPh, 3-MePh, 2-MePh, 3,4-di-OCH_3Ph, 2-Thienyl, Cyclohexyl, Isopropyl, *n*Bu, Ethyl.



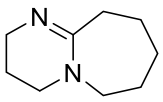
Scheme 23. Chiral Phosphine-Catalyzed (3+2) Annulation to Form Spiro-oxindole Cyclopentanes **76**.[95]

This work highlights the potential of amino acid-derived chiral phosphines, particularly valine-based systems, as a powerful platform for asymmetric annulations. The modularity of the amino acid backbone allows precise tuning of steric and electronic properties, thereby enabling highly selective access to enantioenriched spiro-oxindoles, which are widely regarded as privileged scaffolds in medicinal chemistry.

Further, this work marks a significant advance compared to earlier chiral phosphine systems. For instance, Fu in 2006 employed binaphthyl phosphine (Scheme 22) for asymmetric (3+2) cycloadditions of allenes with enones, achieving enantioselectivities up to 90% *ee*. While effective, those catalysts were synthetically more complex and limited in substrate scope. By contrast, the valine-derived phosphine catalyst **78a** (Scheme 23) is not only easier to access but also provides higher enantioselectivities and broader functional group tolerance, highlighting the advantages of amino acid derived scaffolds in organocatalysis.

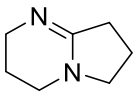
1.3.3 DBU-Catalyzed Transformations

DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) are structurally related bicyclic amidine superbases widely employed in organic synthesis. Both possess strong Brønsted basicity and low nucleophilicity,[96–97] enabling efficient proton abstraction without competing side reactions.



79

1,8-Diazabicyclo[5.4.0]undec-7-ene
(DBU)



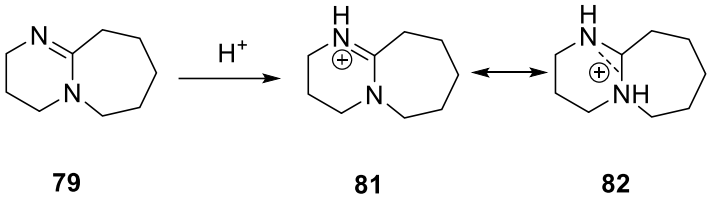
80

1,5-Diazabicyclo[4.3.0]non-5-ene
(DBN)

Figure 1. Structures of DBU and DBN.

The larger bicyclic framework of DBU allows greater delocalization of the positive charge in its conjugate acid, making it slightly more basic ($pK_a \approx 24.3$ in MeCN) than DBN ($pK_a \approx 23.5$)[98] This enhanced delocalization renders DBU thermodynamically more stable and a stronger base, while DBN, with its more compact ring system, exhibits reduced steric hindrance and can be advantageous in reactions involving sterically demanding substrates. Consequently, DBU is often preferred for reactions requiring strong deprotonation, such as deconjugative alkylations and vinylogous Michael additions, whereas DBN is typically favored in cases demanding milder yet efficient base catalysis. Both serve as versatile, metal-free promoters of C-C and C-X bond formations under mild and environmentally benign conditions.[99]

Protonation of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) at the imine nitrogen generates a delocalized amidinium cation (Scheme 24) The positive charge is effectively stabilized through resonance within the bicyclic framework, accounting for the high basicity of DBU (pK_a of $DBU{\cdot}H^+ \approx 24.3$ in MeCN) and its ability to act as a strong yet nucleophilic base. This delocalization enhances thermodynamic stability and contributes to DBU's broad applicability in metal-free deprotonation and condensation reactions.[57]



79 **81** **82**

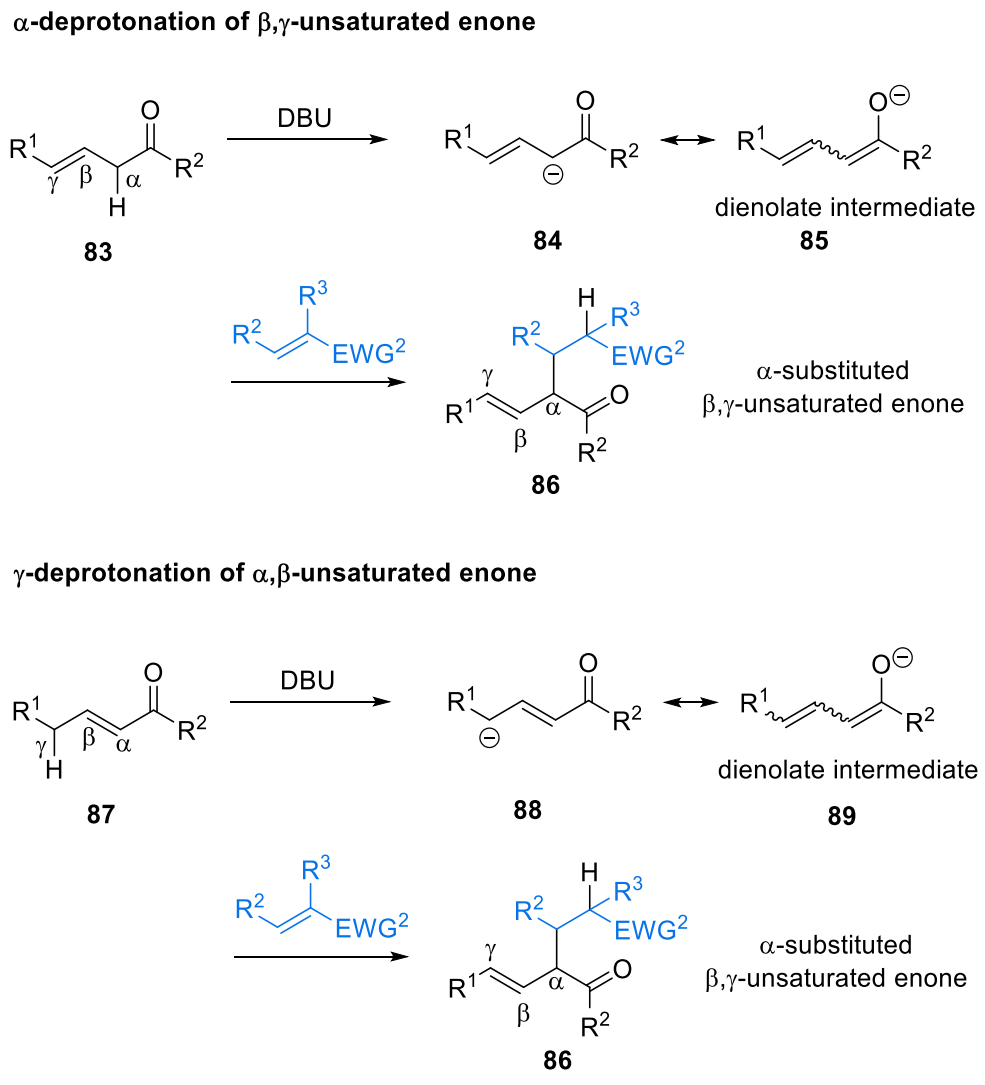
Scheme 24. Protonation and Resonance Stabilization of DBU.

Recent comprehensive reviews have highlighted DBU's broad utility across organic synthesis. For instance, DBU has been shown to catalyze heterocyclic ring-forming reactions, including annulations, cyclizations, and rearrangements leading to nitrogen- and oxygen-containing frameworks. Furthermore, its applications in DBU-mediated organic transformations, ranging from enolate generation and Michael additions to Rauhut-Currier-type couplings and transesterifications, underscore its role as a powerful, environmentally benign organocatalyst.[99]

A key feature of DBU catalysis is its ability to generate enolates and related nucleophilic intermediates mechanistic insight that differentiates DBU from other bases, thereby enabling reactions such as the formal Michael addition of acetone to α,*β*-unsaturated esters and amides.[100] DBU-mediated reactions include cyclization and annulation reactions, where DBU initiates intramolecular nucleophilic attack, often leading to carbocyclic or heterocyclic frameworks.[101] It also mediates isomerization and proton transfer processes, acting as a proton shuttle, facilitating tautomerizations or rearrangements under mild conditions,[102] such as the elimination of SO_2 and subsequent aromatization in pyridine synthesis. Compared to transition-metal catalysis, DBU-mediated reactions are operationally simple and avoid the need for expensive catalysts. This aligns well with the principles of green chemistry, making

DBU a practical and sustainable choice for large-scale applications like transesterification for biodiesel production.[103-104]

In recent years, DBU catalysis has found increasing use in the synthesis of complex enone derivatives, spirocyclic scaffolds, and functionalized heterocycles, highlighting its complementarity to phosphine and NHC-catalyzed processes. Its broad scope, simplicity, and compatibility with diverse functional groups underscore its value as a robust organocatalyst in modern organic synthesis.



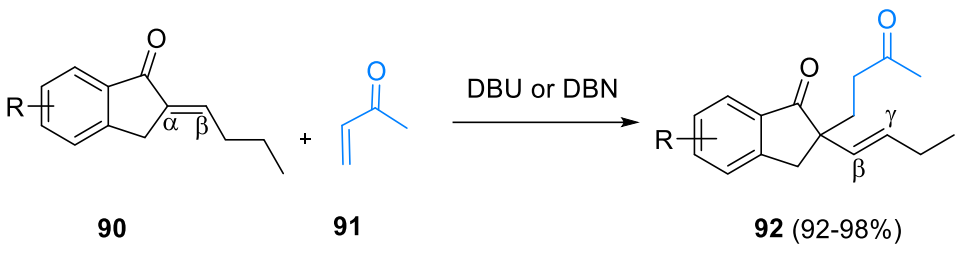
Scheme 25. General DBU-Catalyzed Deconjugative α-Alkylation Reaction.

In this transformation (Scheme 25), DBU acts as a strong, non-nucleophilic or Brønsted base, promoting deprotonation at either the α- or γ-position of conjugated enones to

generate a resonance-stabilized dienolate intermediate. This ambident nucleophile can then undergo selective conjugate addition to an electron-deficient alkene (bearing EWG_2 substituents such as CN, CO_2R, or SO_2Ph), forming a new C-C bond and affording α-substituted β,γ-unsaturated enone products, respectively. The reaction proceeds efficiently under mild, metal-free conditions, demonstrating the ability of DBU to mediate deconjugative alkylation and vinylogous transformations with high selectivity. This process exemplifies the synthetic versatility of DBU in promoting base-induced functionalization of conjugated carbonyl compounds, expanding its utility in the construction of complex molecular frameworks.

Representative examples are outlined below.

DBU and its structural analogue DBN have also proven highly effective in promoting intermolecular deconjugative α-alkylation reactions between cyclic enones (**90**) and ketones (**91**). As reported by Cragoe and co-workers in 1986 (Scheme 26),[105] treatment of indanone derivatives with aliphatic ketones in the presence of DBU affords fused polycyclic ketones through a base-promoted deconjugative α-alkylation pathway. In this transformation, deprotonation at the γ-position of the enone leads to a dienolate intermediate, which subsequently reacts at the α-position of the carbonyl acceptor, resulting in migration of conjugation.This reaction provides a direct and efficient route to complex polycyclic frameworks of medicinal importance, underscoring the value of bicyclic amidine bases such as DBU and DBN in drug-oriented synthetic methodologies.

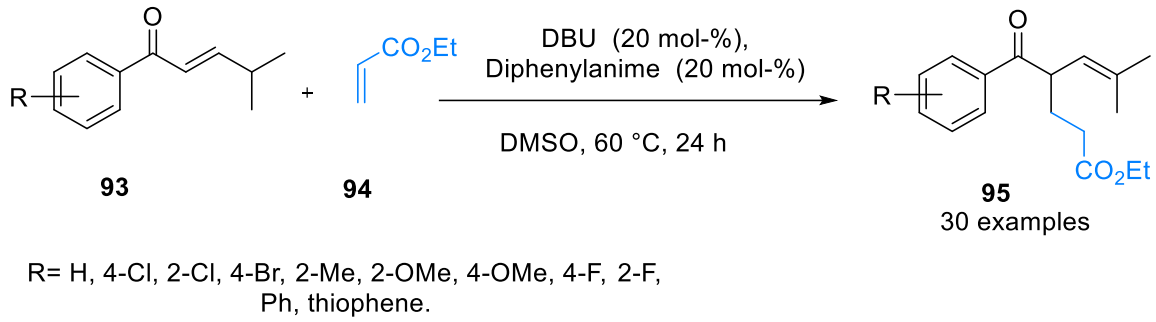


90 **91** **92** (92-98%)

Scheme 26. DBU-Catalyzed Regioselective α-Alkylation of Enones **90.**[105]

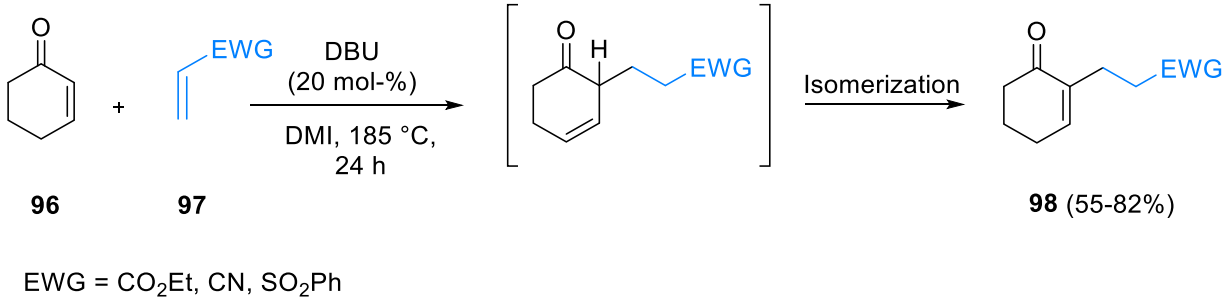
In 2021 Tian and co-workers (Scheme 27) reported a DBU-catalyzed deconjugative coupling of chalcones **93** with acrylates **94**, assisted by diphenylamine as an additive. Under optimized conditions (20 mol-% DBU, 20 mol-% diphenylamine, DMSO, 60 °C,

24 h),[106] the reaction efficiently furnished γ-alkylated chalcone derivatives in moderate to excellent yields across a broad substrate scope (30 examples). Both electron-donating and electron-withdrawing substituents on the aryl ring were well tolerated, including halogens, methoxy, thiophene, and phenyl groups.



Scheme 27. DBU-Catalyzed Regioselective α-Alkylation of Enones **93** via Vinylogous Enolate Formation.[106]

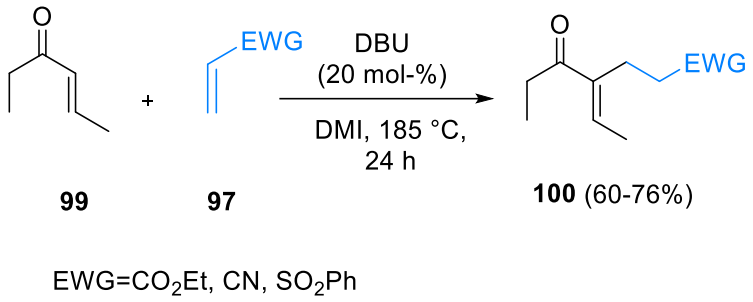
In 1992, Hwu and co-workers developed a DBU-catalyzed coupling between cyclic ketones **96** and electron-deficient alkenes **97**.[107] Using 20 mol-% DBU in DMI (1,3-Dimethyl-2-imidazolidinone) at the very high temperature of 185 °C for 24 h, the transformation delivered α-substituted α,β-unsaturated ketone derivatives in 55-82% yield, obviously as a consequence of a base-catalyzed isomerization of the initial addition product (Scheme 28). The method tolerated various electron-withdrawing substituents on the alkene, such as ester, nitrile, and sulfone groups.



Scheme 28. DBU-Catalyzed Coupling of Cyclic Ketones **96** with Electron-Deficient Alkenes **97**.[107]

Hwu and co-workers further extended the DBU-catalyzed coupling to α,β-unsaturated ketones[107] Treatment of enones **99** with electron-deficient alkenes **97** (20 mol-% DBU,

DMI, 185 °C, 24 h) furnished α-alkylated ketone derivatives in 60-76% yield. A range of activated olefins, including acrylates, acrylonitrile, and vinyl sulfones, participated smoothly in the reaction. This study demonstrated the versatility of DBU in promoting C-C bond formation, expanding the scope from simple cyclic ketones to conjugated enones.



Scheme 29. DBU-Catalyzed Coupling of Enones **99** with Electron-Deficient Alkenes **97**.[107]

1.4 Synthetic Challenges

Despite the impressive progress in C-C bond-forming methodologies, the synthesis of heterocycles and polycyclic scaffolds continues to present significant synthetic challenges. These structures are common in natural products, pharmaceuticals, and functional materials, and their construction often requires precise control over multiple bond-forming events within a single sequence.

One major challenge lies in achieving selectivity. Regioselectivity must be controlled to ensure bond formation at the desired site, stereoselectivity is required to establish the correct three-dimensional architecture, and chemoselectivity is essential to avoid undesired side reactions in the presence of multiple functional groups. Furthermore, the formation of small or highly fused rings introduces issues of ring strain and conformational rigidity, which can limit reactivity or lead to undesired byproducts.

To overcome these difficulties, chemists have increasingly turned to cascade (or tandem) reactions, annulations, and pericyclic processes, which enable the construction of multiple bonds and rings in a single operation. These strategies not only increase synthetic efficiency by reducing the number of steps but also improve overall atom economy and minimize waste generation.

In this context, the development of catalytic methods that are mild, efficient, and broadly applicable is of great importance. Such approaches allow access to diverse heterocyclic and polycyclic frameworks from relatively simple starting materials. The methodologies explored in this thesis-including Lewis acid-promoted Oxa-Diels-Alder reactions, phosphine-mediated annulations and DBU-catalyzed deconjugative alkylations address these challenges by providing practical and efficient routes to rigid, functionalized, and biologically relevant heterocyclic scaffolds.

1.5 Aims and Scope of This Thesis

The work presented in this thesis is motivated by the continuing need for efficient, selective, and sustainable methods for the construction of heterocyclic and polycyclic scaffolds. As outlined above, Lewis acid catalysis, phosphine organocatalysis, and DBU-mediated catalysis each provide powerful yet complementary strategies for carbon-carbon bond formation. However, despite important progress, several challenges remain: extending the scope of catalytic Oxa-Diels-Alder reactions to new substrates, developing phosphine-catalyzed annulations that enable divergent pathways, and harnessing DBU catalysis for regioselective transformations under mild, metal-free conditions.

The aims of this thesis are therefore threefold

1. To explore Lewis acid-catalyzed Oxa-Diels-Alder reactions of 3-ylideneoxindoles and related systems, with the goal of developing efficient routes to fused heterocycles of biological interest.

2. To investigate phosphine-catalyzed transformations, including Rauhut-Currier-type couplings and (3+2) annulations, for the construction of oxindole frameworks. Particular emphasis is placed on understanding how catalyst structure governs pathway selectivity and stereochemical outcome.

3. To develop DBU-catalyzed deconjugative α-alkylations of α,β-unsaturated enones with alkenes, providing a mild, metal-free strategy for accessing functionalized carbon frameworks with broad substrate scope.

The central theme of this work is to illustrate how carefully tailored catalytic systems, including Lewis acids, phosphines, and DBU, can exert control over reactivity,

regioselectivity, and stereoselectivity in C-C bond-forming reactions. By systematically exploring these catalysts, the methodologies established herein contribute to the broader field of Organocatalysis and Lewis acid mediated synthesis, offering robust and adaptable strategies for assembling architecturally complex molecular frameworks.

In addition, mechanistic studies including NMR investigations, stereochemical analysis, and X-ray crystallography were carried out to gain deeper insight into the pathways of these reactions and to rationalize observed selectivities. Collectively, these studies aim to expand the synthetic toolbox for the preparation of biologically relevant heterocyclic scaffolds, with potential applications in natural product synthesis and medicinal chemistry.

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2 Results and Discussion

2.1 Synthesis of Azepane-Fused Pyrano[3,2-*b*]indoles via Lewis Acid Catalyzed Oxa Diels-Alder Reactions

The isolation, biological evaluation, and chemical synthesis of novel polycyclic indoles remain areas of significant scientific interest.[1] Medicinally relevant indole-containing scaffolds also include the pyranoindole class of compounds. Several biologically active members of this class exhibit antiinflammatory, analgesic, and antiproliferative properties, such as the CRTH2 receptor antagonist **101**,[2] the clinical drug cebranopadol (**102**),[3] and soyalkaloid A (**103**),[4] a natural product isolated from the soybean plant. In particular, pyrano[3,2-*b*]indoles are found in various antibacterial agents, including the synthetic small molecules **104**[5] and **105**,[6] as well as in antitumor agents such as the estrogen receptor α-binding inhibitor **106**.[7]

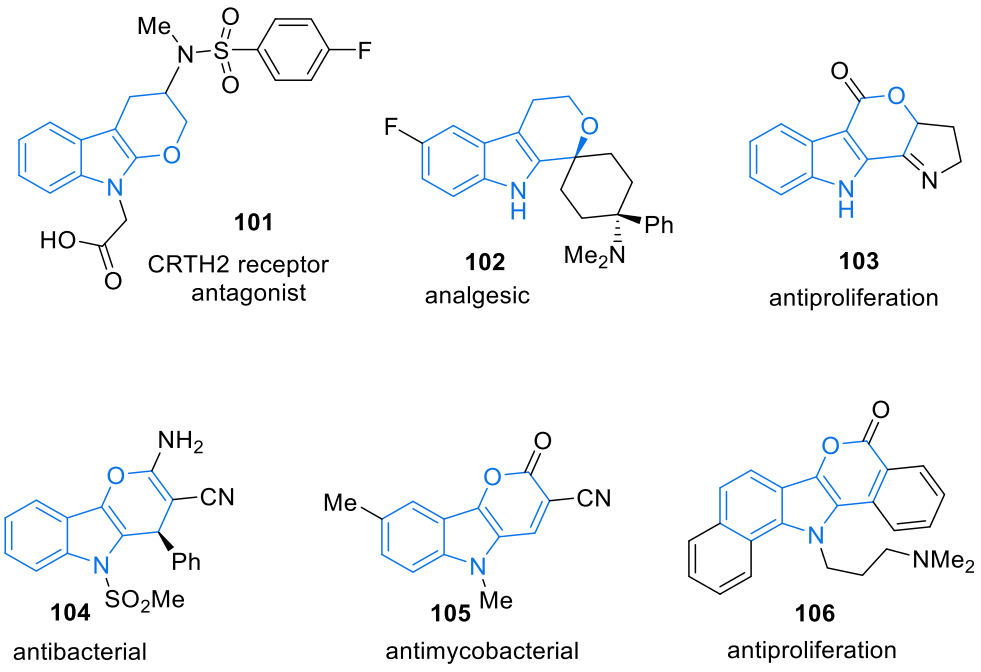
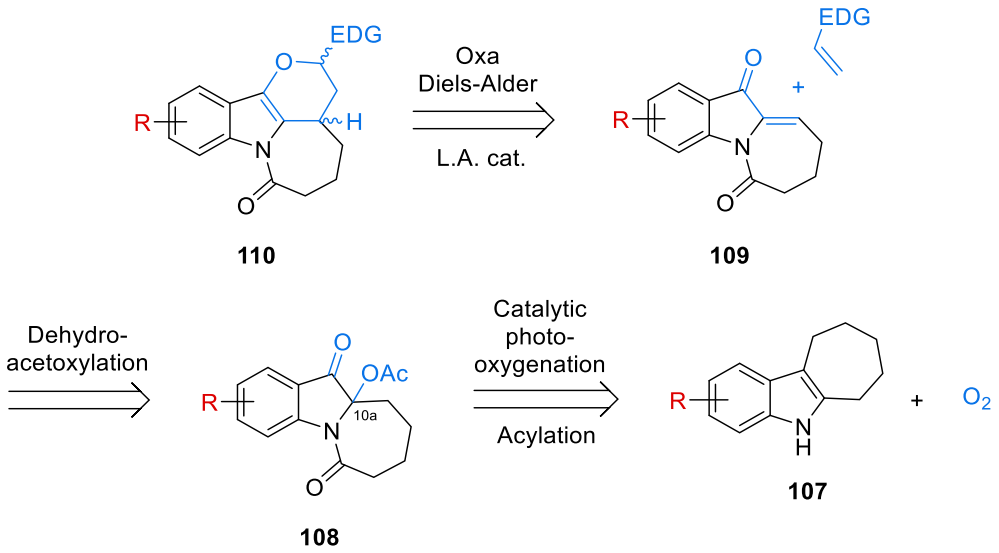


Figure 2. Biologically active pyranoindole compounds.

The primary objective of our investigation was to develop a synthetic strategy for the construction of novel polycyclic pyrano[3,2-*b*]indoles, and the approach centered on exploiting the inverse electron demand Oxa Diels-Alder (ODA) reaction of α,β-unsaturated ketones with alkenes, a powerful cycloaddition method for (4+2)

annulation under Lewis acid catalysis to generate dihydropyrans.[8] Specifically, we wished to utilize the tricyclic dihydroazepino[1,2-*a*]indole-6,11-diones **109** as 1-oxabutadiene components in the (4+2) cycloaddition reaction with electron-rich alkenes, to access the tetracyclic, azepane-fused pyrano[3,2-*b*]indole derivatives **110**. The enones **109** would be derived from the C10a-acetoxylated azepino[1,2-*a*]indoles **108**, which in turn are accessible by a catalytic cascade photooxygenation of cyclohepta[*b*]indoles **113**, which was previously developed in our group (Scheme 30).[9]

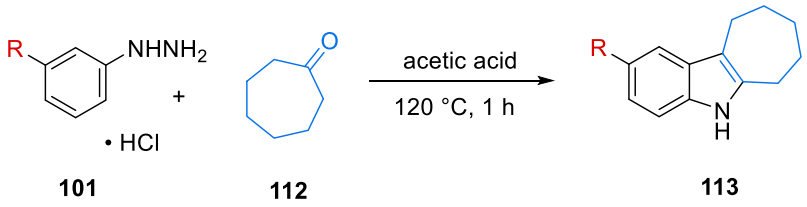


Scheme 30. Inverse electron demand Oxa Diels-Alder reaction of dihydroazepino[1,2-*a*]indole-6,11-diones **109** with electron-rich alkenes, and preparation of enones **109** by catalytic photooxygenation of cyclohepta[*b*]indoles **107**.

2.1.1 Synthesis of dihydroazepino[1,2-*a*]indole-6,11-diones 109

Synthesis of Substituted Cyclohepta[*b*]indoles via Fischer Indole Synthesis

The synthesis of the desired tricyclic enones **109** began with the preparation of cyclohepta[*b*]indoles **113** via a classical Fischer Indole synthesis.[10] The acid-catalyzed condensation of arylhydrazines **111** with cycloheptanone (**112**) gave rise to cyclohepta[*b*]indoles **113**[9] with diverse substituents on the aromatic ring (Scheme 31). As shown in Figure 3, these encompassed substituents like fluoro (F), chloro (Cl), bromo (Br), methoxy (OMe) and methyl (Me), and the corresponding products **113-117** were isolated in 65-86% yield.



Scheme 31. Fischer Indole synthesis utilizing 4-substituted aryl hydrazine chlorides **101** and cycloheptanone (**112**).

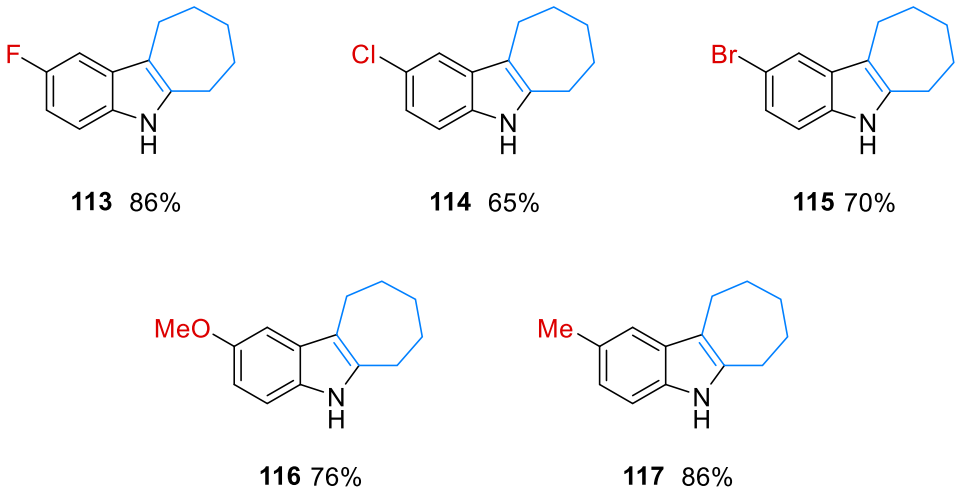
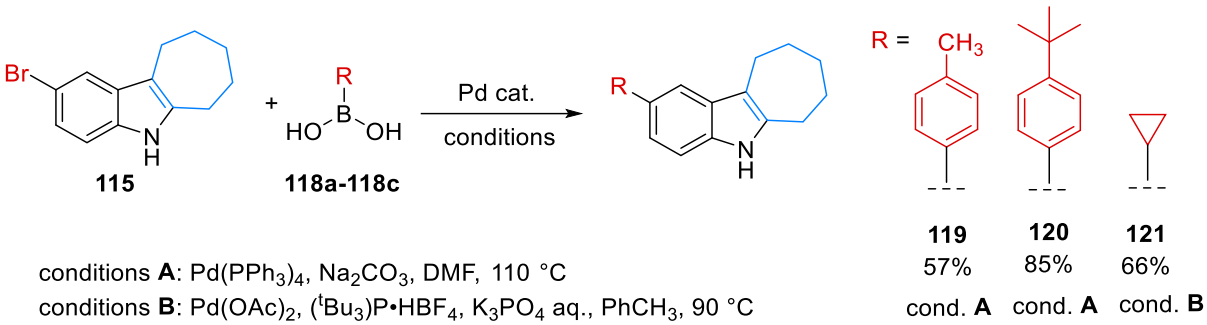


Figure 3. Overview of synthesized of cyclohepta[*b*]indole products.



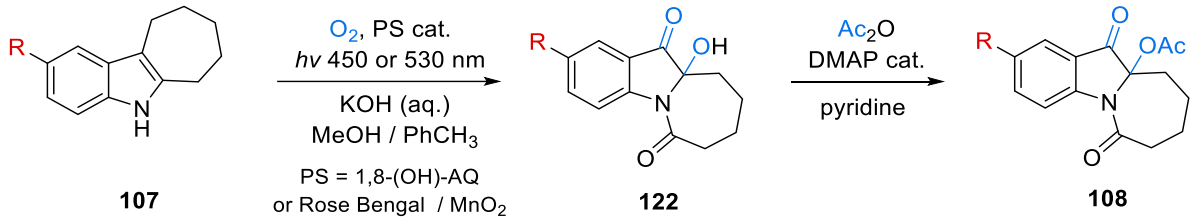
Scheme 32. Suzuki coupling reaction between 2-bromocyclohepta[*b*]indole **115** and boronic acids **118a-118c**.

Three additional cyclohepta[*b*]indoles with aromatic substituents were synthesized via Palladium-catalyzed Suzuki-Miyaura cross-coupling of the 2-bromocyclo-hepta[*b*]indole **115**, which was reacted with *p*-tolylboronic acid (**118a**), 4-(*tert*-butyl)phenylboronic acid (**118b**) and cyclopropylboronic acid (**118c**), either with

$Pd(PPh_3)_4$ or $Pd(OAc)_2$ along with $(^tBu_3)P{\bullet}HBF_4$ (tri(*tert*-butyl)phosphonium tetrafluroborate) as the precatalysts, to give **119**, **120** and **121** in yields between 57-85% (Scheme 32).[9]

Catalytic photooxygenation and acylation

A key innovation in this work lies in the preparation of the azepinoindole enones **119** through a photooxygenation-based protocol.[9] The cyclohepta[*b*]indoles were first subjected to photooxygenation using molecular oxygen under visible light irradiation, and the reaction proceeds in the presence of a photosensitizer (PS), such as 1,8-dihydroxyanthraquinone (1,8-(OH)-AQ), or Rose Bengal in combination with MnO_2. Under 450 or 530 nm LED light irradiation in a mixed solvent system of methanol and toluene, along with aqueous potassium hydroxide solution, a cascade oxidation sequence occurs to produce the C10a-hydroxylated perhydroazepino[1,2-*a*]indoles **122** as the primary products (Scheme 33).



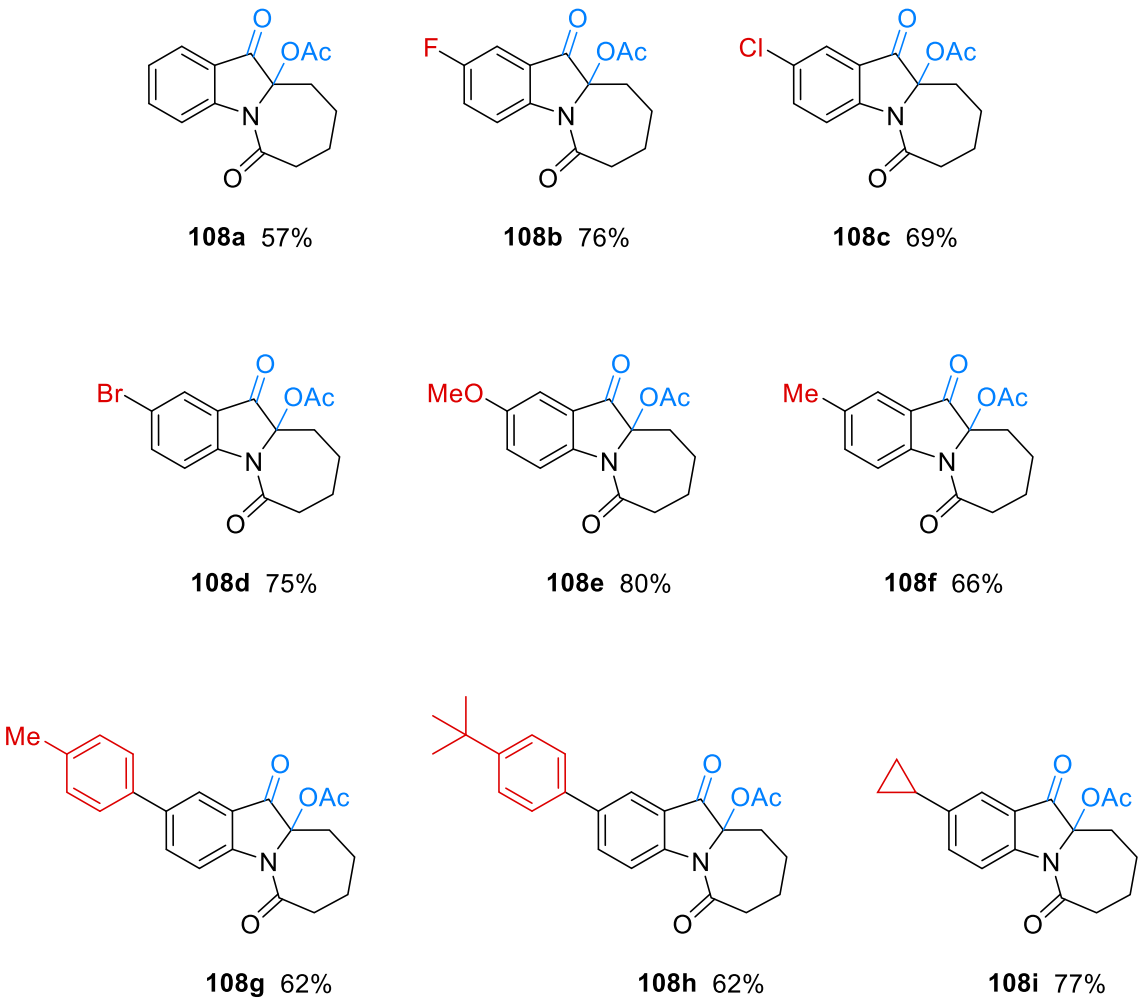
Scheme 33. Photooxygenation of cyclohepta[*b*]indoles and acetylation to perhydroazepino[1,2-*a*]indole acetates **108**.

The crude hemiaminal-type intermediates **122** were subsequently acetylated without prior purification, using acetic anhydride (Ac_2O) and a catalytic amount of 4-dimethyl-aminopyridine (DMAP) in pyridine.[11] This two-step protocol afforded the perhydroazepino[1,2-*a*]indole acetates **108** in good to excellent yields of 57-80% as shown below in Figure 4.

Organophosphate-catalyzed dehydroacetoxylation of perhydroazepino[1,2-*a*]indole acetates 108

Following the preparation of perhydroazepino[1,2-*a*]indole acetates **108**, their dehydroacetoxylation to the dihydroazepino[1,2-*a*]indole-6,11-diones **122** needed to be performed. This reaction was achieved under Brønsted acid catalysis, facilitating

elimination of the acetate and formation of the conjugated enone system. The transformation was conducted using bis(4-nitrophenyl) phosphoric acid as the catalyst (10 mol-%) in toluene solution at 120° C (Scheme 34). A larger number of substituted perhydroazepino[1,2-*a*]indole acetates **108** were successfully transformed to enones **109** under these conditions, which were obtained in moderate to high yields between 60-94% (Figure 5). The reaction was tolerant to both electron-donating and electron-withdrawing substituents on the indole ring.

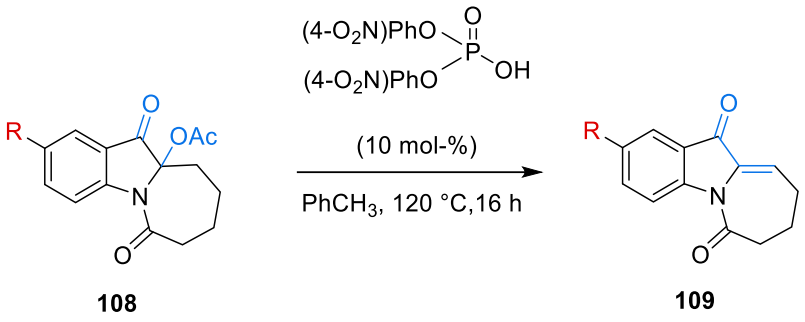


108a 57% **108b** 76% **108c** 69%

108d 75% **108e** 80% **108f** 66%

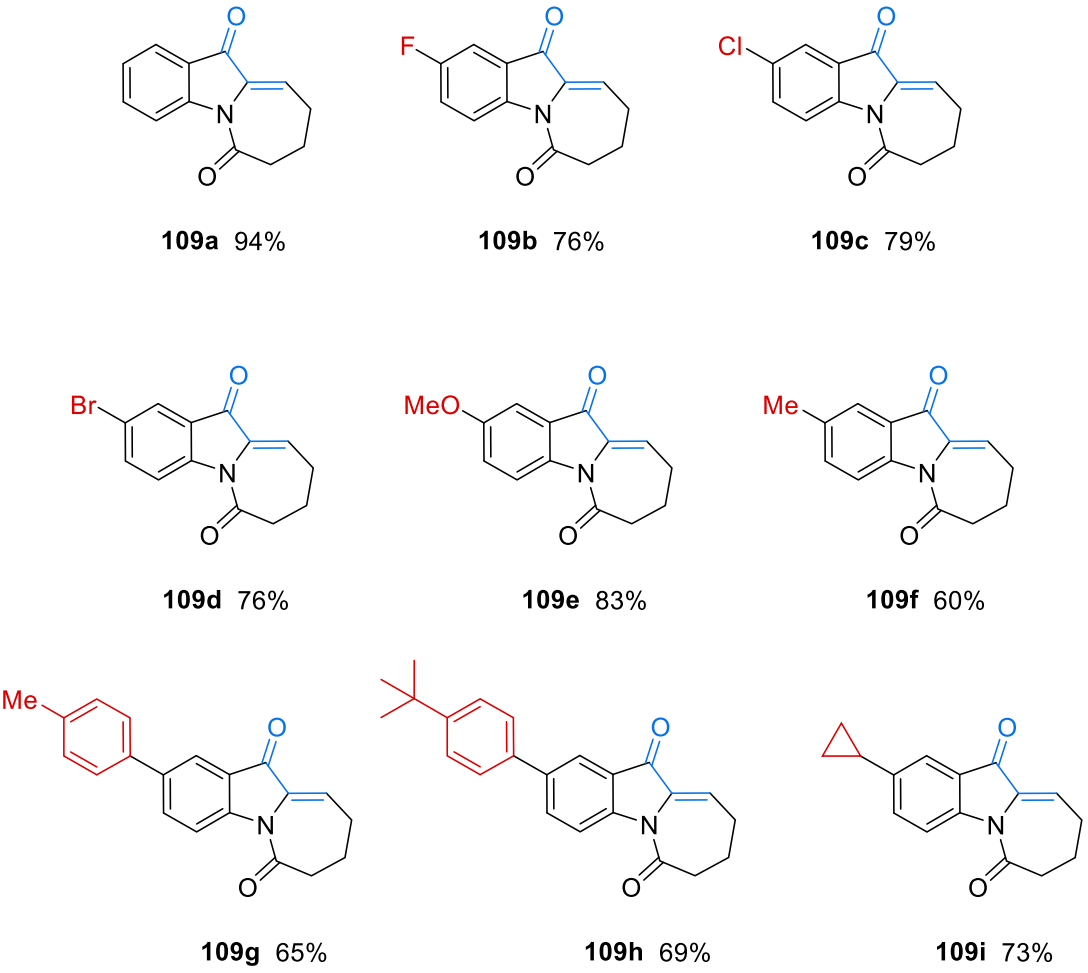
108g 62% **108h** 62% **108i** 77%

Figure 4. Overview of the synthesized perhydroazepino[1,2-*a*]indole acetates **108**.



108 **109**

Scheme 34. Organophosphate-catalyzed dehydroacetoxylation of perhydroazepino[1,2-*a*]indole Acetates **108** to give enones **109**.



109a 94% **109b** 76% **109c** 79%

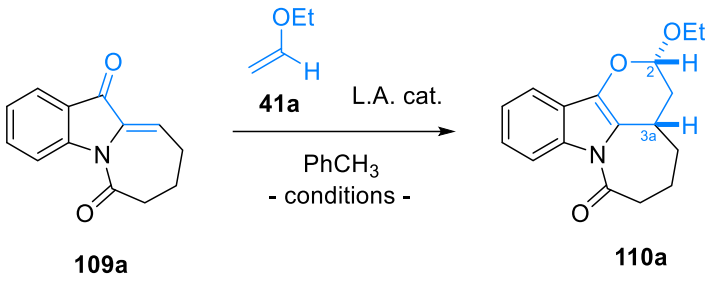
109d 76% **109e** 83% **109f** 60%

109g 65% **109h** 69% **109i** 73%

Figure 5. Overview of the synthesized dihydroazepino[1,2-*a*]indole-6,11-diones **109**.

2.1.2 Inverse electron demand Oxa Diels-Alder reaction of enones 109 with vinyl ethers

Table 1. Optimization of reaction conditions of the Oxa Diels-Alder reaction between enone **109a** and ethyl vinylether (**41a**).



Entry	Catalyst	mol-%	41a (equiv.)	Temp (°C)	Time (h)	Conv. of 109a (%)[a]	Yield of 110a (%)[a]
1	AgOTf	10	100	100	20	Decomposition	n.d.
2	$Cu(OTf)_2$	10	100	100	20	Decomposition	n.d.
3	$Sc(OTf)_3$	10	100	100	20	72	47
4	$Yb(OTf)_3$	10	100	100	20	60	52
5	$Yb(fod)_3$	10	100	100	20	61	58
6	$Yb(fod)_3$	10	100	40	100	100	51
7	$Yb(fod)_3$	20	100	20	100	54	
8	$Yb(fod)_3$	20	10	100	20	100	62
9	$Yb(fod)_3$	15	10	75	20	100	51
10	$Yb(fod)_3$	15	10	50	20	97	71 (70)[b]
11	$Yb(fod)_3$	15	10	22	20	60	57
12	$Yb(fod)_3$	10	10	50	20	93	64
13	None	–	10	50	20	0	0

a) Determined by ^{1}H-NMR against CH_2Br_2 standard. b) Isolated yield afterchromatography.

Reaction development

With a set of tricyclic enones **109a** in hand, a screening for suitable alkenes and Lewis acids for the inverse electron demand Oxa Diels-Alder reaction was initiated. Enone **109a** was chosen as model substrate and reacted with ethyl vinylether (**41a**) under varied reaction conditions (Table 1).

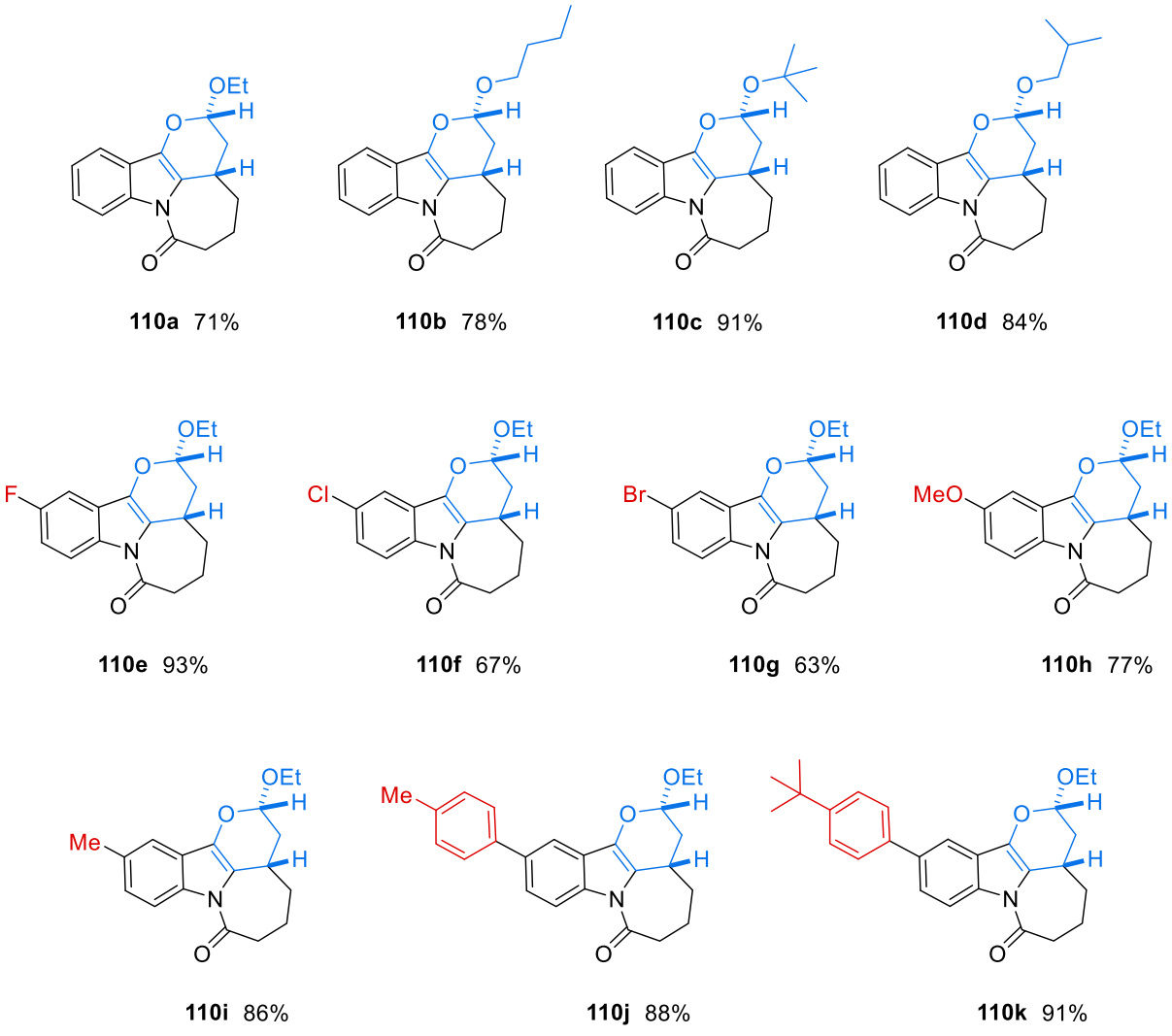
Initial trials using AgOTf and $Cu(OTf)_2$, at 100°C in toluene solution, resulted in decomposition of the starting material **109a** under standard conditions (Table 1, entries 1 and 2). By contrast, $Sc(OTf)_3$ and $Yb(OTf)_3$ cleanly promoted the cycloaddition between enone **109a** and ethyl vinylether (**41a**), to generate the tetracyclic pyrano[3,2-*b*]indole **110a**, with moderate conversions of enone **109a** after 20 h reaction time, and to give the cycloadduct in 47% and 57% yield, respectively (Table 1, entries 3 and 4).

Subsequently, $Yb(fod)_3$, ytterbium(III) tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate), emerged as the most effective catalyst, delivering significantly improved yields. Further optimization revealed that using 15 mol-% $Yb(fod)_3$ with 10 equivalents of ethyl vinyl ether (**41a**) in toluene at 50 °C for 20 hours resulted in the best outcome, affording cycloadduct **110a** in 70% isolated yield with excellent diastereoselectivity in favor of the C2,C3a-*cis*-configured compound (*d.r.* = 97:3; Table 1, entries 5-12). In summary, $Yb(fod)_3$ emerged as the most suitable homogeneous catalyst for the Oxa Diels-Alder reaction between enone **109a** and ethyl vinylether (**41a**). This lathanide catalysts enables the (4+2)-cycloaddition under mild conditions, and has been utilized in a number of homogeneously catalyzed Diels-Alder and hetero Diels-Alder reactions in the past.[12]-[16]

Scope of the Oxa Diels-Alder reaction

The scope of the Oxa Diels-Alder reaction was further explored using a variety of enones **109a** and vinyl ether partners (Figure 7). The reaction conditions optimized for the preparation of compound **110a**, that is, 15 mol-% of $Yb(fod)_3$, 10 equivalents of vinyl ether dienophile, in toluene at 50 °C for 20 h, proved generally applicable across these substrate pairs, affording a range of azepane-fused pyrano[3,2-b]indoles **110a**-**110k** in good to excellent yields (63-93%) and consistently with high diastereoselectivity in favor of the C2,C3a-*cis*-configured cycloadducts (*dr* ≥ 95:5). The use of alkyl vinylethers like *n*-butyl vinyl ether (**41b**), tert-butyl vinyl ether (**41c**), and isobutyl vinyl

ether (**41d**) allowed further diversification of the pyran ring substitution pattern. Utilization of enones **109b** to **109h** allowed for variation of the substituents of the indole core. All the enones **109a-h** with aromatic substituents again underwent the cycloaddition with ethyl vinylether (**41a**) with high diastereoselectivity (*d.r.* ≥ 95:5) and yielded the corresponding products in good to excellent isolated yields, ranging from 63% to 92%.



110a 71% **110b** 78% **110c** 91% **110d** 84%

110e 93% **110f** 67% **110g** 63% **110h** 77%

110i 86% **110j** 88% **110k** 91%

Figure 6. Overview of the synthesized pyrano[3,2-*b*]indoles **110**.

The robustness of the protocol was further validated by scaling up the reaction between enone **109a** and ethyl vinylether (**41a**) to a 1 mmol scale, yielding cycloadduct **110a** in 79% isolated yield, consistent with small scale results. This underscores the method's scalability and operational simplicity, making it able for larger-scale synthesis and library generation.

Attempts to react aromatic enol ethers such as phenyl vinylether (**123**) and heterocyclic dienophiles like *N*-Boc-dihydropyrrole (**124**) failed under standard conditions, showing no conversion. Similarly, reactions with 2,3-dihydrofuran (**125**) resulted in only partial conversion without significant by product formation.

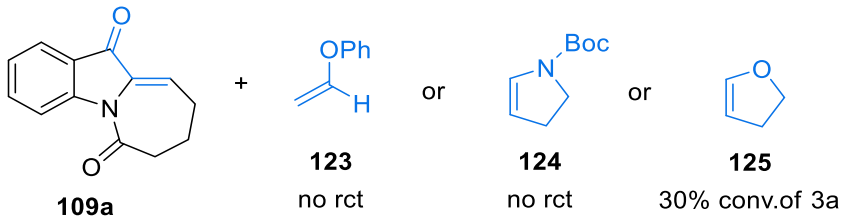
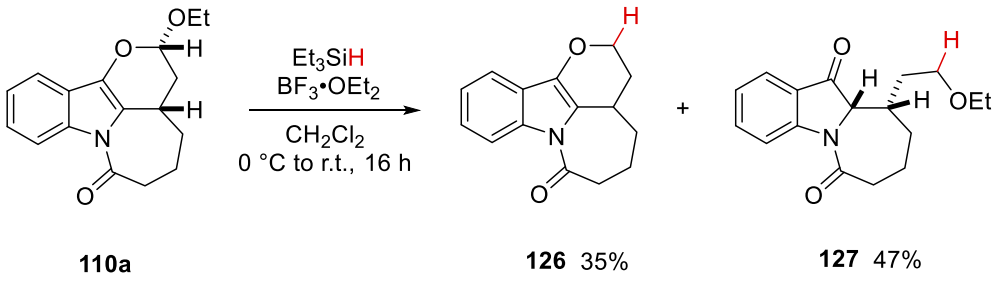


Figure 7. Unsuccessful alkenes in the Yb(fod)$_3$-catalyzed Oxa Diels-Alder reaction with enone **109a**.

Subsequent transformations of cycloadduct 110a

The reactivity of pyranoindole **110a** in reductive transformations was studied. Treatment of compound **110a** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid at 0 °C led to partial reduction of the pyran ring, yielding the dihydropyran derivative **126** in 35% yield, along with a ring-opened azepinoindole **127** in 47% yield, as a single diastereomer (Scheme 35).



Scheme 35. Reductive transformation of pyranoside **110a** with triethylsilane and boron trifluoride etherate.

Mechanistic aspects of the Oxa Diels-Alder reaction

The constitution and relative configuration of the azepane-fused pyrano[3,2-*b*]indoles were unambiguously confirmed by X-ray crystallographic analysis of compound **110a** as well as 2D NOESY-NMR spectroscopy.

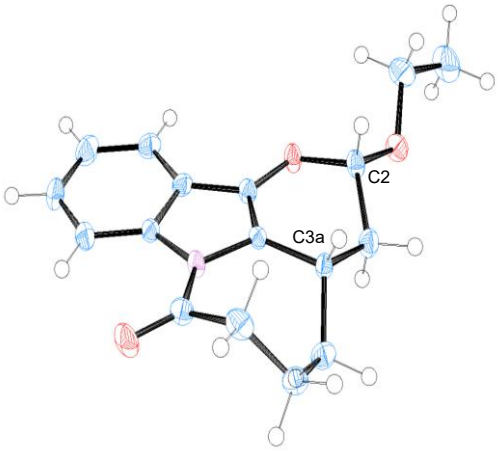


Figure 8. Single crystal X-ray structure of compound **110a**. Thermal ellipsoid contours are shown at 50% probability level.

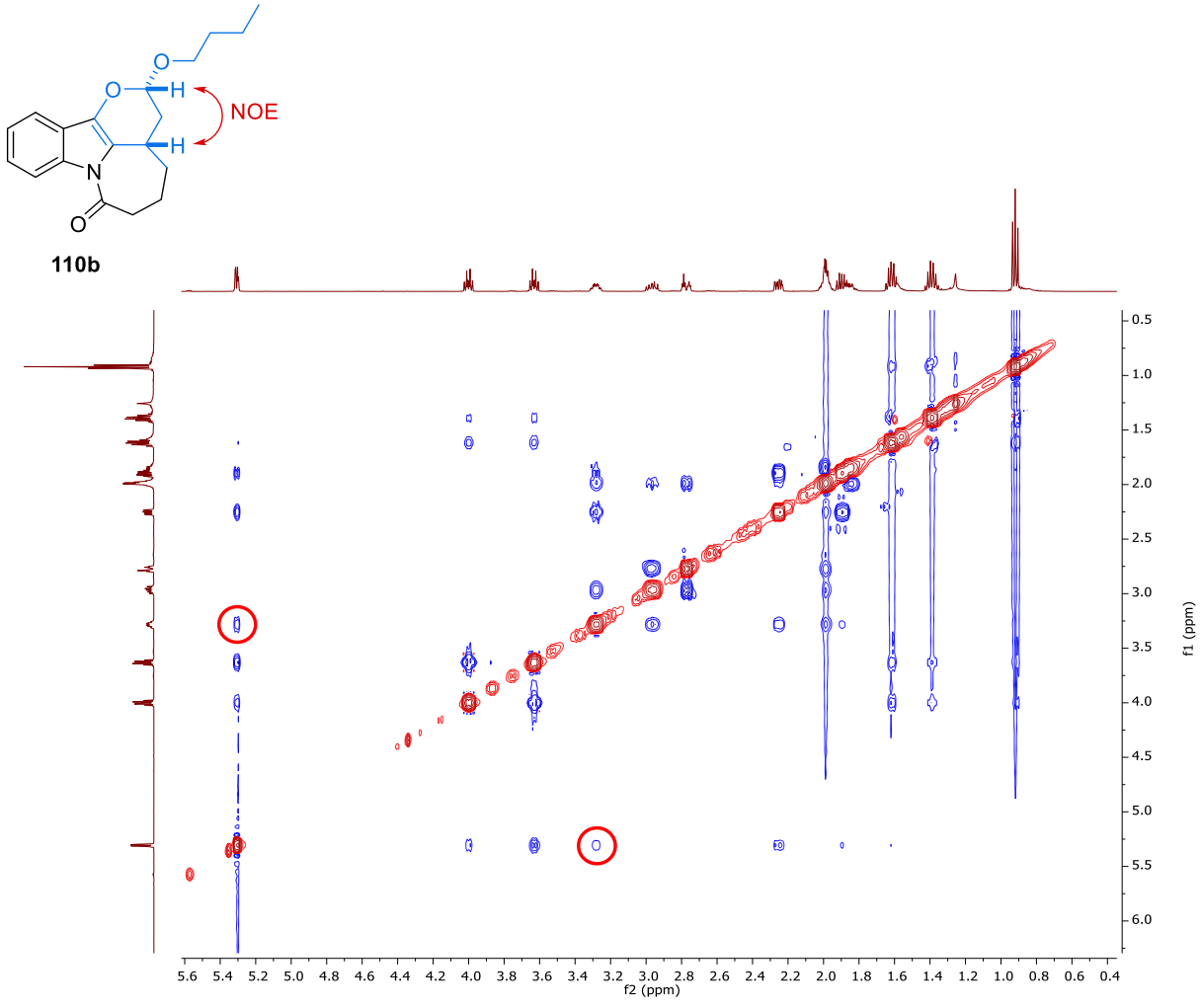
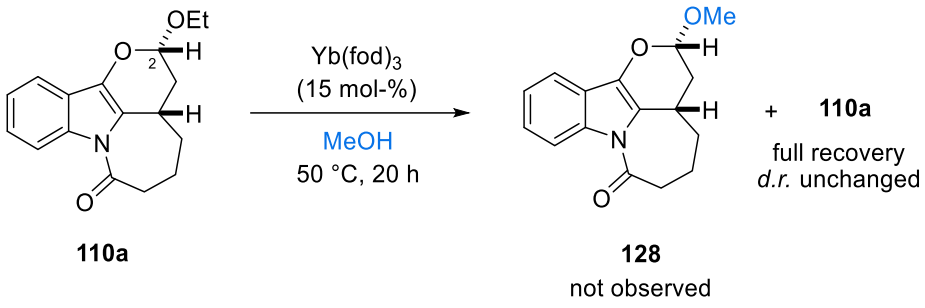


Figure 9. 2D-NOESY NMR spectrum of compound **110b**.

The single crystal X-ray diffraction analysis of product **110a** showed that the proton at C2 of the newly formed tetrahydropyran ring and the methine proton at C3a are *cis*-oriented (Figure 8). Consistent with the crystallographic analysis of compound **110a**, the 2D NOESY spectra of all cycloadducts **110** display a distinct NOE interaction between the protons at C2 and C3a, confirming their relative *cis*-orientation. An exemplary 2D-NOESY spectrum of compound **110b** is depicted in Figure 9. The Oxa Diels-Alder reaction between enones **110** and vinylethers **41** produces almost exclusively (*d.r.* > 95:5) the pyranoindole products with the anomeric C2-alkoxy substituent in the equatorial position of the pyranoside ring. To probe whether an epimerization at the C2 position occurs under the reaction conditions, cycloadduct **110a** was heated in methanol solution in the presence of the Lewis acid catalyst, at 50 °C for 24 h. No transacetalization at the anomeric carbon with methanol was observed, and the C2-configuration of compound **110a** remained unaltered (Scheme 36). This outcome proved that cycloadduct **110a** is stable under the reaction conditions, despite the presence of both a Lewis acid and a nucleophilic solvent (MeOH), which could potentially induce epimerization or ring-opening. There was no evidence of stereochemical scrambling at the C-2 or C-3a positions, nor was the pyran ring susceptible to retro-Diels-Alder reaction or nucleophilic attack under these conditions.



Scheme 36. Attempted transacetalization and anomeric epimerization of pyranoside **110a** under the typical reaction conditions.

The C2,C3a-*cis*-configured cycloadducts **110a**, with an equatorial C2-alkoxy substituent, do not benefit from any stabilization by the anomeric effect. Along with their evidently high stability towards anomeric epimerization under the Lewis-acidic reaction conditions, this suggests a concerted rather than a stepwise (4+2)-cycloaddition. The relative configuration found in cycloadducts **110a** would result from a pericyclic

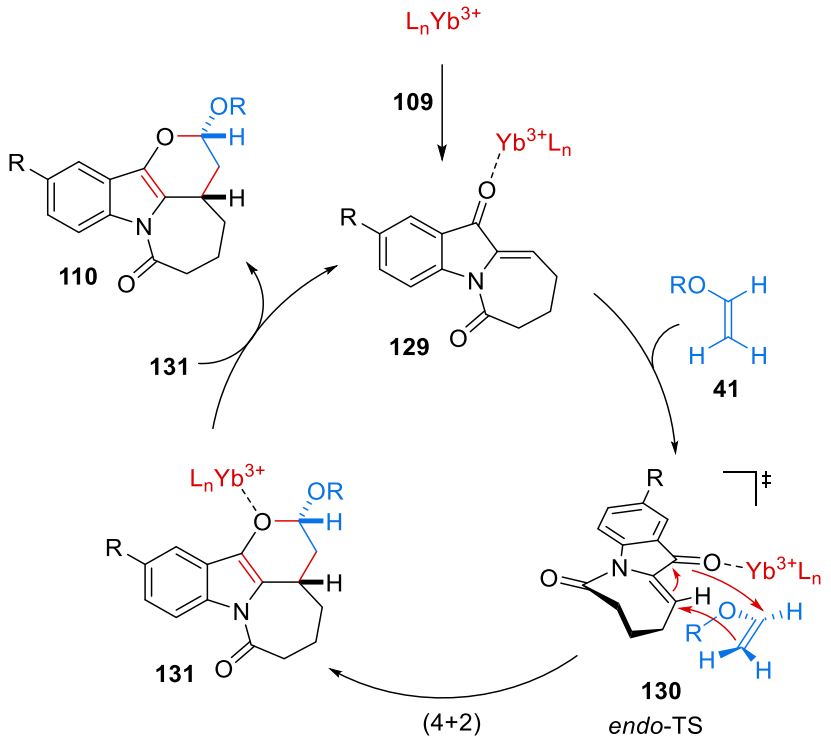
cycloaddition reaction via an *endo* transition state. A high *endo* selectivity is frequently observed in Oxa Diels-Alder reactions catalyzed by $Yb(fod)_3$, and a concerted cycloaddition mechanism is generally accepted.[12-16] Experimental evidence supports its essential catalytic function, as no product formation is observed in the absence of $Yb(fod)_3$ (Table 1, Entry 13), confirming its crucial role in promoting the transformation.

A proposed catalytic cycle for the Oxa Diels-Alder reaction is depicted in Scheme 37. The 1-oxadiene, enone **110**, initially binds to Yb^{3+} with its Lewis-basic carbonyl oxygen, to give substrate-catalyst complex **129**, in which the LUMO energy of the 1-oxadiene π-system is lowered through the Lewis acid activation. Vinylether **41** subsequently interacts with complex **129** in the *endo* transition state **130**. After the (4+2)-cycloaddition, the dihydropyran product is loosely bound to the Yb^{3+} center with is endocyclic pyran oxygen atom in complex **131**. Reaction of complex with another enone molecule **109** releases cycloadduct **110** and regenerates substrate-catalyst complex **130**.

Both, the solid state structure and the solution structure of $Yb(fod)_3$ in toluene are not known, however, Yb^{3+} with its [Xe] $4f^{13}$ electron configuration is known to readily adopt the coordination numbers seven or eight.[17] Therefore, it is considered unlikely that $Yb(fod)_3$ looses one of its chelating heptafluoro-2,2-dimethyl-3,5-octanedionate (fod) ligands upon binding of the enone **109**, but rather forms a seven-coordinate substrate-catalyst complex **132**. While the orientational selectivity of the cycloaddition is dictated by the polarization of the enone and vinylether reactants, the well-established *endo*-diastereoselectivity of the cycloaddition reaction catalyzed by $Yb(fod)_3$ so far has not been explained by a detailed transition state model in the literature. Herein, it is proposed that the *endo* selectivity is a result of steric interactions in the transition state structure of the cycloaddition reaction, and Figure 10 depicts two proposed structures for the *endo* transition state **132** and the *exo* transition state **133'**.

A known crystal structure[18] of the heptacoordinate Terbium(III)-(fod)-complex tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-5-oxooct-3-en-3-olate)-(1*H*-benzimidazole) terbium(III) can serve as a tentative model for the coordination geometry of the *endo* and *exo* transition states **132** and **133'**. In the *exo* transition state **133'**, an unfavorable steric repulsion between the enolether alkoxy substituent and one heptafluoropropyl groups on the neighboring (fod) ligand occurs, rendering the *exo* transition state **133'**

significantly higher in energy than the *endo* transition state **132**. The endo transition state on the other hand may benefit from additional stabilization through π–π* orbital overlap between the vinylether oxygen lone pairs and the CO π* orbital of the enone. The observed *endo* selectivity of the cycloaddition is thus a result of kinetic product control.



Scheme 37. Proposed catalytic cycle for the Oxa Diels-Alder reaction between enones **109** and vinylethers **41** catalyzed by $Yb(fod)_3$.

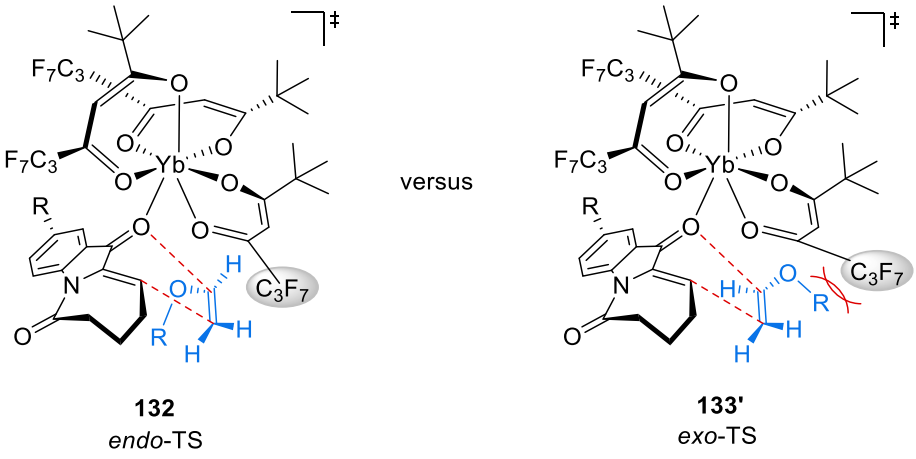


Figure 10. Proposed structures of the *endo* and *exo* transition states **132** and **133'**.

Conclusion

The azepane-fused pyrano[3,2-*b*]indoles synthesized via the Yb(fod)$_3$-catalyzed inverse electron demand oxa Diels-Alder reaction between enones **109** and vinylethers **41** represent a valuable class of densely functionalized *N*,*O*-heterocyclic compounds. Their modular synthesis, broad functional group display, and potential for downstream modifications render this methodology as a synthetically highly useful approach. Future efforts may encompass biological testing of the new tetracyclic pyrano[3,2-*b*]indoles, their pharmacokinetic profiling, and further derivative syntheses.

2.1.3 References

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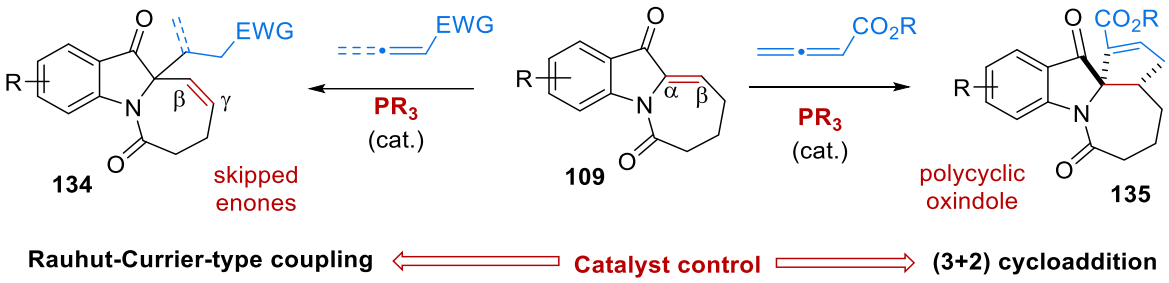
2.2 Phosphine-Catalyzed Crossed Rauhut-Currier-Type Coupling and (3+2) Cycloaddition of 2-Alkylidene-3-indolones 109 with Alkenes and Allenes

In this chapter, we explore the catalyst-controlled product selectivity in tertiary phosphine-organocatalyzed functionalizations of the 2-alkylidene-3-indolones **109** with electron-deficient alkene and allene partners. The study is based on the initial experimental observation that the tricyclic enones **109** in their phosphine-catalyzed reactions with allene carboxylate **64** undergo (3+2)-cycloaddition[1-6] as well as a deconjugative alkylation to yield the α-alkylated β,γ-unsaturated "skipped" enones **134** (Scheme 38). The latter reaction can be classified as a special case of the Rauhut-Currier reaction[7-8] between enones and electrophilic alkenes. During the course of the study, it was established that the skipped enones **134** can be efficiently synthesized via phosphine catalysis utilizing a range of acceptor-substituted alkenes. Further, it was discovered that the product selectivity of the reaction between enones **109** and allene carboxylate **64** can be controlled by the choice of the phosphine catalyst. Through systematic variation of the catalyst, alkene electrophile, and substitution pattern, we demonstrate how catalyst control enables selective access to structurally distinct products from common starting materials.



Scheme 38. Phosphine-catalyzed (3+2)-cycloaddition and deconjugative α-alkylation of enones with alkenes and allene carboxylate.

2.2.1 Phosphine-Catalyzed Crossed Rauhut-Currier-Type Coupling of enones 109 with alkenes

After our initial observation that enones **109**, when reacted with allene carboxylate **65** under phosphine organocatalysis, give the skipped enone **134** in mixture with the tetracyclic (3+2)-adduct **135**, we first aimed at simplying the reaction manifold, by

employing mono-substituted electron-deficient alkenes as coupling partners in the reaction. The reaction between enone **109** and methyl acrylate (**62a**) served as a model transformation, and several classes of nucleophilic catalysts were evaluated. Table 2 shows the reaction development and optimization.

A catalyst screening with 20 mol-% catalyst loading and 16 h reaction time at r.t. in CH_2Cl_2 (under an argon atmosphere) showed that while NEt_3 gave no product, the *N*-heterocyclic bases DABCO and especially DBU promote the reaction between enone **109a** and methyl acrylate (**62a**) to deliver ketone **134a** (Table 2, entries 2-5).

Diverse phosphines could as well be employed with success, with PPh_3 offering complete conversion of enone **109a** after 16 h and the formation of product **134a** in 54% yield (entry 6). Use of the comparatively more electron-rich triarylphosphines P(4-MePh)$_3$, P(4-MeOPh)$_3$, and DPPF led to noticeably poorer conversions of enone **109a** within the same reaction time (entries 7-9).

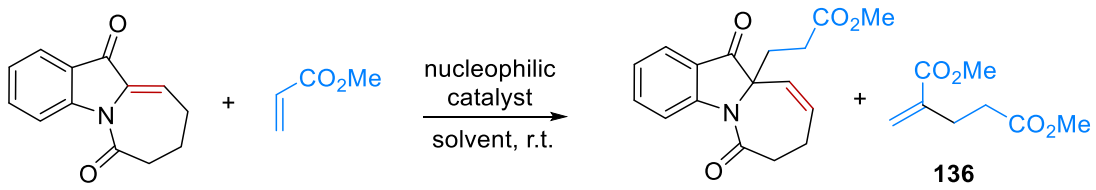
Among trialkylphosphines, PCy_3 showed only 40% conversion, probably owing to its very large cone angle, while PBu_3 gave 92% conversion of enone **109a** and generated compound **134a** in 80% yield (entries 10-11).

The mixed alkylarylphosphines $PMePh_2$ and PMe_2Ph gave the best results (entries 12 and 13), and ultimately, using 10 mol-% of PMe_2Ph and along with a slightly extended reaction duration of 20 h at r.t. in CH_2Cl_2, complete conversion of enone **109a** and an isolated yield of ketone **134a** of 85% could be achieved (entry 16).

Reducing the amount of catalyst to 5 mol-% led to a significant decrease in productivity (entry 17). The reaction with 10 mol-% of PMe_2Ph as the catalyst could as well be performed using EtOAc and acetone as the solvent to give 72% and 68% yields of product **134a**, while use of MeOH led to a halving of the yield.

In summary, the optimal conditions were established as 10 mol-% of PMe_2Ph in CH_2Cl_2 at r.t. for 20 hours, delivering the product **134a** in high yield and excellent selectivity.

Table 2. Development and optimization of reaction conditions of the phosphine-organocatalyzed reaction between enone **109** and methyl acrylate (**62a**).



109a **62a** **134a** **136**

Entry	catalyst	mol-%	solvent	Equiv. of 62a	T (°C)	t (h)	conversion of 109a (%)[a]	yield of 134a (%)[b]	yield of 136 (%)[b,d]
1	–	–	DCM	10	r.t.	16	0	0	0
2	NEt_3	20	DCM	10	r.t.	16	0	0	0
3	DMAP	20	DCM	10	r.t.	16	42	12	0
4	DABCO	20	DCM	10	r.t.	16	48	11	0
5	DBU	20	DCM	10	r.t.	16	100	86	54
6	PPh_3	20	DCM	10	r.t.	16	100	54	quant.
7	$P(4\text{-}MePh)_3$	20	DCM	10	r.t.	16	62	17	trace
8	$P(4\text{-}OMePh)_3$	20	DCM	10	r.t.	16	84	33	trace
9	DPPF	20	DCM	10	r.t.	16	71	19	trace
10	PCy_3	20	DCM	10	r.t.	16	40	18	trace
11	PBu_3	20	DCM	10	r.t.	16	92	80	16
12	$PMePh_2$	20	DCM	10	r.t.	16	100	76	5
13	PMe_2Ph	20	DCM	10	r.t.	16	100	87	60
14	PMe_2Ph	10	DCM	10	r.t.	16	92	69	7
15	PMe_2Ph	15	DCM	10	r.t.	20	100	83	22
16	PMe_2Ph (152)	10	DCM	10	r.t.	20	100	87 (85)[c]	20
17	PMe_2Ph	5	DCM	10	r.t.	20	38	13	0
18	PMe_2Ph	2.5	DCM	10	r.t.	20	36	9	0
19	PMe_2Ph	10	DCM	20	r.t.	20	100	90	14

20	PMe_2Ph	10	DCM	5	r.t.	20	100	83	4
21	PMe_2Ph	10	MeOH	10	r.t.	20	85	50	trace
22	PMe_2Ph	10	Acetone	10	r.t.	20	100	68	9
23	PMe_2Ph	10	EtOAc	10	r.t.	20	100	72	7

General conditions: Reaction performed on 0.10 mmol scale **109a.** [a] Determined by ^{1}H-NMR analysis. [b] Determined by ^{1}H-NMR analysis against CH_2Br_2 standard. [c] Isolated yield. [d] Yield with respect to excessive **61a** used.

Scope of the deconjugative alkylation reaction of enones 109 and alkenes



109 **62** **134**

Scheme 39. Phosphine-catalyzed crossed Rauhut-Currier (RC) coupling with substituted enones **109** and alkenes **62**.

With optimized reaction conditions established, the scope of the transformation was investigated using various enones and acceptor-substituted alkenes. The reaction was tolerant to a range of aromatic substituents on the 2-alkylidene-3-oxoindole framework(Figure 11).

Applying the optimized cross-coupling protocol, a series of tricyclic C10*a*-functionalized β,γ-unsaturated ketones **109** were synthesized. As depicted in Scheme 39**,** the reaction of enone **109a** with various acrylates (**62a**) produced derivatives **134a-134p** in yields ranging from 51% to 96%. Acrylonitrile (**53**) and phenyl vinyl sulfone (**61b**) also served as effective partners, yielding products **134g** and **134h** in 71% and 65%, respectively. Additionally, ethyl propiolate (**62c**) afforded α,β-unsaturated ester in 87% yield (*trans* **134c***/cis* **134c'** = 1.2:1).

Enones **109a, 109b, 109c** bearing halogen substitutions (F, Cl, Br) on the aromatic ring, reacted smoothly with methyl acrylate (**62a**) to products **134j-134l** in 73%−89% yield. Furthermore, methyl and cyclopropyl-substituted enones **109f** and **109i** gave

derivatives **134m** and **134n** in 65% and 92% yield, respectively. The 4-tolyl-substituted enone **109g** and methoxy-substituted **109e** provided products **134o** and **134p** in 96% and 60% yield, respectively.

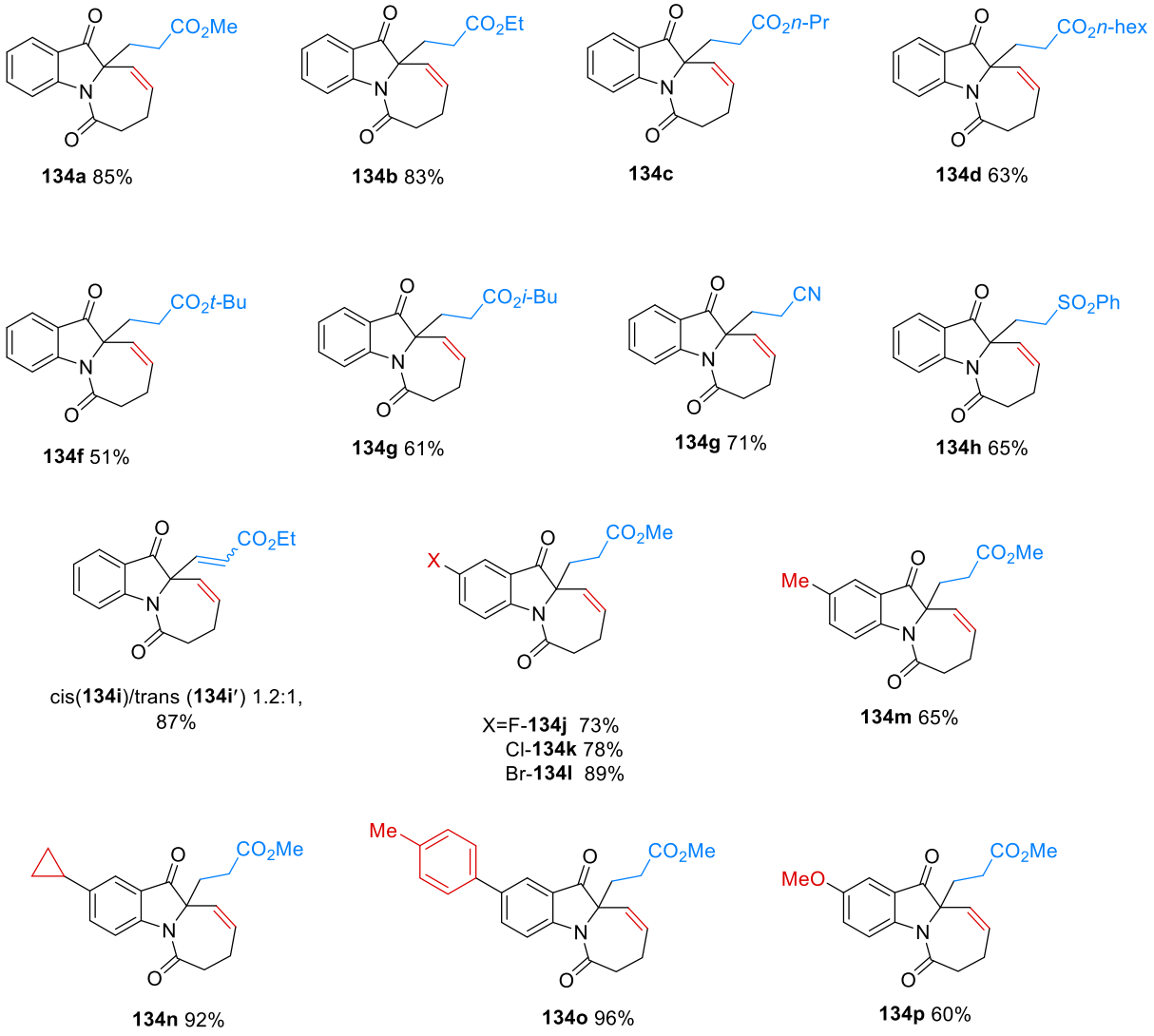
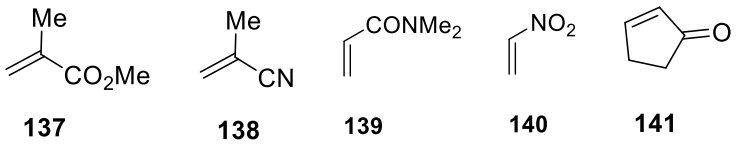


Figure 11. Overview of products formed via phosphine-catalyzed crossed Rauhut-Currier (RC) coupling reactions.

This methodology demonstrates broad applicability for coupling of eneones **109** with mono-acceptor-substituted alkenes. However, *N*,*N*-Dimethyl Acrylamide (**139**) was unreactive under standard conditions, and nitroethylene (**140**) underwent polymerization. Moreover 1,1 or 1,2-disubstituted alkenes, such as methyl methacrylate (**137**), methacrylonitrile (**138**), and cyclopentanones (**141**), were not suitable for this transformation (Figure 12).

In addition to NMR spectroscopic characterization, the structure assignment was additionally secured by X-ray crystallography for the derivatives **134g** and **134j** (Figures 13 and 14).



137 **138** **139** **140** **141**

Figure 12. Unsuccessful alkenes in the phosphine-catalyzed crossed Rauhut-Currier (RC) coupling with enone **109**.

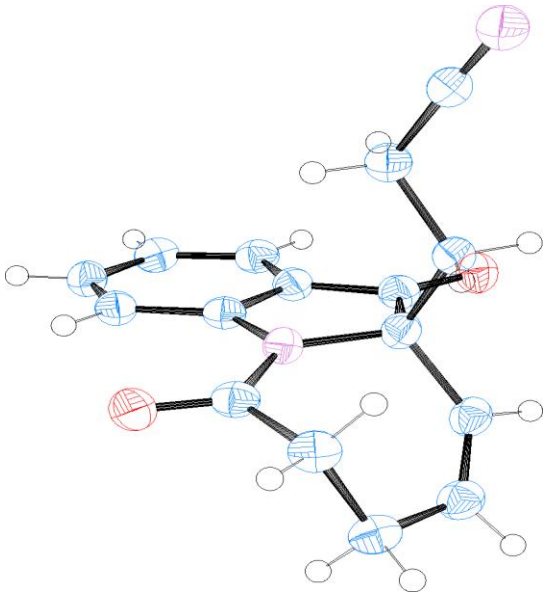


Figure 13. Single crystal X-ray structure of compound **134g**. Thermal ellipsoid contours are shown at 50% probability level.

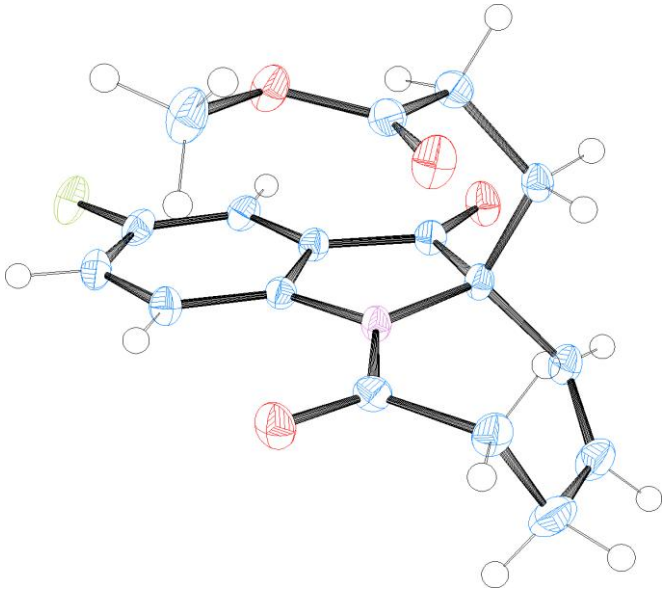
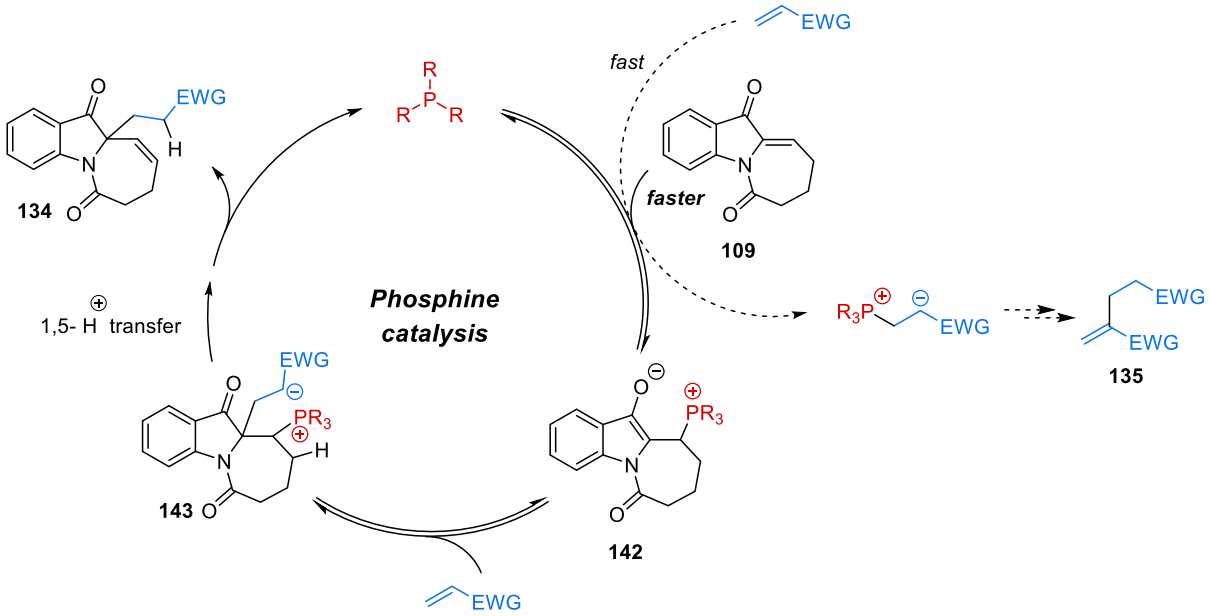


Figure 14. Single crystal X-ray structure of compound **134j**. Thermal ellipsoid contours are shown at 50% probability level.

Mechanistic Insights and Proposed Reaction Pathway



Scheme 40. Proposed mechanism of the phosphine-catalyzed crossed Rauhut-Currier (RC) reaction between enones **109** and mono-acceptor-substituted alkenes.

With regard to the reaction mechanism, it is proposed that the phosphine catalyst first engages in a nucleophilic attack on the activated enone, generating a zwitterionic

phosphonium-enolate intermediate **142**. This reactive species subsequently undergoes a Michael-type addition of the 2-alkylidene-3-oxoindole, thereby forming a new C-C bond in a crossed Rauhut-Currier fashion. The resulting secondary intermediate **143** then undergoes a 1,5-proton transfer, followed by elimination to release the product and the active phosphine catalyst, thus completing the catalytic cycle.

Mechanistic Studies and Control Experiments

Several control reactions were conducted to validate the proposed mechanism. When the reaction was run without phosphine catalyst, no product formation was observed, confirming the essential role of nucleophilic phosphine catalysis. Use of substituted phosphines with bulky groups reduced the yields, suggesting a delicate balance between nucleophilicity and steric properties of the phosphine. Furthermore, monitoring the reaction by ^{1}H-NMR allowed to detect transient intermediates consistent with the proposed RC-type addition. These findings support a stepwise mechanism rather than a concerted addition, aligning with prior mechanistic studies of related phosphine-catalyzed processes.[9]

^{31}P-NMR Spectral Analysis

To gain insight into the behavior of the phosphine catalyst under the reaction conditions, ^{31}P-NMR spectroscopy was employed (Figure 15). Spectra were recorded for both the free phosphine catalyst (PMe_2Ph) and the reaction mixtures to probe possible catalyst–substrate interactions and to identify key phosphorus-containing intermediates.[9]

The ^{31}P-NMR spectrum of PMe_2Ph in CD_2Cl_2 showed a singlet at δ −45.5 ppm, corresponding to the free tertiary phosphine. A minor signal at δ +32.4 ppm was attributed to the corresponding phosphine oxide, which was present in trace quantity in the commercial-grade phosphine reagent. When a mixture of PMe_2Ph and enone **109a** (1:10 ratio) was examined, a new signal appeared at δ +35.4 ppm, consistent with the formation of zwitterionic adduct **142** between the phosphine and the enone. In the third experiment, PMe_2Ph was combined with methyl acrylate **62a** a 1:10 ratio. No significant new peaks were observed, implying no formation of a stable adduct between the phosphine with arylate.

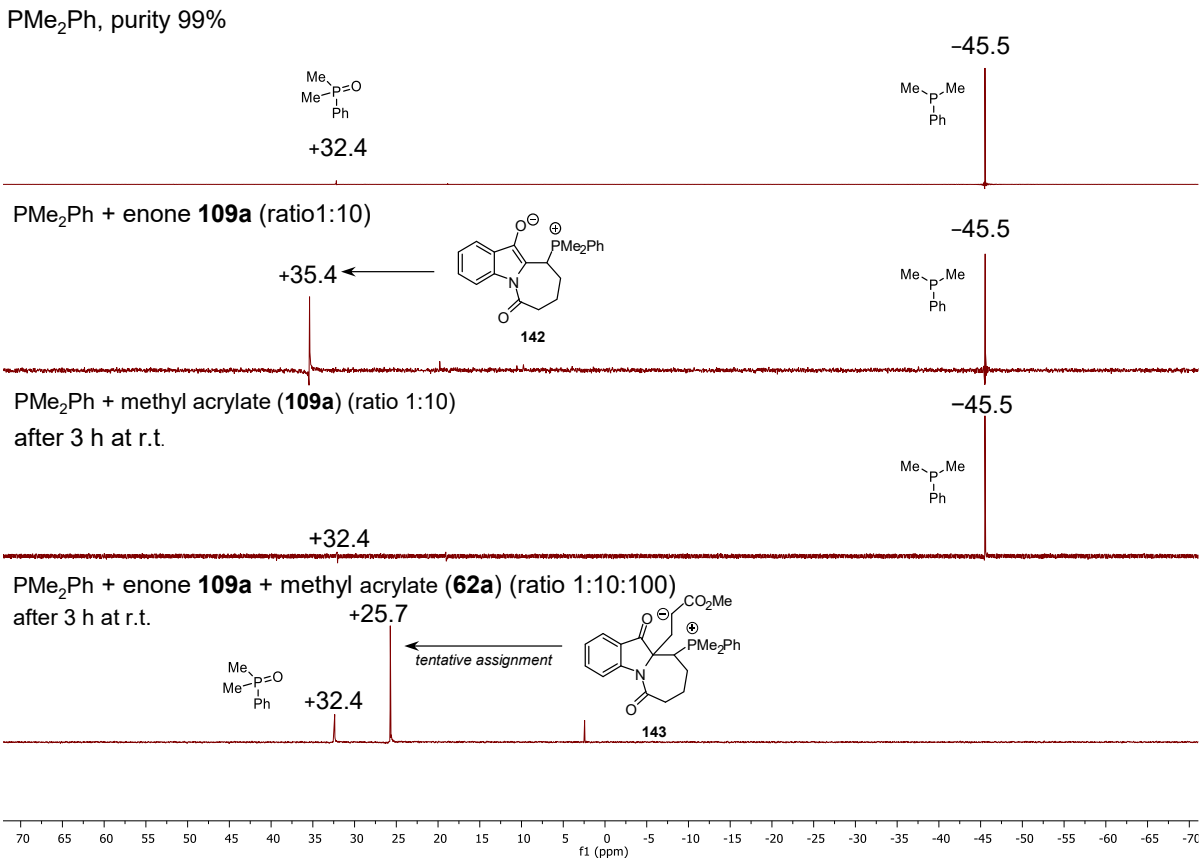


Figure 15. ^{31}P-NMR spectrum phosphine-catalyzed crossed Rauhut-Currier (RC) reaction. ^{31}P-NMR (202 MHz) spectra obtained of isolated and mixed components of reference reaction **109a** + **62a** → **134a** catalyzed by PMe_2Ph. Samples were stirred at r.t. for 3 h prior to NMR measurements.

Finally, in the fourth experiment, a mixture of all three components PMe_2Ph, enone **109a**, and methyl acrylate **62a** in a 1:10:100 ratio after stirring for 3 hours at room temperature was analyzed. A new resonance at δ +25.7 ppm was observed which we tentatively assign to secondary phosphonium intermediate **143**. Collectively, these ^{31}P NMR results lend good support to proposed catalytic mechanism. The disappearance of the free phosphine signal over time, together with the emergence of new resonances, underscores the involvement of phosphine-bound intermediates in the reaction pathway. The broad resonances observed at later time points suggest the presence of multiple species or dynamic equilibria among catalytic intermediates. These findings are consistent with literature reports[9] on phosphine-catalyzed nucleophilic activation of electron-deficient alkenes.

Effect of Additives

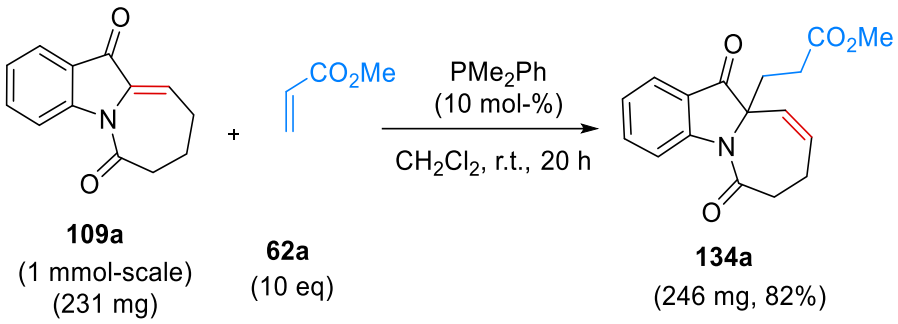
As shown in Figure 16, the reference reaction **(109a+61a→134a)** catalyzed by PMe_2Ph was largely unaffected by the addition of NEt_3, as this tertiary amine does not catalyze the reaction. In contrast, the inclusion of acidic additives had a detrimental effect on conversion. Specifically, *p*-cresol and, more notably, acetic acid significantly inhibited the reaction, with the extent of suppression correlating with increasing acid strength.[10] The impact of water and oxygen was also assessed. The presence of water resulted in an approximate 50% reduction in product yield, highlighting the sensitivity of the reaction to moisture. Furthermore, performing the reaction under an atmosphere of air, instead of inert gas, completely suppressed the transformation. ^{1}H-NMR analysis confirmed rapid oxidation of the phosphine catalyst under aerobic conditions, accounting for the observed deactivation. These findings emphasize the importance of strictly anhydrous and oxygen-free conditions, and demonstrate how basic additives can be beneficial, whereas acidic or oxidative environments are detrimental.

109a + **62a** → **134a**, PMe_2Ph cat. (10 mol-%)

additive (1 eq.)	none	NEt_3	*p*-cresol	HOAc	H_2O	air (1 atm)
yield	87%	93%	73%	2%	51%	0%

Figure 16: Effect of Additives in crossed Rauhut-Currier (RC) coupling between enone **109a** and acrylate **61a**.

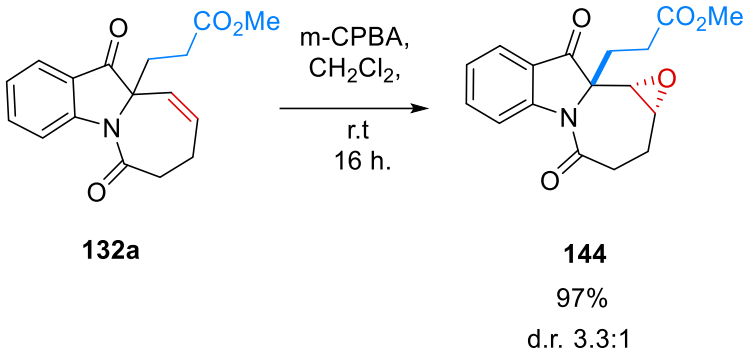
To validate the scalability of the protocol, the synthesis of **134a** was performed on a 1.0 mmol scale under the optimized conditions. Pleasingly, the reaction proceeded smoothly without erosion of yield, affording **134a** in 82% isolated yield (246 mg). This result underscores the practicality and robustness of the method for preparative applications.



Scheme 41. 1 mmole scale reaction of Rauhut-Currier (RC) coupling with enone **109a** and acrylate **62a**.

Further Synthetic Transformations

To demonstrate the synthetic utility of the C10*a*-functionalized β,γ-unsaturated enone scaffold, compound **134a** was subjected to further functional transformations. Treatment of enone **134a** with m-CPBA in dichloromethane at room temperature furnished the corresponding epoxide **144** in 97% yield as a mixture of diastereomers (d.r. 3.3:1, Scheme 42).[11] The relative configuration of the major diastereomer of epoxide **144** could be established unambiguously by single crystal X-ray crystallography (Figure 17).



Scheme 42. Epoxidation of β,γ-unsaturated enone **134a** with m-CPBA.

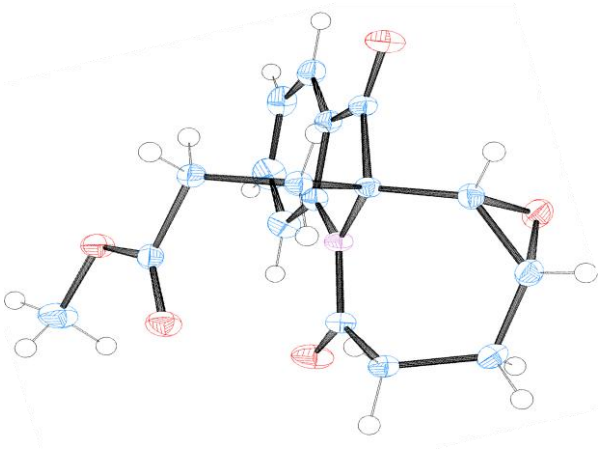
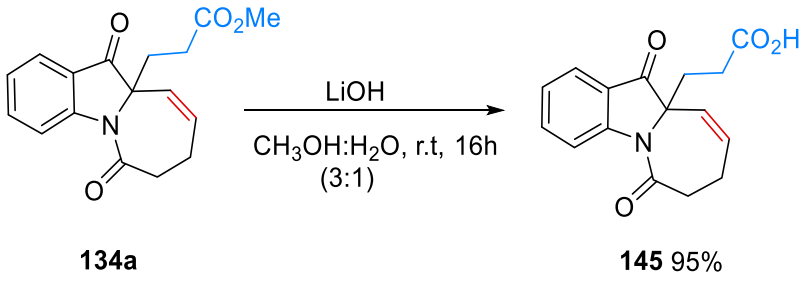


Figure 17. Single crystal X-ray structure of compound **144**. Thermal ellipsoid contours are shown at 50% probability level..

Treatment of methyl ester **134a** with aqueous lithium hydroxide (1.5 equiv.) in a mixture of CH_3OH and H_2O (3:1) at room temperature for 16 hours[12] resulted in smooth conversion to the carboxylic acid **145**. Following acidic workup, compound **145** was obtained in 95% isolated yield as a white solid which was used in the subsequent step without further purification.

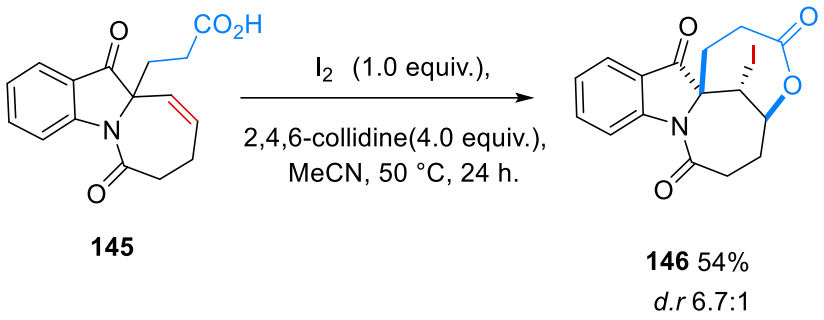


134a **145** 95%

Scheme 43. Saponification of methyl ester **134a** with lithium hydroxide

To further elaborate the carboxylic acid intermediate **145**, an iodolactonization reaction was explored. Treatment of **145** with iodine (1.0 equiv.) and 2,4,6-collidine (4.0 equiv.) in MeCN at 50 °C for 24 h[13] resulted in a clean 7-*endo-tet* cyclization of the intermediary cyclic iodonium species, and the iodolactone **146** was isolated in 54% yield and with good diastereoselectiviy (*d.r.* 6.7:1) after purification. The reaction proceeded with complete regioselectivity, affording a seven-membered lactone fused to the tricyclic core. This transformation highlights the ability of the β,γ-unsaturated acid

intermediate **145** to undergo synthetically valuable oxidative cyclization, thereby enhancing the structural complexity of the scaffold.



145

146 54%
d.r 6.7:1

Scheme 44. Iodolactonization of carboxylic acid **145** with iodine.and 2,4,6-collidine.

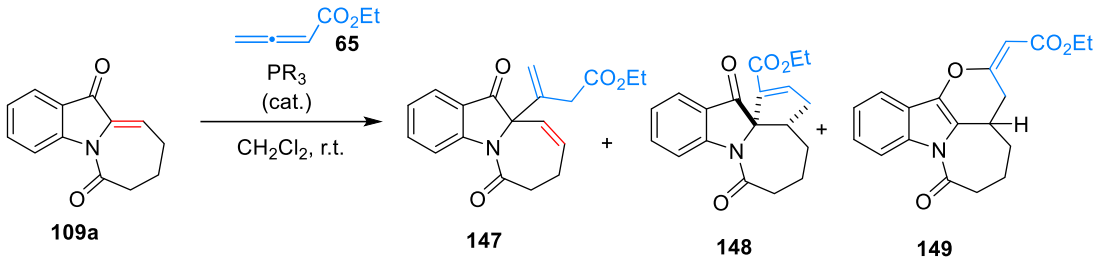
2.2.2 Phosphine-Catalyzed Crossed (3+2)-cycloaddition of enones 109a with allene carboxylate 65

The reactivity of enone **109a** with an allene carboxylate partner was studied. Specifically, the phosphine-catalyzed reaction of enone **109a** with ethyl 2,3-butadienoate (**65**) was examined in depth using a range of tertiary phosphine catalysts (Table 3).[14-15]

The results summarized in Table-3 demonstrate distinct variations in product distribution based on the organocatalyst employed. Triphenylphosphine (PPh_3) predominantly gave the (3+2)-cycloadduct **148,** along with the (4+2)-adduct **149** in a ratio of 79:21, affording a 66% isolated yield of compound **148**. Similarly, mixed alkylaryl phosphines like $PMePh_2$ and PMe_2Ph provided (3+2)-cycloproduct **148** as the major product, with product ratios (**147: 148: 149**) of 11:66:23 and 16:54:30, respectively, with $PMePh_2$ to give 46% and PMe_2Ph delivering 53% and isolated yield of product **148**.

In contrast, bulky or more electron-rich catalysts like P(*t*-Bu)$_3$ and PCy_3 led to the exclusive formation of the Rauhut-Currier product **147**, without any formation of **148** or **149**. These results indicate that phosphine nucleophilicity and steric bulk play critical roles in governing the reaction pathway. Electron-deficient arylphosphines such as

Table 3. Achiral phosphine catalyst screening for the reaction of enone **109a** with allene carboxylate **65**



Entry	Catalyst	mol-%	time [h]	Conversion[a] of 109a (%)	Product ratio [a] 147 / 148 / 149	Yield
1	PPh_3	20	24	86	0 : 79 : 21	**148** 66%[a]
2	$P(4\text{-}MePh)_3$	20	24	80	76 : 24 : 0	n.d.
3	$P(4\text{-}OMePh)_3$	20	24	100	64 : 18 : 18	**147** 48%
		10	48	5	n.d.	n.d.
		5	48	0	–	–
4	$P(4\text{-}FPh)_3$	20	24	7	0 : 100 : 0	n.d.
5	$PMePh_2$	20	24	100	11 : 66 : 23	**148** 46%
6	$PBnPh_2$	20	24	13	0 : 100 : 0	n.d.
7	PMe_2Ph	20	24	100	16 : 54 : 30	**148** 53%
8	PCy_2Ph	20	24	67	63 : 37 : 0	n.d.
9	$P(t\text{-}Bu)_3$	20	24	100	100 : 0 : 0	**147** 61%
		10	48	0	–	–
		5	48	0	–	–
10	PCy_3	20	24	47	100 : 0 : 0	n.d.
11	Di-(1-adamantyl)-*n*-butylphosphine	20	24	0	–	–

General conditions: Reaction performed on 0.10 mmol scale **109a.** [a] Determined by ^{1}H-NMR analysis. (where needed against CH_2Br_2 standard). n.d. = not determined.

$P(4\text{-}FPh)_3$ and also $P\text{-}BnPh_2$ showed complete selectivity for (3+2)-adduct **147**, though with varying leves of conversion.

The constitution and relative configuration of (3+2)-cycloadduct **148** could be established by single crystal X-ray crystallography (Figure 18).

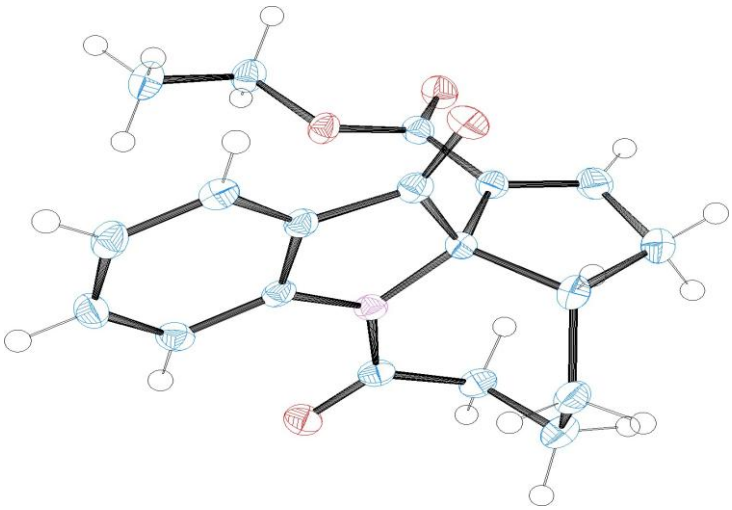


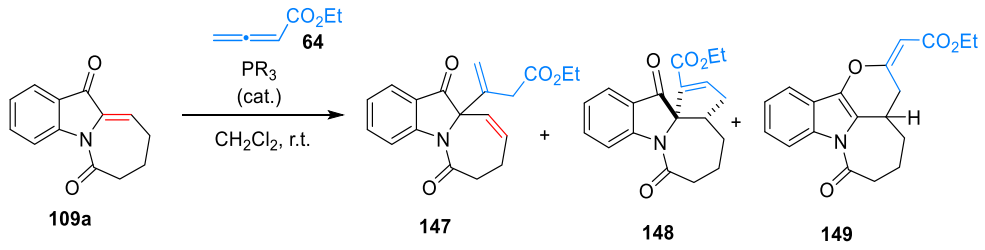
Figure 18. Single crystal X-ray structure of compound **148**. Thermal ellipsoid contours are shown at 50% probability level.

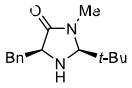
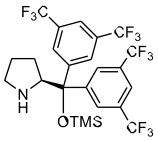
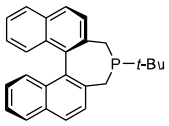
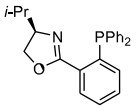
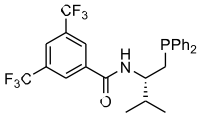
Further, the utilization of chiral phosphine organocatalysts was studied. (Table 4) summarizes the evaluation of nine chiral phosphine catalysts in the asymmetric annulation of enone **109a** with allenoate **65**. The results indicate that only certain structural classes of phosphines are competent in promoting the transformation.

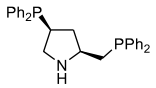
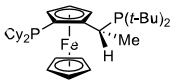
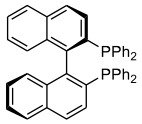
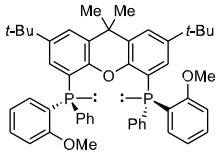
Catalyst Screening with Chiral Phosphines

The screening of chiral phosphines for the reaction of enone **109a** with allene carboxylate **65** (Table 4) revealed pronounced differences in reactivity and selectivity depending on the catalyst structure.

Table 4. Chiral phosphine catalyst screening for the reaction of enone **109a** with allene carboxylate **65.**



Entry	Catalyst	mol-%	time [h]	Conversion[a] of 109a (%)	Product ratio[a] 147: 148: 149	*e.r* of 148[b]	*e.r* of 148 [b]	Yield
1		20	24	0	0: 0: 0	–	–	–
2		20	24	0	0: 0: 0	–	–	–
3		20	24	15	0: 100: 0	–	n.d.	n.d.
4		20	24	0	0: 0: 0	–	–	–
5		20 20 30	24 48 48	35 39 100	0: 100: 0 0: 100: 0 0: 100: 0	–	82:18 82:18 82:18	**146** 25% **146** 28% **146** 47% (–)
6		20	24	100	0 : 78 : 22	–	54:46	n.d.

								
7		20	24	100	100 : 0 : 0	50:50	–	n.d.
8		20	24	100	100 : 0 : 0	52:48	–	n.d.
9		20	24	25	100 : 0 : 0	50:50	–	–

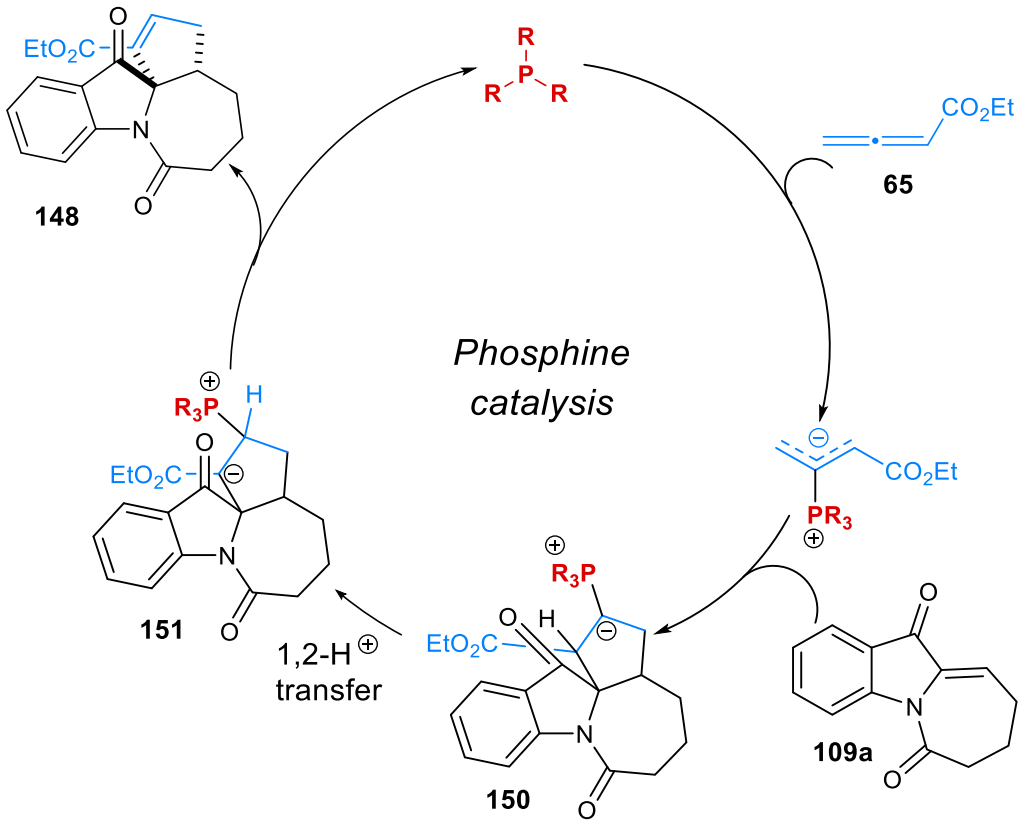
General conditions: Reaction performed on 0.20 mmol scale **109a.** [a] Determined by ^{1}H-NMR analysis. [b] Determined by chiral HPLC. n.d. = not determined.

Entry 1 (a bulky tert-butyl-substituted binaphthyl derivative) and entry 2 (a tris(trifluoromethyl)-aryl-substituted silyl system) are not phosphine catalysts but were included as controls, as they represent scaffolds used in other types of organocatalysis (e.g., imidazolium- or amine-derived systems reported by McMillan or Hayashi–Jørgensen). As expected, these non-phosphine systems were completely inactive and showed no conversion under the reaction conditions. entry 3, a rigid naphthyl-based phosphine, furnished the (3+2) cycloadduct **148** exclusively, but only in 15% conversion, indicating limited reactivity despite complete chemoselectivity. entry 4, a pyrrolidine-functionalized phosphine, was also inactive and produced no detectable product. entry 5, an L-valine-derived tertiary phosphine, displayed the best overall performance. At a loading of 10 mol-% and reaction times of 24-48 h, it consistently afforded the (3+2) cycloadduct **148** in isolated yields of 25%, 28%, and 47%, respectively, while maintaining an enantiomeric ratio of 82:18 across all time intervals. This outcome highlights the ability of amino acid-derived chiral phosphines to achieve both reactivity and enantioinduction in this transformation. entry 6, a diphenylmethylphosphine, achieved complete conversion but poor selectivity: a

mixture of (3+2) **148** and (4+2) **149** was obtained in a 78:22 ratio, with low enantioselectivity (54:46 *e.r.*). entries 7-9, sterically congested binaphthyl-derived phosphines, each provided the (3+2) adduct **148** exclusively and in full conversion. However, enantioselectivity remained modest, with *e.r.* values ranging from 50:50 to 52:48, limiting their usefulness for asymmetric induction despite excellent reactivity.

In summary, the results identify the L-valine-derived phosphine (entry 5) as uniquely effective in combining good reactivity with asymmetric induction. In contrast, non-phosphine catalysts (entries 1 and 2) were completely inactive, and other bulky or rigid phosphines either lacked reactivity or delivered poor stereocontrol. These findings validate the utility of amino acid-based chiral phosphines in the enantioselective synthesis of oxindole scaffolds.

Proposed mechanism



Scheme 45. Proposed mechanism (3+2) cycloaddition between enone **109a** and allenoate substrates **65**.

The catalytic cycle begins with nucleophilic attack of the phosphine catalyst (PR_3) on the allenoate (**65**), generating a zwitterionic phosphonium-enolate intermediate **150** (Scheme 45).[5,16-18]. In adduct **150**, the *γ*-position is nucleophilic and undergoes conjugate addition to the activated enone (**109a**), establishing a new C-C bond. Intramolecular cyclization then furnishes a five-membered cyclic key intermediate **151**, and a subsequent 1,2-proton shift followed by elimination of the phosphine regenerate the catalyst and release the annulated oxindole product **148**.

Conclusion

In summary, phosphine catalysis enables both crossed Rauhut-Currier-type couplings and (3+2) cycloadditions between enones **109a** and alkenes or allene carboxylate **65** respectively, for constructing spirooxindole frameworks. Product selectivity was found to depend strongly on the phosphine catalyst nucleophilicity and steric properties. Bulky phosphines such as P(*t*-Bu)$_3$ gave exclusively the Rauhut-Currier product, while less hindered arylalkylphosphines such as PMe_2Ph favored the (3+2) annulation in the reactions with allene carboxylate **65**. Chiral phosphines further allowed enantioselective access to tetracyclic oxindole **148** with promising stereocontrol.

Together, these results highlight how catalyst identity and structure dictate divergent pathways, providing valuable insights for the rational design of selective organocatalytic transformations of electron-deficient alkenes.

2.2.3 References

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2.3 DBU-Catalyzed Deconjugative α-Alkylation of α-Substituted Enones with Electron-Deficient Alkenes

The α-functionalization of carbonyl compounds remains a cornerstone transformation in synthetic organic chemistry. Traditionally, this has involved enolate alkylation or conjugate addition methods that favor reactions at the β-position of enones due to electronic stabilization of the conjugated system. However, selective functionalization at the α-position of α,β-unsaturated carbonyl compounds remains a challenging yet strategically valuable transformation, particularly when designing methods that break the extended conjugation to access non-conjugated functionalized frameworks.[1-6]

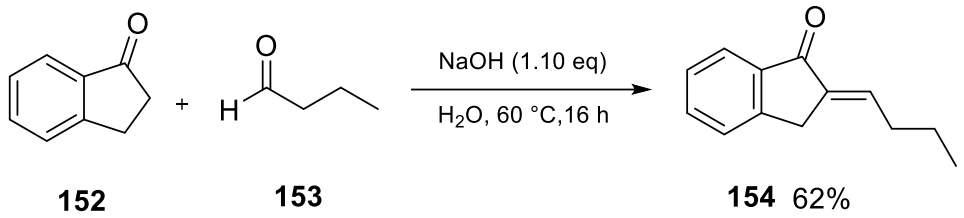
We report the development of a DBU-catalyzed deconjugative α-alkylation protocol that enables the direct coupling of α-substituted enones with various alkene partners.[7-8] This method proceeds under metal-free, mild conditions, offering a practical and selective route to α,α-*bis*-alkylated carbonyl compounds. Importantly, this process leverages the unique basic and nucleophilic properties of 1,8-diaza-bicyclo[5.4.0]undec-*7*-ene (DBU), which plays a dual role in substrate activation and proton transfer.

The α-alkylation of α-substituted enones with electron-deficient alkenes was initially approached via nucleophilic catalysis strategies, including trialkyl phosphines and *N*-heterocyclic carbenes (NHCs), inspired by Rauhut-Currier (RC)-type couplings (Chapter 2.1).[9] However, these attempts yielded poor or inconsistent results. This prompted us to explore a Brønsted base catalysis approach, leading to the identification of DBU as a uniquely effective promoter of the deconjugative α-alkylation.[10]

2.3.1 Reaction Development and Optimization

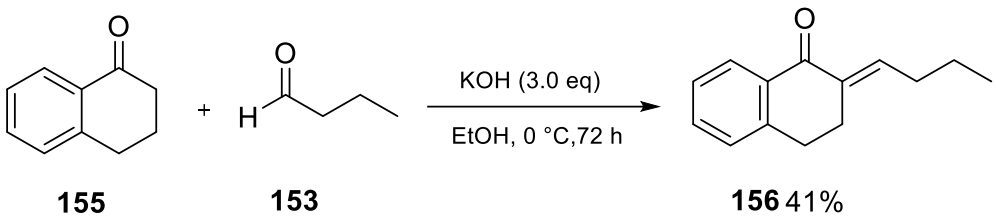
Synthesis of Starting Materials

The α-alkylation methodology developed relies on two key enone substrates, (*E*)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (**154**) and (*E*)-2-butylidene-3,4 dihydro-naphthalen-1(*2H*)-one (**156**). These enones were selected for their structural similarity and capacity to evaluate the generality of the developed base-catalyzed α-functionalization reaction.



Scheme 46. Aldol condensation between 1-indanone (**152**) and butyraldehyde (**153**).

Enone **154** was synthesized through a base-promoted aldol condensation between 1-indanone (**152**) and butyraldehyde (**153**) (Scheme 46). The reaction was performed in aqueous sodium hydroxide (NaOH) at 60 °C,[11] allowing for efficient enolate formation and condensation under mild conditions. After completion, the product was isolated by standard extraction and recrystallization procedures to afford compound **154** in 62% yield.

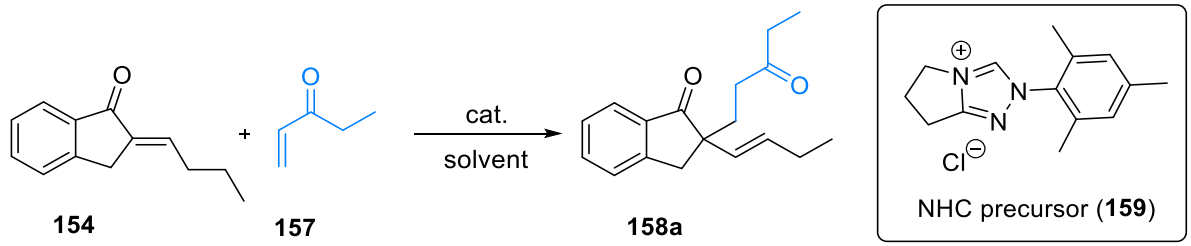


Scheme 47. Aldol condensation between 1-tetralone (**155**) and butyraldehyde (**153**).

To probe the effect of ring size on the α-alkylation process, the structurally extended analog compound **156** was synthesized using an analogous aldol condensation strategy The starting materials, 1-tetralone (**155**) and butyraldehyde (**153**), were condensed under basic (KOH) conditions at 0 °C temperature for 72 h (Scheme 47),[12] leading to the formation of the desired product **156** in 41% yield.

Optimization of Reaction

Table 5. Reaction Optimization with PR_3 and NHC Catalysts for the Coupling of Enone **154** and Ethyl vinyl ketone (**157**).



Entry	Equiv. 157	Catalyst	mol-%	Base (25 mol-%)	Solvent	Temp. (°C)	Time (h)	Conversion of 154 (%)[a]	Yield of 158a (%)[a]
1.	10	PMe_2Ph	20	-	CH_2Cl_2	r.t	20	0	0
2.	10	PMe_2Ph	10	-	$PhCH_3$	40	24	0	0
3	10	PMe_2Ph	10	-	$PhCH_3$	120	24	0	0
4	10	$PMePh_2$	20	-	CH_2Cl_2	r.t	24	0	0
5	10	PBu_3	10	-	$PhCH_3$	40	24	0	0
6	10	PBu_3	10	-	$PhCH_3$	100	24	0	0
7	10	NHC	10	Cs_2CO_3	MeCN	r.t.	24	33	28
8	10	NHC	10	Cs_2CO_3	MeCN	40	24	34	28
9	10	NHC	10	Cs_2CO_3	MeCN	80	24	77	68[b]
10	10	NHC	10	Cs_2CO_3	$PhCH_3$	80	24	0	0
11	10	NEt_3	10	-	MeCN	r.t	24	0	0
12	10	Cs_2CO_3	25	-	MeCN	r.t	24	54	30
13	10	Cs_2CO_3	25	-	MeCN	80	24	60	32

a) Determined by ^{1}H-NMR against CH_2Br_2 standard. b) Isolated yield after chromatography.

The model reaction consisted of (*E*)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (**154**) and ethyl vinyl ketone (**157**)**.** A variety of phosphine catalysts (Table 5),, including PMe_2Ph, $PMePh_2$, and PBu_3, were tested under both mild and elevated temperatures in solvents such as CH_2Cl_2 and $PhCH_3$. However, in all cases (entries 1-6(, no reaction was observed; the starting materials were fully recovered even after prolonged heating.

Encouraged by literature reports on NHC-catalyzed C-C bond formation,[13–14] we next examined the reactivity of enone **154** under NHC catalysis. Using 2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-*c*][1,2,4]triazol-4-ium (**159**) (10 mol-%) as the precatalyst in combination with Cs_2CO_3 (25 mol-%) in acetonitrile, moderate conversion and product formation were observed at room temperature and at 40 °C (entries 7-8). The best performance was achieved at 80 °C, where 77% conversion and 68% isolated yield of product **158a** were obtained (entry 9).

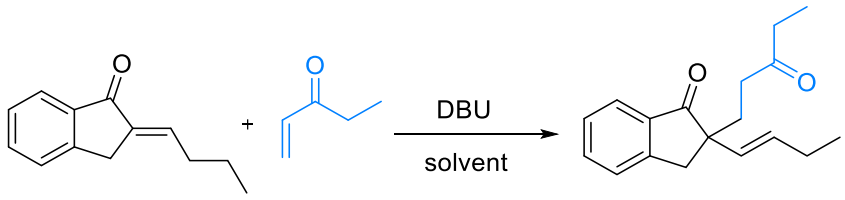
Control experiments clarified the role of the catalyst and base (entries 12-13). In the absence of the NHC precursor, Cs_2CO_3 alone promoted product formation, albeit in only ~30% yield, confirming the existence of a background base-mediated pathway. Conversely, when the NHC precursor was used without base, no reaction occurred. These results demonstrate that while the base alone can trigger some reactivity, the NHC-base combination is essential for efficient catalysis and high yields.

Given the limitations of the RC-based methods (Table 6), we turned to explore Brønsted base-mediated strategies. Screening common organic base revealed that DBU (10 mol-%) in acetonitrile promoted smooth coupling of the enone with ethyl vinyl ketone (**157**, 6.*eq*.) at room temperature, delivering the α-alkylated product **158a** in 98% isolated yield after 20 hours.

This transformation was notable for its mild conditions (room temperature, no metals), high efficiency, and operational simplicity, requiring neither an inert atmosphere nor catalyst pre-activation. Other bases such as triethylamine, DABCO, and DIPEA failed to initiate the reaction, underscoring the unique properties of DBU. The base likely facilitates reversible enone deprotonation and subsequent Michael-type attack onto the activated alkene, promoting deconjugative alkylation.

Optimization of Reaction with DBU (Shift to Brønsted Base Catalysis)

Table 6. Optimization of the Reaction between Enone **154** and Ethyl vinyl ketone (**157**) using DBU.



154 **157** **158a**

Entry	Equi. 157	Catalyst	mol-%	Solvent	T (°C)	Time (h)	Conversion of 154 (%)[a]	Yield of 158a (%)[a]
1	10	DBU	10	CH_2Cl_2	r.t	20	100	95
2	10	DBU	20	CH_2Cl_2	r.t	20	100	90
3	10	DBU	20	$PhCH_3$	r.t	20	100	98
4	10	DBU	10	$PhCH_3$	r.t	20	91	72
5	10	DBU	5	$PhCH_3$	r.t	20	99	70
6	6	DBU	10	$PhCH_3$	r.t	20	98	65
7	3	DBU	10	$PhCH_3$	r.t	20	94	56
8	10	DBU	10	MeOH	r.t	20	100	75
9	6	DBU	10	MeOH	r.t	20	100	71
10	3	DBU	10	MeOH	r.t	20	100	64
11	10	DBU	10	MeCN	r.t	20	100	95
12	6	DBU	10	MeCN	r.t	20	100	98[b]

13	3	DBU	10	MeCN	r.t	20	100	64
14	3	DBU	10	Acetone	r.t	20	100	68
15	6	DBU	10	Acetone	r.t	20	100	96
16	10	DBU	10	Acetone	r.t	20	100	97

a) Determined by ^{1}H-NMR against CH_2Br_2 standard. b) Isolated yield afterchromatography.

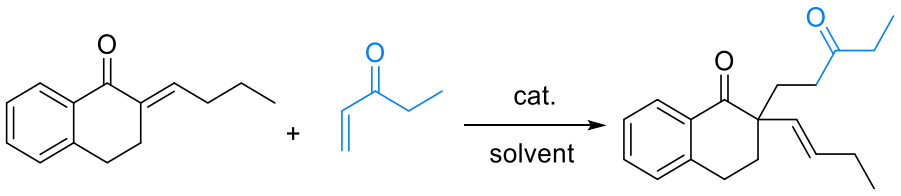
These results established DBU as a superior catalyst for α-alkylation, outperforming phosphine and NHC systems in terms of product formation, ease of handling, and mildness of conditions.

After establishing effective α-alkylation conditions for the indanone-derived enone (**154**), we turned our attention to a structurally extended analog, (*E*)-2-butylidene-3,4-dihydronaphthalen-1(2*H*)-one (**156**)**,** derived from 1-tetralone. This substrate features a larger six-membered carbocyclic ring fused to the benzene and was designed to probe the impact of ring size, electronic distribution, and conformational flexibility on reaction performance.

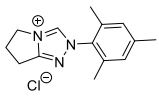
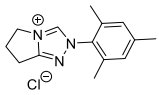
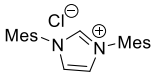
A systematic optimization study was conducted to improve the catalytic transformation of enone substrate **156** using ethyl vinyl ketone (**157**) as the coupling partner. The key variables screened included catalyst type, solvent, temperature, and reaction time. The results of these experiments are summarized in Table 7

The first series of experiments investigated the activity of phosphine-based catalysts (PR_3) and an organic base (DBU). As shown in entries 1 to 4 of Table 7, the use of PMe_2Ph in either dichloromethane (CH_2Cl_2) or toluene ($PhCH_3$) afforded negligible conversion of the starting enone. In CH_2Cl_2 at room temperature, only 10% conversion was observed after 90 hours (entry 2), with a corresponding product yield of just 2%. Reactions in $PhCH_3$ at elevated temperatures (40 °C and 80 °C; entries 3 and 4) failed to promote any product formation, suggesting that the phosphine catalyst is ineffective under these conditions.

Table 7. Reaction Optimization with PR_3 and NHC and DBU Catalysts for the Coupling of Enone **156** and Ethyl vinyl ketone (**157**).



156 **157** **160a**

Entry	Equi of 157	Catalyst	mol-%	Base (25 mol-%)	Solvent	T (°C)	Time (h)	Conversion of 156 (%)[a]	Yield of 160a (%)[a]
1	10	DBU	10	-	$PhCH_3$	r.t	24	28	28
2	10	PMe_2Ph	10	-	CH_2Cl_2	r.t.	90	10	2
3	10	PMe_2Ph	10	-	$PhCH_3$	40	24	0	0
4	10	PMe_2Ph	10	-	$PhCH_3$	80	24	0	0
5	10		10	Cs_2CO_3	MeCN	r.t.	24	7	1
6	10		10	Cs_2CO_3	MeCN	40	24	3	3
7	10		10	Cs_2CO_3	MeCN	r.t	24	10	8
8	10	DBU	10	-	MeCN	40	24	75	49 (48)[b]
9	10	DBU	10	-	$PhCH_3$	80	24	55	19

a) Determined by ^{1}H-NMR against CH_2Br_2 standard. b) Isolated yield after chromatography.

In contrast, the use of the organic base DBU demonstrated catalytic activity. In toluene at 40 °C, DBU provided a modest conversion of 28% with a 28% yield of the desired

product (entry 1). Further increasing the reaction temperature to 40 °C (entry 8) significantly improved the conversion to 75%, with a corresponding product yield of 48%. However, increasing the temperature further to 80 °C (entry 5) led to a decrease in both conversion (55%) and product yield (19%), suggesting possible thermal decomposition of either the catalyst or the product at higher temperatures.

Next, the effect of using cesium carbonate (Cs_2CO_3) as a base was explored in acetonitrile (MeCN) with presumed NHC catalysis.[13-14] or as a background reaction (entries 5-7). These attempts showed low levels of reactivity. Under various conditions (room temperature and 40 °C), only minor conversion of the enone **156** was observed (3-10%), with corresponding product yields of 1-8%. These results suggest that Cs_2CO_3 alone or in combination with an NHC catalyst precursor is insufficient to promote the desired reaction efficiently.

Based on these initial studies, the optimal reaction conditions were identified as follows: DBU (10 mol-%) as the catalyst/base, acetonitrile as the solvent, a reaction temperature of 40 °C, and a reaction time of 24 hours. Under these conditions, a conversion of 75% and a product yield of 48% were achieved. Although moderate, this represents the best performance among the conditions tested.

Scope of the DBU-deconjugative α-alkylation reaction of enones 154 and alkenes

The generality of this method was tested using a variety of acrylate and alkene partners. Enones **154** was reacted with diverse activated alkenes, in the presence of DBU (10 mol-%) in MeCN at room temperature. Both underwent smooth coupling with ethyl vinyl ketone, methyl acrylate, ethyl acrylate, propyl acrylate, *iso*-butyl acrylate, *tert*-butyl acrylate, and hexyl acrylate to give the corresponding products **158a-158i** in 77–98% yield (Figure 19). Electron-deficient olefins such as acrylonitrile and phenyl vinyl sulfone also participated efficiently.

The deconjugative α-alkylation of six-membered tetralone enones was next examined. When the tetralone substrate **156** was treated with acrylates in the presence of DBU (10 mol-%) in MeCN at room temperature, no significant conversion was observed, indicating that the standard conditions effective for the five-membered indanone system were not suitable for the larger ring analogue. Upon increasing the reaction temperature to 40 °C, product formation was achieved.

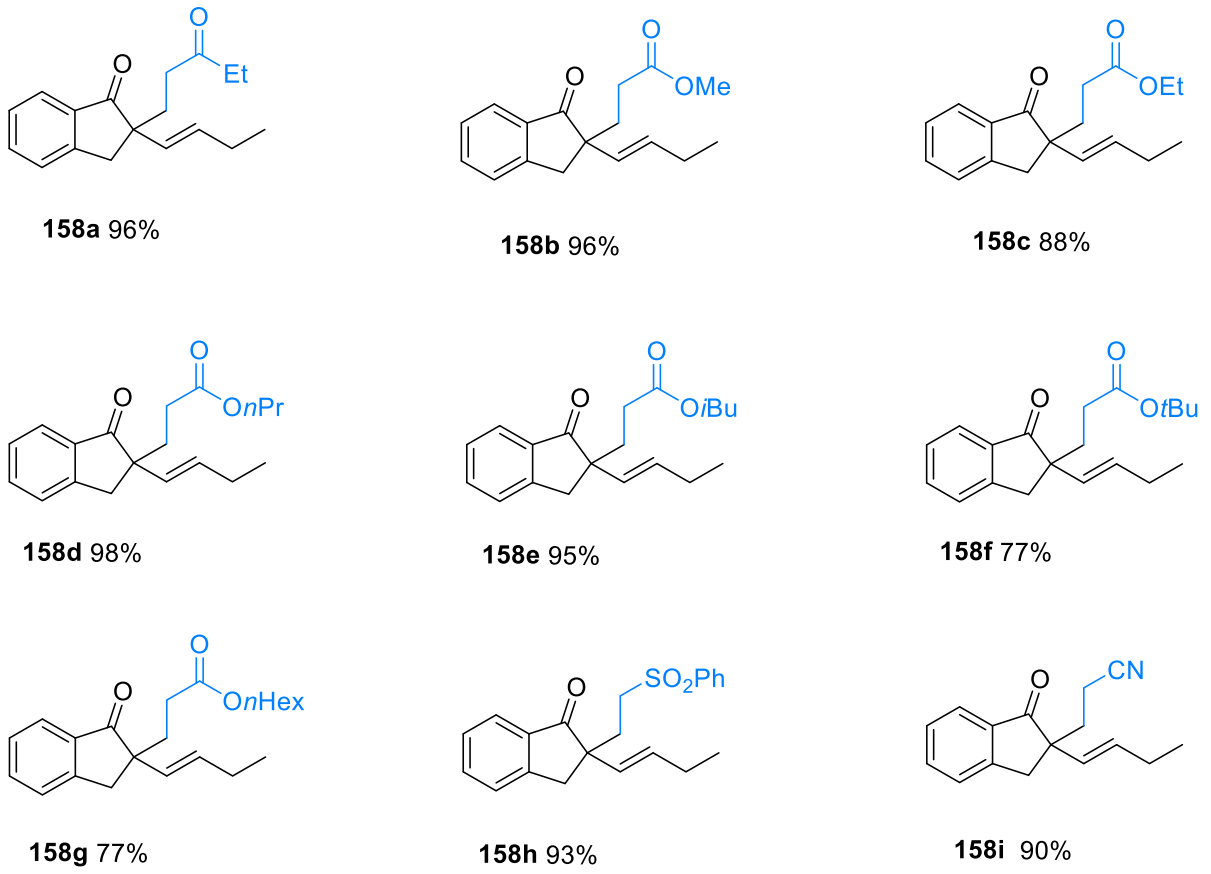


Figure 19. Overview of the DBU-Catalyzed-Deconjugative α-Alkylation Indanone-derived Enone **154**.

Under these conditions, the expected α-alkylated adducts **160** were obtained, incorporating a new substituent at the α-position of the tetralone framework. The scope was explored with a range of electron-deficient alkenes, including acrylonitrile (**53**), methyl acrylate (**62a**), ethyl acrylate (**62b**), *n*-propyl acrylate (**62c**), and *iso*-butyl acrylate (**62d**), all of which furnished the corresponding α-alkylated products **160a-160e** in 40-72% yield (Figure 20).

This outcome demonstrates that the tetralone-derived enone **156** is less reactive than the indanone analogue, likely due to the reduced acidity of the α-protons and the lower thermodynamic driving force for deconjugation. Nevertheless, under slightly elevated temperatures, the reaction proceeded smoothly to give functionalized tetralone derivatives bearing versatile nitrile or ester groups suitable for further transformations. To explore the breadth of substrate compatibility, structurally modified enones incorporating oxygen heteroatom were tested under the optimized catalytic conditions. Specifically, benzofuranone-derived enone **160** was treated with ethyl vinyl ketone

(**156**) in the presence of DBU and a phosphine catalyst (PR_3) under standard conditions in acetonitrile. As illustrated in Scheme 48, these substrates failed to undergo the desired reaction. Instead of yielding any isolable products, the reactions led to complete decomposition of the starting material **160** within 24 hours, as confirmed by ^1H NMR and TLC analysis. Attempts to prepare the corresponding N-acyl enone were unsuccessful, as the compound decomposed during purification on silica gel column chromatography and could not be isolated.

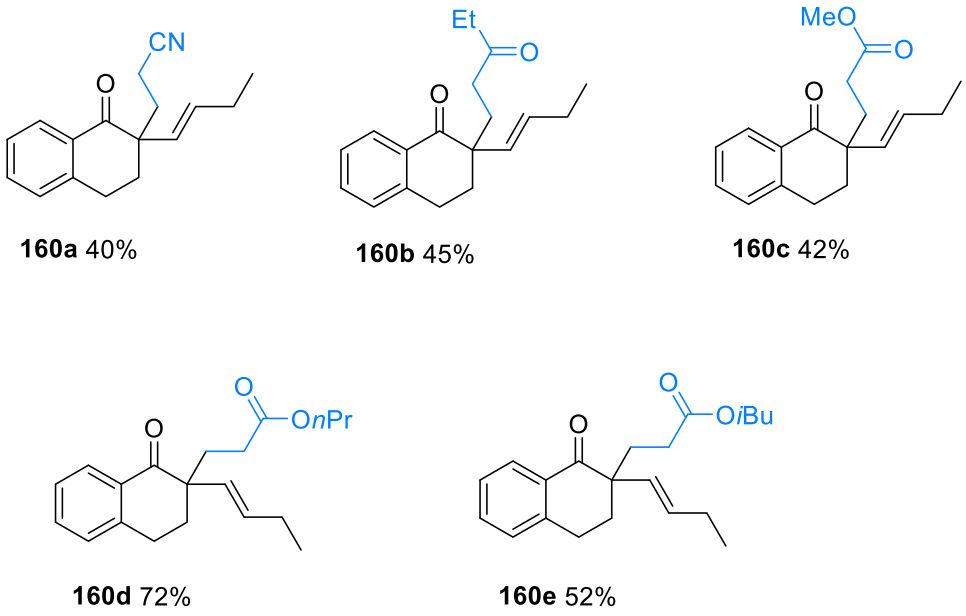
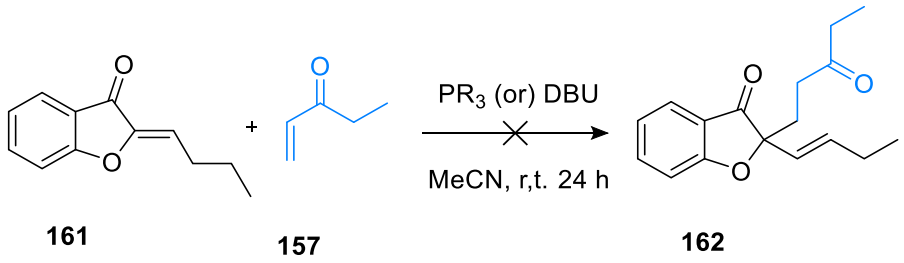


Figure 20. Overview of the DBU-Catalyzed-Deconjugative α-Alkylation of Tetralone-derived Enone **156**.



Scheme 48. Decomposition of Benzofuranone-derived Enone **161** under PR_3/DBU Catalysis.

While the DBU-catalyzed deconjugative α-alkylation method proved broadly effective across various α-substituted enones and electron-deficient alkenes, certain substrate limitations were observed. Representative examples are is shown in Figure 21.

Ongoing studies to overcome these limitations may involve the use of stronger Brønsted bases, modified catalysts, or activation of the enone via Lewis acid co-catalysis.

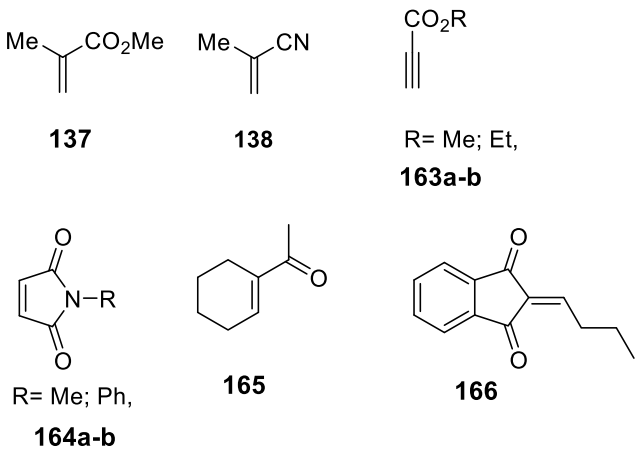
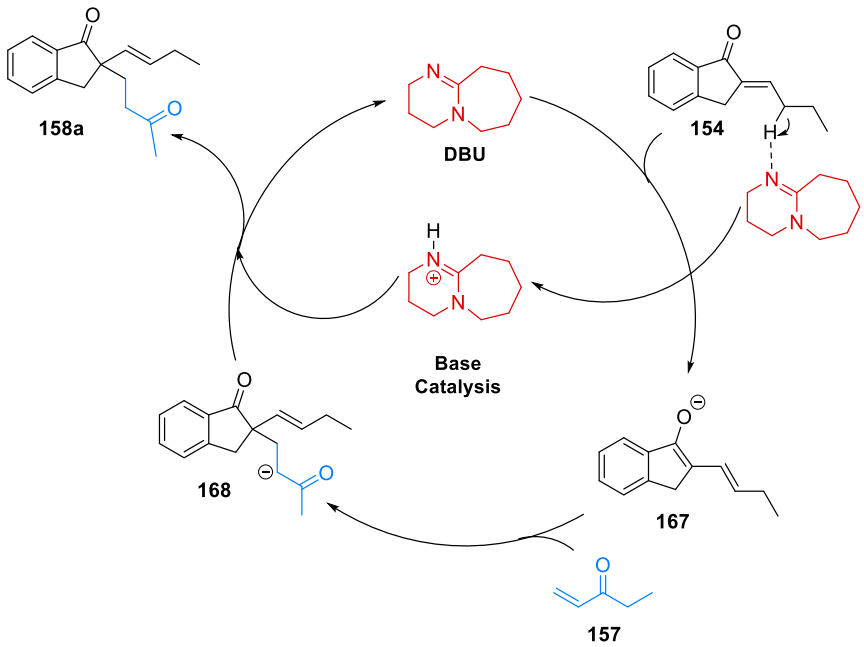


Figure 21. Unreactive Alkenes and Enones in the DBU-Catalysed Deconjugative α-Alkylation Reactions.

Proposed Mechanism for DBU-Catalyzed α-Alkylation of *α, β*-Unsaturated Enone



Scheme 49. Proposed Mechanism for DBU-Catalyzed α-Alkylation of *α, β*-Unsaturated Enone (**154**) and Ethyl vinyl ketone (**157**).

Mechanistically, DBU is believed to abstract the γ-proton from the enone to form a stabilized dienolate, which undergoes conjugate addition to the electron-deficient alkene. The reaction then proceeds via proton transfer to regenerate DBU and furnish the β,γ-unsaturated product.[15]

Basicity and Reactivity Comparison

The distinct reactivity profiles of DBU and PMe_2Ph can be rationalized by considering the basicity of their conjugate acids in acetonitrile (Table 8). DBU is a strong Brønsted base with a conjugate acid pK_a of 24.13,[16] making it highly effective for deprotonation and enolate generation. In contrast, PMe_2Ph has a significantly lower conjugate acid pK_a of 12.64,[17] indicating much weaker basicity but it possesses sufficient nucleophilicity to engage directly in conjugate addition to activated alkenes. This nucleophilic addition step generates a zwitterionic phosphonium-enolate intermediate, which serves as the key reactive species in phosphine catalysis (Chapter 2.2).

Table 8. Comparison of pKa Values for the Conjugate acids of DBU and $PPhMe_2$.

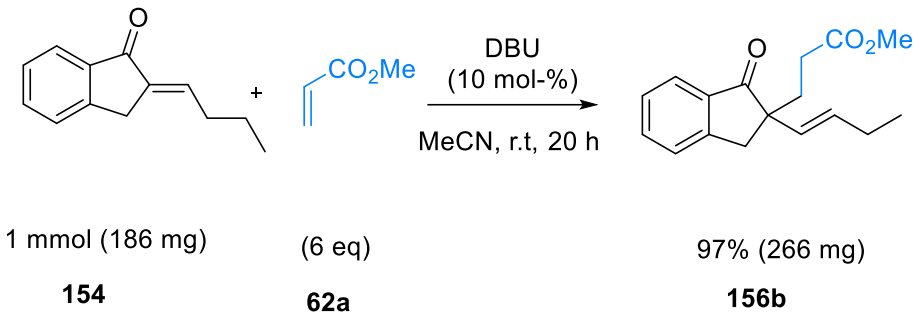
Catalyst	Type	pk_a H^+(MeCN)	Primary Function
DBU	Strong Bronsted Base	24.13	Deprotonation, enolate generation
PMe_2Ph	Nucleophilic catalyst	12.64	Conjugate addition (zwitterionic adduct)

Thus, while DBU promotes reactivity through enolate formation under purely Brønsted basic conditions, phosphine catalysts such as PMe_2Ph operate by a nucleophilic activation pathway highlighting a fundamental difference in activation mode. The higher basicity of DBU explains its efficiency in promoting deconjugative α-functionalization of enones, whereas the unique nucleophilic properties of trialkylarylphosphines enable access to zwitterionic intermediates central to annulation pathways.

DBU serves as a strong, non-metallic base that is well-suited for generating enolates under mild conditions. In contrast, trialkyl and triaryl phosphines (PR_3) function as softer nucleophiles, making them effective catalysts in reactions such as the Morita-Baylis-Hillman and Rauhut-Currier transformations. The choice between a base like DBU and a nucleophile like PR_3 depends on the desired mode of reactivity enolate-

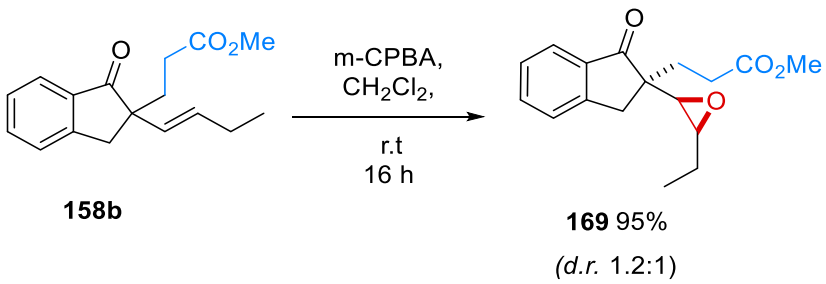
driven pathways are best promoted by DBU, whereas nucleophilic catalysis is favored using phosphine-based systems.

2.3.2 Synthetic Elaboration of the β,γ-Unsaturated products 154 and 160.



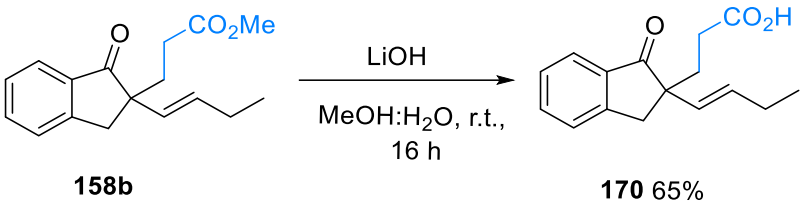
Scheme 50. 1 mmol Scale Synthesis of Ester Compound (**158b**).

The reaction of (*E*)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (**154**) with methyl acrylate (**62a**) (10 equivalents) in the presence of DBU (10 mol-%) in acetonitrile at room temperature proceeded smoothly on a one millimole scale, to afford the desired α-alkylated enone product **158b** in 97% yield (266 mg) after 20 hours (Scheme 50).



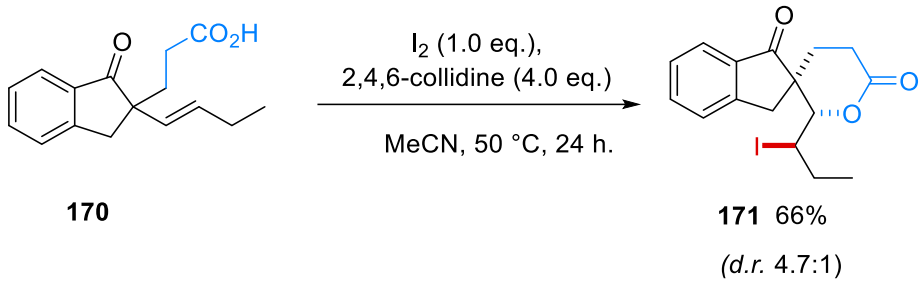
Scheme 51. Epoxidation of the Ester (**158b**). with m-CPBA.

The α-alkylated methyl ester (**158b**) was subjected to epoxidation with *meta*-chloroperbenzoic acid (m-CPBA) in dichloromethane at room temperature.[18] The resulting epoxide (**169**) was obtained in 95% yield with *d.r.* 1.2.1 (Scheme 51), demonstrating the reactivity of the enone moiety toward electrophilic oxidants and the potential for downstream stereoselective transformations.



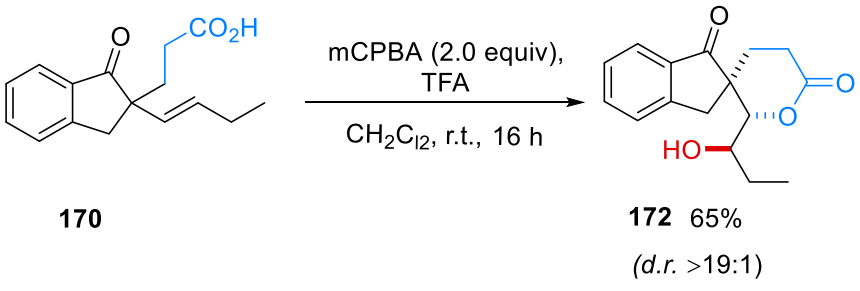
Scheme 52. Saponification of the Ester (**158b**). with LiOH.

The methyl ester (**158b**) was hydrolyzed using lithium hydroxide (LiOH) in a 3:1 mixture of methanol and water at room temperature.[19] This reaction yielded the corresponding carboxylic acid (**170**) in 65% yield (Scheme 52), providing a versatile intermediate for further derivatization.



Scheme 53. Iodolactonization of Acid (**170**). with I_2.

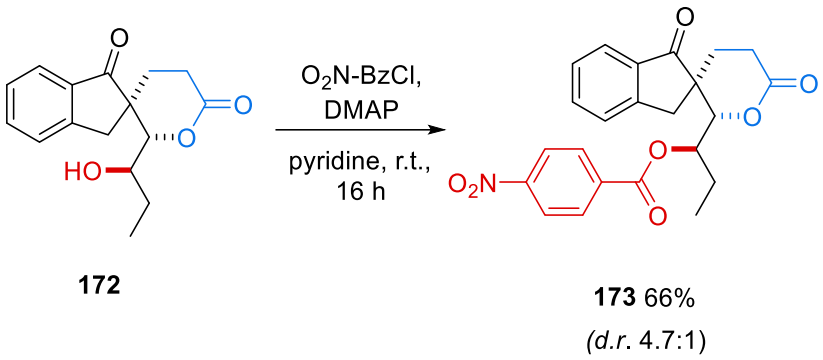
The carboxylic acid intermediate **170** was subjected to iodolactonization using iodine (I_2) and 2,4,6-collidine as base in acetonitrile at 50 °C.[20] This transformation involves electrophilic iodination of the alkene followed by intramolecular nucleophilic attack of the carboxylate, yielding the corresponding iodolactone **171** in 66% yield (*d.r.* 4.7:1) (Scheme 53). The relative configuration of the three contiguous steroegenic centers in iodolactone **171** was assigned based on NOESY spectroscopy.



Scheme 54. Hydroxy lactonization of Acid (**170**) with m-CPBA and TFA.

Finally, the carboxylic acid (**170**) was subjected to acid-promoted intramolecular hydroxy lactonization using a mixture of m-CPBA and trifluoroacetic acid in acetonitrile (Scheme 54) [18] The transformation yielded a fused hydroxy lactone product (**172**) in 65% yield (*d.r.* >19:1), the relative configuration of which could again be assigned by NOESY spectroscopy.

The hydroxyl-containing intermediate (**172**) was subjected to acylation using 4-nitrobenzoyl chloride in the presence of 4-dimethylaminopyridine and pyridine as a base at room temperature for 16 hours.[22] This reaction led to the formation of the corresponding 4-nitrobenzoyl product (**173**) in 66% yield (*d.r.* 4.7:1) (Scheme 55).



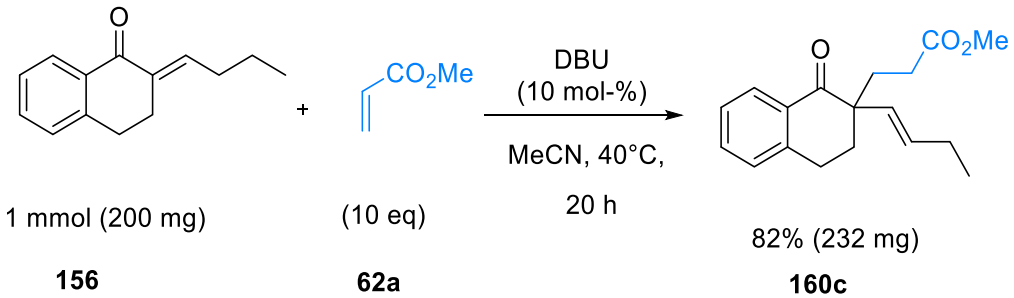
172

173 66%
(*d.r.* 4.7:1)

Scheme 55. Benzoylation of Alcohol (**172**) with *p*-nitro Benzoyl Chloride.

Synthetic Elaboration of the Tetralone-Derived α-Alkylated Product 160c

To further illustrate the synthetic flexibility of the DBU-catalyzed α-alkylation platform, we performed downstream transformations on the tetralone-derived product **160c**. The sequence highlights the feasibility of accessing various functionalized frameworks from a single α-alkylated intermediate using operationally simple procedures.



1 mmol (200 mg)

156

(10 eq)

62a

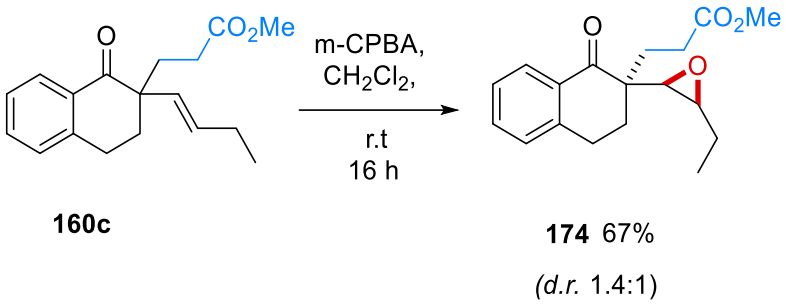
82% (232 mg)

160c

Scheme 56.1 mmol Scale Reaction for Synthesis of Ester (**160**).

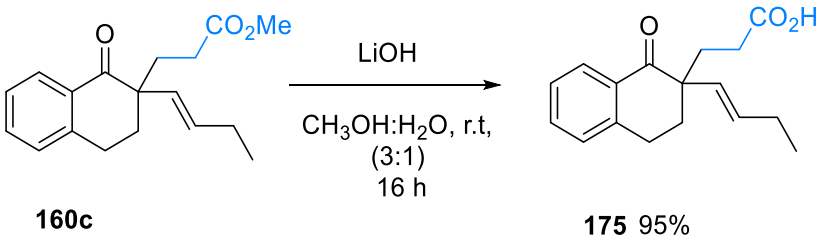
The reaction of (*E*)-2-butylidene-3,4-dihydronaphthalen-1(2*H*)-one (**156**) with methyl acrylate (**62a**) 10. *eq*. in the presence of DBU (10 mol-%) in MeCN at 40 °C for 20 hours provided the desired α-alkylated product (**160c**) in 82% yield (232 mg) (Scheme 56).

Epoxidation of the methyl ester (**160c**) was carried out using mCPBA (2.0 *equiv*) in CH_2Cl_2 at room temperature for 16 hours.[21] The corresponding epoxide (**174**) was obtained in 67% yield (*d.r.* 1.4:1) (Scheme 57).



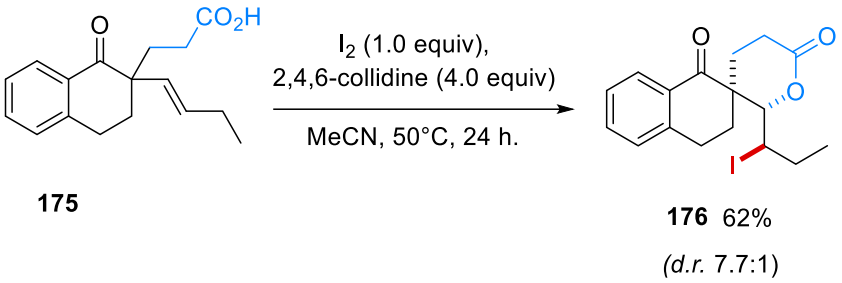
Scheme 57. Epoxidation of Ester (**160C**) with m-CPBA.

The ester (**160c**) was hydrolyzed using LiOH in a 3:1 mixture of MeOH/H_2O at room temperature over 16 hours.[19] This yielded the carboxylic acid derivative **175** in 95% yield (Scheme 58).



Scheme 58. Saponification of the Ester (**160c**) with LiOH.

The carboxylic acid (**175**) underwent iodolactonization using iodine (1.0 *equiv*) and 2,4,6-collidine (1.0 *eq*) in MeCN at 50 °C for 24 hours.[20] This reaction afforded the iodolactone (**176**) in 62% (*d.r.* 7.7:1) (Scheme 59) yield via electrophilic iodination followed by intramolecular lactonization.



Scheme 59. Iodolactonization of Acid (**175**) with I_2.

The NOESY spectrum of iodolactone **176** shows a distinct cross-peak between the methylene proton 5'-H and the proton at 2'-H, indicating a through-space nuclear Overhauser effect (NOE). Since NOESY cross-peaks arise from dipolar interactions rather than scalar couplings, this observation directly reflects the spatial proximity of these two protons.

In the corresponding stereochemical model (Figure 22), the 5'-H and 2'-H protons are positioned on the same molecular face, consistent with the strong NOE detected between them. This correlation supports the *cis* relationship between 5'-H and 2'-H, as their orientation brings them into close contact within the three-dimensional framework. Conversely, if 5'-H were trans to 2'-H, the distance between the two protons would be significantly larger, and the NOESY cross-peak would be absent or much weaker. Thus, the observed NOE between 5'-Ha and 2'-H provides unambiguous evidence for their spatial adjacency and is crucial for confirming the stereochemical assignment of the molecule (**176**).

To complement the NOESY analysis, a 3D molecular model of compound **176** (Figure 23) was constructed to visualize the spatial arrangement of key protons. The model clearly shows that 5′-Ha and 2′-H reside on the same molecular face, placing them in close proximity and thereby rationalizing the strong NOE observed between these protons. This spatial representation provides an intuitive confirmation of the stereochemical assignment and further supports the cis relationship deduced from NMR spectroscopy.

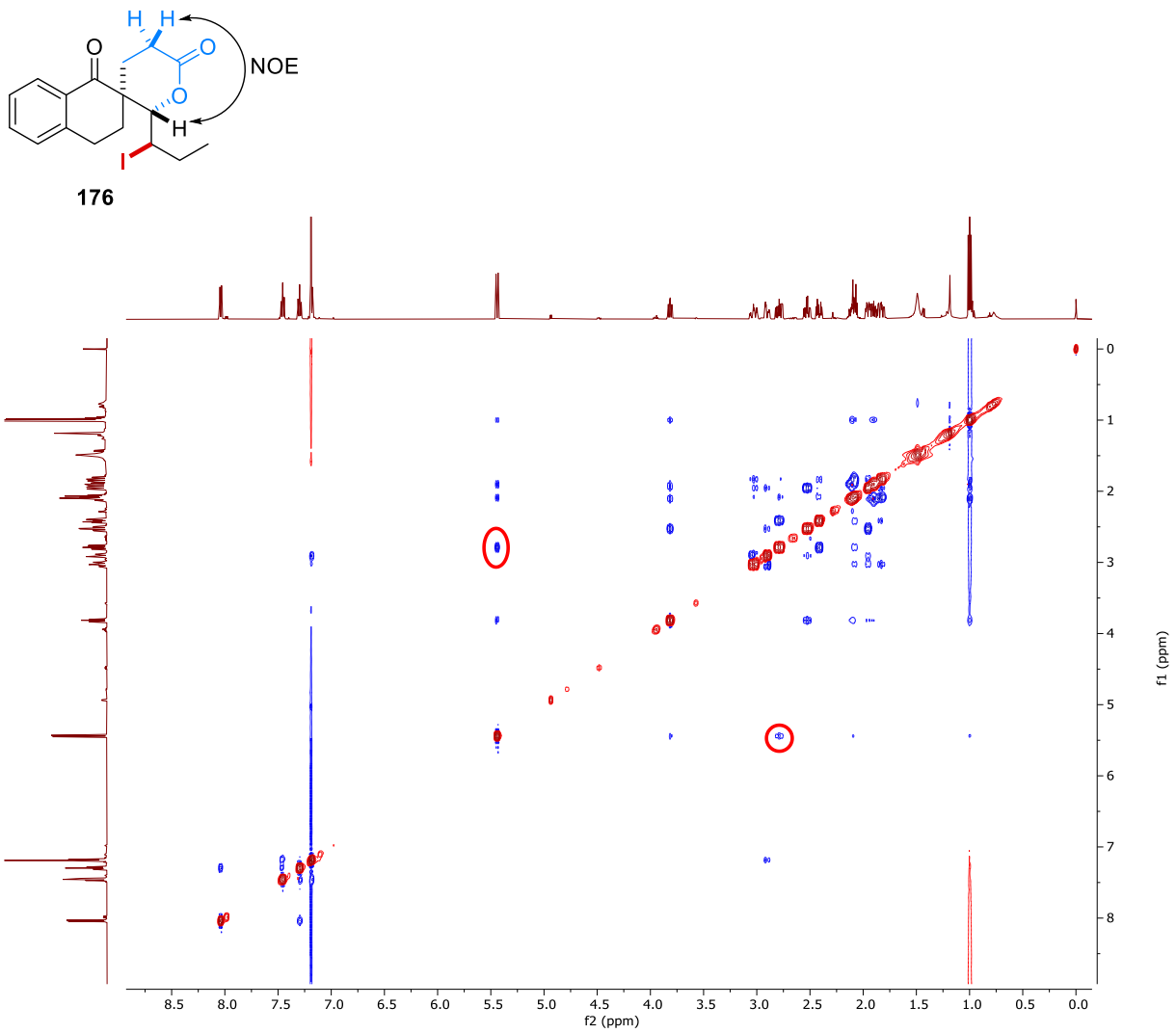


Figure 22. 2D-NOESY NMR spectrum of compound **176**.

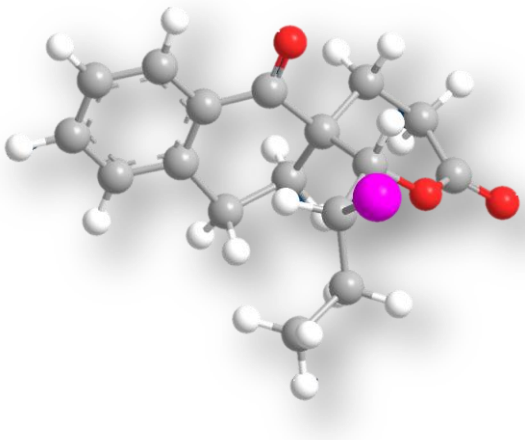
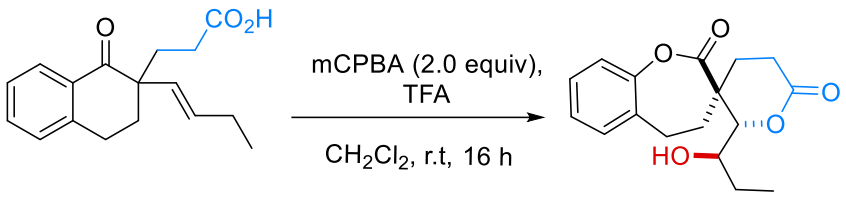


Figure 23. 3D molecular model of compound **176**.



175

177 73%
(d.r. >19:1)

Scheme 60. Baeyer-Villiger Oxidation-Triggered Intramolecular Lactonization of Acid 175 Using m-CPBA.

Treatment of acid **175** with *m*-chloroperbenzoic acid (m-CPBA, 2.0 equiv) in the presence of trifluoroacetic acid (TFA) in dichloromethane at room temperature for 16 h resulted in an oxidative rearrangement (Scheme 60).[20] Under these conditions, a Baeyer-Villiger oxidation[23] of the cyclic ketone occurred, the transformation likely involves oxidation of the cyclic ketone and intramolecular lactonization, resulting in formation of the oxygen-bridged fused hydroxy lactone **177** in 73% yield with a diastereomeric ratio of >19:1.

This transformation highlights the dual role of m-CPBA in promoting Baeyer-Villiger oxidation and enabling intramolecular lactone formation, providing an efficient route to oxygen-bridged polycyclic architectures.

These synthetic elaborations demonstrate that indanone and tetralone-derived α-alkylated products are highly versatile intermediates. The ability to access epoxides, carboxylic acids, iodolactones, and hydroxy-fused polycycles from a single intermediate highlight the robustness and utility of the DBU-catalyzed α-alkylation strategy. These downstream transformations provide an efficient entry point to complex molecular architectures, with potential applications in natural product synthesis and pharmacophore design.

Conclusion

This chapter has described a concise, mild, and metal-free method for the deconjugative α-alkylation of α-substituted enones with alkenes catalyzed by DBU. The transformation exhibits broad substrate scope, high yields, and functional group tolerance. The use of DBU avoids harsh reagents and metals, aligning with principles of green chemistry. Mechanistic observations support a base-mediated enolate pathway, and further derivatization of the products demonstrates synthetic versatility for complex molecule synthesis.

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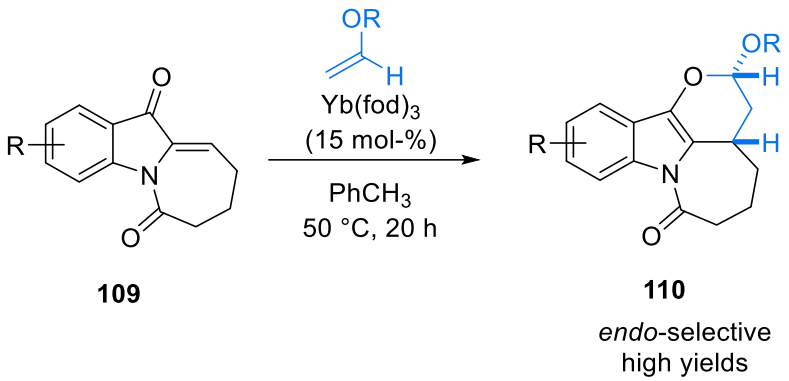
Summary and Outlook

3.1 Summary of the Work

The development of novel catalytic strategies for the stereoselective synthesis of polycyclic heterocycles remains a central challenge in organic synthesis, particularly due to the complex architectures and diverse biological activities these molecules often display. This thesis has presented the design, development, and mechanistic understanding of three distinct catalytic systems-Lewis acid catalysis, phosphine Organocatalysis, and Brønsted base catalysis for the synthesis of azepane-fused pyrano[3,2-b]indoles, Oxindoles, and related frameworks. The work demonstrates not only synthetic efficiency but also broad substrate scope, stereoselectivity, and functional group compatibility, all of which are critical for potential drug discovery applications.

Lewis Acid-Catalyzed Synthesis of Azepane-Fused Pyrano[3,2-b]indoles

A robust and stereoselective oxa Diels-Alder (ODA) reaction was developed using ytterbium (III) catalysts ($Yb(fod)_3$) for the annulation of tricyclic enones with vinyl ethers. The key dienophiles, azepino[1,2-*a*]indole enones, were synthesized via a modular and scalable route involving sensitized photooxygenation of cyclohepta[*b*]indoles followed by organophosphate-catalyzed dehydroacetoxylation.



Scheme 61. Lewis acid-catalysed oxa Diels-Alder reaction of dihydroazepino[1,2-a]indole diones with ethers.

Optimization studies revealed that $Yb(fod)_3$ effectively activated the enone, facilitating the endo-selective (4+2) cycloaddition. The reaction consistently delivered azepane-

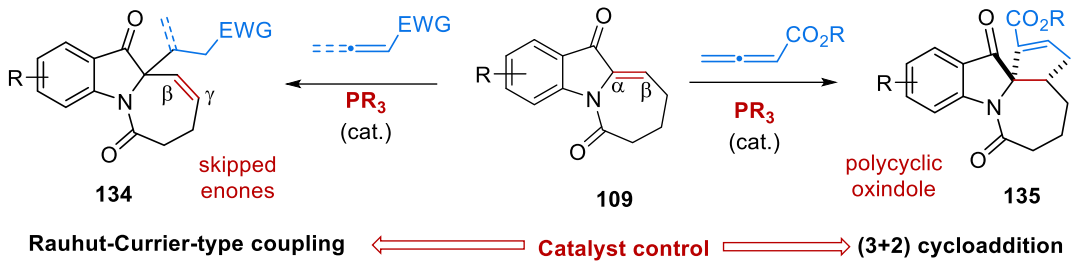
fused pyranoindoles with high diastereoselectivity (*dr* ≥ 95:5) and moderate to excellent yields (63-93%). Mechanistic investigations, including NOESY-NMR and X-ray crystallography, confirmed the *endo*-stereochemistry of the products.

This methodology offers significant synthetic utility for accessing biologically relevant heterocycles and demonstrates scalability, as shown by gram-scale synthesis. The reaction tolerates a wide range of electronic and steric variations on both the enone and the vinyl ether partners, thus enabling rapid library generation.

Phosphine-Catalyzed Divergent Annulations of Oxindoles

A catalyst-controlled divergent synthesis of oxindoles and skipped enones was achieved via phosphine catalyzed annulations. Depending on the substrate structure and catalyst electronics, two distinct pathways were selectively accessed:

- Crossed Rauhut-Currier (RC) coupling afforded β,γ-unsaturated ketones with high selectivity.
- (3+2) Cycloadditions between enones and allenoates led to the formation of fused tricyclic oxindoles with stereochemical complexity.



Scheme 62. the phosphine-catalyzed annulations of α-substituted enones with electron-deficient alkene partners.

Key findings from this study include the observation that trialkylphosphines promote Rauhut-Currier-type coupling, while aryl-substituted phosphines tend to favor cycloaddition pathways. Mechanistic investigations using ^{31}P NMR revealed the formation of zwitterionic phosphonium intermediates, supporting their role as key species in the catalytic cycle. Additionally, the use of a chiral phosphine catalyst enabled enantioselective (3+2)-annulation, affording oxindoles with enantiomeric ratios of up to 82:18. This dual reactivity underscores the versatility of phosphine

catalysis in constructing structurally diverse heterocyclic architectures from common starting materials.

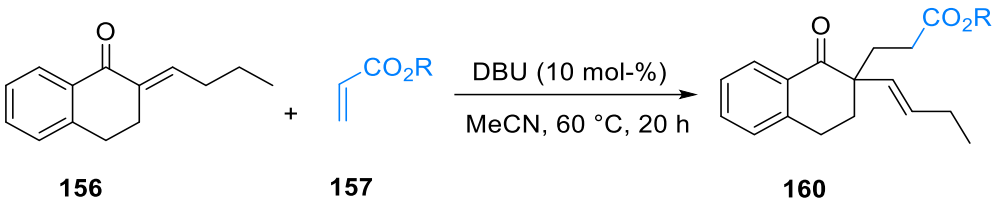
DBU-Catalyzed Deconjugative α-Alkylation of α-substituted enones with electron-deficient alkenes

In an effort to develop metal-free approaches to α-functionalized enones, a Brønsted base-catalyzed α-alkylation was explored. DBU proved uniquely effective in promoting the deconjugative alkylation of α-substituted enones with electron-deficient alkenes under mild, metal-free conditions.



Scheme 63. DBU-Catalyzed α-Alkylation of Indanone Derivative enones **154** with Alkenes **157**.

The reaction enabled regioselective α-functionalization by proceeding through reversible deprotonation of the enone substrate, followed by selective C-C bond formation at the α-position. This approach effectively avoided typical β-conjugate additions, highlighting the distinct reactivity mode of the DBU-catalyzed system.



Scheme 64. DBU-Catalyzed α-Alkylation of Tetralone Derivative enones **156** with Alkenes **157**.

Mechanistic proposals suggest a dual role for DBU as both a Brønsted base and a nucleophilic catalyst. This reaction demonstrates broad applicability across structurally diverse enones and alkenes, offering a new tool for constructing non-conjugated alkylated frameworks.

3.2 Outlook and Future Directions

Synthetic Methodology Expansion

While this thesis has demonstrated the utility of Lewis acid, phosphine, and base catalysis, future efforts may focus on expanding the synthetic scope further. One promising direction is the development of enantioselective catalysis. Although enantioselective variants were briefly explored in the phosphine-catalyzed reactions, broader application of chiral catalysts could enable the asymmetric synthesis of azepane-fused heterocycles and oxindoles with improved enantiomeric excess. Additionally, catalyst design remains a valuable avenue; the creation of tailored Lewis acids or phosphine ligands with fine-tuned steric and electronic properties may further enhance selectivity and expand substrate compatibility. Finally, integrating these catalytic annulations into tandem or cascade processes could significantly improve step economy, minimize purification steps, and streamline the synthesis of structurally complex molecules.

Biological Evaluation

The polycyclic heterocycles synthesized in this work incorporate scaffolds commonly found in bioactive molecules. For example, azepane-fused pyranoindoles resemble core structures present in known anti-inflammatory and CNS-active agents, while oxindoles are widely recognized motifs in natural products and kinase inhibitors. Looking ahead, future efforts should focus on biological screening of these compounds in relevant assays, including anti-cancer, anti-inflammatory, and antimicrobial evaluations. Additionally, structure-activity relationship (SAR) studies through late-stage functionalization could provide insights into pharmacological potential. The development of compound libraries suitable for high-throughput screening (HTS) would further support their potential as lead structures in drug discovery.

Mechanistic Investigations

While this work provides substantial mechanistic evidence through NMR analysis, X-ray crystallography, and optimization studies, further computational investigations could significantly enhance mechanistic understanding. In particular, analysis of transition state geometries and energetics in the Oxa Diels-Alder reaction would clarify key stereocontrol elements. Additionally, exploring the electronic effects of substituents

on reaction pathways in both phosphine and DBU catalysis could provide predictive insight into reactivity and selectivity. Computational evaluation of competing pathways in divergent annulations may also reveal factors governing pathway preference. Together, these insights would aid in predicting reactivity trends and guiding the rational design and optimization of catalysts for improved performance.

Green Chemistry and Sustainability

The use of mild, metal-free catalysts such as Organophosphines and DBU in this work aligns well with the core principles of green chemistry, emphasizing reduced toxicity and improved environmental compatibility. Looking ahead, future research could explore solvent-free or aqueous reaction conditions, as well as the use of biodegradable catalysts and reagents to further reduce the environmental footprint. In addition, the adoption of photochemical or electrochemical activation methods in place of traditional thermal processes could offer more energy-efficient alternatives. Together, these strategies would significantly enhance the sustainability and eco-friendliness of the developed methodologies.

Application in Material and Polymer Chemistry

Beyond their relevance in medicinal chemistry, the polycyclic scaffolds synthesized in this study hold potential for broader application in materials science. These structures could serve as building blocks in organic electronics, such as OLED materials and semiconductors, due to their conjugated frameworks and rigid architectures. Furthermore, their incorporation into polymeric materials may impart rigidity or optoelectronic functionality, making them attractive for advanced material design. Additionally, some of these frameworks may be adapted as chiral ligands or auxiliaries in other catalytic systems, expanding their utility in asymmetric synthesis.

3.3 Concluding Remarks

This thesis has established robust, stereoselective, and modular synthetic methodologies for the construction of structurally complex polycyclic heterocycles using catalyst-controlled annulation strategies. By harnessing the distinct reactivity of Lewis acids, phosphines, and bases, it has been possible to generate diverse heterocyclic frameworks relevant to both synthetic and medicinal chemistry.

The synthetic strategies described herein provide:

- New tools for rapid access to medicinally privileged scaffolds.
- Mechanistic insights that inform catalyst and substrate design.
- A platform for further exploration of complex heterocycle synthesis.

The work sets the stage for continued exploration in asymmetric catalysis, drug discovery, and green synthetic chemistry. Building upon the foundations of Lewis acid, phosphine, and base-mediated transformations, future efforts are expected to further refine catalyst design, improve reaction efficiency, and expand substrate diversity. Ultimately, these advances will help translate synthetic innovations into practical applications in therapeutics, materials science, and sustainable chemical processes, underscoring the enduring importance of catalyst-controlled C-C bond formation in modern organic synthesis.

Appendix

4. Experimental Section

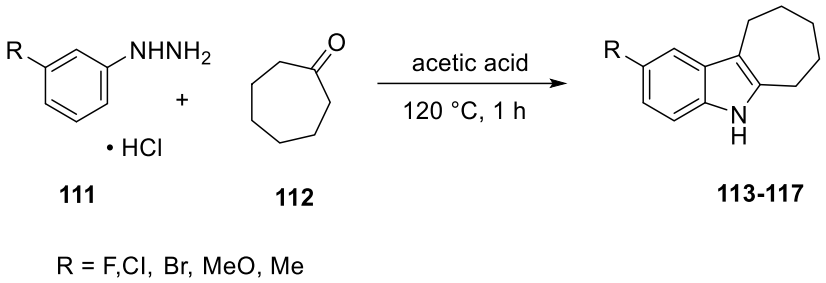
General information

All reactions involving moisture or air-sensitive reagents were carried out in oven dried pressure tubes under argon atmosphere.

Commercially available chemicals were used as received from suppliers unless otherwise noted. Dry solvents used were obtained from suppliers in serum-cap quality. Solvents for chromatographic separation were distilled twice prior to use. Thin-layer chromatography was carried out using silica-coated aluminium plates, silica 60 F254, *Merck*. Column chromatography was performed with silica 60 (230-400 mesh, *Macherey-Nagel*). NMR spectra were recorded on *Bruker AVANCE 500 NEO* and *Bruker AVANCE 300 III* instruments, and spectra were calibrated against the (residual) solvent resonances of CDCl3 (δH = 7.26 ppm, δC = 77.0 ppm), CD3OD (δH = 3.31 ppm, δC = 49.0 ppm) and CD3CN (δH = 1.94 ppm, δC = 118.3 ppm).1H- and 13C-NMR peak assignments were made based on 2D NMR spectra. IR spectra were obtained using a *Nicolet 380 FT-IR* spectrometer by *Thermo Fisher Scientific*. ESI-TOF HRMS spectrometry was performed using an *Agilent* 1200/6210 Time-of-Flight LC-MS instrument. EI HR mass spectra were obtained from a Thermo Electron MAT 95-XP instrument. X-Ray crystallographic analyses were performed on *Apex Kappa-II* and *D8 QUEST* instruments by *Bruker-AXS*.

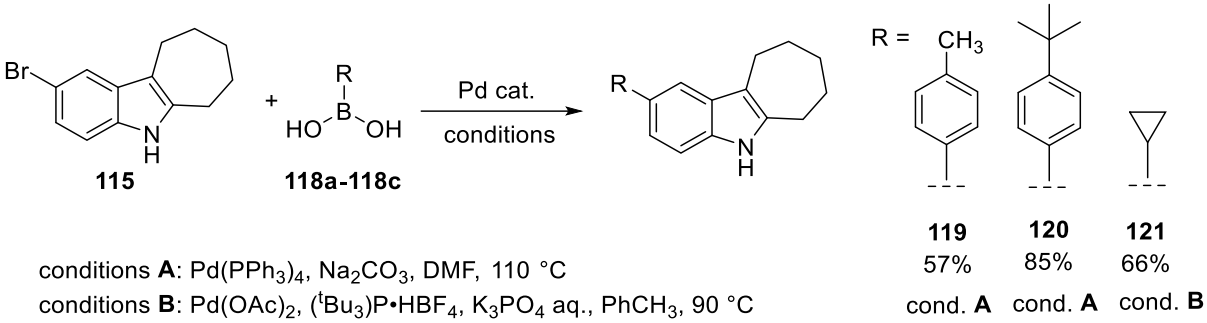
Synthesis of Substituted Cyclohepta[*b*]indoles via Fischer Indole Synthesis

The synthesis of the desired tricyclic enones **109** began with the preparation of cyclohepta[*b*]indoles **113** via a classical Fischer Indole synthesis.[1] The acid-catalyzed condensation of arylhydrazines **111** with cycloheptanone (**112**) gave rise to cyclohepta[*b*]indoles **113**[2] with diverse substituents on the aromatic ring (Scheme 65). As shown in Figure X, these encompassed substituents like fluoro (F), chloro (Cl), bromo (Br), methoxy (OMe) and methyl (Me), and the corresponding products **113-117** were isolated in 65-86% yield. according to the protocols described in detail previously in references.[1-2]



Scheme 65. Fischer Indole synthesis utilizing 4-substituted aryl hydrazine chlorides **111** and cycloheptanone (**112**).

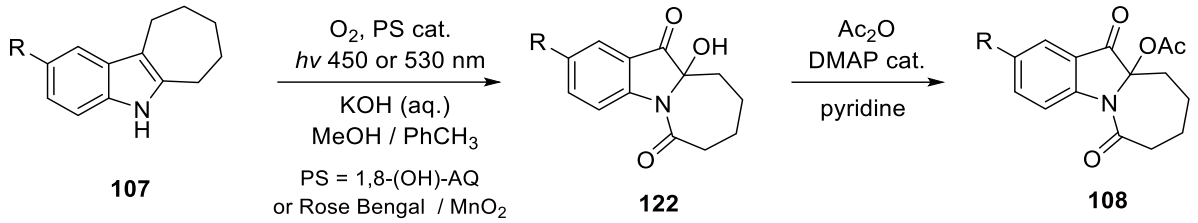
Three additional cyclohepta[*b*]indoles with aromatic substituents were synthesized via Palladium-catalyzed Suzuki–Miyaura cross-coupling of the 2-bromocyclohepta[*b*]indole **115**, which was reacted with *p*-tolylboronic acid (**118a**), 4-(*tert*-butyl)phenylboronic acid (**118b**) and cyclopropylboronic acid (**118c**), either with $Pd(PPh_3)_4$ or $Pd(OAc)_2$ along with $(^tBu_3)P•HBF_4$ (tri(*tert*-butyl)phosphonium tetrafluroborate) as the precatalysts, to give **119**, **120** and **121** in yields between 57-85% according to the protocols described in detail previously in reference.[2]



Scheme 66. Suzuki coupling reaction between 2-bromocyclohepta[*b*]indole **115** and boronic acids **118a-118c**.

Synthesis of perhydroazepino[1,2-*a*]indole acetates

The synthesis of the **108a-108i** was performed by sensitized cascade photooxygenation of cycloheptaindoles **107** followed by acetylation, according to the protocols described in detail in references.[2-3]

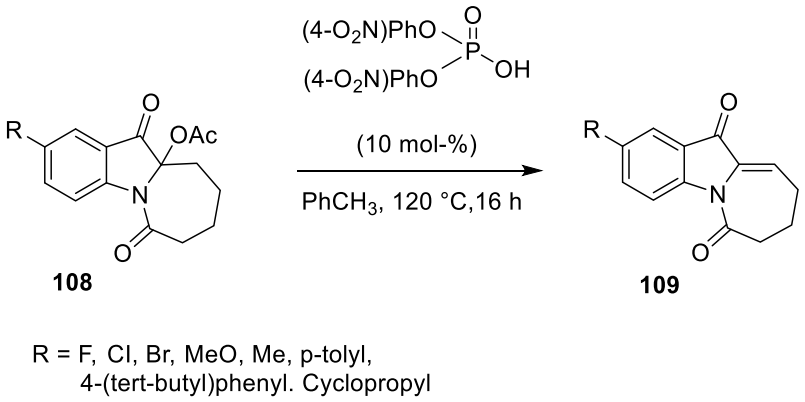


Scheme 67. Photooxygenation of cyclohepta[*b*]indoles and acetylation to perhydroazepino[1,2-*a*]indole acetates **108**.

Organophosphate-catalyzed dehydroacetoxylation of perhydroazepino[1,2-*a*]indole acetates 108.

General procedure 1

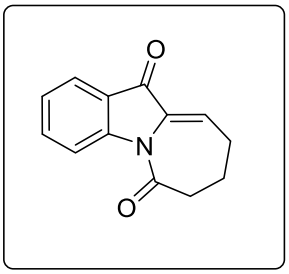
Azepinoindole acetate **108** was dissolved in $PhCH_3$ in a 10 mL crimp cap vial. Bis(4-nitrophenyl) phosphoric acid (BNPP, 10 mol-%) was added. The vial was sealed and air was replaced by argon via cannula during three freeze-pump-thaw cycles. The mixture was stirred at 120 °C for 16 h (heating in an oil bath), then cooled to r.t. and concentrated to dryness. Column chromatography over silica gel afforded pure enone product **109a-109i**.



Scheme 68 Organophosphate-catalyzed dehydroacetoxylation of perhydroazepino[1,2-*a*]indole Acetates **108** to give enones **109**.

8,9-Dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109a)

According to general procedure **1**, acetate **108a** (250.0 mg, 0.91 mmol), and BNPP (30.0 mg,88.1 µmol) in $PhCH_3$ (3.00 mL) gave enone **109a** (colorless solid, 185.0 mg, 94%) after chromatography (silica gel, $Et_2O/PhCH_3$ 1:3).



R*f* = 0.21 (silica, $Et_2O/PhCH_3$ 1:3), **m.p.** = 120-130 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.48 (dt, *J* = 8.4, 0.7 Hz, 1 H), 7.82 (ddd, *J* = 7.6, 1.4,0.7 Hz, 1 H), 7.64 (ddd, *J* = 8.4, 7.6, 1.4 Hz, 1 H), 7.25 (td, *J* = 7.6, 0.7 Hz, 1 H), 6.72 (t, *J* = 4.5 Hz, 1 H,), 2.88 – 2.81 (m, 2 H,), 2.64 (td, *J* = 6.3, 4.5 Hz, 2 H), 2.12 – 2.00 (m, 2 H) ppm.

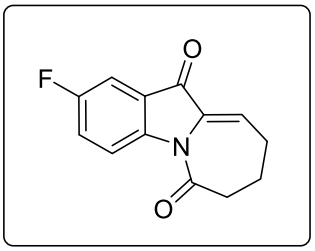
^{13}C-NMR (126 MHz, CDCl3): δ = 183.6, 171.7, 149.3, 136.5, 134.3, 124.8, 124.1, 123.8, 122.3, 118.7, 39.1, 29.4, 19.9 ppm.

IR: $\tilde{\nu}$ = 3330, 2950, 2840, 1720, 1660, 1470, 1450, 1405, 1310, 1120, 1025, 620 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{13}H_{12}NO_2$+[M+H]$^+$: 214.0868, found: 214.0873.

2-Fluoro-8,9-dihydro-6*H*-azepino[1,2-*a*] indole-6,11(7*H*)-dione (109b)

According to general procedure **1**, acetate **108b** (131.0 mg, 0.45 mmol), and BNPP (16.9 mg,49.7 µmol) in $PhCH_3$ (3.00 mL) gave enone **109b** (colorless solid, 75.0 mg, 72%) after chromatography (silica gel, $Et_2O/PhCH_3$ 1:3).



R*f* = 0.45 (silica, $Et_2O/PhCH_3$ 1:3), **m.p.** = 123-127 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.54 (ddd, *J*H,H = 9.1, 0.5 Hz, *J*F,H = 4.2 Hz, 1 H), 7.45 (ddd, *J*H,H = 2.8, 0.5 Hz, *J*F,H = 6.8 Hz, 1 H), 7.34 (ddd, *J*H,H = 9.1, 2.8 Hz, *J*F,H = 8.6 Hz, 1 H), 6.74 (t, *J* = 4.6 Hz, 1 H), 2.87 – 2.81 (m, 2 H), 2.64 (td, *J* = 6.4, 4.6 Hz, 2 H), 2.11 – 2.01 (m, 2 H) ppm.

^{13}C-NMR (75 MHz, CDCl3): δ = 182.7, 171.5, 159.7, 145.6, 134.5, 125.2, 123.6, 123.3, 120.3, 109.8, 38.9, 29.4, 19.8 ppm.

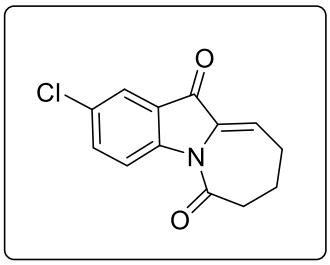
^{19}F-NMR (282 MHz, CDCl3): δ = -116.74 ppm.

IR: $\tilde{\nu}$ = 3210, 2965, 2930, 2880, 1735, 1675, 1525, 1485, 1455, 1380, 1265, 1235, 1195, 1105, 1035, 810, 755 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{13}H_{11}FNO_2$+[M+H]$^+$: 232.0773, found: 232.0776.

2-Chloro-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109c)

According to general procedure **1**, acetate **108c** (138.0 mg, 0.45 mmol), and BNPP (16.9 mg, 49.7 µmol) in PhCH3 (3.00 mL) gave enone **109c** (colorless solid, 96.0 mg, 86%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.28 (silica, Et_2O/heptane 1:3), **m.p.** = 127-132 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.49 (d, *J* = 8.9 Hz, 1 H), 7.74 (d, *J* = 2.3 Hz, 1 H), 7.56 (dd, *J* = 8.9, 2.3 Hz, 1 H,), 6.73 (t, *J* = 4.5 Hz, 1 H), 2.86 – 2.82 (m, 2 H), 2.64 (td, *J* = 6.4, 4.5 Hz, 2 H), 2.08 – 2.02 (m, 2 H) ppm.

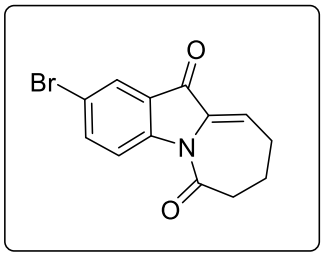
^{13}C-NMR (126 MHz, CDCl3): δ = 182.2, 171.5, 147.5, 136.0, 134.1, 130.5, 125.0, 123.6, 123.3, 119.9, 38.9, 29.4, 19.7 ppm.

IR: $\tilde{\nu}$ = 3315, 2970, 2925, 2880, 1715, 1680, 1600, 1515, 1465, 1375, 1265, 1185, 1100, 1030, 875, 800, 755 cm-1.

HRMS (ESI+): *m/z* calc. for $C_{13}H_{11}ClNO_2$+[M+H]$^+$: 248.0478, found: 248.0485.

2-Bromo-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109d)

According to general procedure **1**, acetate **108d** (157.0 mg, 0.45 mmol), and BNPP (15.3 mg, 44.9 µmol) in $PhCH_3$ (3.00 mL) gave enone **109d** (colorless solid, 102.0 mg, 78%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.28 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.** = 129-134 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.44 (dd, *J* = 8.9, 0.4 Hz, 1 H), 7.91 (dd, *J* = 2.2, 0.4 Hz, 1 H), 7.71 (dd, *J* = 8.9, 2.2 Hz, 1 H), 6.73 (t, *J* = 4.5 Hz, 1 H), 2.87 – 2.80 (m, 2 H), 2.64 (td, *J* = 6.3, 4.5 Hz, 2 H), 2.10 – 2.00 (m, 2 H) ppm.

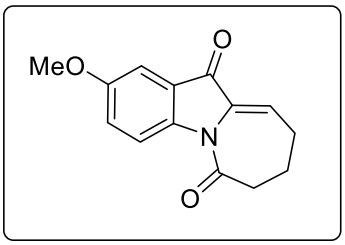
^{13}C-NMR (75 MHz, CDCl3): δ = 182.1, 171.6, 147.9, 138.8, 134.0, 126.7, 125.5, 123.2, 120.3, 117.9, 39.0, 29.4, 19.7 ppm.

IR: $\tilde{\nu}$ = 3315, 2970, 2925, 2880, 1715, 1675, 1600, 1515, 1465, 1380, 1260, 1185, 1100, 1030, 875, 800, 755 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{13}H_{11}BrNO_2$+$[M+H]^+$: 291.9973, found: 291.9973.

2-Methoxy-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109e)

According to general procedure **1**, acetate **108e** (137.0 mg, 0.45 mmol), and BNPP (15.3 mg, 45.0 µmol) in $PhCH_3$ (3.00 mL) gave enone **109e** (colorless solid, 91.0 mg, 83%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.20 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.** = 145-151 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.47 (d, *J* = 9.0 Hz, 1 H), 7.26 (d, *J* = 2.9 Hz, 1 H), 7.23 (dd, *J* = 9.0, 2.9 Hz, 1 H), 6.72 (t, *J* = 4.5 Hz, 1 H), 3.84 (s, 3 H), 2.86-2.81 (m, 2 H), 2.63 (td, *J* = 6.3, 4.5 Hz, 2 H), 2.09 – 2.03 (m, 2 H) ppm.

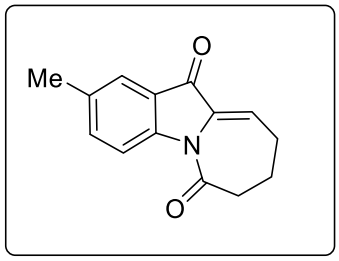
^{13}C-NMR (126 MHz, CDCl3): δ = 183.5, 171.3, 156.9, 144.0, 134.7 , 124.9 , 124.7 , 122.5, 119.9, 105.4, 55.8, 39.0, 29.4, 19.9 ppm.

IR: $\tilde{\nu}$ = 2965, 2940, 2845, 1725, 1680, 1655, 1490, 1450, 1440, 1380, 1320, 1285, 1245, 1130, 1060, 1035, 940, 805, 740 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{14}H_{14}NO_3$+$[M+H]^+$: 244.0974, found: 244.0977.

2-Methyl-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109f)

According to general procedure **1**, acetate **108f** (261.0 mg, 0.91 mmol), and BNPP (30.0 mg,88.1 µmol) in $PhCH_3$ (3.00 mL) gave enone **109f** (colorless solid, 125.0 mg, 60%) after chromatography (silica gel, $Et_2O/PhCH_3$ 1:3).



R*f* = 0.41 (silica, $Et_2O/PhCH_3$ 1:3), **m.p.** = 122-129 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.42 (dd, *J* = 8.5, 0.7 Hz, 1 H), 7.61 (dt, *J* = 2.0, 0.7 Hz, 1 H), 7.45 (ddd, *J* = 8.5, 2.0, 0.7 Hz, 1 H), 6.70 (t, *J* = 4.5 Hz, 1 H), 2.86 – 2.81 (m, 2 H), 2.63 (td, *J* = 6.4, 4.5 Hz, 2 H), 2.40 (s, 3 H), 2.11 – 2.00 (m, 2 H) ppm.

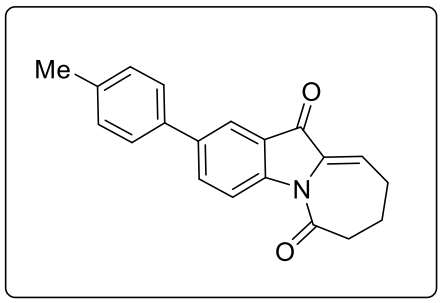
^{13}C-NMR (75 MHz, CDCl3): δ = 183.6, 171.5, 147.5, 137.5, 134.7, 134.6, 123.90, 123.86, 122.0, 118.4, 39.1, 29.4, 20.8, 19.9 ppm.

IR: $\tilde{\nu}$ = 3350, 3050, 2945, 1710, 1685, 1645, 1590, 1485, 1435, 1370, 1340, 1290, 1170, 1065, 960, 820, 770 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{14}H_{14}NO_2$+[M+H]$^+$: 228.1024, found: 228.1025.

2-(*p*-Tolyl)-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109g)

According to general procedure **1**, acetate **108g** (163.0 mg, 0.45 mmol), and BNPP (15.3 mg, 45.0 µmol) in $PhCH_3$ (3.00 mL) gave enone **109g** (colorless solid, 78.0 mg, 57%) after chromatography (silica gel, $Et_2O/PhCH_3$ 1:3).



R*f* =0.25 (silica, $Et_2O/PhCH_3$ 1:3), **m.p.**=129-136 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.58 (dd, *J* = 8.7, 0.6 Hz, 1 H), 8.02 (dd, *J* = 2.1, 0.6 Hz,1 H), 7.88 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.51 (mc, 2 H), 7.26 (mc, 2 H), 6.75 (t, *J* = 4.5 Hz, 1 H), 2.90 – 2.83 (m, 2 H), 2.65 (td, *J* = 6.3, 4.5 Hz, 2 H), 2.40 (s, 3 H), 2.13 – 2.03 (m, 2 H) ppm.

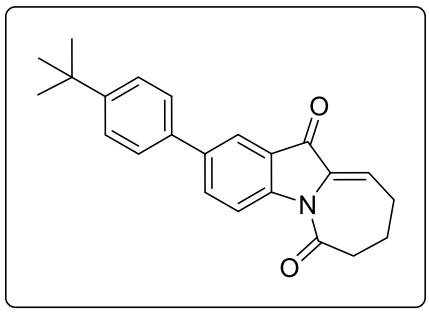
^{13}C-NMR (126 MHz, CDCl3): δ = 183.7, 171.7, 148.3, 137.9, 137.6, 136.4, 135.1, 134.6, 129.7, 126.7,124.3, 122.5, 121.8, 118.9, 39.1, 29.4, 21.1, 19.9 ppm.

IR: $\tilde{\nu}$ = 3035, 2935, 2870, 1725, 1685, 1655, 1620, 1485, 1375, 1345, 1310, 1265, 1195, 1130, 1065, 815, 735 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{20}H_{18}NO_2$+[M+H]$^+$: 303.1337, found: 303.1344.

2-(4-(*tert*-Butyl) phenyl)-8,9-dihydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (109h)

According to general procedure **1**, acetate **108h** (182.0 mg, 0.45 mmol), and BNPP (15.3 mg, 45.0 µmol) in $PhCH_3$ (3.00 mL) gave enone **109h** (colorless solid, 114.0 mg, 73%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* =0.26 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.**= 194-207 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.59 (d, *J* = 8.7 Hz, 1 H), 8.05 (d, *J* = 2.1 Hz, 1 H), 7.90 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.56 (mc, 2 H), 7.48 (mc, 2 H), 6.76 (t, *J* = 4.5 Hz, 1 H), 2.89 – 2.85 (m, 2 H), 2.66 (td, *J* = 6.4, 4.5 Hz, 2 H), 2.11 – 2.05 (m, 2 H), 1.37 (s, 9 H) ppm.

^{13}C-NMR (126 MHz, CDCl3): δ = 183.6, 171.7, 150.9, 148.4, 137.8, 136.4, 135.2, 134.6, 126.5, 125.9, 124.3, 122.4, 121.8, 118.9, 39.1, 34.6, 31.3, 29.4, 19.9 ppm.

IR: $\tilde{\nu}$ = 2970, 2910, 2875, 1725, 1685, 1660, 1620, 1475, 1370, 1310, 1260, 1195, 1090, 1030, 800, 735 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{23}H_{24}NO_2$+[M+H]$^+$: 346.1807, found: 346.1811.

Lewis acid-catalyzed oxa Diels-Alder reactions

General procedure 2.

Enones **109a-109i** was dissolved in $PhCH_3$ in a 10 mL crimp cap vial. $Yb(fod)_3$ (15 mol-%) was added to the stirred solution, followed by vinyl ethers **41a-41k** (10 equiv.). The vial was sealed and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at 50 °C for 20 h (heating in an oil bath). The mixture was concentrated to dryness, and the crude product was analyzed by ^{1}H-NMR spectroscopy to determine diastereomer ratio (*d.r.*). Thereafter, column chromatography over silica gel afforded the pure cycloadducts **110a-110k**.

Reaction on 1 mmol scale:

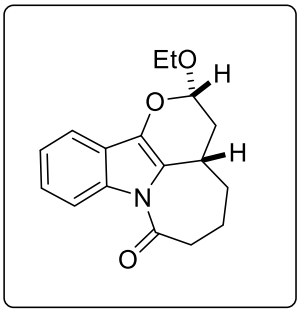
Enone **109a** (213.0 mg, 1.00 mmol) was dissolved in $PhCH_3$ (5.00 mL) in a 10 mL crimp cap vial. Yb(fod)3 (159.0 mg, 0.15 mmol) was added to the stirred solution, followed by ethyl vinyl ether (**41a**, 950.0 µL, 9.92 mmol). The vial was sealed and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at 50 °C for 20 h (heating in an oil bath). The mixture was concentrated to dryness, and column chromatography (silica gel, Et_2O/$PhCH_3$ 1:3) gave compound **110a** (colorless solid, 227.0 mg, 79%).

Technical note:

Even though cycloadducts **110** are well-soluble in $CDCl_3$, several derivatives showed broadened ^{1}H-NMR signals in this solvent. In these cases, use of CD_3OD or CD_3CN led to well-resolved ^{1}H-NMR spectra.

(2*S,3a*S**)-2-Ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110a)**

According to general procedure **2**, enone **109a** (21.3 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110a** (colorless solid, 20.0 mg, 70%) after chromatography (silica gel, Et$_2$O/PhCH$_3$ 1:3).



R*f* = 0.32 (silica, Et$_2$O/heptane 1:3), **m.p.** = 125-131 °C.

^{1}H-NMR (500 MHz, CD3CN): δ = 8.44 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.47 (dt, *J* = 7.6, 1.2, Hz, 1 H), 7.30 (ddd, *J* = 8.1, 7.6, 1.2 Hz, 1 H), 7.26 (td, *J* = 7.6, 1.2 Hz, 1 H), 5.34 (dd, *J* = 7.6, 2.1 Hz, 1 H), 4.00 (dq, *J* = 9.7, 7.1 Hz, 1 H), 3.72 (dq, *J* = 9.7, 7.1 Hz, 1 H), 3.39 – 3.30 (m, 1 H), 3.04 (mc, 1 H), 2.67 (dt, *J* = 14.6, 3.7 Hz, 1 H), 2.23 (ddd, *J* = 13.6, 6.7, 2.1 Hz, 1 H), 2.04 – 1.88 (m, 3 H), 1.81 – 1.69 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H) ppm.

^{13}C-NMR (126 MHz, CD3CN): δ = 173.6, 136.9, 134.9, 125.8, 124.3, 123.4, 120.5, 117.3, 117.1, 101.4, 65.4, 36.6, 35.5, 30.5, 30.2, 21.3, 15.6 ppm.

IR: $\tilde{\nu}$ = 3385, 2940, 1690, 1460, 1305, 1235, 1125, 985, 750 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{20}NO_3$+[M+H]$^+$: 286.1443, found: 286.1446.

Minor diastereomer:

The minor *exo*-diastereomer could as well be isolated and characterized by NMR spectroscopy:

(2*R,3a*S**)-2-Ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110a')**

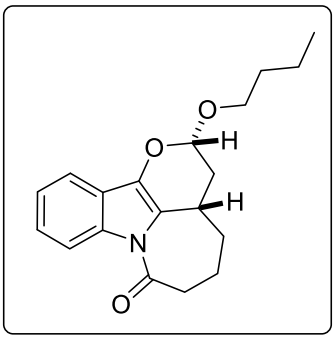
^{1}H-NMR (500 MHz, CD3OD): δ = 8.38 (dt, *J* = 8.2, 1.2 Hz, 1 H), 7.44 (mc, 1 H), 7.27 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1 H), 7.23 (td, *J* = 7.3, 1.2 Hz, 1 H), 5.41 (t, *J* = 2.5 Hz, 1 H), 3.92 (dq, *J* = 9.8, 7.1 Hz, 1 H), 3.75 (dq, *J* = 9.8, 7.1 Hz, 1 H), 3.38-3.33 (m, 1 H), 3.13 – 3.05 (m, 1 H), 2.66 (dt, *J* = 14.0, 4.1 Hz, 1 H), 2.23 (ddd, *J* = 13.3, 6.0, 2.5 Hz, 1 H),

2.15 – 2.01 (m, 3 H), 1.66 (ddd, *J* = 13.3, 10.7, 2.5 Hz, 1 H), 1.59 – 1.50 (m, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H) ppm.

^{13}C-NMR (126 MHz, CD3OD): δ = 174.4, 136.6, 135.1, 125.9, 124.6, 124.1, 120.7, 117.4, 117.3, 99.2, 65.3, 37.0, 35.6, 31.1, 27.8, 22.0, 15.5 ppm.

(2*S**,3a*S**)-2-Butoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110b)

According to general procedure **2**, enone **109a** (21.3 mg, 0.10 mmol), *n*-butyl vinyl ether (**41b**,128.0 µL, 1.00 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110b** (colorless solid, 24.0 mg, 77%) after chromatography (silica gel, Et$_2$O/PhCH$_3$ 1:3).



R*f* = 0.35 (silica, Et$_2$O/heptane 1:3), **m.p.** = 136-139 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.48 (dt, *J* = 8.3, 1.0 Hz, 1 H), 7.51 (dt, *J* = 7.6, 1.0 Hz, 1 H), 7.32 (ddd, *J* = 8.3, 7.6, 1.0 Hz, 1 H), 7.26 (td, *J* = 7.6, 1.0 Hz, 1 H), 5.31 (dd, *J* = 6.9, 2.1 Hz, 1 H), 4.00 (dt, *J* = 9.6, 6.6 Hz, 1 H), 3.63 (dt, *J* = 9.6, 6.6 Hz, 1 H), 3.28 (dtd, *J* = 11.5, 6.9, 3.5 Hz, 1 H), 3.01 – 2.92 (m, 1 H), 2.77 (dt, *J* = 15.1, 4.0 Hz, 1 H), 2.25 (ddd, *J* = 13.6, 6.9, 2.1 Hz, 1 H), 2.03 – 1.95 (m, 3 H), 1.90 (dt, *J* = 13.6, 6.9 Hz, 1 H), 1.87 – 1.81 (m, 1 H), 1.65 – 1.58 (m, 2 H), 1.39 (mc, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H) ppm.

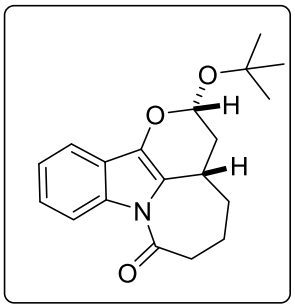
^{13}C-NMR (126 MHz, CDCl3): δ = 172.4, 136.7, 134.1, 125.2, 123.4, 122.5, 118.2, 116.7, 116.5, 100.1, 69.1, 35.9, 34.4, 31.7, 29.9, 29.4, 20.6, 19.2, 13.8 ppm.

IR: $\tilde{\nu}$ = 3360, 2945, 1735, 1655, 1470, 1380, 1305, 765 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{19}H_{24}NO_3$+[M+H]$^+$: 314.1756, found: 314.1760.

(2*S,3a*S**)-2-(*tert*-Butoxy)-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110c)**

According to general procedure **2,** enone **109a** (21.3 mg, 0.10 mmol), *tert*-butyl vinyl ether (**41c**, 131.0 µL, 1.00 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110c** (colorless solid, 28.0 mg, 89%) after chromatography (silica gel, Et$_2$O/PhCH$_3$ 1:3).



R*f* = 0.34 (silica, Et$_2$O/heptane 1:3), **m.p.** = 110 °C.

^{1}H-NMR (500 MHz, CD3CN): δ = 8.44 (dt, *J* = 8.2, 1.1 Hz, 1 H), 7.44 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.30 (ddd, *J* = 8.2, 7.6, 1.1 Hz, 1 H), 7.25 (td, *J* = 7.6, 1.1 Hz, 1 H), 5.59 (dd, *J* = 7.8, 2.1 Hz, 1 H), 3.42 – 3.35 (m, 1 H), 3.08 – 3.00 (m, 1 H), 2.68 (dt, *J* = 14.4, 3.8 Hz, 1 H), 2.14 (ddd, *J* = 13.5, 6.6, 2.1 Hz, 1 H), 2.04 - 1.90 (m, 3 H), 1.78 – 1.69 (m, 2 H), 1.32 (s, 3 H) ppm.

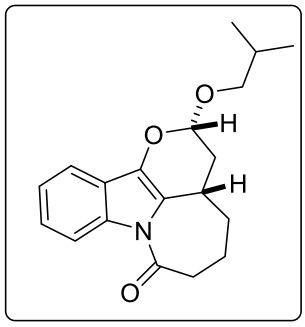
^{13}C-NMR (126 MHz, CD3CN): δ = 173.6, 137.4, 134.9, 125.7, 124.2, 123.6, 120.3, 117.3, 117.1, 96.3, 76.4, 36.9, 36.6, 30.6, 30.5, 28.9, 21.3 ppm.

IR: $\tilde{\nu}$ = 3375, 2975, 2930, 2875, 1730, 1685, 1465, 1380, 1345, 1260, 1185, 1155, 1120, 935, 760 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{19}H_{24}NO_3$+[M+H]$^+$: 314.1756, found: 314.1758.

(2*S,3a*S**)-2-Isobutoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110d)**

According to general procedure **2**, enone **109a** (21.3 mg, 0.10 mmol), isobutyl vinyl ether (**41d**, 130.0 µL, 1.00 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110d** (colorless solid, 26.0 mg, 83%) after chromatography (silica gel, Et$_2$O/PhCH$_3$ 1:3).



R*f* = 0.59 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.** = 87-96 °C.

^{1}H-NMR (500 MHz, CD3CN): δ = 8.40 (dt, *J* = 8.2, 0.8 Hz, 1 H), 7.46 (dt, *J* = 7.4, 0.8 Hz, 1 H), 7.30 (ddd, *J* = 8.4, 7.4, 0.8 Hz, 1 H), 7.26 (td, *J* = 7.4, 0.8 Hz, 1 H), 5.33 (dd, *J* = 6.5, 2.2 Hz, 1 H), 3.71 (dd, *J* = 9.4, 6.6 Hz, 1 H), 3.42 (dd, *J* = 9.4, 6.6 Hz, 1 H), 3.35 (mc, 1H), 3.06 – 2.98 (m, 1 H), 2.68 – 2.62 (m, 1 H), 2.24 (ddd, *J* = 13.7, 6.9, 2.2 Hz, 1 H), 2.00 – 1.96 (m, 2 H), 1.89 – 1.80 (m, 4 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H), ppm.

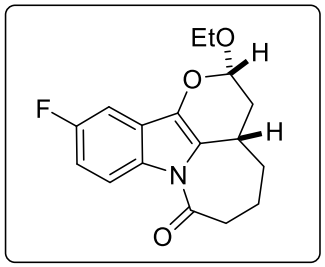
^{13}C-NMR (126 MHz, CD3CN): δ = 173.6, 136.6, 134.8, 125.7, 124.2, 123.4, 120.3, 117.2, 117.0, 101.3, 76.4, 36.5, 34.8, 30.5, 29.7, 29.3, 21.3, 19.4 ppm.

IR: $\tilde{\nu}$ = 3290, 2965, 2935, 2875, 1725, 1675, 1610, 1465, 1385, 1310, 1260, 1185, 920, 750, 670 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{19}H_{24}NO_3$+$[M+H]^+$: 314.1756, found: 314.1755.

(2*S,3a*S**)-2-Ethoxy-10-fluoro-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110e)**

According to general procedure **2**, enone **109b** (23.1 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and $Yb(fod)_3$ (15.9 mg, 15 µmol) in $PhCH_3$ (1.00 mL) gave compound **110e** (colorless solid, 28.0 mg, 92%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.26 (silica, Et_2O/heptane 1:3), **m.p.** = 112-117 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.42 (ddd, *J*H,H = 9.1, 0.5 Hz, *J*F,H = 4.7 Hz, 1 H), 7.15 (ddt, *J*H,H = 2.7, 0.5 Hz, *J*F,H = 9.1 Hz, 1 H), 7.01 (td, *J*H,H = 9.1, 2.7 Hz, *J*F,H = 9.1 Hz, 1 H), 5.30 (dd, *J* = 7.0, 2.1 Hz, 1 H), 4.04 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.70 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.26 (mc, 1 H), 3.01 – 2.86 (m, 1 H), 2.76 (dt, *J* = 15.0, 4.3 Hz, 1 H), 2.26 (ddd, *J* = 13.6, 6.8, 2.1 Hz, 1 H), 2.06 – 1.94 (m, 3 H), 1.93 – 1.79 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H) ppm.

^{13}C-NMR (75 MHz, CDCl3): δ = 172.1, 159.5, 136.3, 130.3, 123.4, 120.0,117.7, 112.6, 102.6,100.0, 64.8, 35.7, 34.5, 29.8, 29.5, 20.5, 15.2 ppm.

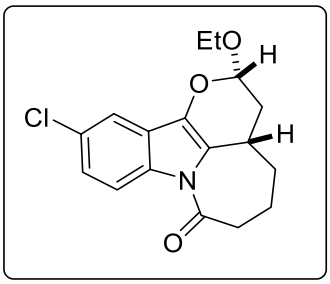
19F-NMR (282 MHz, CDCl3): δ = -118.93 ppm.

IR: $\tilde{\nu}$ = 3335, 2950, 2880, 1735, 1680, 1485, 1380, 1270, 840, 760 cm-1.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{19}FNO_3$+[M+H]$^+$: 304.1349, found: 304.1356.

(2*S,3a*S**)-10-Chloro-2-ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110f)**

According to general procedure **2**, enone **109c** (24.7 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110f** (colorless solid, 21.0 mg, 66%) after chromatography (silica gel, Et2O/PhCH3 1:3).



R*f* = 0.28 (silica, Et$_2$O/heptane1:3), **m.p.** = 89-95 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 8.69 (br. s, 1 H), 7.51 (d, *J* = 2.2 Hz, 1 H), 7.26 (dd, *J* = 8.8, 2.1 Hz, 1 H), 5.35 (dd, *J* = 6.9, 2.1 Hz, 1 H), 4.07 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.72 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.40 – 3.32 (m, 1 H), 3.19 – 3.00 (m, 2 H, 6-Ha), 2.30 (ddd, *J* = 13.7, 6.8, 2.1 Hz, 1 H), 2.14 – 2.00 (m, 3 H), 1.98 – 1.89 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H) ppm.

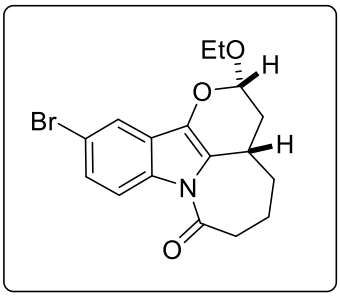
^{13}C-NMR (126 MHz, CDCl3): δ = 173.1, 136.0, 132.6, 129.1, 125.2, 123.8, 119.9, 117.8, 116.6, 100.0, 64.9, 36.1, 34.5, 29.9, 29.6, 20.6, 15.2 ppm.

IR: $\tilde{\nu}$ = 3325, 2940, 2880, 1735, 1680, 1465, 1375, 1340, 1315, 1270, 1185, 1120, 980, 840, 755 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{19}ClNO_3$+[M+H]$^+$: 320.1053, found: 320.1060.

(2*S,3a*S**)-10-Bromo-2-ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110g)**

According to general procedure **2**, enone **109d** (29.0 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110g** (colorless solid, 23.0 mg, 63%) after chromatography (silica gel, Et2O/PhCH3 1:3).



R*f* = 0.28 (silica, Et$_2$O/heptane 1:3), **m.p.** = 99-104 °C.

^{1}H-NMR (300 MHz, CD3OD): δ = 8.27 (dd, *J* = 8.8, 0.5 Hz, 1 H), 7.54 (dd, *J* = 2.0, 0.5 Hz, 1 H), 7.36 (dd, *J* = 8.8, 2.0 Hz, 1 H), 5.35 (dd, *J* = 6.8, 2.1 Hz, 1 H), 4.01 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.72 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.36 (mc, 1 H), 3.13 – 3.00 (m, 1 H), 2.73 – 2.64 (m, 1 H), 2.26 (ddd, *J* = 13.7, 6.8, 2.1 Hz, 1 H), 2.08 – 1.93 (m, 2 H), 1.89 – 1.75 (m, 3 H), 1.24 (t, *J* = 7.1 Hz,3 H) ppm.

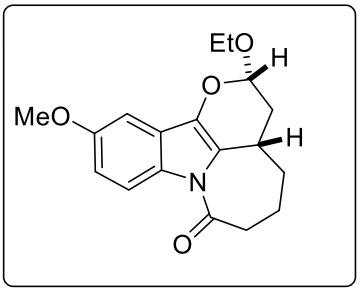
^{13}C-NMR (75 MHz, CD3OD): δ = 174.4, 136.5, 133.9, 128.6, 125.6, 121.9, 120.2, 118.9, 117.5, 101.6, 65.8, 36.5, 35.4, 30.9, 30.3, 21.6, 15.6 ppm.

IR: $\tilde{\nu}$ = 3325, 2940, 2880, 1735, 1680, 1465, 1375, 1340, 1315, 1270, 1185, 1120, 980, 840,755 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{19}BrNO_3$+[M+H]$^+$: 364.0548, found: 364.0550.

(2*S,3a*S**)-2-Ethoxy-10-methoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110h)**

According to general procedure **2**, enone **109e** (24.3 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110h** (colorless solid, 24.1 mg, 76%) after chromatography (silica gel, Et2O/PhCH3 1:3).



R*f* = 0.26 (silica, Et_2O/heptane 1:3), **m.p.** = 211-214 °C.

^{1}H-NMR (300 MHz, CDCl3): δ = 8.41 (d, *J* = 9.0 Hz, 1 H), 6.96 (d, *J* = 2.6 Hz, 1 H), 6.90 (dd, *J* = 9.0, 2.6 Hz, 1 H), 5.31 (dd, *J* = 7.2, 2.1 Hz, 1 H), 4.08 (dq, *J* = 9.5, 7.1 Hz, 1 H), 3.85 (s, 3 H), 3.71 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.27 (mc, 1 H), 3.03 – 2.89 (m, 1 H), 2.80 (dt, *J* = 14.7, 3.8 Hz, 1 H), 2.26 (ddd, *J* = 13.7, 6.8, 2.1 Hz, 1 H), 2.06 – 1.94 (m, 3 H), 1.94 – 1.77 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H) ppm.

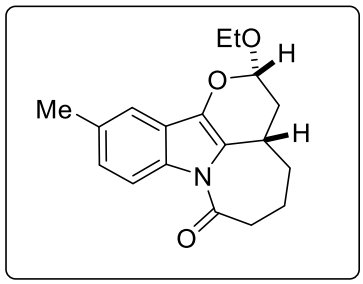
^{13}C-NMR (75 MHz, CDCl3): δ = 172.1, 156.4, 136.7, 128.8, 123.3, 119.0, 117.6, 113.6, 100.1, 99.4, 64.8, 55.7, 35.7, 34.7, 29.9, 29.6, 20.5, 15.2 ppm.

IR: $\tilde{\nu}$ = 3380, 2980, 2850, 1730, 1680, 1490, 1460, 1340, 1380, 1330, 1260, 1190, 1120, 1040, 920, 845, 745 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{18}H_{22}NO_4$+$[M+H]^+$: 316.1549, found: 316.1550.

(2*S,3a*S**)-2-Ethoxy-10-methyl-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110i)**

According to general procedure **2**, enone **109f** (22.7 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and $Yb(fod)_3$ (15.9 mg, 15 µmol) in $PhCH_3$ (1.00 mL) gave compound **110i** (colorless solid, 25.0 mg, 84%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.61 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.** = 107-109 °C.

^{1}H-NMR (300 MHz, CD3OD): δ = 8.22 (d, *J* = 8.5 Hz, 1 H), 7.24 – 7.19 (m, 1 H), 7.11 – 7.05 (m, 1 H), 5.31 (dd, *J* = 7.1, 2.1 Hz, 1 H), 4.01 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.74 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.35 – 3.24 (m, 1 H), 3.10 – 2.97 (m, 1 H), 2.67 – 2.57 (m, 1 H), 2.40 (s, 3 H), 2.22 (ddd, *J* = 13.6, 6.8, 2.1 Hz, 1 H), 2.05 – 1.90 (m, 3 H), 1.82 – 1.68 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm.

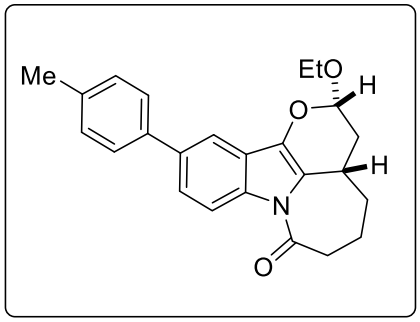
^{13}C-NMR (75 MHz, CD3OD): δ = 174.4, 137.7, 134.4, 133.6, 127.2, 124.2, 120.2, 117.4, 117.1, 101.6, 65.8, 36.5, 35.7, 31.0, 30.4, 21.7, 21.4, 15.6 ppm.

IR: $\tilde{\nu}$ = 3335, 2935, 2875, 1725, 1685, 1490, 1460, 1380, 1320, 1170, 1135, 1065, 990, 815 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{18}H_{22}NO_3$+$[M+H]^+$: 300.1600, found: 300.1607.

(2*S,3a*S**)-2-Ethoxy-10-(*p*-tolyl)-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110j)**

According to general procedure **2**, enone **109g** (30.0 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and $Yb(fod)_3$ (15.9 mg, 15 µmol) in $PhCH_3$ (1.00 mL) gave compound **110j** (colorless solid, 32.5 mg, 87%) after chromatography (silica gel, Et_2O/$PhCH_3$ 1:3).



R*f* = 0.48 (silica, Et2O/toluene 1:3), **m.p.** = 92-96 °C.

^{1}H-NMR (300 MHz, CD3OD): δ = 8.41 (br. d, *J* = 8.6 Hz, 1 H), 7.62 (mc, 1 H), 7.57- 7.49 (m, 3 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 5.38 (dd, *J* = 7.1, 1.9 Hz, 1 H), 4.05 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.73 (dq, *J* = 9.6, 7.1 Hz, 1 H), 3.44 – 3.35 (m, 1 H), 3.17 – 3.02 (m, 1 H), 2.73 – 2.62 (m, 1 H), 2.37 (s, 3 H), 2.29 (ddd, *J* = 13.7, 6.8, 1.9 Hz, 1 H), 2.10 – 1.90 (m, 3 H), 1.90 – 1.73 (m, 2 H),1.26 (t, *J* = 7.1 Hz, 3 H) ppm.

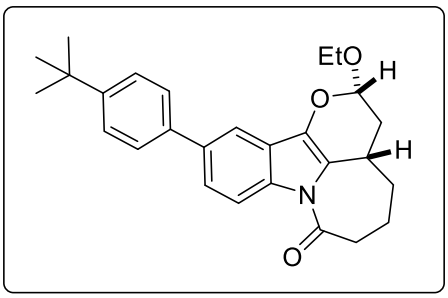
^{13}C-NMR (75 MHz, CD3OD): δ = 174.5, 139.7, 138.2, 137.93, 137.91, 134.6, 130.5, 128.0, 125.1, 124.6, 120.8, 117.6, 115.4, 101.7, 65.8, 36.5, 35.8, 31.0, 30.5, 21.7, 21.1, 15.6 ppm.

IR: $\tilde{\nu}$ = 3285, 2960, 2930, 2880, 1725, 1685, 1655, 1620, 1590, 1480, 1370, 1335, 1310, 1265,1130, 1005, 810, 745 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{24}H_{26}NO_3$+$[M+H]^+$: 376.1913, found: 376.1913.

(2*S,3a*S**)-10-(4-(*tert*-Butyl)phenyl)-2-ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]-fluoren-7-one (110k)**

According to general procedure **2**, enone **109h** (34.0 mg, 0.10 mmol), ethyl vinyl ether (**41a**, 95.0 µL, 0.99 mmol) and Yb(fod)$_3$ (15.9 mg, 15 µmol) in PhCH$_3$ (1.00 mL) gave compound **110k** (colorless solid, 37.0 mg, 89%) after chromatography (silica gel, Et2O/PhCH3 1:3).



R*f* = 0.47 (silica, Et$_2$O/PhCH$_3$ 1:3), **m.p.** = 87-94 °C.

^{1}H-NMR (500 MHz, CDCl3): δ = 10.82 – 9.81 (br. m, 1 H), 8.00 (br. s, 1 H), 7.66 (mc, 2 H), 7.63 (br. d, J = 7.1 Hz, 1 H), 7.48 (mc, 2 H), 5.66 – 5.57 (m, 1 H), 4.31 – 4.22 (m, 1H), 3.93 – 3.84 (m, 1 H), 3.22 – 3.00 (br. m, 1 H), 2.89–2.69 (br. m, 1 H), 2.61 – 2.53 (m, 1 H), 2.49 – 2.30 (m, 3 H), 2.28 – 2.17 (m, 1 H), 1.41 (t, *J* = 7.0 Hz, 3 H), 1.37 (s, 9 H) ppm.

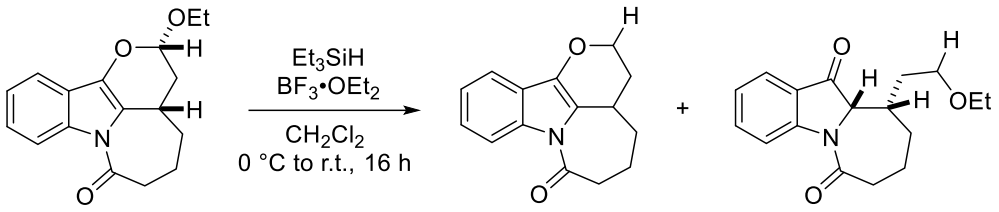
^{13}C-NMR (126 MHz, CDCl3): δ = 171.1, 150.0, 138.6, 137.6, 137.0, 135.0, 127.0, 125.7, 124.9, 123.8, 119.9, 118.0, 115.3, 100.4, 65.0, 38.1, 35.0, 34.5, 31.4, 30.5, 30.3, 21.5, 15.3 ppm.

IR: $\tilde{\nu}$ = 3285, 2960, 2930, 2880, 1725, 1685, 1655, 1620, 1590, 1480, 1370, 1335, 1310, 1265, 1130, 1005, 810, 745 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{27}H_{32}NO_3$+[M+H]$^+$: 418.2382, found: 418.2386.

Reaction of pyranoside **110a** to compounds **126** and **127**.

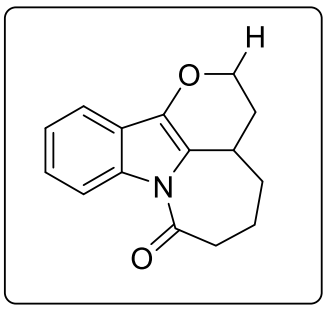
Pyranoside **110a** (28.5 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (5.00 mL) at 0 °C. Et_3SiH (70.0 µL, 0.44 mmol) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (30.0 µL, 0.23 mmol). The mixture was allowed to warm to r.t. over 16 h. $NaHCO_3$ (aq.) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3×). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (silica gel, Et2O/PhCH3 1:3) afforded compound **126** (colorless solid, 8.5 mg, 35%) and compound **127** (colorless oil, 13.5 mg, 47%).



110a **126** 35% **127** 47%

Scheme 70. Reductive transformation of pyranoside **110a** with triethylsilane and boron trifluoride etherate.

2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]fluoren-7-one (126)



R*f* = 0.58 (silica, Et_2O/$PhCH_3$ 1:3), **m.p.** = 155-157 °C.

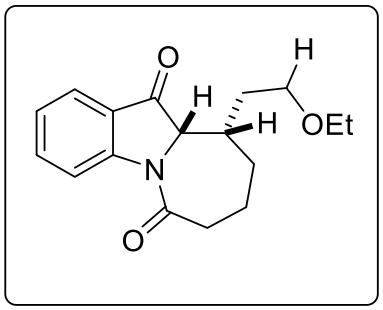
^{1}H-NMR (300 MHz, CDCl3): δ = 8.48 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1 H), 7.49 (mc, 1 H), 7.36-7.29 (m, 1 H), 7.26 (td, *J* = 7.6, 1.4 Hz, 1 H), 4.34 (ddd, *J* = 11.0, 5.7, 3.2 Hz, 1 H), 4.25 (ddd, *J* = 11.0, 9.1, 2.6 Hz, 1 H), 3.26 – 3.14 (m, 1 H), 3.05-2.92 (m, 1 H), 2.78 (dt, *J* = 14.7, 4.0 Hz, 1 H), 2.16 (dtd, *J* = 14.0, 6.0, 2.5 Hz, 1 H), 2.11 – 1.96 (m, 3 H), 1.76 (dddd, *J* = 14.0, 9.1, 7.5, 3.3 Hz, 1 H), 1.63 – 1.53 (m, 1 H) ppm.

^{13}C-NMR (75 MHz, CDCl3): δ = 172.2, 139.4, 133.8, 125.3, 123.5, 122.4, 118.3, 116.6, 116.5, 65.8, 36.0, 30.7, 30.4, 29.7, 20.9 ppm.

IR: $\tilde{\nu}$ = 3335, 2950, 2835, 1675, 1450, 1415, 1120, 1025, 630 cm^{-1}.

HRMS (EI): *m/z* calc. for $C_{15}H_{15}NO_2$+[M+H]$^+$: 241.1097, found: 241.1097.

(10*S,10a*S**)-10-(2-Ethoxyethyl)-8,9,10,10a-tetrahydro-6*H*-azepino[1,2-*a*]indole-6,11(7*H*)-dione (127)**



R*f* = 0.23 (silica, Et_2O/$PhCH_3$ 1:3).

^{1}H-NMR (300 MHz, CDCl3): δ = 8.57 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.72 (ddd, *J* = 7.7, 1.5, 0.8 Hz, 1H), 7.65 (ddd, *J* = 8.4, 7.7, 1.5 Hz, 1H), 7.20 (td, *J* = 7.7, 0.8 Hz, 1H), 4.29 (d, *J* = 1.5 Hz, 1H), 3.33 (mc, H), 3.30 – 3.23 (m, 2H), 2.80 – 2.67 (m, 2H), 2.66 – 2.54 (m, 1H), 2.19 – 2.09 (m, 1H),1.95 – 1.71 (m, 3H), 1.49 (mc, 1H,), 1.26 – 1.13 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm.

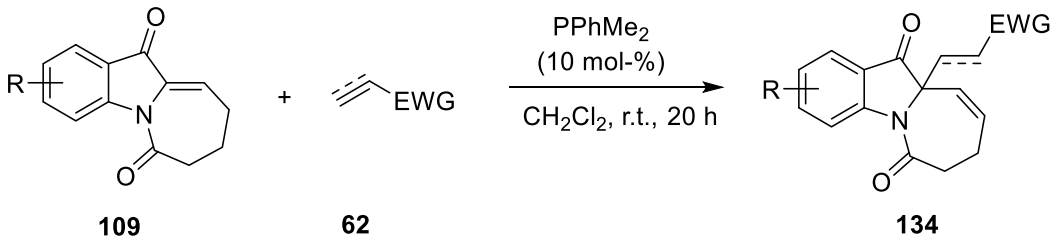
^{13}C-NMR (75 MHz, CDCl3): δ = 198.3, 172.4, 153.7, 137.4, 124.5, 124.2, 123.5, 118.5, 69.7, 68.2, 66.1, 39.7, 37.1, 32.7, 24.5, 18.9, 15.1 ppm.

IR: $\tilde{\nu}$ = 3330, 2950, 2840, 1720, 1660, 1470, 1450, 1405, 1310, 1120, 1030, 620 cm^{-1}.

HRMS (EI): *m/z* calc. for $C_{17}H_{21}NO_2$+$[M+H]^+$: 287.1516, found: 287.1518.

General procedure 3 for the Synthesis of β,γ-Unsaturated Ketones 134a-134p

Enone **109** was dissolved in CH_2Cl_2 in a 10 mL crimp cap vial. Alkene **62**(10 equiv) was added to solution, followed by dimethylphenylphosphine (10 mol-%) via a micropipette. The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 20 h and then concentrated to dryness. Column chromatography over silica gel afforded the pure products **134a-134p**.

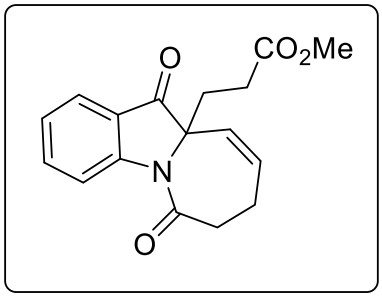


109 **62** **134**

Scheme 71. Phosphine-catalyzed crossed Rauhut-Currier (RC) coupling with substituted enones **109** and alkenes **62**.

Methyl-3-(6,11-dioxo-7,8-dihydro-6*H*-azepino(1,2-*a*)indol-10*a*(11*H*)-yl)propanoate (134a)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), methyl acrylate (**62a**, 90.0 µL, 0.99 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134a** (colorless solid, 25.5 mg, 85%).



R*f* = 0.26 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 113−114 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.6,1.5, 0.8 Hz, 1H), 7.70 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m,1H), 5.92 − 5.87 (m, 1H), 5.82 (ddd, J = 11.7, 2.5, 1.5 Hz, 1H), 3.58 (s, 3H), 3.27 (td, J = 13.3, 4.7 Hz, 1H), 2.74 − 2.68 (m, 1H), 2.62 (ddd, J = 15.7, 8.7, 7.3 Hz, 1H), 2.57 − 2.42 (m, 3H), 2.15 − 2.02 (m, 2H) ppm.

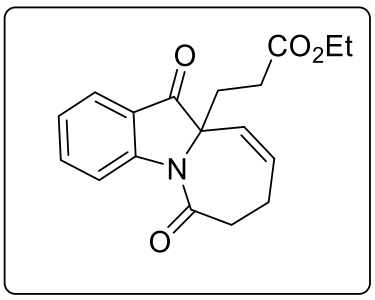
^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.9, 172.4, 172.2, 153.2, 137.9, 131.1, 127.5, 124.5, 123.9, 122.5, 118.8, 71.4, 59.9, 36.4, 35.3, 28.1, 25.5, ppm.

IR: $\tilde{\nu}$ = 3032, 2937, 1716, 1675, 1605, 1582, 1469, 1438, 1363, 1250, 1151, 893, 796, 741, 724, 629 cm^{-1}.

HRMS(ESI-TOF):*m*/*z*.calc for $C_{17}H_{17}NO_4$+[M+Na]$^+$:322.1049; found, 322.1046.

Ethyl-3-(6,11-dioxo-7,8-dihydro-6*H*-azepino(1,2-a)indol-10a(11*H*)-yl)propanoate (134b)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), ethyl acrylate (**62b,** 106.0 µL, 1.00 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134b** (colorless solid, 25.6 mg, 82%).



R*f* = 0.23 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 127−128 °C.

^{1}H-NMR(500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.7,1.4, 0.7 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26 − 7.22 (m,1H), 5.92 − 5.87 (m, 1H), 5.82 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 4.03 (qd, 7.2, 1.2 Hz, 2H), 3.28 (td, J = 13.1, 4.7 Hz, 1H), 2.74 − 2.68 (m, 1H), 2.63 (ddd, J = 15.8, 8.8, 7.3 Hz, 1H), 2.55 − 2.45 (m, 3H), 2.13 - 2.00 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H) ppm.

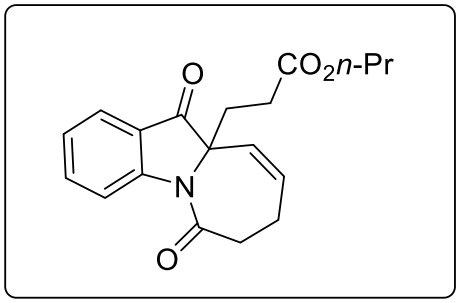
^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.9, 172.3, 172.0, 153.2, 137.8, 131.0, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 60.9, 36.4, 35.2, 28.3, 25.5, 14.1 ppm.

IR: $\tilde{\nu}$ = 3011, 2955, 1756, 1657, 1601, 1594, 1471, 1438, 1361, 1256, 1153, 755, 723, 629 cm^{-1}.

HRMS (ESI-TOF): m/z calc for $C_{18}H_{19}NO_4$+[M+Na]$^+$: 336.1206; found, 336.1210.

Propyl-3-(6,11-dioxo-7,8-dihydro-6*H*-azepino(1,2-*a*)indol-10*a*(11*H*)-yl)propanoate (134c)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), propyl acrylate (**62c,** 123.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134c** (colorless solid, 24.7 mg, 75%).



R*f* = 0.37 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 157−158 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.66 (dt, J = 8.5, 0.7 Hz, 1H), 7.77 (ddd, J = 7.7, 1.5, 0.7 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26 - 7.22 (m, 1H), 5.92 − 5.87 (m, 1H), 5.82 (ddd, J = 11.8, 2.5, 1.5 Hz, 1H), 3.93 (t, J = 6.8 Hz, 2H), 3.28 (td, J = 13.7, 4.7 Hz, 1H), 2.73 - 2.68 (m, 1H), 2.62 (ddd, J = 14.7, 8.8, 7.2 Hz, 1H), 2.54 − 2.44 (m, 3H), 2.14 − 2.01 (m, 2H), 1.54 (sext., J = 7.4 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H) ppm.

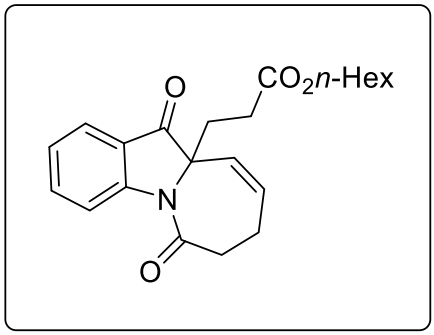
^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.9, 172.3, 172.1, 153.1, 137.8, 131.1, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 66.5, 36.4, 35.2, 28.3, 25.5, 21.8, 10.3 ppm.

IR: $\tilde{\nu}$ = 2975, 2937, 1724, 1675, 1607, 1465, 1378, 1186, 1157, 1083, 761, 687 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{19}H_{21}NO_4$+[M+Na]$^+$: 350.1363; found, 350.1373.

Hexyl-3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2*a*]indol10*a*(11*H*)yl)propanoate (137d).

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), *n*-hexyl acrylate (**62d**, 175.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **137d** (colorless solid, 23.3 mg, 63%).



R*f* = 0.38 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 136−138 °C.

^{1}H-NMR (500 MHz, CDCl3): δ 8.66 (d, *J* = 8.5 Hz, 1H), 7.77 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 1H), 7.69 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 7.26 − 7.22 (m, 1H), 5.92 − 5.86 (m, 1H), 5.82 (ddd, *J* = 11.7, 2.4, 1.4 Hz, 1H), 3.96 (t, *J* = 7.0 Hz, 2H), 3.28 (td, *J* = 13.4, 4.6 Hz, 1H), 2.73−2.68 (m,1H), 2.62 (ddd, *J* = 14.7, 8.8, 7.2 Hz, 1H), 2.54 − 2.43 (m, 3H), 2.13 - 2.00 (m, 2H), 1.55 − 1.47 (m, 2H), 1.29 − 1.21 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm.

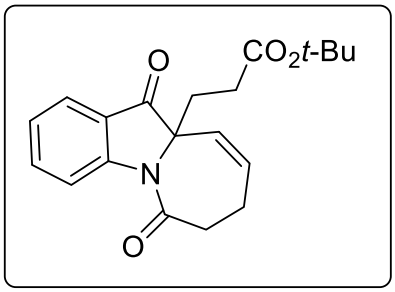
13C-NMR (126 MHz, $CDCl_3$): δ 198.9, 172.2, 172.1, 153.2, 137.8, 131.0, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 65.1, 36.4, 35.2, 31.4, 28.4, 28.3, 25.5, 25.4, 22.5, 14.0 ppm.

IR: $\tilde{\nu}$ = 2968, 2933, 2865, 1729, 1683, 1467, 1378, 1262, 1085, 1023, 796, 761, 687 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{22}H_{27}NO_4$+[M+Na]$^+$:392.1832; found,392.1833.

Tert-Butyl3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]indol-10*a*(11*H*)-yl)propanoate (134f)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), *tert*-butyl acrylate (**62e**, 144.0 µL, 0.99 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134f** (colorless solid, 17.4 mg, 51%).



R*f* = 0.45 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 123−124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.70 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.26 − 7.22 (m, 1H), 5.91 - 5.86 (m, 1H), 5.82 (ddd, J = 11.7, 2.1, 1.1 Hz, 1H), 3.29 (td, J = 13.3, 4.5 Hz, 1H), 2.74 − 2.68 (m, 1H), 2.58 − 2.42 (m, 4H), 1.99 (t, J = 7.8 Hz, 2H), 1.36 (s, 9H).

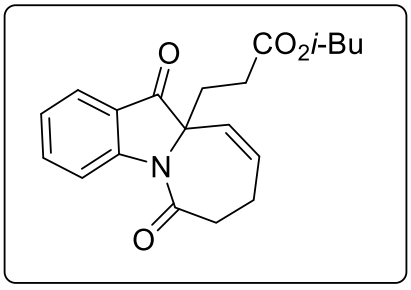
^{13}C-NMR (126 MHz, $CDCl_3$): δ 199.0, 172.2, 171.2, 153.1, 137.7, 130.9, 127.7, 124.5, 123.9, 122.6, 118.9, 81.0, 71.4, 36.4, 35.3, 29.3, 28.0, 25.6.

IR: $\tilde{\nu}$ = 2975, 2937, 1724, 167, 1607, 1465, 1378, 1186, 1157, 1083, 761, 687 cm^{-1}.

HRMS(ESI-TOF): *m*/*z* calc for $C_{20}H_{23}NO_4$+[M+Na]$^+$:364.1525;
found,364.1525.

Isobutyl-3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]indol-10*a*-(11*H*)-yl)propanoate (134g)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), isobutyl acrylate (**62f**, 142.0 µL, 0.99 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), (colorless solid, 20.8 mg, 61%) compound **134f**.



R*f* = 0.41 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 112−113 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.7, 1.4, 0.6 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.26 − 7.22 (m, 1H), 5.92 − 5.86 (m, 1H), 5.82

(ddd, *J* = 11.7, 2.4, 1.4 Hz, 1H), 3.80 − 3.73 (m, 2H), 3.28 (td, *J* = 13.2, 4.7 Hz, 1H), 2.73 − 2.68 (m, 1H), 2.61 (ddd, *J* = 14.6, 8.6, 7.2 Hz, 1H), 2.54 − 2.42 (m, 3H), 2.11 − 2.06 (m, 1H), 1.81 (hept., *J* = 6.7 Hz, 1H), 0.842 (d, *J* = 6.7 Hz, 3H), 0.838 (d, *J* = 6.7 Hz, 3H) ppm.

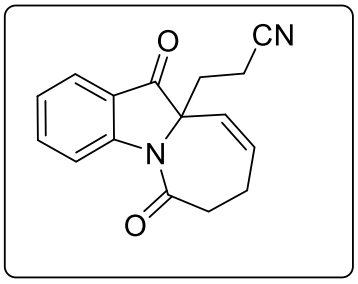
^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 198.9, 172.2, 172.1, 153.1, 137.8, 131.1, 127.6, 124.5, 123.9, 122.5, 118.8, 71.4, 71.0, 36.4, 35.2, 28.2, 27.5, 25.5, 19.0 ppm.

IR: $\tilde{\nu}$ = 2968, 2882, 1727, 1683, 1611, 1465, 1378, 1300, 1157, 761, 689 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{20}H_{23}NO_4$+[M+Na]$^+$: 364.1519; found, 364.1525.

3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]-10a(11H)-yl)propanenitrile (134g)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), acrylonitrile **62g,** 65.0 *µ*L, 0.99 mmol), and PMe_2Ph (1.4 *µ*L, 10 *µ*mol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134g** (colorless solid, 18.8 mg, 71%).



R*f* = 0.26 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 128−132 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 8.69 (d, *J* = 8.4 Hz, 1H), 7.79 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.74 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.29 − 7.25 (m, 1H), 6.01 − 5.96 (m, 1H), 5.81 (ddd, *J* = 11.7, 2.5, 1.8 Hz, 1H), 3.12 (ddd, *J* = 12.4, 5.1, 1.5 Hz, 1H), 2.82 − 2.77 (m, 1H), 2.64 − 2.52 (m, 3H), 2.48 (ddd, *J* = 14.5, 9.4, 6.3 Hz, 1H), 2.27 − 2.14 (m, 2H) ppm.

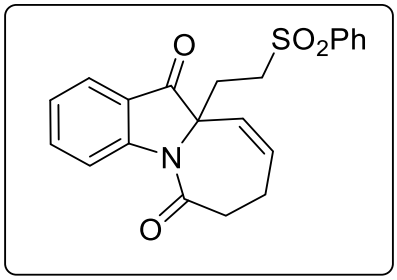
^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 197.8, 171.5, 153.0, 138.4, 132.5, 126.3, 125.0, 124.2, 122.0, 119.0, 118.0, 70.2, 36.5, 35.7, 25.5, 11.9 ppm.

IR: $\tilde{\nu}$ 3287, 2923, 1714, 1683, 1609, 1465, 1374, 1293, 1151, 1044, 763, 689, 536, 435 cm^{-1}.

HRMS (ESI-TOF) *m/z* calc. for $C_{16}H_{14}N_2O_2$+[M+Na]$^+$,289.0947; found, 289.0934.

10*a*-(2-(Phenylsulfonyl)ethyl-8,10*a*-dihydro-6*H*-azepino[1,2-a]-indole-6,11(7*H*)-dione (134h)

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), phenyl vinyl sulfone (**62h**, 168.0 mg, 1.00 mmol), and PMe_2Ph (14.2 µL, 0.10 mmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134h** (colorless solid, 24.6 mg, 64%).



R*f* = 0.25 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 135−137 °C.

^{1}H-NMR (400 MHz, CDCl3): δ 8.65 (dt, J = 8.4, 0.7 Hz, 1H), 7.84 - 7.81 (m, 2H), 7.74 - 7.70 (m, 2H), 7.69 - 7.64 (m, 1H), 7.59 - 7.54 (m, 2H), 7.26 - 7.22 (m, 1H), 5.96 − 5.89 (m, 1H), 5.73 (ddd, J = 11.6, 2.6, 1.7 Hz, 1H), 3.03 - 2.92 (m, 2H), 2.81 (ddd, J = 13.7, 12.3, 5.3 Hz, 1H), 2.71 - 2.63 (m, 1H), 2.62 - 2.45 (m, 4H) ppm.

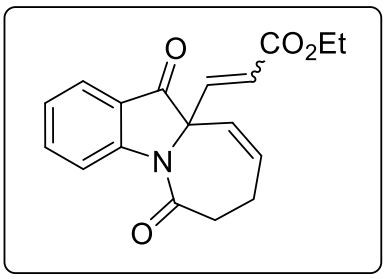
^{13}C-NMR (100 MHz, $CDCl_3$): δ 197.7, 171.6, 152.8, 138.32, 138.28, 134.1, 132.3, 129.5, 128.0, 126.4, 124.9, 124.2,121.8, 118.9, 69.8,50.1, 36.3, 30.0, 25.4 ppm.

IR: $\tilde{\nu}$ 2966, 2925, 2861, 1720, 1673, 1605, 1465, 1378, 1304, 1147, 1087, 745, 685, 604, 536 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{21}H_{19}NO_4S$+$[M+H]^+$:382.1113, found: 382.1120.

Ethyl-3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]indol-10*a*-(11*H*)-yl)acrylate (134i,134i')

According to the general procedure **3**, enone **109a** (21.3 mg, 0.10 mmol), ethyl propiolate (**62i**, 101.2 µL, 1.00 mmol), and PMe_2Ph (14.2 µL, 0.10 mmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound *cis*-**134i** (**R*f*** = 0.47, colorless solid, 10.9 mg, 35%) and compound *trans*-**134i'** (**R*f*** = 0.39, colorless solid, 13.3 mg, 42%).



cis-**134i**: mp: 160−161 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 8.5 Hz, 1H), 7.80 − 7.76 (m, 1H), 7.70 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.27−7.23 (m, 1H), 6.06 − 6.01 (m, 1H), 5.98 − 5.94 (m, 2H), 5.92 (d, J = 12.6 Hz, 1H), 4.05 (dq, J = 10.9, 7.2 Hz, 1H), 3.87 (dq, J = 10.9, 7.2 Hz, 1H), 3.26 (td, J = 13.4, 4.8 Hz, 1H), 2.63−2.56 (m, 1H), 2.56−2.44 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H) ppm.

^{13}C- NMR (126 MHz, $CDCl_3$): δ 195.3, 172.0, 165.5, 152.8, 137.7, 134.9, 132.5, 127.1, 124.7, 124.6, 121.8, 121.5, 118.4, 71.8, 61.4, 35.5, 25.8, 13.7 ppm.

trans-**134i'**: mp: 153−154 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.69 (dt, J = 8.5, 0.7 Hz, 1H), 7.78 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.74 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.29 − 7.24 (m, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.09 − 6.02 (m, 3H), 4.18 (q, J = 7.1 Hz, 2H), 3.05 (td, J = 13.3, 3.6 Hz, 1H), 2.62 − 2.52 (m, 2H), 2.52 − 2.44 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H) ppm.

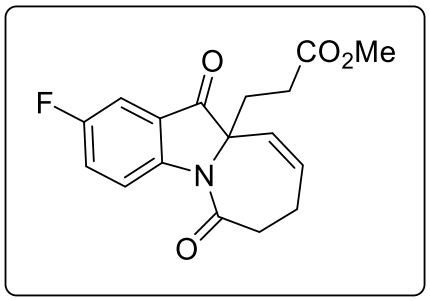
^{13}C-NMR (126 MHz, $CDCl_3$): δ 194.2, 171.8, 165.2, 152.3, 144.7, 138.2, 133.3, 125.1, 125.0, 124.9, 123.8, 121.4, 118.7, 72.4, 61.0, 35.5, 25.8, 14.1 ppm.

IR: $\tilde{\nu}$ 2991, 2948, 1788, 1657, 1658, 1467, 1375, 1260, 1197, 1051, 796, 696 cm^{-1}.

HRMS (ESI-TOF): m/z calc for $C_{18}H_{18}NO_4$+$[M+H]^+$: 312.1236; found, 312.1239.

Methyl-3-(2-Fluoro-6,11-dioxo-7,8-dihydro-6*H*azepino[1,2*a*]-indol-10*a*(11*H*)-yl)propanoate (134j)

According to the general procedure **3**, enone **109b** (23.1 mg, 0.10 mmol), methyl acrylate (**62a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:9), compound **134j** (colorless solid, 23.3 mg, 73%).



R*f* = 0.24 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 95−97 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 8.68 (ddd, *J* = 8.7, 1.0 Hz, $J_{F,H}$ =4.3 Hz, 1H), 7.43 − 7.38 (m, 2H), 5.93 − 5.88 (m, 1H), 5.79 (ddd, *J* = 11.7, 2.5, 1.6 Hz, 1H), 3.58 (s, 3H), 3.28 − 3.20 (m, 1H), 2.73 − 2.67 (m, 1H), 2.62 (ddd, *J* = 15.7, 8.6, 7.3 Hz, 1H), 2.54 − 2.45 (m, 3H), 2.16 − 2.00 (m, 2H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 198.2, 172.3, 171.9, 159.2, 149.2, 131.4, 127.2, 125.2, 123.8, 120.4, 109.1, 72.0, 51.9, 36.2, 35.3, 28.1, 25.5 ppm.

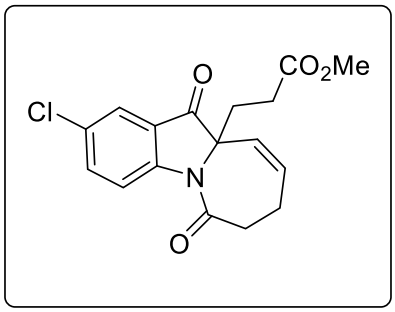
^{19}F-NMR (470 MHz, $CDCl_3$): *δ*−116.7.

IR: $\tilde{\nu}$ = 2960, 2925, 1739, 1724, 1675, 1487, 1438, 1378, 1258, 1240, 1149, 1009, 835, 802 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{17}H_{16}FNO_4$+[M+Na]$^+$: 340.0955; found, 340.0961.

Methyl-3-(2-Chloro-6,11-dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]-indol-10a(11*H*)-yl)propanoate (134k)

According to the general procedure **3**, enone **109c** (25.3 mg, 0.10 mmol), methyl acrylate (**62a,** 90.0 *µ*L, 0.99 mmol), and PMe_2Ph (1.4 *µ*L, 10 *µ*mol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134k** (colorless solid, 26.7 mg, 78%).



R*f* = 0.27 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 119−121 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 8.63 (d, *J* = 8.9 Hz, 1H), 7.72 (br s, 1H), 7.63 (dt, *J* = 8.8, 1.6 Hz, 1H), 5.94−5.88 (m, 1H), 5.81 − 5.75 (m, 1H), 3.58 (s, 3H), 3.25 (td, *J* = 13.1, 5.1 Hz, 1H), 2.75 − 2.67 (m, 1H), 2.66 − 2.58 (m, 1H), 2.54−2.45 (m, 3H), 2.36 (s, 3H), 2.17 − 1.98 (m, 2H) ppm.

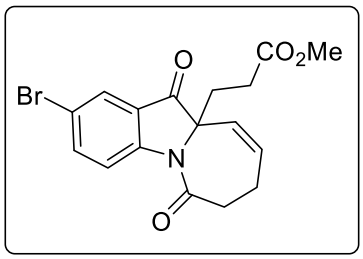
^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 197.8, 172.3, 172.1, 151.5, 137.6, 131.4, 130.1, 127.1, 123.8, 123.3, 120.0, 71.9, 52.0, 36.3, 35.3, 28.1, 25.4 ppm.

IR: $\tilde{\nu}$ = 2896, 2821, 1799, 1756, 1615, 1467, 1439, 1396, 1244, 1210, 1118, 1001, 865, 811 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{17}H_{16}ClNO_4$+[M+Na]$^+$: 356.0660; found, 356.0667.

Methyl-3-(2-Bromo-6,11-dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]-indol-10*a*(11*H*)-yl)propanoate (134l)

According to the general procedure **3**, enone **109d** (29.0 mg, 0.10 mmol), methyl acrylate (**62a**, 90.0 µL, 0.99 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134l** (colorless solid, 33.3 mg, 89%).



R*f* = 0.35 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 126−127 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 2.1 Hz, 1H), 7.76 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.94 − 5.87 (m, 1H), 5.78 (ddd, *J* = 11.8, 2.5, 1.8 Hz, 1H), 3.59 (s, 3H), 3.30 − 3.19 (m, 1H), 2.75 − 2.67 (m, 1H), 2.62 (ddd, *J* = 15.8, 8.4, 7.6 Hz, 1H), 2.54 - 2.46 (m, 3H), 2.15 − 1.99 (m, 2H) ppm.

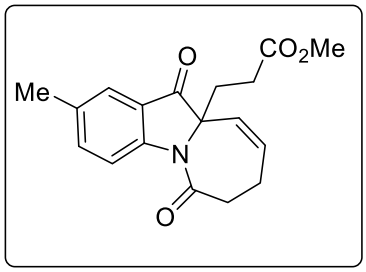
^{13}C-NMR (100 MHz, $CDCl_3$): δ 197.7, 172.3, 172.2, 151.9, 140.3, 131.4, 127.1, 126.4, 124.2, 120.3, 117.4, 71.8, 52.0, 36.3, 35.3, 28.1, 25.4 ppm.

IR: $\tilde{\nu}$ = 2950, 2925, 1726, 1715, 1659, 1497, 1421, 1366, 1252, 1210, 1119, 958, 835, 812 cm^{-1}.

HRMS (ESITOF):*m*/*z* calc for $C_{17}H_{16}BrNO_4$+[M+Na]$^+$: 400.0155; found, 400.0161.

Methyl-3-(2-Methyl-6,11-dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]-indol-10*a*(11*H*)-yl)propanoate (134m)

According to the general procedure **3**, enone **109f** (22.7 mg, 0.10 mmol), methyl acrylate (**62a**, 90.0 µL, 0.99 mmol), and PMe_2Ph (1.4 µL, 10 µmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:9), compound **134m** (colorless solid, 19.9 mg, 65%).



R*f* = 0.17 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 182−183 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.51 (d, J = 8.5 Hz, 1H), 7.53−7.51 (m, 1H), 7.48 (dd, J = 8.5, 1.7 Hz, 1H), 5.88 − 5.83 (m, 1H), 5.78 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 3.55 (s, 3H), 3.22 (td, J = 13.3, 4.6 Hz, 1H), 2.69 − 2.63 (m, 1H), 2.59 (ddd, J = 15.7, 8.7, 7.2 Hz, 1H), 2.50 − 2.40 (m, 3H), 2.36 (s, 3H), 2.10 − 1.97 (m, 2H).

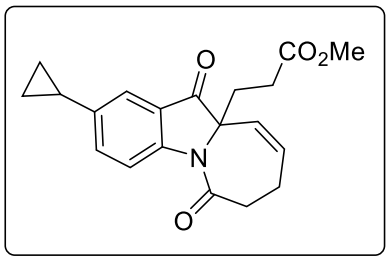
^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.8, 172.4, 171.9, 151.4, 139.0, 134.5, 131.0, 127.6, 123.4, 122.7, 118.5, 71.5, 51.8, 36.3, 35.2, 28.1, 25.5, 20.7.

IR: $\tilde{\nu}$ = 2992, 2985, 1745, 1725, 1654, 1491, 1460, 1332, 1286, 1222, 1125, 1008, 825, 811 cm^{-1}.

HRMS (ESI-TOF): m/z calc for $C_{18}H_{19}NO_4$+[M+Na]$^+$: 336.1206; found, 336.1210.

Methyl-3-(2-Cyclopropyl-6,11-dioxo-7,8-dihydro-6*H*-azepino-[1,2-*a*]indol-10a(11*H*)-yl)propanoate (134n)

According to the general procedure **3**, enone **XXi** (24.7 mg, 97.5 μmol), methyl acrylate (**62a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134n** (colorless solid, 30.7 mg, 92%).



R*f* = 0.31 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 131−134 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.1 Hz, 1H), 7.41 (d, J = 2.1 Hz, 1H), 5.91 − 5.85 (m, 1H), 5.79 (ddd, J = 11.7, 2.4, 1.3 Hz, 1H), 3.58 (s, 3H), 3.24 (td, J = 13.7, 5.1 Hz, 1H), 2.71 − 2.65 (m, 1H), 2.59 (ddd, J = 14.8, 8.6, 7.4 Hz, 1H), 2.52 − 2.43 (m, 3H), 2.10 − 2.02 (m, 2H), 1.97 − 1.90 (m, 1H), 1.03 − 0.97 (m, 2H), 0.74−0.68 (m, 2H) ppm.

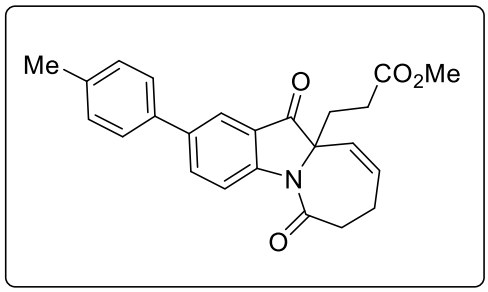
^{13}C-NMR (100 MHz, $CDCl_3$): δ 198.9, 172.4, 171.9, 151.3, 141.0, 136.3, 131.0, 127.6, 122.7, 119.7, 118.5, 71.6, 51.9, 36.3, 35.3, 28.1, 25.5, 14.9, 9.4, 9.3 ppm.

IR: $\tilde{\nu}$ = 2972, 2915, 1789, 1729, 1663, 1474, 1431, 1362, 1294, 1263, 1190, 1015, 823 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{21}NO_4$+[M+Na]$^+$: 362.1363; found, 362.1367.

Methyl-3-(6,11-dioxo2-(p-tolyl)-7,8-dihydro-6*H*-azepino[1,2-*a*]-indol-10*a*(11*H*)-yl)propanoate (134o)

According to the general procedure **3**, enone **109g** (30.3 mg, 0.10 mmol), methyl acrylate (**62a,** 90.0 *µ*L, 0.99 mmol), and PMe_2Ph (1.4 *µ*L, 10 *µ*mol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, Et_2O/$PhCH_3$ 1:6), compound **134o** (colorless solid, 37.7 mg, 96%).



R*f* = 0.37 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 165−167 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 8.70 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.96 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.52 − 7.48 (m, 2H), 7.28 − 7.25 (m, 2H), 5.94 − 5.88 (m, 1H), 5.84 (ddd, *J* = 11.6, 2.1, 1.2 Hz, 1H), 3.59 (s, 3H), 3.28 (td, *J* = 13.7, 4.8 Hz, 1H), 2.75 − 2.70 (m, 1H), 2.65 (ddd, *J* = 14.8, 8.6, 7.5 Hz, 1H), 2.58 − 2.47 (m, 3H), 2.40 (s, 3H), 2.18 − 2.09 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 198.9, 172.4, 172.1, 152.2, 137.8, 137.7, 136.6, 136.2, 131.1, 129.7, 127.5, 126.7, 123.1, 121.3, 119.0, 71.8, 51.9, 36.3, 28.2, 25.5, 21.1 ppm.

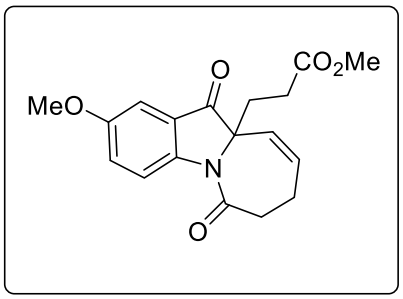
IR: $\tilde{\nu}$ = 2953, 2905, 1750, 1719, 1695, 1487, 1458, 1368, 1251, 1248, 1153, 1002, 835 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{24}H_{23}NO_4$+[M+Na]$^+$: 412.1519; found, 412.1527.

Methyl-3-(2-Methoxy-6,11-dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]-indol-10a(11*H*)-yl)propanoate (134p)

According to the general procedure **3**, enone **109e** (24.2 mg, 0.10 mmol), methyl acrylate (**62a**, 90.0 *µ*L, 0.99 mmol), and PMe_2Ph (1.4 *µ*L, 10 *µ*mol) in CH_2Cl_2 (1.00 mL)

gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **134p** (colorless solid, 19.9 mg, 60%).



R*f* = 0.19 (silica gel, $Et_2O/PhCH_3$ 1:6), mp: 102−105 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.59 (d, J = 9.1 Hz, 1H), 7.29 (dd, J = 9.1, 2.8 Hz, 1H), 7.16 (d, J = 2.8 Hz, 1H), 5.92 − 5.86 (m, 1H), 5.81 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 3.84 (s, 3H), 3.58 (s, 3H), 3.23 (td, J = 13.2, 4.6 Hz, 1H), 2.72 − 2.65 (m, 1H), 2.61 (ddd, J = 15.7, 8.6, 7.2 Hz, 1H), 2.54 − 2.43 (m, 3H), 2.13 − 2.00 (m, 2H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ 198.8, 172.4, 171.6, 156.7, 148.2, 131.1, 127.5, 126.9, 123.4, 120.0, 71.8, 55.8, 51.9, 36.3, 35.2, 28.1, 25.6 ppm.

IR: $\tilde{\nu}$ = 2961, 2855, 1721, 1672, 1497, 1449, 1373, 1320, 1249, 1249, 1163, 1042, 888, 696 cm^{-1}.

HRMS(ESI-TOF): m/z calc for $C_{18}H_{19}NO$+[M+Na]$^+$: 352.1155; found, 352.1158.

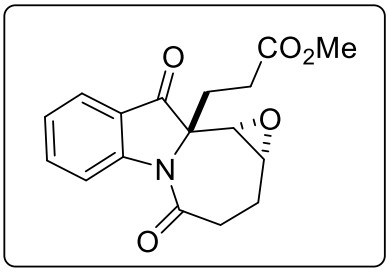
Preparation of Compound 134a on a 1 mmol Scale.

According to the general procedure, enone **109a** (213.2 mg, 1.00 mmol), methyl acrylate (**62a**, 905 μL, 9.99 mmol), and PMe_2Ph (14.2 μL, 0.10 mmol) in CH2Cl2 (10 mL) gave, after chromatography (silica gel, Et2O/PhCH3 1:6), compound **134a** (246.6 mg, 82%).

Methyl3-(4,10-Dioxo-1*a*,3,4,10*b*-tetrahydro-2*H*-oxireno-[2',3',3,4]azepino[1,2-*a*]-indol-10*a*(10*H*)-yl)propanoate (144a-144b)

Compound **134a** (100.0 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (3.00 mL), and *m*CPBA (77 weight-%, 113.5 mg, 0.51 mmol) was added. The mixture was stirred at r.t. for 16 h)[11] and then sat. aq $NaHSO_3$ (3 mL) was added. After 10 min of additional stirring, the layers were separated, and the organic layer was washed with sat. aq $NaHSO_3$, sat. aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. obtained from this fraction were characterized by X-ray crystallography). Column chromatography (silica gel, $Et_2O/PhCH_3$ 1:6 and a major diastereomer **144b**

with (1*aR**,10*aS**,10*bS**)- configuration (R_f = 0.12, colorless solid, 78.8 mg, 75%; single crystals obtained from this fraction were characterized by X-ray crystallography).



Minor diastereomer **144a**:

Rf = 0.12 (silica gel, Et_2O/$PhCH_3$ 1:6), mp: 155−157 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 8.61 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.78 (ddd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.70 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.28 − 7.23 (m, 1H), 3.57 (s, 3H), 3.56 (d, *J* = 4.0 Hz, 1H), 3.34 − 3.31 (m, 1H), 2.81 (td, *J* = 13.6, 2.1 Hz, 1H), 2.66 (ddd, *J* = 16.2, 9.2, 7.2 Hz, 1H), 2.53 − 2.44 (m, 2H), 2.40 (dddd, *J* = 14.1, 6.1, 1.8, 1.0 Hz, 1H), 2.29 − 2.23 (m, 1H), 2.23 (ddd, *J* = 10.9, 9.2, 5.7 Hz, 1H), 2.07 (ddd, *J* = 16.2, 8.9, 7.2 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 198.8, 172.23, 172.20, 153.5, 138.1, 124.8, 123.9, 122.4, 118.8, 69.4, 58.5, 55.8, 51.9, 30.8, 30.6, 27.4, 24.6 ppm.

Major diastereomer: **144b** mp: 133−135 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 8.63 (d, *J* = 8.6 Hz, 1H), 7.78 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.68 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.26 − 7.22 (m, 1H), 3.56 (s, 3H), 3.47 (d, *J* = 4.0 Hz, 1H), 3.39 (td, *J* = 4.9, 4.0 Hz, 1H), 2.92 (td, *J* = 13.6, 5.5 Hz, 1H), 2.69 (ddd, *J* = 15.8, 9.0, 7.1 Hz, 1H), 2.56 (ddd, *J* = 15.8, 8.9, 6.1 Hz, 1H), 2.50 (dtd, *J* = 13.9, 4.0, 0.7 Hz, 1H), 2.39 - 2.24 (m, 2H), 2.14 (ddd, *J* = 16.5, 9.0, 6.1 Hz, 1H), 2.06 (ddd, *J* = 16.5, 8.8, 7.1 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 198.8, 172.2, 170.6, 52.0, 34.2, 29.2, 27.6, 22.1. 154.5, 138.0, 124.7, 123.9, 122.8, 119.1, 69.2, 58.1, 54.9. ppm.

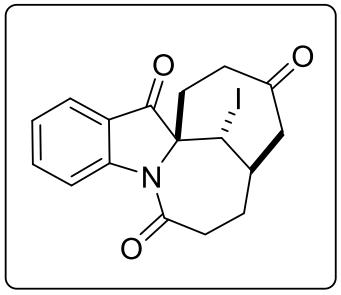
IR: *ṽ* 2962, 2933, 2853, 1714, 1677, 1605, 1440, 1366, 1242, 1155, 835, 476 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{17}H_{17}NO_5$+[M+Na]$^+$: 338.0999; found, 338.0999.

Preparation of Lactone 146

15-Iodo-1,2,6,7-tetrahydro-3H,14H-5,14*a*-menthano[1,6]oxazecino-[6,5-*a*]-indole-3,8,14(5H)-tri-one (146)

Compound **134a** (20.0 mg, 66.8 *µ*mol) was dissolved in a 3:1 mixture of MeOH and H_2O (2.00 mL), and LiOH (3.2 mg, 0.13 mmol) was added. The mixture was stirred for 16 h at r.t. MeOH was removed under reduced pressure, and the remaining aqueous phase was diluted with EtOAc and sat. aq $NaHCO_3$. The layers were separated, and the aqueous layer was acidified with 5% HCl aq the aqueous phase was extracted with EtOAc (2 ×), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield the intermediate acid 10 (yellow solid, 18.0 mg, 95%) which was used in the subsequent step without further purification. A portion of acid **145** (20.0 mg, 70.1 *µ*mol) and 2,4,6-collidine (36.1 *µ*L, 0.27 mmol) were dissolved in MeCN (2.00 mL). A solution of I_2 (17.8 mg, 70.1 *µ*mol) in MeCN (1.00 mL) was added at 0 °C, and the mixture was subsequently heated to 50 °C for 24 h. The mixture was diluted with CH_2Cl_2 and washed with 5% $Na_2S_2O_3$ aq and 0.5 M $KHSO_4$ aq, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (silica gel, Et_2O/ $PhCH_3$ 1:6) gave compound **146** (colorless solid, 15.8 mg, 54%, *d.r.* 6.7:1). as a mixture of inseparable diastereomers.



R*f* = 0.30 (silica gel, Et_2O/ $PhCH_3$ 1:6), mp: 285−287 °C.

Major (5*S**,14a*R**,15*S**)-diastereomer:

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* 7.86 (d, *J* = 8.5 Hz, 1H), 7.74 − 7.69 (m, 2H), 7.31 − 7.27 (m, 1H), 4.44 (d, *J* = 0.7 Hz, 1H), 4.37 (ddd, *J* = 7.5, 6.9, 0.7 Hz, 1H), 3.22 (ddd, *J* = 18.0, 11.7, 9.2 Hz, 1H), 2.87 (ddd, *J* = Hz, 14.9, 9.2, 1.2 Hz, 1H), 2.67 (ddd, *J* = Hz, 18.5, 10.9, 4.4 Hz, 1H), 2.56 (ddd, *J* = Hz, 18.0, 9.9, 1.2 Hz, 1H), 2.50 (ddd, *J* = Hz, 18.5, 10.6, 8.4 Hz, 1H), 2.39 − 2.31 (m, 1H), 2.25 (ddd, *J* = Hz, 14.9, 11.8, 10.2 Hz, 1H), 2.03-1.93 (m, 1H) ppm.

Minor diastereomer, trace signals: *δ* 4.30 (d, *J* = 1.2 Hz, 1H), 4.37 (ddd, *J* = 7.4, 6.9, 1.2 Hz, 1H), 3.33 (ddd, *J* =18.1, 11.4, 9.6 Hz, 1H).

^{13}C-NMR (126 MHz, CDCl3): δ 198.4,175.5, 174.3, 150.1, 137.7, 125.9, 125.3, 125.2, 117.7, 75.1, 74.8, 43.0, 34.9, 27.6, 25.6.

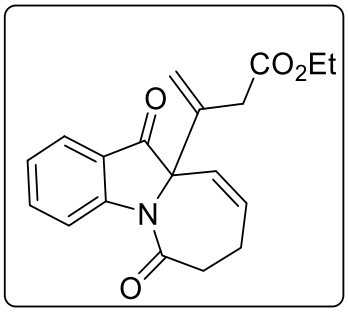
IR: $\tilde{\nu}$ = 2990, 2925, 1731, 1728, 1674, 1483, 1431, 1373, 1256, 1246, 1147, 1003, 822, 813 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{17}H_{16}INO_3$+[M+Na]$^+$: 433.9860; found, 433.9863.

Rauhut-Currier-Type Reaction between Enone 109a and Ethyl 2,3-Butadienoate (65)

Ethyl-3-(6,11-Dioxo-7,8-dihydro-6*H*-azepino[1,2-*a*]indol-10a(11*H*)-yl)but-3-enoate (147)

Enone **109a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**65**, 120 μL, 1.03 mmol) was added to solution, followed by P(*t*-Bu)$_3$ (4.0 mg, 20 μmol 20 mol %). The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 24 h and then concentrated to dryness. Column chromatography (silica gel, EtOAc/$PhCH_3$ 1:10) afforded compound **147**.



^{1}H-NMR (300 MHz, CDCl3): δ 8.67 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.76 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.26 - 7.20 (m, 1H), 6.05 − 5.97 (m, 1H), 5.93 (ddd, *J* = 11.6, 2.2, 1.6 Hz, 1H), 5.39 (br s, 1H), 5.31 (br s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.49 − 3.36 (m, 1H), 3.20 (dd, *J* = 16.1, 0.6 Hz, 1H), 2.85 (d, *J* = 16.1 Hz, 1H), 2.56 − 2.36 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ 196.2, 172.7, 170.4, 152.8, 139.7, 137.8, 133.5, 125.7, 124.6, 124.5, 121.4, 119.3, 118.4, 74.6, 61.1, 37.6, 35.1, 26.1, 14.0 ppm.

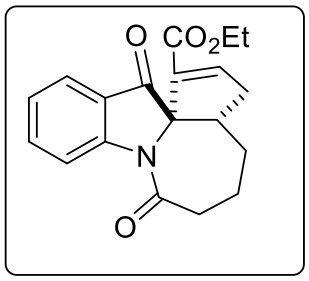
IR: $\tilde{\nu}$ = 2979, 2915, 1746, 1714, 1663, 1497, 1436, 1369, 1266, 1260, 1155, 1002, 815 cm^{-1}

HRMS (ESI-TOF): *m*/*z* calc for $C_{19}H_{19}NO_4$+[M+Na]$^+$: 348.1206; found, 348.1215.

(3+2)-Cycloaddition

Ethyl(3a*S**,13a*S**)-7,13-Dioxo-3,3*a*,4,5,6,7-hexahydro-13*H*-cyclopenta[2,3]azepino-[1,2-*a*]indole-1-carboxylate (148)

Enone **109a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**65**, 120 *µ*L, 1.03 mmol) was added to solution, followed by PMe_2Ph (2.8 *µ*L, 20 *µ*mol, 20 mol %). The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 24 h and then concentrated to dryness. Column chromatography (silica gel, EtOAc/$PhCH_3$ 1:10) afforded compound **148** (colorless solid, 17.1 mg, 53%).



R*f* = 0.23 (silica gel, EtOAc/$PhCH_3$ 1:10), mp: 102−103 °C.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.68 (dt, *J* = 8.5, 0.7 Hz, 1H), 7.75 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.32 (t, *J* = 2.5 Hz, 1H), 7.26 − 7.19 (m, 1H), 3.99 − 3.80 (m, 2H), 3.20− 3.11 (m, 1H), 3.04 (ddd, *J* = 19.3, 9.5, 2.5 Hz, 1H), 2.83 − 2.72 (m, 1H), 2.66 (ddd, *J* = 19.3, 3.8, 2.5 Hz, 1H), 2.46 − 2.37 (m, 1H), 1.94 − 1.73 (m, 3H), 1.70 − 1.56 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H) ppm.

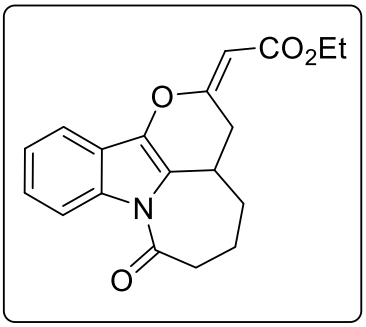
^{13}C-NMR (126 MHz, $CDCl_3$): *δ* 200.3, 171.4, 162.1, 153.5, 149.9, 137.2, 135.9, 124.2, 123.8, 123.2, 118.7, 80.9, 60.8, 41.3, 34.8, 34.2, 25.2, 18.1, 13.2. ppm.

IR: *ṽ* 2925, 1739, 1720, 1677, 1605, 1467, 1374, 1300, 1151, 1085, 761, 683 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{19}H_{19}NO$+[M+Na]$^+$: 348.1206; found, 348.1215.

Analytical Data of Side Product 149.

Ethyl(*E*)-2-(7-Oxo-3,3*a*,4,5,6,7-hexahydro-2*H*-1-oxa-7a-azacyclohepta[*jk*]fluoren-2-ylidene) acetate (149)



R*f* = 0.50 (EtOAc/$PhCH_3$ 1:10), colorless solid, mp: 157−159 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.45 (dt, *J* = 8.3, 0.7 Hz, 1H), 7.53 (br. d, *J* = 7.6 Hz, 1H), 7.36 (ddd, *J* = 8.3, 7.4, 1.3 Hz, 1H), 7.32 − 7.28 (m, 1H), 5.83 (d, *J* = 1.6 Hz, 1H), 4.27 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.25 − 3.17 (m, 1H), 2.91 (td, *J* = 13.8, 6.1 Hz, 1H), 2.79 (dt, *J* = 13.8, 4.3 Hz, 1H), 2.41 (ddd, *J* = 14.8, 10.6, 1.6 Hz, 1H), 2.22 (ddt, *J* = 11.1, 8.4, 2.9 Hz, 1H), 2.16 − 1.96 (m, 2H), 1.64 (ddd, *J* = 11.1, 3.6, 1.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

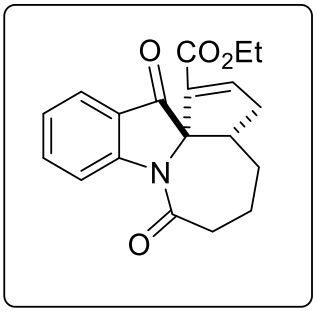
^{13}C-NMR (126 MHz, $CDCl_3$): δ 171.8, 167.2, 165.8, 136.4, 133.7, 125.7, 123.8, 120.6, 119.8, 116.5, 116.4, 101.0, 60.0, 36.4, 30.6, 29.7, 29.6, 20.7, 14.3 ppm.

IR: $\tilde{\nu}$ = 3330, 2950, 2840, 1720, 1660, 1470, 1450, 1405, 1310, 1120, 1030, 620 cm^{-1}.

HRMS (ESI-TOF): *m*/*z* calc for $C_{19}H_{20}NO_4$+[M+H]$^+$: 326.1387; found, 326.1393.

Preparation of (-) 148 Using Chiral Phosphine Catalyst

Enone **109a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**65**, 120 μL, 1.03 mmol) was added to solution, followed by (*S*)-*N*-(1-(diphenylphosphaneyl)-3-methylbutan-2-yl)-3,5-bis(trifluoromethyl)-benzamide (Chiral Phosphine Catalyst 15.3 mg, 30 μmol, 30 mol %).



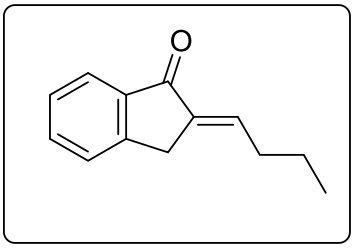
The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 48 h and then concentrated to dryness. Column chromatography (silica gel, EtOAc/$PhCH_3$ 1:10) afforded compound **(−)-148** colorless solid, 15.0 mg, 47%, *e.r.* 82:18.

R*f* = 0.23 (EtOAc/$PhCH_3$ 1:10), [*a*] ^{22} = -30.4 (*c* = 1.0, $CHCl_3$).

Synthesis of (*E*)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (154)

A mixture of 1-indanone (**152**,0.264 g, 2 m moles), butyraldehyde (**153**, 0.18mL, 2 m moles) and sodium hydroxide (0.088 g, 2.20 m moles) in water (2 mL) was heated at 60 °C for 16 h, and the progress of the reaction followed by TLC. The crude product obtained by the usual work-up was purified on silica gel (10% EE: Heptane) to afford as compound **154**. 233.1 mg 62%.

(E)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (154)



^{1}H-NMR (500 MHz, $CDCl_3$) δ δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 3.67 (s, 2H), 2.30 (q, *J* = 7.4 Hz, 2H), 1.58 (hex, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm.

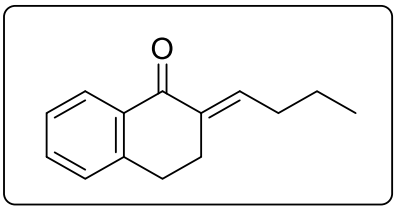
^{13}C-NMR (126 MHz, $CDCl_3$) δ 193.6, 149.5, 139.0, 138.3, 136.7, 134.5, 127.6, 126.4, 124.5, 32.0, 30.1, 21.9, 14.1 ppm.

HRMS (ESI-TOF): m/z calc. for $C_{13}H_{15}O^+$ $[M+H]^+$: 187.1117, found: 187.1115.

Synthesis of (*E*)-2-butylidene-3,4-dihydronaphthalen-1(2*H*)-one (156)

Powdered KOH (1.15 g, 20.52 mmol) was weighed into a Schlenk flask and the remaining air was replaced by argon with three pump-purge cycles. Afterwards dry ethanol (34mL) was added in portions and the mixture was stirred at 0 °C until the KOH was fully dissolved. 1-Tetralone (**155**, 1.00 g, 6.8404 mmol) was added slowly. Subsequently butyraldehyde (**153**, 1.85mL, 20.52 mmol) was added very slowly over the course of 10 min and the reaction mixture was stirred at 0 °C for 72 h. The reaction mixture was combined with an equal volume of water and extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and subsequently evaporated. After column chromatography (silica gel, heptane/ethyl acetate 20:1) compound **156** (R*f* = 0.36, yellow oil, 566 mg, 41 %) was obtained.

(*E*)-2-butylidene-3,4-dihydronaphthalen-1(2*H*)-one (156)



R_f (heptane/EtOAc 20:1) = 0.36.

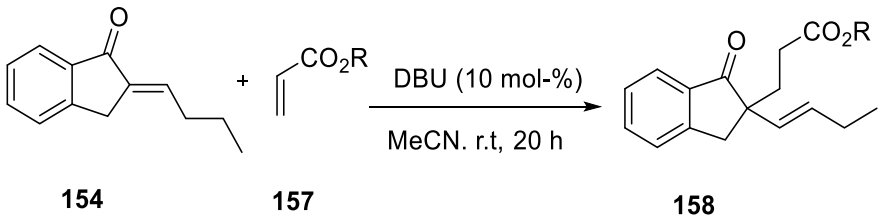
^{1}H-NMR (CDCl3, 500MHz): δ = 8.09 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 2.95 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.24 (q, *J* = 7.4 Hz, 2H), 1.54 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C-NMR (CDCl3, 126MHz): δ = 187.6, 143.7, 140.0, 135.1, 133.6, 132.9, 128.20, 128.15, 126.9, 30.2, 29.1, 25.6, 22.1, 13.9 ppm.

HRMS MS (EI): m/z calc for $C_{14}H_{16}O^+$ $[M]^+$: 200.12; found 200.00

General Procedure 4 for the Synthesis of *β,γ*-Unsaturated Ketones 158a-158i.

Enone **154** was dissolved in MeCN in a 10 mL crimp cap vial. Alkene **157** (6 equiv.). was added to the stirred solution, followed by DBU (10 mol-%). The vial was sealed and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t for 20 h and then concentrated to dryness. column chromatography over silica gel afforded the pure Compound **158a-158i.**

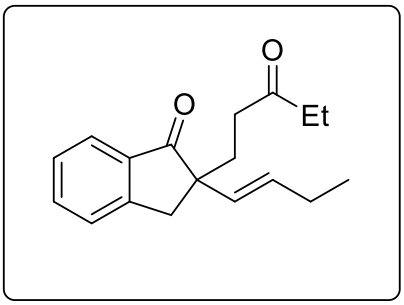


154 **157** **158**

Scheme 69. DBU-Catalyzed α-Alkylation of Indanone Derivative enones **154** with Alkenes **157**.

(*E*)-2-(but-1-en-1-yl)-2-(3-oxopentyl)-2,3-dihydro-1*H*-inden-1-one (158a)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), ethyl vinyl ketone (**157**, 59.6µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158a** (colorless oil, 26.1 mg, 97%) after chromatography (silica gel, EtOAC/Heptane 1:4).



R*f* = 0.23 (silica, EtOAc/Heptane 1:4)

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.74 (dt, *J* = 7.5, 1.0 Hz,1H), 7.59 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.43 (dt, *J* = 7.5, 1.0 Hz,1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 5.61 (dt, *J* = 15.8, 6.0 Hz, 1H), 5.52 (dt, *J* = 15.8, 0.9 Hz, 1H), 3.24 (d, *J* = 17.2 Hz, 1H), 3.03 (d, *J* = 17.2 Hz, 1H), 2.46 – 2.32 (m, 4H), 2.06 – 1.93 (m, 4H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H) ppm.

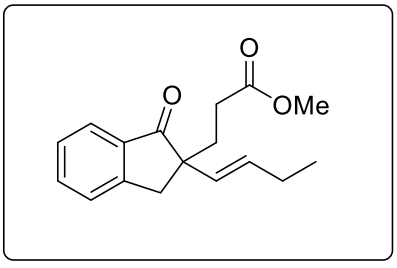
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 211.0, 207.8, 152.2, 135.7, 134.9, 132.9, 130.0, 127.5, 126.3, 124.4, 54.3, 38.8, 37.7, 35.9, 31.6, 25.7, 13.6, 7.8 ppm.

IR: $\tilde{\nu}$ = 2963, 1706, 1607, 1463, 1324, 1269, 1209, 972, 923, 795, 737, 469 cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{18}H_{22}NaO_2^+$ $[M+Na]^+$: 293.1512, found: 293.1517.

Methyl (*E*)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl) Propionate (158b)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), methyl acrylate (**62a**, 54.3µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158b** (colorless oil, 26.3mg, 97%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.46 (silica, EtOAc/Heptane 1:4)

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.74 (td, *J* = 7.7, 0.9 Hz, 1H), 7.58 (td, *J* = 7.5, 0.9 Hz, 1H), 7.43 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.36 (td, *J* = 7.5, 0.9 Hz, 1H), 5.62 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.51 (dt, *J* = 15.7, 1.3 Hz, 1H), 3.64 (s, 3H), 3.25 (d, *J* = 17.2 Hz, 1H), 3.04 (d, *J* = 17.2 Hz, 1H), 2.39 (ddd, *J* = 15.9, 11.0, 5.4 Hz, 1H), 2.27 (ddd, *J* = 15.9, 11.0, 5.4 Hz, 1H), 2.12 (ddd, *J* = 13.6, 10.8, 5.3 Hz, 1H), 2.05 – 1.92 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 207.3, 173.7, 152.1, 135.6, 134.9, 133.2, 129.6, 127.6, 126.3, 124.5, 54.4, 51.6, 38.3, 32.6, 29.7, 25.7, 13.5 ppm.

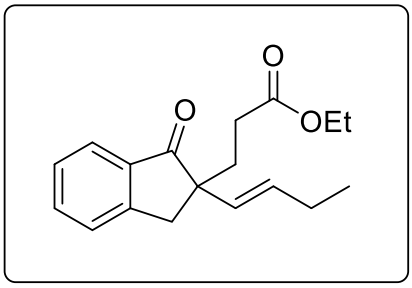
IR: $\tilde{\nu}$ = 3022, 2925, 1722,1634,1619, 1438, 1403, 1283, 1213, 1182, 1069, 984,

927, 855, 811, 745, 667, 626 cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{17}H_{21}O_3^+$ [M+H]$^+$: 273.1485, found: 273.1491.

Ethyl (*E*)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl) Propionate (158c)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), ethyl acrylate (**62b**, 60.0µL, 0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158c** (colorless oil, 25.3 mg, 88%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.40 (silica, EtOAc/Heptane 1:4)

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.74 (d, *J* = 7.6 Hz, 1H), 7.58 (td, *J* = 7.6, 1.0 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 5.61 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.52 (dt, *J* = 15.7, 1.4 Hz, 1H), 4.09 (q, *J* = 7.4 Hz, 2H), 3.26 (d, *J* = 17.1 Hz, 1H), 3.05 (d, *J* = 17.1 Hz, 1H), 2.37 (ddd, *J* = 15.9, 11.1, 5.2 Hz, 1H), 2.25 (ddd, *J* = 15.9, 11.1, 5.2 Hz, 1H), 2.11 (ddd, *J* = 13.7, 11.1, 5.2 Hz, 1H), 2.04 – 1.93 (m, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm.

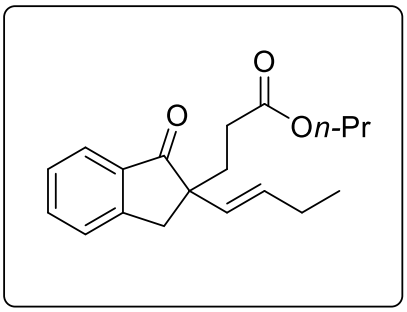
^{13}C-NMR ($CDCl_3$, 126 MHz): δ = 207.4, 173.3, 152.1, 135.6, 134.9, 133.1, 129.6, 127.6, 126.3, 124.5, 60.4, 54.5, 38.2, 32.6, 30.0, 25.7, 14.2, 13.5 ppm.

IR: $\tilde{\nu}$ = 3018, 2928, 1704,1648,1607, 1465, 1213, 925, 743, 667, 473 cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{18}H_{22}O_3^+$ [M+Na]$^+$: 309.1461, found: 309.1470.

Propyl (*E*)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)Propionate (158d)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), propyl acrylate (**62c**, 74.4 µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158d** (colorless oil, 29.5 mg, 98%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.34 (silica, EtOAC/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.74 (d, *J* = 7.6 Hz, 1H), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H), 7.44 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.37 (td, *J* = 7.6, 1.0 Hz, 1H), 5.61 (dt, *J* = 15.7, 6.1 Hz,1H), 5.52 (dt, *J* = 15.7, 1.4 Hz, 1H), 4.00 (t, *J* = 6.7 Hz, 2H), 3.26 (d, *J* = 17.2 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 2.38 (ddd, *J* = 16.1, 11.2, 5.2 Hz, 1H), 2.26 (ddd, *J* = 16.1, 11.2, 5.2 Hz, 1H), 2.12 (ddd, *J* = 13.7, 11.2, 5.2 Hz, 1H), 2.05 – 1.94 (m, 3H), 1.65 – 1.58 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H) ppm.

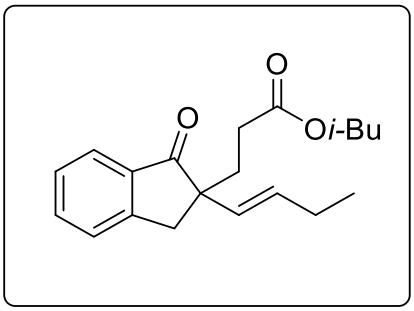
^{13}C-NMR ($CDCl_3$, 126 MHz): δ = 207.4, 173.4, 152.1, 135.6, 134.9, 133.1, 129.6, 127.6, 126.4, 124.5, 66.1, 54.5, 38.3, 32.6, 30.0, 25.7, 21.9, 13.5, 10.4 ppm.

IR: $\tilde{\nu}$ = 3053, 2983, 2305, 1712, 1421, 1263, 822, 908, 710, 651cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{19}H_{24}O_3^+$ [M+Na]$^+$: 323.1618, found: 323.1626.

Iso-butyl(*E*)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)Propionate (158e)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), iso-butyl acrylate (**62d**, 86.4 µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158e** (colorless oil, 30.0 mg, 95%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.36 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.74 (d, *J* = 7.6 Hz, 1H), 7.59 (td, *J* = 7.6, 1.1 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 5.62 (dt, *J* = 15.7, 6.0 Hz, 1H), 5.52 (dt, *J* = 15.7, 1.3 Hz, 1H), 3.82 (d, *J* = 6.7 Hz, 2H), 3.26 (d, *J* = 17.3 Hz, 1H), 3.06 (d, *J* = 17.3 Hz, 1H), 2.38 (ddd, *J* = 16.0, 11.2, 5.3 Hz, 1H), 2.27 (ddd, *J* = 16.0, 11.2, 5.3 Hz, 1H), 2.11 (ddd, *J* = 13.7, 10.9, 5.3 Hz, 1H), 2.05 – 1.96 (m, 3H), 1.89 (hept, *J* = 6.8 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 6H) ppm.

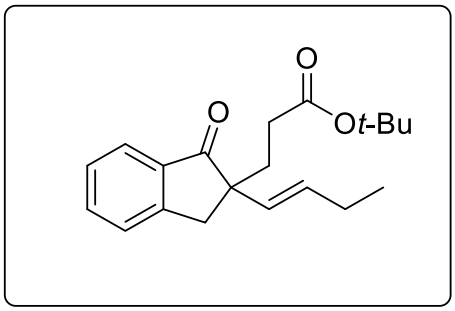
^{13}C-NMR ($CDCl_3$, 100 MHz): δ 207.4, 173.4, 152.1, 135.6, 134.9, 133.1, 129.7, 127.6, 126.4, 124.6, 70.6, 54.5, 38.3, 32.6, 30.0, 27.6, 25.7, 19.1, 13.5 ppm.

IR: $\tilde{\nu}$ = 3020, 2967, 1716, 1409, 1213, 1061, 929, 743, 667cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{20}H_{26}O_3^+$ [M+Na]$^+$: 337.1774, found: 337.1772.

Tert-butyl(*E*)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)Propionate (158f)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), tert butyl acrylate (**62e**, 87.4 µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158f** (colorless oil, 24.4 mg, 78%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.34 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.74 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.59 (td, *J* = 7.6, 0.9 Hz, 1H), 7.44 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.36 (td, *J* = 7.6, 0.9 Hz, 1H), 5.61 (dt, *J* = 15.7, 5.9 Hz, 1H), 5.52 (dt, *J* = 15.7, 1.1 Hz, 1H), 3.24 (d, *J* = 17.2 Hz, 1H), 3.06 (d, *J* = 17.2 Hz, 1H), 2.26 (ddd, *J* = 15.1, 11.3, 4.9 Hz, 1H), 2.19 – 1.90 (m, 5H), 1.41 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 207.6, 172.6, 152.2, 135.7, 134.9, 132.9, 129.8, 127.5, 126.4, 124.5, 80.3, 54.5, 38.3, 32.7, 31.2, 28.1, 25.7, 13.6 ppm.

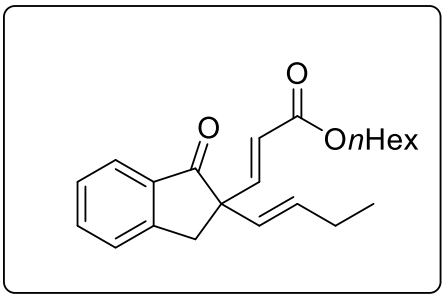
IR: $\tilde{\nu}$ = 3020, 2965, 1714, 1469,1409, 1397, 1283, 1061, 984, 743, 667cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{20}H_{26}NaO_3^+$ [M+Na]$^+$: 337.1774, found: 337.1773.

Hexyl(E)-3-2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)Propionate (158g)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), hexyl acrylate (**62f**, 105.6 µL,0.60 mmol) and DBU (1.50 µL,10µmol) in MeCN (1.00 mL) gave

compound **158g** (colorless oil, 26.1 mg, 77%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.31 (silica, EtOAc/Heptane 1:4)

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.74 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.58 (td, *J* = 7.6, 1.0 Hz, 1H), 7.43 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.37 (td, *J* = 7.6, 1.0 Hz, 1H), 5.62 (dt, *J* = 15.8, 6.0 Hz, 1H), 5.52 (dt, *J* = 15.8, 1.3 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.26 (d, *J* = 17.3 Hz, 1H), 3.05 (d, *J* = 17.3 Hz, 1H), 2.36 (ddd, *J* = 15.7, 11.1, 5.3 Hz, 1H), 2.26 (ddd, *J* = 15.7, 11.1, 5.3 Hz, 1H), 2.11 (ddd, *J* = 13.6, 10.9, 5.3 Hz, 1H), 2.06 – 1.93 (m, 3H), 1.62 – 1.55 (m, 2H), 1.35 – 1.23 (m, 7H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm.

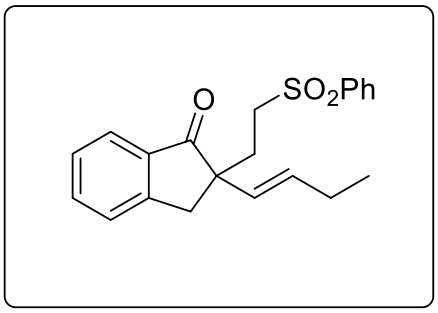
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 207.4, 173.4, 152.1, 135.6, 134.9, 133.1, 129.7, 127.6, 126.4, 124.5, 64.6, 54.5, 38.3, 32.6, 31.4, 30.0, 28.5, 25.7, 25.5, 22.5, 14.0, 13.5 ppm.

IR: $\tilde{\nu}$ = 3022, 2959, 1718, 1638, 1467,1409, 1296, 1063, 984, 811, 748, 641.cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{22}H_{30}O_3^+$ $[M+Na]^+$: 365.2087, found: 365.2086.

(*E*)-2-(but-1-en-1-yl)-2-(2-(phenylsulfonyl)ethyl)-2,3-dihydro-1*H*-inden-1-one (158h)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), phenyl vinyl sulfone (**62g**, 100.9 mg,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158h** (colorless oil, 33.1 mg, 93%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.23 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.90 – 7.86 (m, 2H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.59 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 – 7.54 (m, 2H), 7.42 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.36 (td, *J* = 7.6, 1.1 Hz, 1H), 5.56 (dt, *J* = 15.7, 6.3 Hz, 1H). 5.39 (dt, *J* = 15.7, 1.5 Hz, 1H), 3.29 – 3.23 (m, 2H), 3.09 (ddd, *J* = 14.1, 12.5, 4.5 Hz, 1H), 2.99 (d, J = 17.0 Hz, 1H), 2.13 (ddd, *J* = 13.4, 12.6, 4.3 Hz, 1H), 2.05 – 1.95 (m, 3H), 0.90 (t, *J* = 7.4 Hz, 3H) ppm.

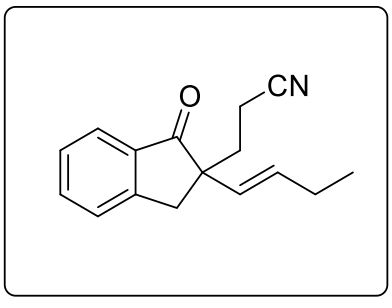
^{13}C-NMR ($CDCl_3$, 126 MHz): ^{13}C-NMR ($CDCl_3$, 126 MHz): δ = 206.4, 151.6, 138.8, 135.3, 135.1, 134.3, 133.8, 129.3, 128.6, 128.0, 127.8, 126.4, 124.6, 53.5, 52.4, 38.9, 30.2, 25.6, 13.4 ppm.

IR: $\tilde{\nu}$ = 3034, 1710, 1367, 1429, 1263, 1149,1088, 918, 729, 710, 651.cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{21}H_{22}O_3S^+$ $[M+H]^+$: 355.1362, found: 355.1368.

(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)propanenitrile (158i)

According to general procedure **4**, enone **154** (18.6 mg, 0.10 mmol), acrylonitrile (**53**, 39.3 µL,0.60 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **158i** (colorless oil, 21.6 mg, 90%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.38 (silica, EtOAc/Heptane 1:4).

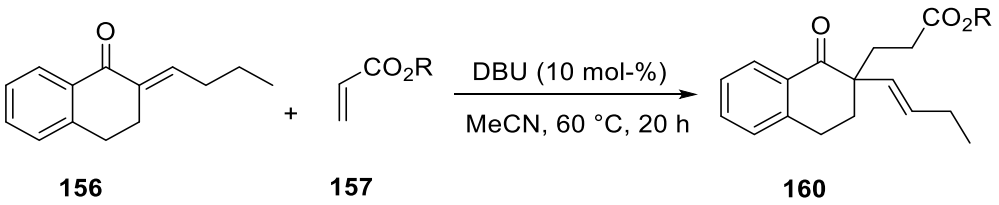
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.75 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.62 (td, *J* = 7.6, 1.0 Hz, 1H), 7.46 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.39 (td, *J* = 7.6, 1.0 Hz, 1H), 5.68 (dt, *J* = 15.8, 6.3 Hz, 1H), 5.47 (dt, *J* = 15.8, 1.5 Hz, 1H), 3.35 (d, *J* = 17.4 Hz, 1H), 3.13 (d, *J* = 17.4 Hz 1H), 2.49 (ddd, *J* = 17.0, 9.5, 5.5 Hz, 1H), 2.39 (ddd, *J* = 17.0, 9.5, 6.7 Hz, 1H), 2.18 (ddd, *J* = 13.8, 9.5, 5.5 Hz, 1H), 2.08 – 1.96 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 206.4, 151.7, 135.3, 135.1, 134.6, 128.3, 127.9, 126.5, 124.7, 119.7, 54.2, 38.5, 33.0, 25.7, 13.4, 13.0 ppm.

IR: $\tilde{\nu}$ = 3053, 2987, 1718, 1421,1112, 908, 755, 703, 644, 598. cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{16}H_{17}NO^+$ [M+H]$^+$: 240.1383, found: 240.1382.

General Procedure 5. for the Synthesis of *β,γ*-Unsaturated Ketones 160a-160e



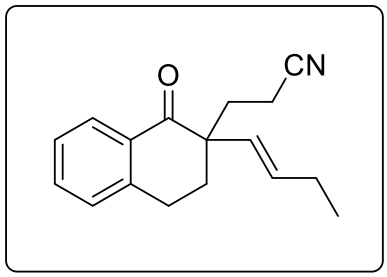
156 **157** **160**

Scheme 70. DBU-Catalyzed α-Alkylation of Tetralone Derivative enones **156** with Alkenes **157**

Enone **156** was dissolved in MeCN in a 10 mL crimp cap vial. Alkene **157** (10 equiv.) was added to the stirred solution, followed by DBU (10 mol-%). The vial was sealed and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at 40 °C for 24 h. column chromatography over silica gel afforded the pure Compound **160a-160e**.

(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanenitrile (160a)

According to general procedure **5**, enone **156** (20.0 mg, 0.10 mmol), acrylonitrile (**53**, 65.5µL,1.00 mmol) and DBU (1.50µL,10 µmol) in MeCN (1.00 mL) gave compound **160a** (colorless oil, 10.0 mg, 40%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R_f = 0.19 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.03 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 5.46 – 5.37 (m, 2H), 3.08 (ddd, *J* = 17.0, 11.3, 5.2 Hz, 1H), 2.86 (dt, *J* = 17.0, 4.1 Hz, 1H), 2.60 (ddd, *J* = 17.0, 9.8, 6.0 Hz, 1H), 2.44 (ddd, *J* = 17.0, 9.8, 6.0 Hz, 1H), 2.17 – 1.95 (m, 6H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm.

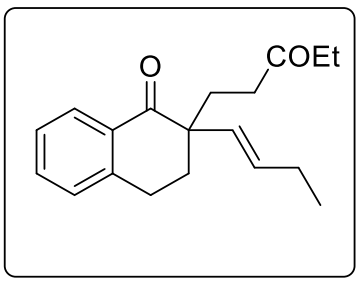
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 199.3, 143.1, 136.0, 133.5, 131.9, 128.6, 127.8, 127.5, 126.8, 120.4, 50.4, 33.6, 33.3, 25.8, 25.7, 13.4, 13.1 ppm.

IR: $\tilde{\nu}$ = 2954, 2852, 1712, 1460, 923, 765, 714, 647, 555. cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{19}NO^+$ $[M+H]^+$: 253.15; found 253.00.

(*E*)-2-(but-1-en-1-yl)-2-(3-oxopentyl)-3,4-dihydronaphthalen-1(2*H*)-one (160b)

According to general procedure **5**, enone **156** (18.6 mg, 0.10 mmol), ethyl vinyl ketone (**157**, 99.6µL,1.00 mmol) and DBU (1.50µL,10µmol) in MeCN (1.00 mL) gave compound **160b** (colorless oil, 16.1 mg, 57%) after chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.23 (silica, EtOAc/Heptane 1:4)

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.04 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.44 (td, *J* = 7.7, 1.2 Hz, 1H), 7.30 (t, *J* = 7.7, 1H), 7.19 (d, *J* = 7.7, 1H), 5.50 (dt, *J* = 16.1, 1.4 Hz, 1H), 5.38 (dt, *J* = 16.0, 6.1 Hz, 1H), 3.04 (ddd, *J* = 17.0, 10.1, 5.0 Hz, 1H), 2.87 (dt, *J* = 17.0, 4.8 Hz, 1H), 2.53 – 2.40 (m, 4H), 2.12 – 1.89 (m, 6H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm.

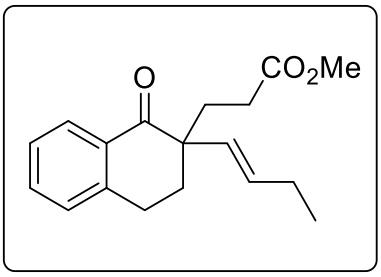
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 211.8, 200.3, 143.5, 134.1, 133.3, 132.4, 129.6, 128.7, 127.9, 126.7, 50.5, 38.0, 36.1, 33.1, 31.4, 26.0, 25.9, 13.7, 8.0 ppm.

IR: $\tilde{\nu}$ = 3041, 2963, 1747, 1336, 994, 748, 716, 635, 592.cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{19}H_{24}NaO_2^+$ $[M+Na]^+$: 307.1669, found: 307.1675.

Methyl(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (160c)

According to the general procedure **5**, enone **156** (20.0 mg, 0.10 mmol), methylacrylate **62a** (90.6 µL, 1 mmol) and DBU (1.54 µL, 10 mol%) in MeCN (1.00 mL) gave compound **160c** (colorless oil, 12.2 mg, 43%) after column chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.28 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.05 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.51 (dt, *J* = 16.0, 1.2 Hz, 1H), 5.40 (dt, *J* = 16.0, 6.1 Hz, 1H), 3.65 (s, 3H), 3.05 (ddd, *J* = 16.9, 10.2, 5.3 Hz, 1H), 2.86 (dt, *J* = 16.9, 4.7 Hz, 1H), 2.48 - 2.32 (m, 2H), 2.13 - 1.95 (m, 6H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm.

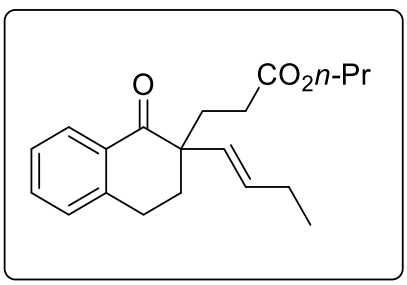
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 199.7, 174.3, 143.2, 134.3, 133.1, 132.1, 128.9, 128.5, 127.9, 126.6, 51.6, 50.3, 32.5, 32.3, 29.6, 25.9, 25.7, 13.5 ppm.

IR: $\tilde{\nu}$ = 3032, 2992, 1734, 1415, 956, 744, 719, 651.cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{18}H_{22}NaO_3^+$ $[M+Na]^+$: 309.1461, found: 309.1460.

Propyl(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (160d)

According to the general procedure **5**, enone **156** (20.0 mg, 0.10 mmol) n-propylacrylate **62c** (124.1 µL, 1.00 mmol) and DBU (1.50 µL, 10 mol%) in MeCN (1.00 mL) gave compound **160d** (colorless oil, 12.2 mg, 39%) after column chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.23 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.04 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 5.51 (dt, *J* = 16.1, 1.3 Hz, 1H), 5.40 (dt, *J* = 16.1, 6.0 Hz, 1H), 4.01 (t, *J*

= 6.8 Hz, 2H), 3.05 (ddd, *J* = 17.0, 10.0, 5.3 Hz, 1H), 2.86 (dt, *J* = 17.0, 4.7 Hz, 1H), 2.47 - 2.31 (m, 2H), 2.11 - 1.95 (m, 6H), 1.69 – 1.58 (m, 2H) 0.92 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm.

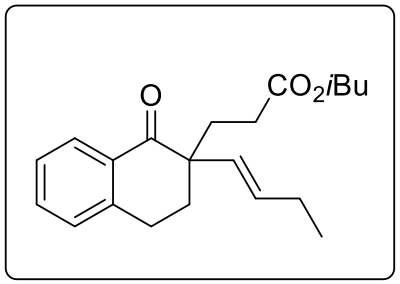
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 199.7, 173.9, 143.3, 134.2, 133.1, 132.1, 129.0, 128.5, 127.8, 126.5, 66.0, 50.3, 32.4, 32.3, 29.7, 25.9, 25.7, 21.9, 13.5, 10.4 ppm.

IR: $\tilde{\nu}$ = 3053, 2987, 1718, 1421, 908, 729, 702, 651.cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{20}O_2^+$ [M+H]$^+$: 270.1756, found: 270.1755.

Iso-butyl(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (160d)

According to the general procedure **5**, enone **156** (20.0 mg, 0.1 mmol) *iso*-butylacrylate **62c** (144.1 µL, 1.00 mmol) and DBU (1.50 µL, 10 mol%) in MeCN (1 mL) gave compound **160d** (colorless oil, 12.2 mg, 37%) after column chromatography (silica gel, EtOAc/Heptane 1:4).



R*f* = 0.24 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 8.05 (d, *J* = 7.6 Hz,1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.51 (d, *J* = 16.2 Hz, 1H), 5.41 (dt, *J* = 16.2, 5.9 Hz, 1H), 3.84 (d, *J* = 6.6 Hz, 2H), 3.05 (ddd, *J* = 16.8, 10.4, 4.9 Hz, 1H), 2.87 (dt, *J* = 16.8, 3.9 Hz, 1H), 2.47 – 2.33 (m, 2H), 2.10 – 1.96 (m, 6H), 1.95 – 1.87 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 6H) ppm.

^{13}C-NMR ($CDCl_3$, 126 MHz): δ = 199.7, 173.9, 143.3, 134.2, 133.1, 132.1, 129.0, 128.5, 127.9, 126.6, 70.5, 50.3, 32.4, 32.3, 29.7, 27.7, 25.9, 25.7, 19.1, 13.5 ppm.

IR: $\tilde{\nu}$ = 3053, 2987, 1718, 1421, 908, 729, 702, 651.cm^{-1}.

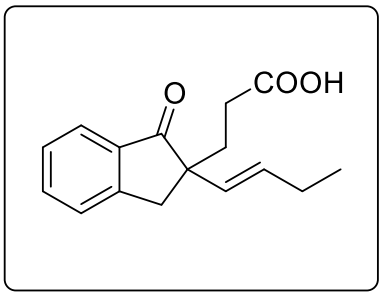
HRMS (ESI+): *m/z* calc for $C_{21}H_{28}NaO_3^+$ [M+H]$^+$: 351.1931; found 351.1927.

Preparation of Compound 158b on a 1 mmol Scale:

According to the general procedure **4**, enone **154** (186.2 mg, 1.00 mmol), methyl acrylate (**62a**, 543.7 µL, 0.60 mmol), and DBU (15.0 µL, 0.10 mmol) in CH_2Cl_2 (10 mL) gave, after chromatography (silica gel, EtOAc/Heptane 1:4), compound **158b** (266.6 mg, 98%).

***(E)*-3-(2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)propanoic acid (170)**

Compound **158b** (122.6 mg, 0.45 mmol) was dissolved in a 3:1 mixture of MeOH and H_2O (4.00 mL), and LiOH (21.4 mg, 0.89 mmol) was added. The mixture was stirred for 16h at r.t. MeOH was removed under reduced pressure, and the remaining aqueous phase was diluted with EtOAc and sat. aq $NaHCO_3$. The layers were separated, and the aqueous layer was acidified with 5% HCl aq the aqueous phase was extracted with EtOAc (2×), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield the intermediate acid **170** (colorless oil, 93.0 mg, 80%) which was used in the subsequent step without further purification.



^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 7.74 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.59 (td, *J* = 7.7, 1.0 Hz, 1H), 7.44 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.37 (td, *J* = 7.7, 1.0 Hz, 1H), 5.63 (dt, *J* = 15.8, 6.3 Hz, 1H), 5.51 (dt, *J* = 15.8, 1.4 Hz, 1H), 3.27 (d, *J* = 17.1 Hz, 1H), 3.04 (d, *J* = 17.1 Hz, 1H), 2.44 (ddd, *J* = 16.3, 10.9, 5.3 Hz, 1H), 2.32 (ddd, *J* = 16.3, 10.9, 5.3 Hz, 1H), 2.12 (ddd, *J* = 13.8, 10.9, 5.4 Hz, 1H), 2.04 – 1.93 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 207.3, 179.2, 152.0, 135.5, 135.0, 133.4, 129.4, 127.6, 126.4, 124.6, 54.4, 38.4, 32.2, 29.7, 25.7, 13.5 ppm.

IR: $\tilde{\nu}$ = 2921, 1706,1615, 1460, 1392,1294,1215, 1180, 1149, 745, 572, 438 cm^{-1}.

HRMS (ESI-TOF): *m/z* calc. for $C_{16}H_{18}NaO_3^+$ $[M+Na]^+$: 281.1148, found: 281.1143.

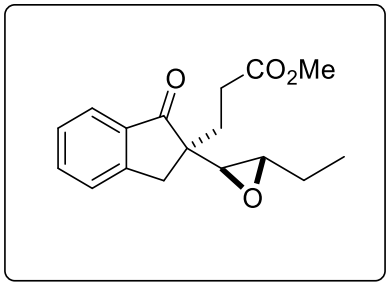
Preparation of Compound 160c on a 1mmol Scale

According to the general procedure **5**, enone **156** (200.2 mg, 1.00 mmol), methyl acrylate (**62a**, 906 μL, 1.00 mmol), and DBU (15.0 μL, 0.10 mmol) in CH_2Cl_2 (10 mL) gave, after chromatography (silica gel, EtOAc/Heptane 10:1), compound **160c** (235.5 mg, 82%).

Preparation of Epoxide 169

Methyl3-((*R**)-2-((2*S**,3*S**)-(3-ethyloxiran-2-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl)propanoate (169)

Compound **158b** (27.2 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL), and *m*CPBA (77 weight-%, 34.5 mg, 0.20 mmol) was added. The mixture was stirred at r.t. for 16 h,[11] Sand then sat. aq $NaHSO_3$ (1 mL) was added. After 10 min of additional stirring, the layers were separated, and the organic layer was washed with sat. aq $NaHSO_3$, sat.aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (silica gel, EtOAc/Heptane, 1:4) gave as a mixture of diastereomers **169** (d.r, 1.5:1) with (colorless oil), 27.4 mg, 95%).



R*f* = 0.27 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.73 (ddt, *J* = 11.8, 7.7, 1.0 Hz, 2H), 7.59 (tdd, *J* = 7.4, 4.0, 1.2 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.40 – 7.34 (m, 2H), 3.65 (s, 2H), 3.63 (s, 3H), 3.11 (d, *J* = 2.3 Hz, 1H), 3.04 (d, *J* = 17.7 Hz, 1H), 2.94 (d, *J* = 17.0 Hz, 1H), 2.90 (d, *J* = 2.2 Hz, 1H), 2.86 (d, *J* = 17.7 Hz, 1H), 2.76 – 2.72 (m, 2H), 2.69 (s, 1H), 2.65 (td, *J* = 5.6, 2.2 Hz, 1H), 2.49 (ddd, *J* = 16.1, 11.2, 5.2 Hz, 1H), 2.42 – 2.17 (m, 4H), 2.17–1.98 (m, 3H), 1.64 – 1.54 (m, 3H), 1.49 – 1.43 (m, 1H), 1.25 (s, 1H), 1.00 (t, *J* = 7.5 Hz, 4H), 0.86 (t, *J* = 7.5 Hz, 3H).

Major diastereomer

^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.7, 173.2, 153.1, 135.5, 135.4, 127.8, 126.5, 124.3, 60.2, 56.1, 52.5, 51.8, 32.0, 30.0, 29.3, 24.8, 9.9 ppm.

Minor diastereomer

^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.3, 173.5, 152.7, 136.1, 135.9, 127.8, 126.4, 124.4, 60.2, 56.1, 52.5, 51.8, 34.0, 31.0, 29.4, 24.7, 9.8 ppm.

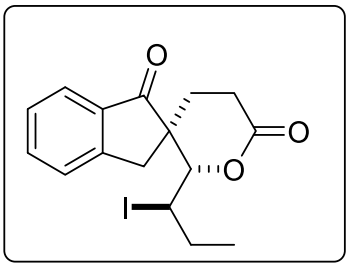
IR: $\tilde{\nu}$ = 2954, 1712,1601, 1296,1250, 1055, 871, 840, 795, 737, 469 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{20}O_4$+[M+Na]$^+$: 311.1254, found: 311.1245.

Hazard statement: Solid mCPBA in dry form is an explosive agent and the reagent should only be used in the H_2O-containing formulation available from commercial suppliers.

(2*R,2'*S**)-2'-((*R**)-1-iodopropyl)-4',5'-dihydro-2'*H*,6'*H*-spiro[indene-2,3'-pyran]-1,6'(3*H*)-dione (171)**

A portion of acid **170** (25.8 mg, 0.10 mmol) and 2,4,6-collidine (52.9 µL, 0.40 mmol) were dissolved in MeCN (2.00 mL). A solution of I_2 (25.3 mg, 0.20 mmol) in MeCN (1.00 mL) was added at 0 °C, and the mixture was subsequently heated to 50 °C for 24 h. The mixture was diluted with CH_2Cl_2 and washed with 5% $Na_2S_2O_3$ aq and 0.5 M $KHSO_4$ aq, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (silica gel, EtOAc/PhCH3 1:4) gave compound **171** as a mixture of diastereomers. (*d.r.* 4.7:1, colorless solid, 25.4 mg, 66%).



R*f* = 0.41 (silica, EtOAc/Heptane 1:4).

Major diastereomer, (2*R**,2'*S**,2'-(1*R**):

^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 7.84 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.44 (td, *J* = 7.5, 0.8 Hz, 1H), 5.10 (d, *J* = 8.8 Hz, 1H), 3.96 (td, *J* = 8.9, 2.9 Hz, 1H), 3.54 (d, *J* = 17.4 Hz, 1H), 2.94 (d, *J* = 17.4 Hz, 1H), 2.86 (dt, *J* = 17.8, 6.4 Hz, 1H), 2.58 (ddd, *J* = 17.8, 9.1, 5.9 Hz, 1H), 2.26 (ddd, *J* = 14.1, 9.1, 6.4 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.93 – 1.86 (m, 1H), 1.71 (dt, *J* = 14.1, 6.4 Hz, 1H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 205.5, 170.0, 151.1, 135.4, 128.2, 126.6, 125.0, 84.0, 52.0, 34.4, 34.1, 32.2, 29.2, 27.06, 13.8 ppm.

Signals of minor diastereomer:

^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 7.78 (dt, *J* = 7.5, 0.8 Hz, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.20 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1H), 3.47 (d, *J* = 17.3 Hz, 1H), 3.12 (d, *J* = 17.3 Hz, 1H), 3.04 (ddd, *J* = 18.0, 8.7, 6.5 Hz, 1H), 0.78 (t, *J* = 7.2 Hz, 3H) ppm.

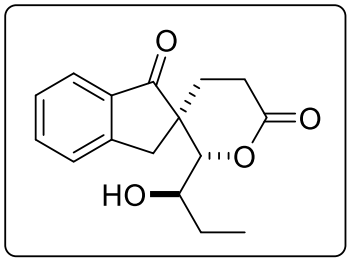
^{13}C-NMR (126 MHz, $CDCl_3$) δ = 205.3, 169.9, 150.3, 135.7, 128,4, 126.5, 124.3, 87.9, 50.5, 40.9, 34.2, 30.8, 29.0, 27.15, 14.2 ppm.

IR: $\tilde{\nu}$ = 2926,1710,1673,1458,1436, 1362,1294, 898, 832, 778, 473 cm^{-1}

HRMS (ESI+): *m/z* calc. for $C_{16}H_{19}IO_3^+$ $[M+H]^+$: 385.0295, found: 385.1145.

(2*R,2'*S**)-2'-((*R**)-1-hydrxypropyl)-4',5'-dihydro-2'*H*,6'*H*-spiro[indene-2,3'-pyran]-1,6'(3*H*)-dione (172)**

A portion of acid **170** (90.0 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (8.00 mL), and *m*CPBA (77 weight-%, 117.3 mg, 0.68 mmol) was added then trifluoroacetic acid (0.20 mL) was added. The mixture was stirred at r.t. for 16 h, and then sat.aq $NaHCO_3$, and brine. The organic layer was dried over MgSO4, filtered, and concentrated to dryness. Column chromatography (silica gel, Et_2OAC/$PhCH_3$,1:4) gave as a mixture of diastereomers (>19:1) **172** colorless solid, 61.4 mg, 65%.



R*f* = 0.21(silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 (td, *J* = 7.6, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 4.61 (d, *J* = 8.9 Hz, 1H), 3.58 – 3.50 (m, 2H), 2.93 (d, *J* = 17.4 Hz, 1H), 2.80 (ddd, *J* = 18.5, 7.2, 3.4 Hz, 1H), 2.64 (ddd, *J* = 18.5, 11.0, 7.4 Hz, 1H), 2.28 (ddd, *J* = 13.8, 10.9, 7.2 Hz, 1H), 1.96 (dqd, *J* = 15.1, 7.6, 2.6 Hz, 1H), 1.71 (ddd, *J* = 13.8, 7.4, 3.4 Hz, 1H), 1.50 – 1.42 (m, 1H), 1.42 – 1.32 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 206.5, 169.8, 151.4, 135.7, 135.1, 127.9, 126.7, 124.5, 86.4, 73.2, 49.7, 33.3, 30.9, 27.6, 27.1, 9.5 ppm.

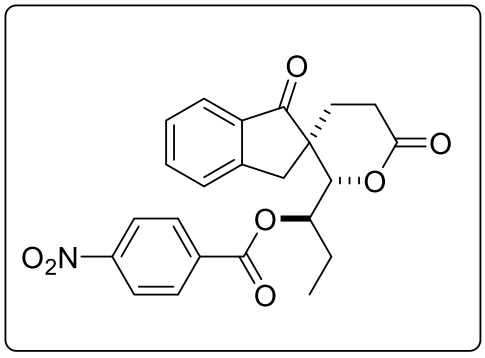
IR: $\tilde{\nu}$ = 2933, 1886, 1728, 1699, 1622, 1460, 1392, 1235, 1205, 1179, 1136, 854, 772, 696, 469 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{16}H_{18}O_4^+$ [M+Na]$^+$: 297.1097, found: 297.1109.

Benzoylation of Alcohol

(*R**)-1-((2*R**,2'*S**)-1,6'-dioxo-1,3,5',6'-tetrahydro-2'*H*,4'*H*-spiro[indene-2,3'-pyran]-2'-yl)propyl 4-nitrobenzoate (173)

To a solution of alcohol **172** (10 mg, 0.036 mmol, 1.0 eq.) in pyridine (1 mL) was added para-nitro benzoyl chloride (40 mg, 0.021 mmol, 6.0 eq.) and DMAP (2.44 mg, 20 µmol, 0.1 eq.). The mixture was stirred at room temperature for 16 h. Then iced-cold H_2O (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous NaCl (1 mL) and concentrated under reduced pressure. column chromatography on silica gel ($PhCH_3$/EtOAc, 9:1) afforded as a mixture of diastereomers **173** (*d.r.*1.5:1), colorless solid.112.7 mg, 82%).



R*f* = 0.40 (silica, EtOAc/$PhCH_3$, 1:9).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.13 (m, 2H), 7.71 (m, 2H), 7.40 – 7.35 (m, 2H), 7.05 (m, 1H), 6.86 – 6.78 (m, 1H), 5.28 – 5.20 (m, 1H), 5.02 (d, *J* = 9.6, 1H), 3.45 (d, *J* = 17.9 Hz,, 1H), 2.93 (d, *J* = 17.9 Hz,, 1H), 2.90 – 2.84 (m, 1H), 2.74 – 2.63 (m, 1H), 2.45 – 2.35 (m, 1H), 2.14 – 1.98 (m, 1H), 1.75 (m, 2H), 0.89 (t, *J* = 7.4 Hz,, 3H) ppm.

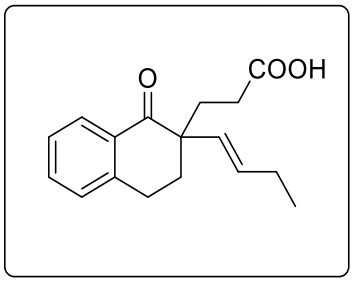
^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.0, 168.8, 162.7, 151.4, 150.6, 135.4, 134.5, 133.9, 130.6, 127.4, 126.8, 124.4, 123.2, 83.8, 73.7, 49.4, 33.1, 30.9, 27.0, 25.1, 8.7 ppm.

IR: $\tilde{\nu}$ = 2920,1861, 1798, 1633, 1615, 1433, 1383, 1282, 1221, 1159, 1106, 824, 795, 656, 479 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{23}H_{21}O_7$+[M+H]$^+$: 424.1391, found: 424.1401.

(*E*)-3-(2-(but-1-en-1-yl)-1-oxo-1,2,3,4-tetrahydronapthalen-2-yl) propanoic acid (175)

Compound **160c** (100.0 mg, 0.35 mmol) was dissolved in a 3:1 mixture of MeOH and H_2O (4.00 mL), and LiOH (16.7 mg, 0.69 mmol) was added. The mixture was stirred for 16 h at r.t. MeOH was removed under reduced pressure, and the remaining aqueous phase was diluted with EtOAc and sat. aq $NaHCO_3$. The layers were separated, and the aqueous layer was acidified with 5% HCl aq the aqueous phase was extracted with EtOAc (2×), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield the intermediate acid **175** (colorless oil, 91.0 mg, 95%) which was used in the subsequent step without further purification.



^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 5.49 (dt, *J* = 16.0, 1.1 Hz, 1H), 5.41 (dt, *J* = 16.0, 6.0 Hz, 1H), 3.06 (ddd, *J* = 17.0, 10.3, 5.4 Hz, 1H), 2.86 (dt, *J* = 17.0, 4.5 Hz, 1H), 2.55 – 2.38 (m, 2H), 2.11 – 1.95 (m, 6H), 0.91 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C-NMR (100MHz, $CDCl_3$) δ = 199.8, 180.0, 143.2, 134.6, 133.2, 132.1, 128.7, 128.5, 127.9, 126.6, 50.3, 32.6, 32.0, 29.6, 25.8, 25.7, 13.4 ppm.

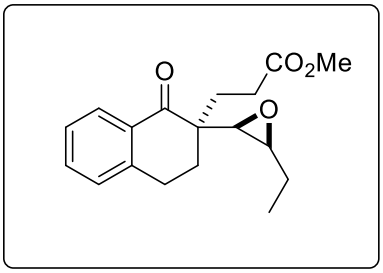
IR: $\tilde{\nu}$ = 2921,1881, 1720, 1642, 1615, 1460, 1392, 1294, 1215, 1180, 1149, 884, 762, 686. 440 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{17}H_{20}NaO_3^+$ [M+Na]$^+$: 295.1305, found: 295.1313.

Preparation of Epoxide 174.

Methyl-3-((*S)-2-((2*R**,3*S**)-3-ethyloxiran-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (174)**

Compound **160c** (28.6 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (3.00 mL), and *m*CPBA (77 weight-%, 34.5 mg, 0.20 mmol) was added. The mixture was stirred at r.t. for 16 h, and then sat. aq $NaHSO_3$ (1 mL) was added. After 10 min of additional stirring, the layers were separated, and the organic layer was washed with sat. aq $NaHSO_3$, sat. aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (silica gel, EtOAc/Heptane,1:4) gave as a mixture of diastereomers **174** (*d.r.* 1.5:1, colorless oil, 20.5 mg, 67%).



R*f* = 0.26 (silica, EtOAc/Heptane 1:4).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.02 (ddd, *J* = 13.2, 7.9, 1.5 Hz, 1H), 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.47 (ttd, *J* = 11.9, 7.5, 1.5 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.20 (m, 2H), 3.72 (s, 1H), 3.12 (d, *J* = 2.3 Hz, 1H), 3.09 – 2.92 (m, 4H), 2.45–2.36 (m, 4H), 7.71–7.68 (m, 0H), 7.11 – 7.08 (m, 0H), 3.65 (d, *J* = 1.4 Hz, 5H), 3.27 (ddd, *J* = 16.9, 9.5, 4.6 Hz, 1H), 2.79 – 2.71 (m, 2H), 2.61 – 2.45 (m, 1H), 2.26 – 2.06 (m, 4H), 2.06 – 1.93 (m, 4H), 1.66 – 1.46 (m, 5H), 1.03 – 0.97 (m, 3H), 0.95 (d, *J* = 7.5 Hz, 3H) ppm.

Major diastereomer-(2*R,3*S**)**

^{13}C-NMR (126 MHz, $CDCl_3$) δ 198.5, 173.7, 143.0, 133.7, 131.9, 128.7, 128.1, 127.0, 61.2, 56.4, 51.8, 47.5, 30.7, 29.2, 28.0, 27.7, 25.2, 25.1, 9.8 ppm.

Minor diastereomer

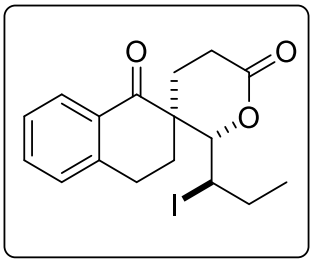
^{13}C-NMR ($CDCl_3$) δ 198.5, 173.8, 143.8, 132.4, 131.9, 128.7, 127.6, 126.8, 61.2, 56.4, 51.8, 47.5, 29.4, 29.3, 28.1, 25.7, 25.0, 10.0 ppm.

IR: $\tilde{\nu}$ = 2954, 2870, 1712, 1601, 1409, 1296, 1055, 894, 737, 500 cm^{-1}.

HRMS (ESI+): *m/z* calc. for $C_{18}H_{22}O_4$+$[M+H]^+$: 303.1591, found: 303.1596.

(2*S,2'*S**)-2'-((*R**)-1-iodopropyl)-3,4,4',5'-terahydro-1*H*,2'*H*,6'*H*-spiro[naphthalene-2,3'-pyran]-1,6'-dione (176)**

A portion of acid **175** (27.2 mg, 0.10 mmol) and 2,4,6-collidine (52.9 μL, 0.40 mmol) were dissolved in MeCN (2.00 mL). A solution of I_2 (25.3 mg, 0.20 mmol) in MeCN (1.00 mL) was added at 0 °C, and the mixture was subsequently heated to 50°C for 24 h. The mixture was diluted with CH_2Cl_2 and washed with 5% $Na_2S_2O_3$ aq and 0.5 M $KHSO_4$ aq, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (silica gel, EtOAc/PhCH3, 1:4) gave compound **176** as a mixture of diastereomers (*Rf* = 0.50, *d.r*. 7.7:1, colorless solid, 24.7 mg, 62%).



R*f* = 0.50 (silica, Et2OAC/Heptane 1:4).

Major diastereomer, (2*S**,2'*S**,2'-(1*R**):

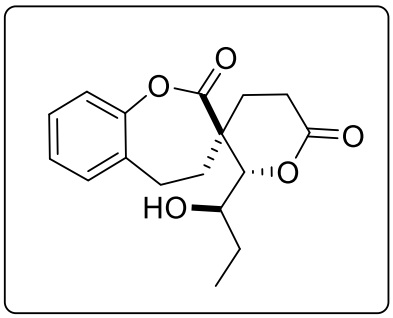
^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 8.11 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 5.51 (d, *J* = 9.6 Hz, 1H), 3.88 (td, *J* = 8.9, 1.6 Hz, 1H), 3.13 – 3.06 (m, 1H), 2.97 (d, *J* = 17.3 Hz, 1H), 2.86 (ddd, *J* = 16.4, 12.4, 5.1 Hz, 1H), 2.60 (td, *J* = 13.2, 4.7 Hz, 1H), 2.48 (dt, *J* = 16.4, 4.3 Hz, 1H), 2.20 – 2.13 (m, 2H), 2.06 – 1.87 (m, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR (126 MHz, CDCl3) δ = 197.7, 171.6, 141.5, 133.9, 130.8, 128.8, 128.7, 127.3, 82.1, 47.0, 32.9, 29.6, 29.2, 26.7, 26.6, 24.2, 13.5 ppm.

HRMS (ESI+): m/z calc. for $C_{17}H_{19}INaO_3^+$ $[M+Na]^+$: 421.0271, found: 421.1345.

(2*S,2'*S**)-2'-((*R**)-1-hydroxypropyl)-,4,4',5,5'-terahydro-2*H*,2'*H*,6'*H*-spiro[benzo[*b*]oxepine-3,3'-pyran]-2,6'-dione (177)**

A portion of acid **175** (60.0 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (5.00 mL), and *m*CPBA (77 weight-%, 75.9 mg, 0.44 mmol) was added then Trifluoroacetic acid (0.12 mL) was added. The mixture was stirred at r.t. for 16 h, and then sat.aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (silica gel, Et2OAC/PhCH3.1:4) gave as a mixture of diastereomers **177** (*d.r* >19:1, colorless solid, 49.2 mg, 73%).



R*f* = 0.22 (silica, EtOAc/$PhCH_3$ 1:4).

^{1}H-NMR (CD_3CN, 400 MHz) δ = 7.12 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.06 (td, *J* = 7.8, 1.6 Hz, 1H), 6.90 (s, 1H), 6.82-6.78 (m, 2H), 4.77 (d, *J* = 4.1 Hz, 1H), 4.33 (td, *J* = 7.2, 4.1 Hz, 1H), 2.71 (ddd, *J* = 13.1, 11.3, 5.8 Hz, 1H), 2.61 (ddd, *J* = 13.1, 11.3, 5.8 Hz, 1H), 2.54 (ddd, *J* = 17.2, 7.8, 4.7 Hz, 1H), 2.34 (ddd, *J* = 17.2, 9.3, 4.7 Hz, 1H), 2.20-2.06 (m, 2H), 2.02-1.89 (m, 2H), 1.82 (quint., *J* = 7.4 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, CD_3CN) δ = 178.8, 170.8, 155.5, 131.0, 128.5, 128.2, 121.1, 116.0, 86.3, 84.6, 46.6, 36.5, 28.6, 27.9, 27.4, 25.6, 9.8 ppm.

HRMS (ESI+): m/z calc. for $C_{17}H_{20}NaO_5^+$ $[M+Na]^+$: 327.1203, found: 327.1209.

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Curriculum Vitae

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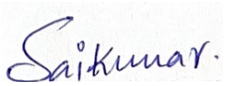
Publikationen

1. S. Banda, A. Villinger, M. Brasholz, *Org. Biomol. Chem*. **2023**, *21*, 4379–4381.
2. S. Banda, M. Brasholz, *J. Org. Chem*. **2024**, *89*, 18, 13263–13271.
3. S. Banda, L. Johannßen, M. Brasholz, *Synlett*, **2026**, in print.

Date: 13.11.2025 Signature: 

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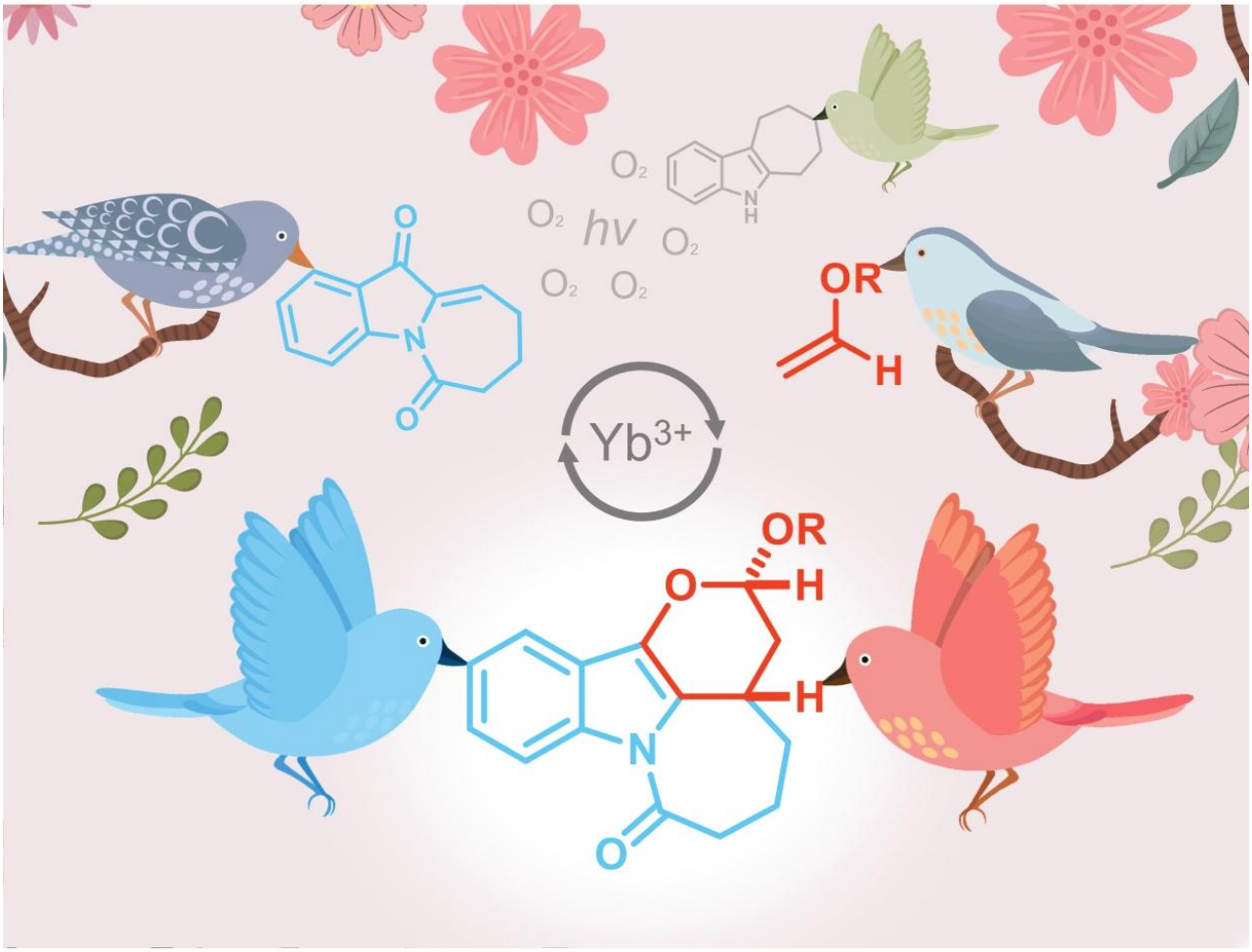

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Synthesis of azepane-fused pyrano[3,2-*b*]indoles by Lewis acid-catalysed oxa Diels–Alder reactions

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Synthesis of azepane-fused pyrano[3,2-*b*]indoles by Lewis acid-catalysed oxa Diels–Alder reactions†

Saikumar Banda, [a] Alexander Villinger [a] and Malte Brasholz *[a,b]

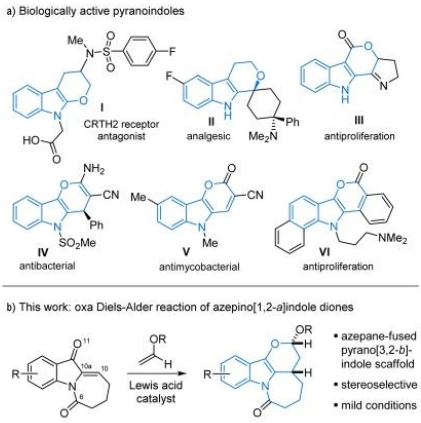
The dihydroazepino[1,2-*a*]indole diones 3 are tricyclic oxindole-type enones which are readily accessible by catalytic photooxygenation of cyclohepta[*b*]indoles 1 followed by dehydration. Lewis acid-catalysed oxa Diels–Alder reactions of enones 3 with enol ethers 4 were developed that lead to novel tetracyclic azepane-fused pyrano[3,2-*b*]indoles 5, with high stereoselectivity and under mild reaction conditions.

The isolation, biological study and chemical synthesis of new polycyclic indoles continue to be of high interest.[1] Indole-containing frameworks that are medicinally relevant also encompass the pyranoindoles. Biologically active members of this class of compounds display anti-inflammatory, analgesic and antiproliferative activities like the CRTH2 receptor antagonist **I**,[2] the drug cebranopadol (**II**)[3] and soyalkaloid A (**III**) from the soybean plant[4] (Scheme 1a). Pyrano[3,2-*b*]indoles in particular can be found in a number of antibacterial agents such as the synthetic small molecules **IV**[5] and **V**[6] as well as antitumor agents like the estrogen receptor α binding inhibitor **VI**.[7]

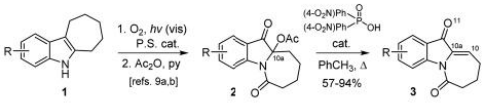
The oxa Diels–Alder ('ODA') reaction is one among the most efficient methods for the synthesis of functionalized pyran derivatives, as it allows for the stereoselective construction of this key motif in a single step.[8] Here, we report the synthesis of novel polycyclic pyrano[3,2-*b*]indoles fused with an azepane ring, by way of the Lewis acid-catalysed ODA reaction between enol ethers and unsaturated azepino[1,2-*a*]indole dione derivatives (Scheme 1b). The latter enone components for the oxa [4 + 2] cycloaddition are readily accessible through a sensitized catalytic cascade photooxygenation of cyclohepta[*b*]indoles previously developed in our laboratory,[9] followed by dehydration.

The preparation of enones **3** began with the photooxygenation of cyclohepta[*b*]indoles (**1**) followed by acetylation.[9a,b] The resulting 10a-*O*-acetyl perhydroazepino[1,2-*a*]indoles **2** subsequently underwent an organophosphate-catalysed dehydroacetoxylation to give the C10,C10a-unsaturated products **3** in yields between 57–94% (Scheme 2).

The oxa Diels–Alder reaction between enone **3a** and ethyl vinyl ether (**4a**) was then developed as shown in Table 1. Initially,



Scheme 1 Bioactive pyranoindoles and Lewis acid-catalysed oxa Diels–Alder reaction of dihydroazepino[1,2-*a*]indole diones with enol ethers.



Scheme 2 Photooxygenation of cyclohepta[*b*]indoles (**1**) and dehydroacetoxylation of 10a-*O*-acetoxy perhydrazepino[1,2-*a*]indole diones **2** to enones **3**. P.S. = photosensitizer.

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† Electronic supplementary information (ESI) available: Full experimental details and compound characterization data. CCDC 2237052. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ob00234a

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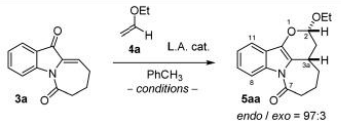
Table 1 Summary of reaction development



#	Catalyst	mol%	**4a** equiv.	*T* (°C)	*t* (h)	Conv. **3a**[a] (%)	Yield **5aa**[a] (%)
1	AgOTf	10	100	100	20	Decomp.	n.d.
2	$Cu(OTf)_2$	10	100	100	20	Decomp.	n.d.
3	$Sc(OTf)_3$	10	100	100	20	72	47
4	$Yb(OTf)_3$	10	100	100	20	60	52
5	$Yb(fod)_3$	10	100	100	20	61	58
6	$Yb(fod)_3$	10	100	100	40	100	51
7	$Yb(fod)_3$	20	100	100	20	100	54
8	$Yb(fod)_3$	20	10	100	20	100	62
9	$Yb(fod)_3$	15	10	75	20	100	51
10	**$Yb(fod)_3$**	**15**	**10**	**50**	**20**	**97**	**71 (70)**[b]
11	$Yb(fod)_3$	15	10	22	20	60	57
12	$Yb(fod)_3$	10	10	50	20	93	64
13	None	n.a.	10	50	20	0	0

[a] Determined by ^{1}H NMR analysis against CH_2Br_2 standard. [b] Yield after chromatography. L.A. = Lewis acid. Reaction conditions: 0.10 mmol of **3a**, sealed vial.

several metal triflates were evaluated as Lewis acid catalysts and enol ether **4a** was used in large excess, *i.e.* as the cosolvent (entries 1–4). 10 mol% of $Sc(OTf)_3$ and $Yb(OTf)_3$ cleanly promoted the reaction at 100 °C in toluene, however the conversion of enone **3a** ranged between 60–72% after 20 h reaction time. Conversely, AgOTf and $Cu(OTf)_2$ mostly led to decomposition of the starting material at 100 °C but also at lower temperatures.

Compared to $Yb(OTf)_3$, $Yb(fod)_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium)[10] showed a similar conversion but a slightly superior yield (entry 5), to generate the pyrano[3,2-*b*]indole product **5aa** in 58%. A subsequent reduction of the molar excess of enol ether **4a** as well as the reaction temperature both led to improved conversion and yield (entries 6–10). Using 15 mol% of $Yb(fod)_3$ together with 10 equiv. of **4a**, at 50 °C in a sealed vial for 20 h, finally gave product **5aa** with 70% isolated yield (entry 10). Under these conditions, cycloadduct **5aa** formed highly selectively as the *endo*-diastereomer with C2,C3a-*cis*-configuration[11] (dr = 97 : 3 by ^{1}H NMR analysis, numbering for 2-ethoxy-2,3,3a,4,5,6-hexahydro-7*H*-1-oxa-7a-azacyclohepta[*jk*]fluoren-7-one).
Further reduction of the temperature or catalyst loading was not beneficial, and no reaction was observed in the absence of the Lewis acid catalyst (entries 11–13).

Utilising the optimised protocol, a number of oxa [4 + 2] cycloadducts were synthesised with good to excellent yields (Fig. 1). The reactions between enone **3a** and alkylated vinyl ethers **4a–d** delivered products **5ab–5ad** in 70–89% yield, and compound **5aa** could additionally be prepared on a 1 mmol scale in 79% yield. Further, enones **3b–h** with varied aromatic substituents were employed to give, in combination with ethyl vinyl ether (**4a**), cycloadducts **5ba–5ha** in 63–92% yield (dr between 95 : 5 and 97 : 3 in all cases).

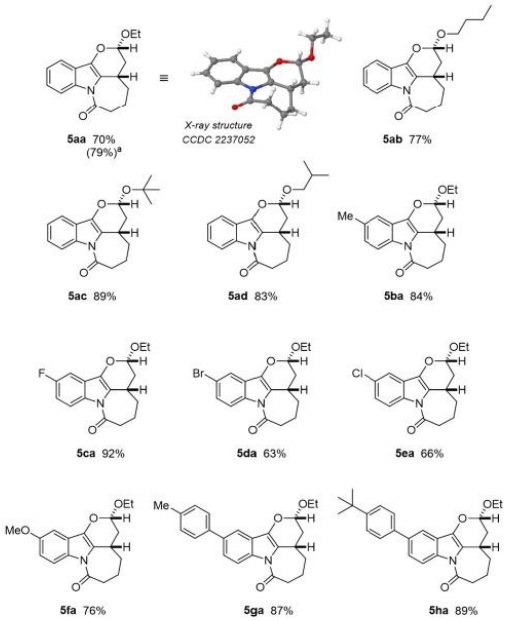
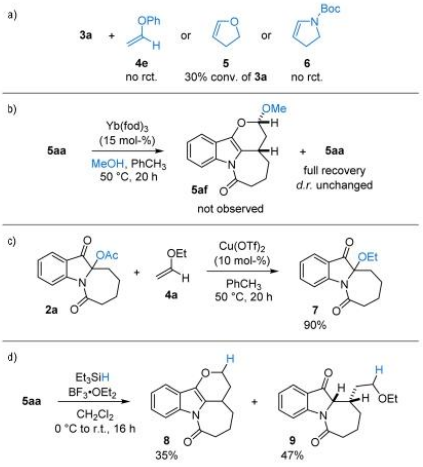


Fig. 1 Scope of reaction products. Reaction conditions: 0.10 mmol of enone **3**, 1.00 mmol of enol ether **4**, 15 mol% $Yb(fod)_3$, $PhCH_3$, sealed vial, 50 °C, 20 h. [a] Yield of reaction on 1.00 mmol scale.

An overview of additional experiments and mechanistic observations is given in Scheme 3. While alkyl enol ethers readily participated in the Lewis acid-catalysed cycloaddition with enones **3**, no conversion was observed in the attempted reactions of enone **3a** with phenyl vinyl ether (**4e**) and *N*-Boc-



Scheme 3 Additional experiments.

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2,3-dihydro-1*H*-pyrrol (**6**). In case of 2,3-dihydrofuran (**5**), some 30% conversion of enone **3a** was observed, however, the expected cycloadduct formed in less than 15% yield along with unidentified side products (Scheme 3a). Secondly, when cycloadduct **5aa** was reacted under the typical conditions in the presence of an excess of methanol, no transacetalisation to methoxy-substituted compound **5af** could be observed, and also no epimerisation occurred at the anomeric C2-carbon of **5aa**, proving that the C2,C3a-*cis*-configuration of **5aa** arised from an *endo*-selective [4 + 2] cycloaddition (Scheme 3b). As $Cu(OTf)_2$ was found to be too reactive as the catalyst in the cycloaddition between enone **3a** and enol ether **4a**, we also attempted to use it together with precursor acetate **2a** and ethyl vinyl ether (**4a**), speculating that enone **3a** would be generated *in situ* under these conditions. Interestingly, the C10a ethoxy-substituted compound **7** was obtained in this case, as the sole product and in 90% yield (Scheme 3d). Finally, the reductive cleavage of the acetal function of pyranoside **5aa** was investigated. Upon treatment of compound **5aa** with $BF_3{\cdot}OEt_2$ and Et_3SiH at 0 °C, the reduced dihydropyran derivative **8** formed in 35% yield, accompanied by 47% of the ring-opened perhydroazepino[1,2-*a*]indole dione **9** as a single diastereomer.

Conclusions

The dihydroazepino[1,2-*a*]indole diones **3**, accessible from cyclohepta[*b*]indoles **1** by photooxygenation and dehydration, readily undergo highly *endo*-selective Lewis acid-catalysed oxa Diels–Alder reactions with enol ethers **4**. The resulting [4 + 2] cycloadducts are azepane-fused pyrano[3,2-*b*]indoles **5**, and our future interest is to explore further the synthetic potential and applications of this new polycyclic indole scaffold.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support of this research by the University of Rostock is gratefully acknowledged.

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11 The X-ray single crystal structure data related to compound **5aa**, CCDC 2237052,† can be obtained from the Cambridge Structural Database, https://www.ccdc.cam.ac.uk.

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Phosphine-Catalyzed Crossed Rauhut–Currier-Type Coupling and [3 + 2]-Cycloaddition of 2-Alkylidene-3-oxindoles with Alkenes and Allenes to Access β,γ-Unsaturated Enones and Polycyclic Oxindoles

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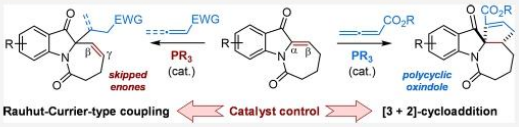
ABSTRACT: Dihydroazepino[1,2-*a*]indole diones are tricyclic *N*-acyl-2-alkylidene-3-oxindole enones that readily engage in tertiary phosphine-catalyzed intermolecular coupling reactions with acceptor-substituted alkenes. In these reactions, the tricyclic α-substituted enones undergo an α-alkylation with concomitant formation of a quaternary stereocenter, as well as the installation of a new double bond within the seven-membered azepane ring. The organocatalytic reaction constitutes a special case of the crossed intermolecular Rauhut–Currier reaction as the presence of the α-substituent in the enones prohibits the formation of an α,β-unsaturated product, but instead, skipped β,γ-unsaturated enones are obtained. With allene carboxylates as alternative coupling partners, the crossed Rauhut–Currier-type reaction competes with a regioselective allene to enone [3 + 2]-cycloaddition, and the product selectivity can be controlled by the choice of the phosphine organocatalyst.



INTRODUCTION

The Rauhut–Currier reaction, which can be regarded as the vinylogous version of the well-known Morita–Baylis–Hillman reaction, is a coupling between two Michael acceptors leading to α-alkylated α,β-unsaturated carbonyl compounds as the products.[1] The reaction is readily initiated by *N*-heterocyclic bases and tertiary phosphines as the catalysts, and its intramolecular version has been well-developed, also in asymmetric variants, utilizing chiral amine and phosphine organocatalysts.[2] While the intermolecular Rauhut–Currier reaction is similarly straightforward for homodimerization reactions of a single acceptor-substituted alkene, the intermolecular crossed Rauhut–Currier coupling of two different alkenes is much more challenging because the role selectivity of the alkene partners is often difficult to control (Scheme 1a).

In general terms, the conventional Rauhut–Currier reaction requires that at least one of the two participating Michael systems carries a hydrogen atom as the substituent on the α-(sp^2)-carbon of the double bond neighboring the acceptor group. According to the commonly accepted mechanism, this hydrogen is shifted during the reaction to the α-position of the electron-withdrawing group of the second coupling partner in a proton transfer. As a consequence, the reaction as such cannot proceed if both Michael acceptors possess an α-substituent other than hydrogen.

Intermolecular crossed Rauhut–Currier reactions where only one of the two components carries an α-substituent other than hydrogen are principally possible, but the α-substituted alkene would need to be the less reactive component in the initial conjugate addition with the nucleophilic catalyst compared to the α-unsubstituted coupling partner for the reaction to proceed. Hence, Rauhut–Currier cross couplings of this type are rare and largely underdeveloped. If, on the other hand, the α-substituted Michael acceptor would react faster with the nucleophilic catalyst than the α-unsubstituted alkene, the overall reaction could not lead to an α,β-unsaturated product ultimately.

In 1986, Cragoe and co-workers reported in one example a deconjugative α-alkylation of a 2-alkylidene-1-indanone with methyl vinyl ketone catalyzed by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[3] and later, other scientists at Merck & Co. repeated this reaction for a closely related indanone substrate[4] (Scheme 1b). The reaction would not only install a new 3-oxobutyl substituent in the α-position of the benzylic ketone, but, at the same time, a new *trans*-configured double bond was placed in the β,γ-position. Therefore, it can be regarded as a special case of the intermolecular crossed Rauhut–Currier reaction to deliver a skipped Michael system as the substructure in the product. Another method allowing to access an α-substituted skipped enone from an α,β-unsaturated carbonyl system was reported by Christoffers who reacted 1-

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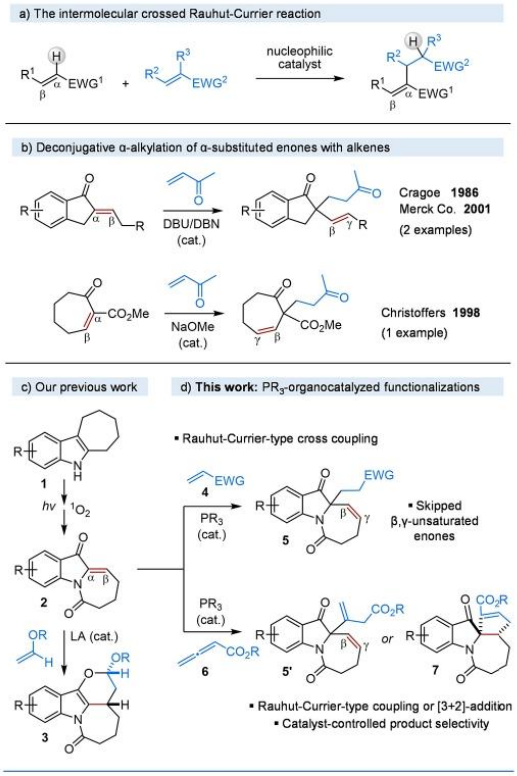
Scheme 1. (a) Intermolecular Crossed Rauhut−Currier Reaction, (b) Deconjugative α-Alkylation of α-Substituted Enones with Alkenes Leading to Skipped β,γ-Unsaturated Enones, and (c) Preparation of Tricyclic Enones 2 and Their Phosphine-Catalyzed Reactions with Alkenes and Allenes



carboxymethylcycloheptenone with methyl vinyl ketone in the presence of NaOMe as a strongly basic catalyst.[5]

Prior to this study, we reported the synthesis of the tricyclic 2-alkylidene-3-oxindole-type enones **2**, which possess a dihydroazepino[1,2-*a*]indole dione structure. Enones **2** can be prepared by the photooxygenation of cyclohepta[*b*]indoles **1**[6] followed by a two-step dehydration, and they were previously engaged in Oxa-Diels−Alder reactions leading to tetracyclic pyrano[3,2-*b*]indole derivatives **3** (Scheme 1c).[7] In recognition of their utility for the synthesis of more complex polycyclic *N*-heterocyclic molecular scaffolds, we subsequently continued to study the reactivity of the enones **2** under a broader range of reaction conditions. As we reacted enones **2** with acceptor-substituted alkenes **4** in the presence of phosphines as nucleophilic organocatalysts, we discovered a selective intermolecular Rauhut−Currier-type cross-coupling reaction to give the α-alkylated ketones **5**, which feature a synthetically highly valuable β,γ-*cis*-unsaturation within the seven-membered ring of the tricyclic oxindole scaffold. In contrast, when reacting enones **2** with allene carboxylates **6**, the Rauhut−Currier product **5′** is obtained along with tetracycle **7**, which arises from a phosphine-catalyzed allene to enone [3 + 2]-cycloaddition first reported by Lu et al.[8]

Pleasingly, we established during this study that the product selectivity of the reaction can be controlled by the choice of the phosphine catalyst.

RESULTS AND DISCUSSION

Following our initial observation that the α,β-unsaturated dihydroazepino[1,2-*a*]indole diones **2** can be coupled with alkenes **4** in the presence of nucleophilic organocatalysts, we began a systematic study of the reaction. As shown in Table 1

Table 1. Summary of Reaction Development



#	catalyst	mol %	*t* (h)	conv. of **2a**[a]	yield of **5a** (%)[a,b]	yield of **8a** (%)[a,c]
1	NEt_3	20	16	0	0	0
2	DABCO	20	16	48	11	0
3	DBU	20	16	100	86	54
4	PPh_3	20	16	100	54	quant.
5	$P(4\text{-}MePh)_3$	20	16	62	17	trace
6	$P(4\text{-}MeOPh)_3$	20	16	84	33	trace
7	DPPF	20	16	71	19	trace
8	PCy_3	20	16	40	18	trace
9	PBu_3	20	16	92	80	16
10	$PMePh_2$	20	16	100	76	5
11	PMe_2Ph	20	16	100	87	60
12	PMe_2Ph	10	16	92	69	7
13	**PMe_2Ph**	**10**	**20**	**100**	**87 (85)**[d]	**20**
14	PMe_2Ph	5	20	38	13	0

[a]Determined by ^1H NMR against CH_2Br_2 standard. [b]Yield with respect to the quantity of **2a** used. [c]Yield with respect to excessive **4a** used (1.00 mmol). [d]Yield after chromatographic isolation.

for the parent tricyclic enone **2a** and methyl acrylate (**4a**), a number of different organocatalysts, especially tertiary phosphines, readily promote the transformation, leading to the C10a-alkylated β,γ-unsaturated ketone **5a**. Depending on the catalyst structure, the catalyst loading, and reaction duration, varied quantities of the homocoupling product of methyl acrylate, the Rauhut−Currier product **8a**, are generated concurrently.

A catalyst screening (with 20 mol % catalyst loading and 16 h reaction time at r.t. in CH_2Cl_2 under an argon atmosphere) showed that while NEt_3 gave no product, the *N*-heterocyclic bases DABCO and especially DBU promote the reaction between enone **2a** and methyl acrylate (**4a**) to deliver ketone **5a** (Table 1, entries 1−3). Diverse phosphines could as well be employed with success, with PPh_3 offering complete conversion of enone **2a** after 16 h and the formation of product **5a** in 54% yield (entry 4). Use of the comparatively more electron-rich triarylphosphines $P(4\text{-}MePh)_3$, $P(4\text{-}MeOPh)_3$, and DPPF led to noticeably poorer conversions of enone **2a** within the same reaction time (entries 5−7). Among trialkylphosphines, PCy_3 showed only 40% conversion, probably owing to its large cone angle, while PBu_3 gave 92% conversion of enone **2a** and generated compound **5a** in 80% yield (entries 8−9). The mixed alkylarylphosphines $PMePh_2$ and PMe_2Ph gave the best results (entries 10 and 11), and ultimately, using 10 mol % of PMe_2Ph along with a slightly extended reaction duration of 20 h at r.t. in CH_2Cl_2, complete

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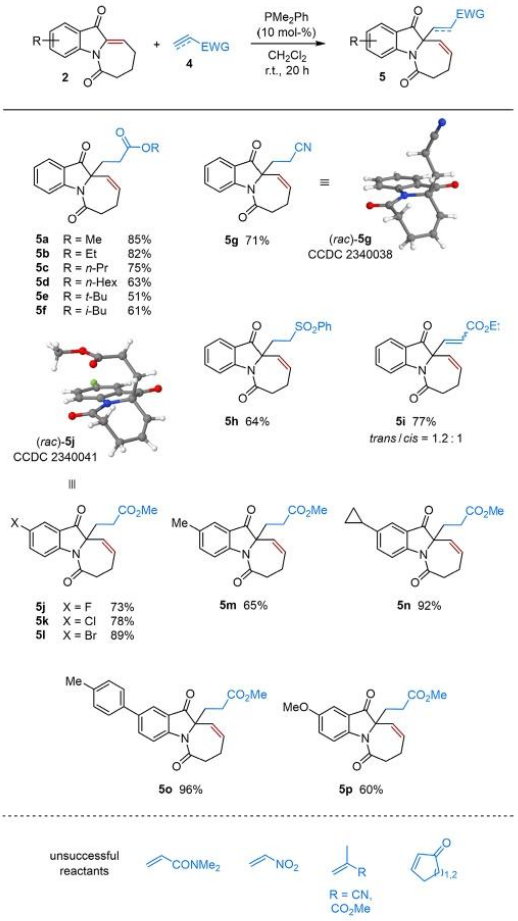
conversion of enone **2a** and an isolated yield of ketone **5a** of 85% could be achieved (entry 13). Reducing the amount of catalyst to 5 mol % led to a significant decrease in productivity (entry 14). The reaction with 10 mol % of PMe_2Ph as the catalyst could as well be performed using EtOAc or acetone as the solvent to give 72% and 68% yields of product **5a**, while use of MeOH led to a halving of the yield (for further details, see Table S1, Supporting Information file).

Utilizing the optimized cross-coupling protocol, a number of tricyclic C10a-functionalized β,γ-unsaturated ketones **5** could be prepared. As shown in Scheme 2, coupling of enone **2a** with diverse acrylates (**4a**–**4f**) led to the derivatives **5a**–**5f** in 85–51% yield. Acrylonitrile (**4g**) and phenyl vinyl sulfone (**4h**) could as well be employed as the alkene partners to give products **5g** and **5h** in 71% and 64% yields. In addition, use of ethyl propiolate (**4i**) allowed for the preparation of the α,β-unsaturated ester **5i** in 77% yield (*trans*/*cis* = 1.2:1).

Scheme 2. Reaction Scope[a]

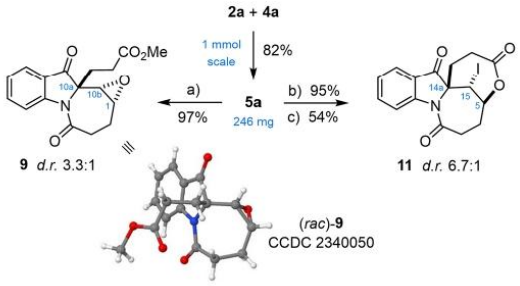


[a]Conditions: enone **2** (0.10 mmol), alkene or alkyne **4** (1.00 mmol, 10 equiv), PMe_2Ph (10 mol-%), CH_2Cl_2 (0.10 M in **2**), r.t., 20 h. Reported yields after chromatography.

Further, the enones **2b**–**2d** with fluorine, chlorine, and bromine substitution on the aromatic ring readily engaged in couplings with methyl acrylate (**4a**) to give products **5j**–**5l** in yields of 89–73%. Likewise, the methyl- and cyclopropyl-substituted derivatives **5m** and **5n** could be made from the corresponding enones **2e** and **2f** in 65% and 92% yields, as well as the 4-tolyl-substituted product **5o** and the methoxy derivative **5p**, which were accessible from the parent enones **2g** and **2h** and methyl acrylate (**4a**) in 96% and 60% yields. The present iteration of the protocol allows for the high-yielding coupling of enones **2** with various mono acceptor-substituted alkenes; however, *N*,*N*-dimethylacrylamide was unreactive under the typical conditions, while nitroethylene underwent polymerization. 1,1- or 1,2-Disubstituted alkenes such as methyl methacrylate, methacrylonitrile, or cyclo-alkenones were further unsuitable reactants.

The β,γ-unsaturated tricyclic ketones **5** are useful intermediate products for further functionalizations. As shown in Scheme 3, the cross coupling of enone **2a** with

Scheme 3. Scaled Synthesis and Subsequent Transformations of Compound 5a[a]



[a](a) *m*CPBA (2.0 equiv), CH_2Cl_2, r.t., 16 h. (b) LiOH (2.0 equiv), $MeOH/H_2O$, r.t., 16 h. (c) I_2 (1.0 equiv), 2,4,6-collidine (4.0 equiv), MeCN, 50 °C, 24 h.

methyl acrylate (**4a**) could well be performed on a 1 mmol scale to give ketone **5a** in 82% yield. The epoxidation of the endocyclic double bond of compound **5a** with *m*CPBA proceeded cleanly, to give epoxide **9** in 97% yield, and with a useful diastereoselectivity in preference of the C10a,C10b-*trans*-configured product (*d.r.* 3.3:1). In addition, the methyl ester function of compound **5a** could be saponified to give the corresponding intermediate acid **10** in 95% yield, and a subsequent I_2-mediated iodolactonization reaction at 50 °C generated the tetracyclic oxindole **11**, via an unexpected 7-*endo* cyclization,[9] in 54% yield (*d.r.* 6.7:1).

The proposed reaction mechanism of the phosphine-catalyzed coupling of enones **2** with acceptor-substituted alkenes **4** is shown in Scheme 4a. Initially, conjugate addition of the nucleophilic phosphine organocatalyst with enone **2** gives a β-phosphonium enolate **12**. While the formation of intermediate **12** is accompanied by the release of some minor strain energy inherent to the cycloheptene portion of enone **2**,[10] the failure of 1-acetylcyclohexene (**14**) to participate in the reaction as an alternative enone (Scheme 4b) indicates that the gain of aromatic stabilization energy in phosphonium enolate **12** is the major contributor shifting the equilibrium toward **12**. In contrast, the competing 1,4-addition between R_3P and alkene **4** appears more easily reversible, and monitoring of the

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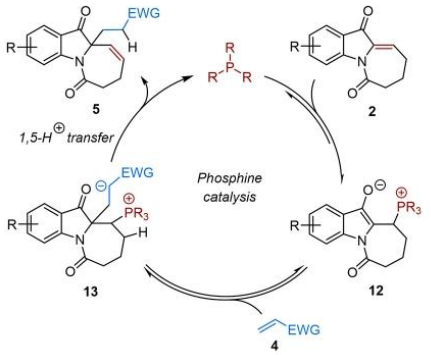
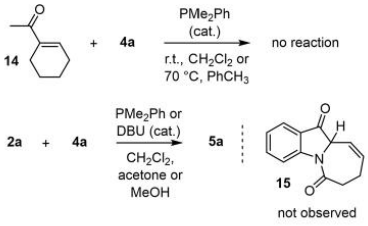
Scheme 4. (a) Proposed Reaction Mechanism, (b) Additional Observations, and (c) Effect of Additives on the Reference Reaction 2a + 4a → 5a

a) Proposed mechanism



b) Further observations



c) Effect of additives

2a + 4a → 5a, PMe_2Ph cat. (10 mol-%)

additive (1 eq.)	none	NEt_3	*p*-cresol	HOAc	H_2O	air (1 atm)
yield	87%	93%	73%	2%	51%	0%

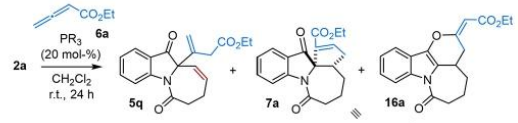
reaction progress of the reference reaction **2a** + **4a** → **5a** by ^{1}H NMR spectroscopy showed that the homodimerization product of methyl acrylate, the diester **8a**, only formed gradually after the consumption of enone **2a**. Subsequent to the formation of the phosphonium enolate **12**, its 1,4-addition with alkene **4** generates a secondary zwitterionic phosphonium intermediate **13**, which is converted into product **5** after a 1,5-proton transfer and the elimination of R_3P to regenerate the catalyst. As shown in Scheme 4b, the reaction **2a** + **4a** → **5a**, in aprotic or protic solvent, and catalyzed by PMe_2Ph or the significantly more basic DBU, generates none of the *β*,*γ*-unsaturated enone **15**, which rules out a base-catalyzed deconjugation via a dienolate intermediate derived from enone **2a**.

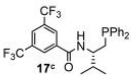
The reaction **2a** + **4a** → **5a** was additionally studied by ^{31}P NMR spectroscopy (see Supporting Information file), and when enone **2a** was mixed with PMe_2Ph in CD_2Cl_2 solution and in the molar ratio of 10:1, a new singlet at +35.4 ppm occurred which we assign to the 1,4-adduct **12a**. In turn, when methyl acrylate (**4a**) and PMe_2Ph were mixed in CD_2Cl_2 in the same ratio, the ^{31}P NMR spectrum after equilibration showed that besides the catalyst signal at −45.5 ppm, any additional species could only be detected in trace amounts. Conversely, the reaction mixture containing catalytic PMe_2Ph with both reactants **2a** and **4a** in the typical concentrations showed a dominant new singlet at +25.7 ppm which we tentatively attribute to the secondary phosphonium species **13a** and which suggests that the 1,5-proton transfer/elimination converting **13** into **5** is the rate-determining step of the catalytic cycle.[11]

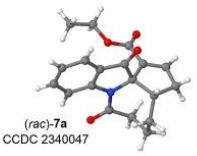
As shown in Scheme 4c, the reference reaction catalyzed by PMe_2Ph is hardly affected by the addition of NEt_3 as a (catalytically inactive) base. Conversely, *p*-cresol and particularly HOAc as acidic additives impede the reaction, more strongly with increasing acid strength. Further, while the presence of H_2O nearly leads to a halving of the yield, an atmosphere of air instead of argon inhibits the reaction entirely due to relatively rapid oxidation of the phosphine catalyst, as evident by ^{1}H NMR analysis.

Finally, we turned our attention to reactions of enones **2** with an allene carboxylate as the second reactant. The phosphine-catalyzed reaction between **2a** and ethyl 2,3-butadienoate (**6a**) was studied using a larger set of phosphine catalysts (20 mol % catalyst loading, see Table S2, Supporting Information file, for full details), and generally, it gives the expected Rauhut−Currier-type cross-coupling product **5q** with most of the catalysts that were employed. However, the [3 + 2]-cycloadduct **7a** is generated concurrently, as well as the [4 + 2]-cycloadduct **16a**, in small amounts (Scheme 5).

Scheme 5. Catalyst-Dependent Product Selectivity of the Reaction between Enone 2a and Ethyl 2,3-Butadienoate (6a) and Chiral Phosphine-Catalyzed Asymmetric [3 + 2]-Cycloaddition Leading to Compound (−)-7a[a]



	ratio[a] **5q** : **7a** : **16a**	yield[b]
$P(t\text{-Bu})_3$	100 : 0 : 0	61% **5q**
$P(4\text{-MeOPh})_3$	64 : 18 : 18	48% **5q**
PPh_3	0 : 79 : 21	66%[c] **7a**
$PMePh_2$	11 : 66 : 23	46% **7a**
PMe_2Ph	16 : 54 : 30	53% **7a**
	0 : 100 : 0	47% (−)-**7a** *e.r.* 82:18



[a](a) Determined by ^{1}H NMR analysis. (b) Isolated yield. (c) 30 mol-% used, 48 h reaction time.

Gratifyingly, we found that the product selectivity of the reaction can be controlled by the choice of the phosphine catalyst. More electron-rich phosphines such as $P(4\text{-MeOPh})_3$ and $P(t\text{-Bu})_3$ preferentially lead to product **5q**, the latter catalyst with complete product selectivity and with 61% isolated yield. On the other hand, PPh_3 and the mixed alkylaryl phosphines $PMePh_2$ or PMe_2Ph offer a good selectivity in favor of the [3 + 2]-adduct **7a**, which was isolated in yields between 46% and 53% and as a single regioisomer. In contrast to the Rauhut−Currier-type reaction leading to **5q**, where the phosphine interacts first with enone **2a**, the [3 + 2]-cycloaddition leading to tetracycle **7a** is initiated by the conjugate addition of R_3P to the allene carboxylate **6a** to give a phosphonium-substituted allylic carbanion as a reactive three-carbon nucleophile.[8] Compared to this mode of [3 + 2]-

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cyclization, the possible alternative [4 + 2]-annulation[12] leading to pyranoindole derivative **16a** is generally of much less significance for all of the catalysts studied.

The reactions between enone **2a** and allene carboxylate **6a** were further examined using a set of chiral amine and phosphine catalysts (see Table S3, Supporting Information file, for full details). While the Rauhut−Currier cross-coupling product **5q** could not be obtained in an enantioenriched form with neither catalyst, the [3 + 2]-cycloadduct (−)-**7a** could be accessed with high product selectivity, in 47% yield and with an enantiomeric ratio of 82:18 by using the L-valine-derived tertiary phosphine **17**.[13,8d,14]

■ CONCLUSIONS

In conclusion, tertiary phosphine-organocatalyzed intermolecular deconjugative alkylations of enones with acceptor-substituted alkenes were developed, which allow for the synthesis of highly functionalized polycyclic 3-oxindole scaffolds. The organocatalytic reaction can be classified as a special variant of the intermolecular crossed Rauhut−Currier reaction that couples α-substituted enones with alkenes to selectively deliver α-alkylated β,γ-unsaturated enone products. Replacing the monosubstituted alkenes by allene carboxylates as the reactants for the tricyclic enones, the Rauhut−Currier-type products are accompanied by [3 + 2]- and [4 + 2]-cycloadducts, and the product selectivity can be steered by choosing the appropriate tertiary phosphine catalyst.

■ EXPERIMENTAL SECTION

General Experimental Methods. Commercially available chemicals were used as received from suppliers unless otherwise noted. Dry solvents used were obtained from suppliers in serum-cap quality. Solvents for chromatographic separation were distilled twice prior to use. Thin-layer chromatography was carried out using silica-coated aluminum plates, silica 60 F254, *Merck*. Column chromatography was performed with silica 60 (230−400 mesh, *Macherey-Nagel*). NMR spectra were recorded on Bruker AVANCE 500 NEO, JEOL JNM-ECZ400, and Bruker AVANCE 300 III instruments, and spectra were calibrated against the solvent resonances of $CHCl_3$ (δ^H = 7.26 ppm) and $CDCl_3$ (δ^C = 77.0 ppm). ESI-TOF HRMS spectrometry was performed using an *Agilent* 1200/6210 Time-of-Flight LC-MS instrument. X-ray crystallographic analyses were performed on an Apex Kappa-II instrument by *Bruker-AXS*.

General Procedure for the Synthesis of β,γ-Unsaturated Ketones 5. Enone **2** was dissolved in CH_2Cl_2 in a 10 mL crimp cap vial. Alkene **4** (10 equiv) was added to solution, followed by dimethylphenylphosphine (10 mol %) via a micropipette. The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 20 h and then concentrated to dryness. Column chromatography over silica gel afforded the pure product **5**.

*Methyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)propanoate (**5a**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5a** (R_f = 0.26, colorless solid, 25.5 mg, 85%). mp: 113−114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.6, 1.5, 0.8 Hz, 1H), 7.70 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m, 1H), 5.92−5.87 (m, 1H), 5.82 (ddd, J = 11.7, 2.5, 1.5 Hz, 1H), 3.58 (s, 3H), 3.27 (td, J = 13.3, 4.7 Hz, 1H), 2.74−2.68 (m, 1H), 2.62 (ddd, J = 15.7, 8.7, 7.3 Hz, 1H), 2.57−2.42 (m, 3H), 2.15−2.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.9, 172.4, 172.2, 153.2, 137.9, 131.1, 127.5, 124.5, 123.9, 122.5, 118.8, 71.4, 51.9, 36.4, 35.3, 28.1, 25.5. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_4^+$, 322.1049; found, 322.1046.

*Ethyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)propanoate (**5b**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), ethyl acrylate (**4b**, 106.0 μL, 1.00 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5b** (R_f = 0.23, colorless solid, 25.6 mg, 82%). mp: 127−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m, 1H), 5.92−5.87 (m, 1H), 5.82 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 4.03 (qd, 7.2, 1.2 Hz, 2H), 3.28 (td, J = 13.1, 4.7 Hz, 1H), 2.74−2.68 (m, 1H), 2.63 (ddd, J = 15.8, 8.8, 7.3 Hz, 1H), 2.55−2.45 (m, 3H), 2.13−2.00 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.9, 172.3, 172.0, 153.2, 137.8, 131.0, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 60.9, 36.4, 35.2, 28.3, 25.5, 14.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{18}H_{19}NNaO_4^+$, 336.1206; found, 336.1210.

*Propyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)propanoate (**5c**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), propyl acrylate (**4c**, 123.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5c** (R_f = 0.37, colorless solid, 24.7 mg, 75%). mp: 157−158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (dt, J = 8.5, 0.7 Hz, 1H), 7.77 (ddd, J = 7.7, 1.5, 0.7 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m, 1H), 5.92−5.87 (m, 1H), 5.82 (ddd, J = 11.8, 2.5, 1.5 Hz, 1H), 3.93 (t, J = 6.8 Hz, 2H), 3.28 (td, J = 13.7, 4.7 Hz, 1H), 2.73−2.68 (m, 1H), 2.62 (ddd, J = 14.7, 8.8, 7.2 Hz, 1H), 2.54−2.44 (m, 3H), 2.14−2.01 (m, 2H), 1.54 (sext., J = 7.4 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.9, 172.3, 172.1, 153.1, 137.8, 131.1, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 66.5, 36.4, 35.2, 28.3, 25.5, 21.8, 10.3. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_4^+$, 350.1363; found, 350.1373.

*Hexyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)propanoate (**5d**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), *n*-hexyl acrylate (**4d**, 175.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5d** (R_f = 0.38, colorless solid, 23.3 mg, 63%). mp: 136−138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.7, 1.5, 0.6 Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m, 1H), 5.92−5.86 (m, 1H), 5.82 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 3.96 (t, J = 7.0 Hz, 2H), 3.28 (td, J = 13.4, 4.6 Hz, 1H), 2.73−2.68 (m, 1H), 2.62 (ddd, J = 14.7, 8.8, 7.2 Hz, 1H), 2.54−2.43 (m, 3H), 2.13−2.00 (m, 2H), 1.55−1.47 (m, 2H), 1.29−1.21 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 198.9, 172.2, 172.1, 153.2, 137.8, 131.0, 127.6, 124.5, 123.9, 122.6, 118.8, 71.4, 65.1, 36.4, 35.2, 31.4, 28.4, 28.3, 25.52, 25.49, 22.5, 14.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{22}H_{27}NNaO_4^+$, 392.1832; found, 392.1833.

*tert-Butyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a(11H)-yl)propanoate (**5e**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), *tert*-butyl acrylate (**4e**, 144.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5e** (R_f = 0.45, colorless solid, 17.4 mg, 51%). mp: 123−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.70 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.26−7.22 (m, 1H), 5.91−5.86 (m, 1H), 5.82 (ddd, J = 11.7, 2.1, 1.1 Hz, 1H), 3.29 (td, J = 13.3, 4.5 Hz, 1H), 2.74−2.68 (m, 1H), 2.58−2.42 (m, 4H), 1.99 (t, J = 7.8 Hz, 2H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 199.0, 172.2, 171.2, 153.1, 137.7, 130.9, 127.7, 124.5, 123.9, 122.6, 118.9, 81.0, 71.4, 36.4, 35.3, 29.3, 28.0, 25.6. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{20}H_{23}NNaO_4^+$, 364.1525; found, 364.1525.

*Isobutyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)propanoate (**5f**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), isobutyl acrylate (**4f**, 142.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5f** (R_f = 0.41, colorless solid, 20.8 mg, 61%). mp: 112−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.7, 1.4, 0.6

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Hz, 1H), 7.69 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.26−7.22 (m, 1H), 5.92−5.86 (m, 1H), 5.82 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 3.80−3.73 (m, 2H), 3.28 (td, J = 13.2, 4.7 Hz, 1H), 2.73−2.68 (m, 1H), 2.61 (ddd, J = 14.6, 8.6, 7.2 Hz, 1H), 2.54−2.42 (m, 3H), 2.11−2.06 (m, 1H), 1.81 (hept., J = 6.7 Hz, 1H), 0.842 (d, J = 6.7 Hz, 3H), 0.838 (d, J = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.9, 172.2, 172.1, 153.1, 137.8, 131.1, 127.6, 124.5, 123.9, 122.5, 118.8, 71.4, 71.0, 36.4, 35.2, 28.2, 27.5, 25.5, 19.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_4^+$, 364.1519; found, 364.1525.

*3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a(11H)-yl)-propanenitrile (**5g**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), acrylonitrile (**4g**, 65.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5g** (R_f = 0.26, colorless solid, 18.8 mg, 71%). mp: 128−132 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, J = 8.4 Hz, 1H), 7.79 (ddd, J = 7.7, 1.4, 0.6 Hz, 1H), 7.74 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 7.29−7.25 (m, 1H), 6.01−5.96 (m, 1H), 5.81 (ddd, J = 11.7, 2.5, 1.8 Hz, 1H), 3.12 (ddd, J = 12.4, 5.1, 1.5 Hz, 1H), 2.82−2.77 (m, 1H), 2.64−2.52 (m, 3H), 2.48 (ddd, J = 14.5, 9.4, 6.3 Hz, 1H), 2.27−2.14 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.8, 171.5, 153.0, 138.4, 132.5, 126.3, 125.0, 124.2, 122.0, 119.0, 118.0, 70.2, 36.5, 35.7, 25.5, 11.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{14}N_2NaO_2^+$, 289.0947; found, 289.0954.

*10a-(2-(Phenylsulfonyl)ethyl)-8,10a-dihydro-6H-azepino[1,2-a]-indole-6,11(7H)-dione (**5h**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), phenyl vinyl sulfone (**4h**, 168.0 mg, 1.00 mmol), and PMe_2Ph (14.2 μL, 0.10 mmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5h** (R_f = 0.25, colorless solid, 24.6 mg, 64%). mp: 135−137 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (dt, J = 8.4, 0.7 Hz, 1H), 7.84−7.81 (m, 2H), 7.74−7.70 (m, 2H), 7.69−7.64 (m, 1H), 7.59−7.54 (m, 2H), 7.26−7.22 (m, 1H), 5.96−5.89 (m, 1H), 5.73 (ddd, J = 11.6, 2.6, 1.7 Hz, 1H), 3.03−2.92 (m, 2H), 2.81 (ddd, J = 13.7, 12.3, 5.3 Hz, 1H), 2.71−2.63 (m, 1H), 2.62−2.45 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.7, 171.6, 152.8, 138.32, 138.28, 134.1, 132.3, 129.5, 128.0, 126.4, 124.9, 124.2, 121.8, 118.9, 69.8, 50.1, 36.3, 33.0, 25.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO_4S^+$, 404.0927; found, 404.0933.

*Ethyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a-(11H)-yl)acrylate (**5i**).* According to the general procedure, enone **2a** (21.3 mg, 0.10 mmol), ethyl propiolate (**4i**, 101.2 μL, 1.00 mmol), and PMe_2Ph (14.2 μL, 0.10 mmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound *cis*-**5i** (R_f = 0.47, colorless solid, 10.9 mg, 35%) and compound *trans*-**5i** (R_f = 0.39, colorless solid, 13.3 mg, 42%). *cis*-**5i**: mp: 160−161 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 8.5 Hz, 1H), 7.80−7.76 (m, 1H), 7.70 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.27−7.23 (m, 1H), 6.06−6.01 (m, 1H), 5.98−5.94 (m, 2H), 5.92 (d, J = 12.6 Hz, 1H), 4.05 (dq, J = 10.9, 7.2 Hz, 1H), 3.87 (dq, J = 10.9, 7.2 Hz, 1H), 3.26 (td, J = 13.4, 4.8 Hz, 1H), 2.63−2.56 (m, 1H), 2.56−2.44 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 195.3, 172.0, 165.5, 152.8, 137.7, 134.9, 132.5, 127.1, 124.7, 124.6, 121.8, 121.5, 118.4, 71.8, 61.4, 35.5, 25.8, 13.7. *trans*-**5i**: mp: 153−154 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (dt, J = 8.5, 0.7 Hz, 1H), 7.78 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.74 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.29−7.24 (m, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.09−6.02 (m, 3H), 4.18 (q, J = 7.1 Hz, 2H), 3.05 (td, J = 13.3, 3.6 Hz, 1H), 2.62−2.52 (m, 2H), 2.52−2.44 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 194.2, 171.8, 165.2, 152.3, 144.7, 138.2, 133.3, 125.1, 125.0, 124.9, 123.8, 121.4, 118.7, 72.4, 61.0, 35.5, 25.8, 14.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}NO_4^+$, 312.1236; found, 312.1239.

*Methyl 3-(2-Fluoro-6,11-dioxo-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5j**).* According to the general procedure, enone **2b** (23.1 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:9), compound **5j** (R_f = 0.24, colorless solid, 23.3 mg, 73%). mp: 95−97 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (ddd, J = 8.7, 1.0 Hz, $J_{F,H}$ = 4.3 Hz, 1H), 7.43−7.38 (m, 2H), 5.93−5.88 (m, 1H), 5.79 (ddd, J = 11.7, 2.5, 1.6 Hz, 1H), 3.58 (s, 3H), 3.28−3.20 (m, 1H), 2.73−2.67 (m, 1H), 2.62 (ddd, J = 15.7, 8.6, 7.3 Hz, 1H), 2.54−2.45 (m, 3H), 2.16−2.00 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.2 (d, $J_{C,F}$ = 3.0 Hz), 172.3, 171.9, 159.2 (d, $J_{C,F}$ = 247.3 Hz), 149.2 (d, $J_{C,F}$ = 1.3 Hz), 131.4, 127.2, 125.2 (d, $J_{C,F}$ = 23.8 Hz), 123.8 (d, $J_{C,F}$ = 7.6 Hz), 120.4 (d, $J_{C,F}$ = 7.6 Hz), 109.1 (d, $J_{C,F}$ = 23.0 Hz), 72.0, 51.9, 36.2, 35.3, 28.1, 25.5. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$): δ − 116.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}FNNaO_4^+$, 340.0955; found, 340.0961.

*Methyl 3-(2-Chloro-6,11-dioxo-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5k**).* According to the general procedure, enone **2c** (25.3 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5k** (R_f = 0.27, colorless solid, 26.7 mg, 78%). mp: 119−121 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 8.9 Hz, 1H), 7.72 (br s, 1H), 7.63 (dt, J = 8.8, 1.6 Hz, 1H), 5.94−5.88 (m, 1H), 5.81−5.75 (m, 1H), 3.58 (s, 3H), 3.25 (td, J = 13.1, 5.1 Hz, 1H), 2.75−2.67 (m, 1H), 2.66−2.58 (m, 1H), 2.54−2.45 (m, 3H), 2.36 (s, 3H), 2.17−1.98 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 197.8, 172.3, 172.1, 151.5, 137.6, 131.4, 130.1, 127.1, 123.8, 123.3, 120.0, 71.9, 52.0, 36.3, 35.3, 28.1, 25.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}{}^{35}ClNNaO_4^+$, 356.0660; found, 356.0667.

*Methyl 3-(2-Bromo-6,11-dioxo-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5l**).* According to the general procedure, enone **2d** (29.0 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5l** (R_f = 0.35, colorless solid, 33.3 mg, 89%). mp: 126−127 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 8.9, 2.1 Hz, 1H), 5.94−5.87 (m, 1H), 5.78 (ddd, J = 11.8, 2.5, 1.8 Hz, 1H), 3.59 (s, 3H), 3.30−3.19 (m, 1H), 2.75−2.67 (m, 1H), 2.62 (ddd, J = 15.8, 8.4, 7.6 Hz, 1H), 2.54−2.46 (m, 3H), 2.15−1.99 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.7, 172.3, 172.2, 151.9, 140.3, 131.4, 127.1, 126.4, 124.2, 120.3, 117.4, 71.8, 52.0, 36.3, 35.3, 28.1, 25.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}{}^{79}BrNNaO_4^+$, 400.0155; found, 400.0161.

*Methyl 3-(2-Methyl-6,11-dioxo-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5m**).* According to the general procedure, enone **2e** (22.7 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:9), compound **5m** (R_f = 0.17, colorless solid, 19.9 mg, 65%). mp: 182−183 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.51 (d, J = 8.5 Hz, 1H), 7.53−7.51 (m, 1H), 7.48 (dd, J = 8.5, 1.7 Hz, 1H), 5.88−5.83 (m, 1H), 5.78 (ddd, J = 11.7, 2.4, 1.4 Hz, 1H), 3.55 (s, 3H), 3.22 (td, J = 13.3, 4.6 Hz, 1H), 2.69−2.63 (m, 1H), 2.59 (ddd, J = 15.7, 8.7, 7.2 Hz, 1H), 2.50−2.40 (m, 3H), 2.36 (s, 3H), 2.10−1.97 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.8, 172.4, 171.9, 151.4, 139.0, 134.5, 131.0, 127.6, 123.4, 122.7, 118.5, 71.5, 51.8, 36.3, 35.2, 28.1, 25.5, 20.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_4^+$, 336.1206; found, 336.1210.

*Methyl 3-(2-Cyclopropyl-6,11-dioxo-7,8-dihydro-6H-azepino-[1,2-a]indol-10a(11H)-yl)propanoate (**5n**).* According to the general procedure, enone **2f** (24.7 mg, 97.5 μmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5n** (R_f = 0.31, colorless solid, 30.7 mg, 92%). mp: 131−134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.1 Hz, 1H), 7.41 (d, J = 2.1 Hz, 1H), 5.91−5.85 (m, 1H), 5.79 (ddd, J = 11.7, 2.4, 1.3 Hz, 1H), 3.58 (s, 3H), 3.24 (td, J = 13.7, 5.1 Hz, 1H), 2.71−2.65 (m, 1H), 2.59 (ddd, J = 14.8, 8.6, 7.4 Hz, 1H), 2.52−2.43 (m, 3H), 2.10−2.02 (m, 2H), 1.97−1.90 (m, 1H), 1.03−0.97 (m, 2H), 0.74−0.68 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.9, 172.4, 171.9, 151.3, 141.0, 136.3, 131.0, 127.6, 122.7, 119.7, 118.5, 71.6, 51.9, 36.3, 35.3, 28.1, 25.5, 14.9, 9.4, 9.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{21}NNaO_4^+$, 362.1363; found, 362.1367.

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*Methyl 3-(6,11-Dioxo-2-(p-tolyl)-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5o**).* According to the general procedure, enone **2g** (30.3 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5o** (R_f = 0.37, colorless solid, 37.7 mg, 96%). mp: 165−167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.96 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.52−7.48 (m, 2H), 7.28−7.25 (m, 2H), 5.94−5.88 (m, 1H), 5.84 (ddd, *J* = 11.6, 2.1, 1.2 Hz, 1H), 3.59 (s, 3H), 3.28 (td, *J* = 13.7, 4.8 Hz, 1H), 2.75−2.70 (m, 1H), 2.65 (ddd, *J* = 14.8, 8.6, 7.5 Hz, 1H), 2.58−2.47 (m, 3H), 2.40 (s, 3H), 2.18−2.09 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.9, 172.4, 172.1, 152.2, 137.8, 137.7, 136.6, 136.2, 131.1, 129.7, 127.5, 126.7, 123.1, 121.3, 119.0, 71.8, 51.9, 36.3, 35.3, 28.2, 25.5, 21.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{23}NNaO_4^+$, 412.1519; found, 412.1527.

*Methyl 3-(2-Methoxy-6,11-dioxo-7,8-dihydro-6H-azepino[1,2-a]-indol-10a(11H)-yl)propanoate (**5p**).* According to the general procedure, enone **2h** (24.2 mg, 0.10 mmol), methyl acrylate (**4a**, 90.0 μL, 0.99 mmol), and PMe_2Ph (1.4 μL, 10 μmol) in CH_2Cl_2 (1.00 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5p** (R_f = 0.19, colorless solid, 19.9 mg, 60%). mp: 102−105 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 9.1 Hz, 1H), 7.29 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.16 (d, *J* = 2.8 Hz, 1H), 5.92−5.86 (m, 1H), 5.81 (ddd, *J* = 11.7, 2.4, 1.4 Hz, 1H), 3.84 (s, 3H), 3.58 (s, 3H), 3.23 (td, *J* = 13.2, 4.6 Hz, 1H), 2.72−2.65 (m, 1H), 2.61 (ddd, *J* = 15.7, 8.6, 7.2 Hz, 1H), 2.54−2.43 (m, 3H), 2.13−2.00 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.8, 172.4, 171.6, 156.7, 148.2, 131.1, 127.5, 126.9, 123.4, 120.0, 71.8, 55.8, 51.9, 36.3, 35.2, 28.1, 25.6. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_5^+$, 352.1155; found, 352.1158.

Preparation of Compound 5a on a 1 mmol Scale. According to the general procedure, enone **2a** (213.2 mg, 1.00 mmol), methyl acrylate (**4a**, 905 μL, 9.99 mmol), and PMe_2Ph (14.2 μL, 0.10 mmol) in CH_2Cl_2 (10 mL) gave, after chromatography (silica gel, $Et_2O/PhCH_3$ 1:6), compound **5a** (246.6 mg, 82%).

Preparation of Epoxide 9. *Hazard statement: Solid mCPBA in dry form is an explosive agent and the reagent should only be used in the H_2O-containing formulation available from commercial suppliers.*

*Methyl 3-(4,10-Dioxo-1a,3,4,10b-tetrahydro-2H-oxireno-[2′,3′:3,4]-azepino[1,2-a]indol-10a(10H)-yl)propanoate (**9**).* Compound **5a** (100.0 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (3.00 mL), and *m*CPBA (77 weight-%, 113.5 mg, 0.51 mmol) was added. The mixture was stirred at r.t. for 16 h, and then sat. aq $NaHSO_3$ (3 mL) was added. After 10 min of additional stirring, the layers were separated, and the organic layer was washed with sat. aq $NaHSO_3$, sat. aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (silica gel, $Et_2O/PhCH_3$ 1:6) gave a minor diastereomer with (1a*S**,10a*S**,10b*R**)-configuration (R_f = 0.26, colorless solid, 23.7 mg, 22%) and a major diastereomer with (1a*R**,10a*S**,10b*S**)-configuration (R_f = 0.12, colorless solid, 78.8 mg, 75%; single crystals obtained from this fraction were characterized by X-ray crystallography). *Minor diastereomer*: mp: 155−157 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.78 (ddd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.70 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.28−7.23 (m, 1H), 3.57 (s, 3H), 3.56 (d, *J* = 4.0 Hz, 1H), 3.34−3.31 (m, 1H), 2.81 (td, *J* = 13.6, 2.1 Hz, 1H), 2.66 (ddd, *J* = 16.2, 9.2, 7.2 Hz, 1H), 2.53−2.44 (m, 2H), 2.40 (dddd, *J* = 14.1, 6.1, 1.8, 1.0 Hz, 1H), 2.29−2.23 (m, 1H), 2.23 (ddd, *J* = 10.9, 9.2, 5.7 Hz, 1H), 2.07 (ddd, *J* = 16.2, 8.9, 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.8, 172.23, 172.20, 153.5, 138.1, 124.8, 123.9, 122.4, 118.8, 69.4, 58.5, 55.8, 51.9, 30.8, 30.6, 27.4, 24.6. *Major diastereomer*: mp: 133−135 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.6 Hz, 1H), 7.78 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.68 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.26−7.22 (m, 1H), 3.56 (s, 3H), 3.47 (d, *J* = 4.0 Hz, 1H), 3.39 (td, *J* = 4.9, 4.0 Hz, 1H), 2.92 (td, *J* = 13.6, 5.5 Hz, 1H), 2.69 (ddd, *J* = 15.8, 9.0, 7.1 Hz, 1H), 2.56 (ddd, *J* = 15.8, 8.9, 6.1 Hz, 1H), 2.50 (dtd, *J* = 13.9, 4.0, 0.7 Hz, 1H), 2.39−2.24 (m, 2H), 2.14 (ddd, *J* = 16.5, 9.0, 6.1 Hz, 1H), 2.06 (ddd, *J* = 16.5, 8.8, 7.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.8, 172.2, 170.6, 154.6, 138.0, 124.7, 123.9, 122.8, 119.1, 69.2, 58.1, 54.9, 52.0, 34.2, 29.2, 27.6, 22.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_5^+$, 338.0999; found, 338.0999.

Preparation of Lactone 11. *15-Iodo-1,2,6,7-tetrahydro-3H,14H-5,14a-methano[1,6]oxazecino-[6,5-a]indole-3,8,14(5H)-trione (**11**).* Compound **5a** (20.0 mg, 66.8 μmol) was dissolved in a 3:1 mixture of MeOH and H_2O (2.00 mL), and LiOH (3.2 mg, 0.13 mmol) was added. The mixture was stirred for 16 h at r.t. MeOH was removed under reduced pressure, and the remaining aqueous phase was diluted with EtOAc and sat. aq $NaHCO_3$. The layers were separated, and the aqueous layer was acidified with 5% HCl aq The aqueous phase was extracted with EtOAc (2 ×), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield the intermediate acid **10** (yellow solid, 18.0 mg, 95%) which was used in the subsequent step without further purification. A portion of acid **10** (20.0 mg, 70.1 μmol) and 2,4,6-collidine (36.1 μL, 0.27 mmol) were dissolved in MeCN (2.00 mL). A solution of I_2 (17.8 mg, 70.1 μmol) in MeCN (1.00 mL) was added at 0 °C, and the mixture was subsequently heated to 50 °C for 24 h. The mixture was diluted with CH_2Cl_2 and washed with 5% $Na_2S_2O_3$ aq and 0.5 M $KHSO_4$ aq, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Column chromatography (silica gel, $Et_2O/PhCH_3$ 1:6) gave compound **11** as a mixture of inseparable diastereomers (R_f = 0.30, *d.r.* 6.7:1, colorless solid, 15.8 mg, 54%). mp: 285−287 °C. *Major* (5*S**,14a*R**,15*S**)-*diastereomer*: ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.74−7.69 (m, 2H), 7.31−7.27 (m, 1H), 4.44 (d, *J* = 0.7 Hz, 1H), 4.37 (ddd, *J* = 7.5, 6.9, 0.7 Hz, 1H), 3.22 (ddd, *J* = 18.0, 11.7, 9.2 Hz, 1H), 2.87 (ddd, *J* = Hz, 14.9, 9.2, 1.2 Hz, 1H), 2.67 (ddd, *J* = Hz, 18.5, 10.9, 4.4 Hz, 1H), 2.56 (ddd, *J* = Hz, 18.0, 9.9, 1.2 Hz, 1H), 2.50 (ddd, *J* = Hz, 18.5, 10.6, 8.4 Hz, 1H), 2.39−2.31 (m, 1H), 2.25 (ddd, *J* = Hz, 14.9, 11.8, 10.2 Hz, 1H), 2.03−1.93 (m, 1H). *Minor diastereomer, trace signals*: δ 4.30 (d, *J* = 1.2 Hz, 1H), 4.37 (ddd, *J* = 7.4, 6.9, 1.2 Hz, 1H), 3.33 (ddd, *J* = 18.1, 11.4, 9.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 198.4, 175.5, 174.3, 150.1, 137.7, 125.9, 125.3, 125.2, 117.7, 75.1, 74.8, 43.0, 34.9, 27.6, 25.6. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{14}INNaO_4^+$ 433.9860; found, 433.9863.

Rauhut−Currier-Type Reaction between Enone 2a and Ethyl 2,3-Butadienoate (6a) to Give Compound 5q. *Ethyl 3-(6,11-Dioxo-7,8-dihydro-6H-azepino[1,2-a]indol-10a(11H)-yl)but-3-enoate (**5q**).* Enone **2a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**6a**, 120 μL, 1.03 mmol) was added to solution, followed by $P(t\text{-}Bu)_3$ (4.0 mg, 20 μmol 20 mol %). The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 24 h and then concentrated to dryness. Column chromatography (silica gel, $EtOAc/PhCH_3$ 1:10) afforded compound **5q** (R_f = 0.37, colorless solid, 20.0 mg, 61%). mp: 122−125 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.67 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.76 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.26−7.20 (m, 1H), 6.05−5.97 (m, 1H), 5.93 (ddd, *J* = 11.6, 2.2, 1.6 Hz, 1H), 5.39 (br s, 1H), 5.31 (br s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.49−3.36 (m, 1H), 3.20 (dd, *J* = 16.1, 0.6 Hz, 1H), 2.85 (d, *J* = 16.1 Hz, 1H), 2.56−2.36 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 196.2, 172.7, 170.4, 152.8, 139.7, 137.8, 133.5, 125.7, 124.6, 124.5, 121.4, 119.3, 118.4, 74.6, 61.1, 37.6, 35.1, 26.1, 14.0. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_4^+$, 348.1206; found, 348.1215.

[3 + 2]-Cycloaddition between Enone 2a and 2,3-Butadienoate (6a) to Give Compound 7a. *Ethyl (3a*S**,13a*S**)-7,13-Dioxo-3,3a,4,5,6,7-hexahydro-13H-cyclopenta[2,3]azepino-[1,2-a]indole-1-carboxylate (**7a**).* Enone **2a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**6a**, 120 μL, 1.03 mmol) was added to solution, followed by PMe_2Ph (2.8 μL, 20 μmol, 20 mol %). The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 24 h and then concentrated to dryness. Column chromatography (silica gel, $EtOAc/PhCH_3$ 1:10) afforded compound **7a** (R_f = 0.23, colorless solid, 17.1 mg, 53%). mp: 102−103 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (dt, *J* = 8.5, 0.7

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Hz, 1H), 7.75 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.67 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.32 (t, J = 2.5 Hz, 1H), 7.26−7.19 (m, 1H), 3.99−3.80 (m, 2H), 3.20−3.11 (m, 1H), 3.04 (ddd, J = 19.3, 9.5, 2.5 Hz, 1H), 2.83−2.72 (m, 1H), 2.66 (ddd, J = 19.3, 3.8, 2.5 Hz, 1H), 2.46−2.37 (m, 1H), 1.94−1.73 (m, 3H), 1.70−1.56 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 200.3, 171.4, 162.1, 153.5, 149.9, 137.2, 135.9, 124.2, 123.8, 123.2, 118.7, 80.9, 60.8, 41.3, 34.8, 34.2, 25.2, 18.1, 13.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_4^+$, 348.1206; found, 348.1215.

Analytical Data of Side Product 16a. *Ethyl (E)-2-(7-Oxo-3,3a,4,5,6,7-hexahydro-2H-1-oxa-7a-azacyclohepta[jk]fluoren-2-ylidene)acetate (16a).* R_f = 0.50 ($EtOAc/PhCH_3$ 1:10), colorless solid, mp: 157−159 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (dt, J = 8.3, 0.7 Hz, 1H), 7.53 (br. d, J = 7.6 Hz, 1H), 7.36 (ddd, J = 8.3, 7.4, 1.3 Hz, 1H), 7.32−7.28 (m, 1H), 5.83 (d, J = 1.6 Hz, 1H), 4.27 (dd, J = 14.8, 5.7 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.25−3.17 (m, 1H), 2.91 (td, J = 13.8, 6.1 Hz, 1H), 2.79 (dt, J = 13.8, 4.3 Hz, 1H), 2.41 (ddd, J = 14.8, 10.6, 1.6 Hz, 1H), 2.22 (ddt, J = 11.1, 8.4, 2.9 Hz, 1H), 2.16−1.96 (m, 2H), 1.64 (ddd, J = 11.1, 3.6, 1.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.8, 167.2, 165.8, 136.4, 133.7, 125.7, 123.8, 120.6, 119.8, 116.5, 116.4, 101.0, 60.0, 36.4, 30.6, 29.7, 29.6, 20.7, 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_4^+$, 326.1387; found, 326.1393.

Preparation of (−)-7a Using Chiral Phosphine Catalyst 17. Enone **2a** (21.3 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1.00 mL) in a 10 mL crimp cap vial. Ethyl 2,3-butadienoate (**6a**, 120 μL, 1.03 mmol) was added to solution, followed by (*S*)-*N*-(1-(diphenylphosphaneyl)-3-methylbutan-2-yl)-3,5-bis(trifluoromethyl)-benzamide (**17**, 15.3 mg, 30 μmol, 30 mol %). The vial was sealed, and argon was bubbled through the mixture via cannula for 5 min. The mixture was stirred at r.t. for 48 h and then concentrated to dryness. Column chromatography (silica gel, $EtOAc/PhCH_3$ 1:10) afforded compound (−)-**7a** (R_f = 0.23, colorless solid, 15.0 mg, 47%, *e.r.* 82:18). $[a]_D^{22}$ = −30.4 (c = 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01402.

Details of substrate syntheses, reaction optimization, catalyst screenings, ^{31}P NMR study, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2340038, 2340041, 2340047, and 2340050 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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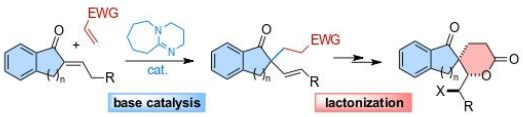
Letter

DBU-Catalyzed Deconjugative Alkylations of 2-Alkylidene Indanones and Tetralones with Alkenes and Synthesis of Spirocyclic δ-Lactones

Saikumar Banda, Lasse Johannßen, Malte Brasholz
Affiliation addresses are listed at the end of the article.

GRAPHICAL ABSTRACT



ABSTRACT

1,8-Diazabicyclo(5.4.0)undec-7-ene catalyzes the deconjugative α-alkylation of 2-butylidene 1-indanone and 1-tetralone with electrophilic alkenes, to give α,α-disubstituted β,γ-unsaturated indanone and tetralone products, under mild conditions, and in moderate to excellent yields. Further elaboration of the 1-indanone and 1-tetralone-derived skipped enones gave δ,ε-unsaturated alkenoic acids, which underwent diastereoselective iodo- and epoxylactonizations, furnishing valuable [4.5]- and [5.5]-spirocyclic δ-lactones in high yields.

Keywords enones, base catalysis, iodolactonization, epoxylactonization, spirocycles

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Introduction

Spirocyclic δ-lactones are a structurally rich and synthetically challenging class of heterocyclic compounds. γ-[4.5]- and [5.5]-spirocyclic δ-lactones that build on the 7-oxaspiro[4.5]decan-8-one and 2-oxaspiro[5.5]undecan-3-one structural motifs can be isolated from various green plants and fungi and possess interesting biological properties (**Fig. 1**). For example, neolaxiflorin A,[1] laxifloride C,[2] and sculponin T[3] are diterpenoid compounds from the genus *Isodon* that display antiproliferative activity against various human cancer cell lines. Ptycholactone[4] and 15-deoxyoxalicine[5] are two further natural terpenoid [5.5]-spiro-δ-lactones, the latter of which shows insect repellent effects. In addition to natural products research, spiro-δ-lactones have also been subject of synthetic library screenings, and the herbicidal small molecule (**I**)[6] is one such example. Due to their attractive biological properties, the development of synthetic routes to access spirocyclic δ-lactones remains a topic of general interest, and here we wish to disclose a concise route leading to several [4.5]- and [5.5]-spirocyclic δ-lactone motifs.

Stimulated by our interest in the synthesis of "skipped" enones,[7] we initially investigated the deconjugative α-alkylation of the (*E*)-2-butylidene-1-indanone **1a** with electrophilic alkenes[8] as Michael acceptors, employing various nucleophilic and base catalysts (**Scheme 1**). Enone **1a** was first reacted with ethyl vinyl ketone **2a** as the electrophile (10 equiv) in the presence of tertiary phosphines as well as several NHC percursors (10 mol% each). We previously found that PBu_3 or $PMePh_2$, weakly basic but strongly nucleophilic phosphines, are highly effective catalysts in addition reactions of 2-alkylidene 3-oxindoles with alkenes.[7] However, in the case of the 2-alkylidene indanone **1a**, no conversion to the desired α,α-disubstituted β,γ-unsaturated ketone **3a** was observed, even at elevated temperatures of up to 120 °C in toluene solution. Triethylamine, less nucleophilic but having a pK_a comparable to the tertiary phosphines, also did not promote the reaction. Conducting the reaction with 2-mesityl-2,5,6,7-tetrahydro-pyrrolo[2,1-*c*][1,2,4]-triazol-4-yliumchlorid (10 mol%) as a carbene precursor, in combination with Cs_2CO_3 (25 mol%) in acetonitrile solution at 80 °C (sealed tube), cleanly afforded

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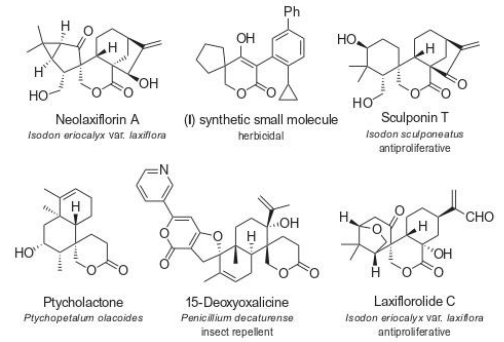
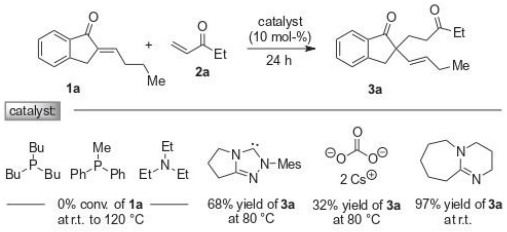


Fig. 1 Natural and synthetic [4.5]- and [5.5]-spirocyclic δ-lactones based on the 7-oxaspiro[4.5]decan-8-one and 2-oxaspiro[5.5] undecan-3-one structural motifs.

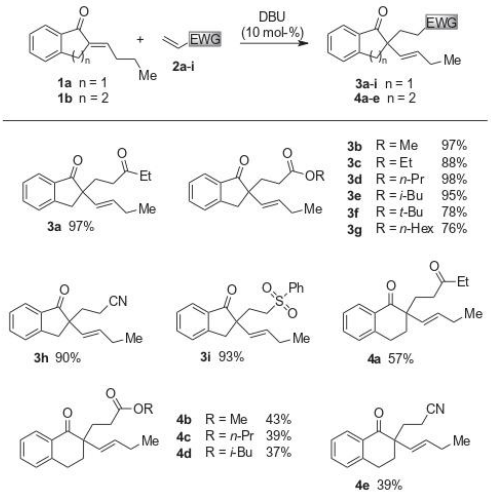


Scheme 1 Survey of reaction conditions for the deconjugative α-alkylation of enone **1a** with ethyl vinyl ketone **2a**.

the skipped enone **3a** in yields of up to 68%; however, Cs_2CO_3 showed significant background reactivity under these conditions, and the yield of compound **3a** with Cs_2CO_3 alone amounted to 32%.

Finally, using 10 mol% of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as base catalyst[9] efficiently promoted the coupling of reactants **1a** and **2a** at room temperature, resulting in quantitative conversion of enone **1a** after 24 h. Diverse solvents were evaluated in the reaction including acetonitrile, dichloromethane, and toluene that gave comparable results, but also methanol was found suitable. Under the optimal conditions, using 10 mol% of DBU and 6 molar equiv of ethyl vinyl ketone **2a** in MeCN at room temperature for 24 h allowed for the isolation of β,γ-unsaturated ketone **3a** in 97% yield. By comparison, a reduction of the quantity of DBU to 5 mol% would reduce the yield of product **3a** to 70%, and when only 3 equiv of the alkene **2a** were employed, the yield dropped to 56%.

Scheme 2 depicts an overview of the α,α-disubstituted β,γ-unsaturated ketone products that could be accessed from 2-butylidene-1-indanone **1a** as well as 2-butylidene-1-tetralone **1b** with diverse electrophilic alkenes **2** under DBU catalysis. All reactions of enone **1a** proceeded readily with 10 mol% of DBU at



Scheme 2 Overview of β,γ-unsaturated ketones derived from enones **1a** and **1b**. Conditions for products **3**: Enone **1a** (0.10 mmol), alkene **2** (0.60 mmol), DBU (10 μmol), and MeCN (0.10 M), room temperature, 20 h. Conditions for products **4**: Enone **1b** (0.10 mmol), alkene **2** (1.00 mmol), DBU (10 μmol), and MeCN (0.10 M), 40 °C, 24 h. Yields after chromatography.

ambient temperature, and in addition to ethyl vinyl ketone **2a**, the acrylates **2b–2g** as electrophiles afforded skipped enones **3b–3g** in high yields ranging from 76% to 98%. Compound **3b** could as well be prepared on a 1 mmol scale, resulting in 98% isolated yield.[10] Acrylonitrile **2h** and phenyl vinyl sulfone **2i** could also be used in the reaction giving products **3h** and **3i** in 90% and 93% yield, respectively.

The DBU-catalyzed α-alkylations of tetralone derivative **1b** with alkenes **2** required slightly more forcing conditions (40 °C in MeCN solution for 24h), and despite high conversion of **1b**, yields of the β,γ-unsaturated ketones **4a–e** were generally moderate, ranging from 39% with acrylonitrile as the alkene partner to 37–57% with acrylates and ethyl vinyl ketone as reactants.

The indanone- and tetralone-derived β,γ-unsaturated ketones **3b** and **4b** could be utilized in the synthesis of valuable spirocyclic lactones, as shown in **Scheme 3**. Saponification of the methyl carboxylates **3b** and **4b** with lithium hydroxide led to the δ,ε-unsaturated carboxylic acids **5** and **8**. Iodolactonization[11] of alkenoic acid **5** with iodine in the presence of 2,4,6-collidine[12] at 50 °C produced a spiro[4.5] δ-lactone, the (1-iodopropyl)-substituted spiroindene-2,3′-pyranone **6** in 66% yield, as a mixture of two diastereomers with d.r. 4.7:1. The reaction of alkenoic acid **8** under the same conditions gave spironaphthalene-2,3′-pyranone **9** in 62% yield and with d.r. 7.7:1. Carboxylic acids **5** and **8** were further subjected to epoxylactonization using *m*-chloroperbenzoic acid in the presence of trifluoroacetic acid at ambient temperature. Compound **5** was converted into (1-hydroxypropyl)-substituted spiroindene-2,3′-pyranone **7** in 64% and as a single diastereomer (d.r. > 19:1).[13] The lactonization of

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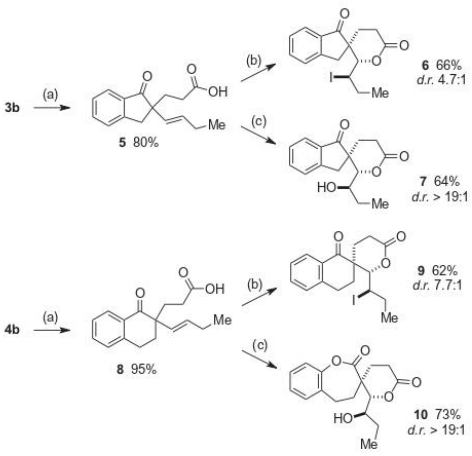

Scheme 3 Synthesis of spirocyclic lactones. Reaction conditions: (**a**) LiOH (2.0 equiv), MeOH, and H_2O, room temperature, 16 h. (**b**) I_2 (2.0 equiv), 2,4,6-collidine (4.0 equiv), MeCN, 50 °C, 24 h. (**c**) *m*CPBA (2.0 equiv), TFA, and CH_2Cl_2, room temperature, 16 h.

acid **8** under identical conditions was however accompanied by a Baeyer–Villiger[14] ring expansion with a remarkable regioselectivity, to produce the [5.6]-spirocyclic spirobenzo[*b*]oxepine-3,3′-pyranone **10**, in 73% and with > 19:1 d.r.

In conclusion, the DBU-catalyzed deconjugative α-alkylation of 2-alkylidene indanone **1a** and tetralone **1b** with electrophilic alkenes **2** affords α,α-disubstituted β,γ-unsaturated ketones **3** and **4** in moderate to excellent yields. These skipped enone products can be transformed into functionalized spirocyclic δ-lactones by efficient and diastereoselective iodo- and epoxylactonization reactions.

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Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

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Contributors' Statement S.B.: Investigation. L.J.: Investigation. M.B.: Conceptualization, Data curation, Project administration, Writing—original draft.

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10 **Procedure for the DBU-catalyzed deconjugative α-alkylation 1a + 2b → 3b** (1 mmol scale). Enone **1a** (186.2 mg, 1.00 mmol) was dissolved in MeCN (10.0 mL). Methyl acrylate (**2b**, 543.7 µL, 6.00 mmol) was added followed by DBU (15.0 µL, 0.10 mmol). The mixture was stirred under argon, at r.t. for 20 h, then concentrated to dryness. Column chromatography (silica gel, EtOAc/heptane 1:4) afforded compound **3b** (colorless oil, 266.6 mg, 98%). Analytical data for methyl (*E*)-3-[2-(but-1-en-1-yl)-1-oxo-2,3-dihydro-1*H*-inden-2-yl]propanoate (**3b**): R_f = 0.46 (silica, EtOAc/heptane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (td, *J* = 7.7, 0.9 Hz, 1H), 7.58 (td, *J* = 7.5, 0.9 Hz, 1H), 7.43 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.36 (td, *J* = 7.5, 0.9 Hz, 1H), 5.62 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.51 (dt, *J* = 15.7, 1.3 Hz, 1H), 3.64 (s, 3H), 3.25 (d, *J* = 17.2 Hz, 1H), 3.04 (d, *J* = 17.2 Hz, 1H), 2.39 (ddd, *J* = 15.9, 11.0, 5.4 Hz, 1H), 2.27 (ddd, *J* = 15.9, 11.0, 5.4 Hz, 1H), 2.12 (ddd, *J* = 13.6, 10.8, 5.3 Hz, 1H), 2.05 – 1.92 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.3, 173.7, 152.1, 135.6, 134.9, 133.2, 129.6, 127.6, 126.3, 124.5, 54.4, 51.6, 38.3, 32.6, 29.7, 25.7, 13.5 ppm. HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{21}O_3^+$ [M+H]$^+$: 273.1485, found: 273.1491.
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13 **Procedure for the epoxylactonization 5 → 7**. Alkenoic acid **5** (90.0 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (8.00 mL). *m*-CPBA (152.3 mg, 77 wt%, 0.68 mmol) was added, then trifluoroacetic acid (0.20 mL). The mixture was stirred at r.t. for 16 h. The mixture was washed with sat. aq. $NaHCO_3$ and brine, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography (silica gel, EtOAc/$PhCH_3$ 1:4) afforded compound **7** (colorless solid, 61.4 mg, 64%). Analytical data for (2*R**,2′*S**)-2′-[(*R**)-1-hydroxypropyl]-4′,5′-dihydro-2′*H*,6′*H*-spiro[indene-2,3′-pyran]-1,6′(3*H*)-dione (**7**): R_f = 0.21 (silica, EtOAc/Heptane 1:4). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ = 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 (td, *J* = 7.6, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 4.61 (d, *J* = 8.9 Hz, 1H), 3.58 – 3.50 (m, 2H), 2.93 (d, *J* = 17.4 Hz, 1H), 2.80 (ddd, *J* = 18.5, 7.2, 3.4 Hz, 1H), 2.64 (ddd, *J* = 18.5, 11.0, 7.4 Hz, 1H), 2.28 (ddd, *J* = 13.8, 10.9, 7.2 Hz, 1H), 1.96 (dqd, *J* = 15.1, 7.6, 2.6 Hz, 1H), 1.71 (ddd, *J* = 13.8, 7.4, 3.4 Hz, 1H), 1.50 – 1.42 (m, 1H), 1.42 – 1.32 (m, 1H), 0.92 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 206.5, 169.8, 151.4, 135.7, 135.1, 127.9, 126.7, 124.5, 86.4, 73.2, 49.7, 33.3, 30.9, 27.6, 27.1, 9.5 ppm. HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{18}NaO_4^+$ [M+Na]$^+$: 297.1097, found: 297.1109
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