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(4+1)-Cycloadditions Exploiting the Biphilicity of Oxyphosphonium Enolates and Rh^{II}/Pd^{II}-Stabilized Metallocarbenes for the Construction of Five-Membered Frameworks

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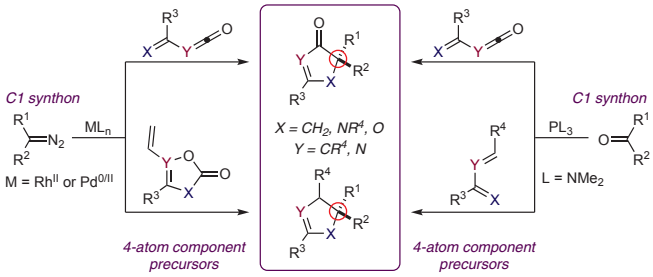

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Abstract (4+1)-Cyclizations are an underutilized disconnect for the formation of five-membered heterocyclic and carbocyclic frameworks. Herein we analyze methods employing oxyphosphonium enolates and Rh^{II}/Pd^{II}-metallocarbenes as C1 synthons in the presence of several four-atom components for the synthesis of 2,3-dihydrobenzofurans, 2,3-dihydroindoles, oxazolones, cyclopentenones, and pyrrolones.

Key words (4+1)-cyclization, carbenes, rhodium, palladium, phosphorus, organocatalysis, carbocycles, heterocycles

1 Introduction

The utilization of cycloaddition reactions, for the efficient and convergent construction of cyclic molecules, has allowed synthetic chemists to make large advancements in the assembly of natural products, pharmaceuticals, and agrochemicals.[1–3] Furthermore, the use of transition metals (TM), organocatalysts, and Lewis acids to catalyze cycloadditions has increased the efficiency of such processes in chemo-, diastereo- and/or stereoselective fashions vastly improving the synthesis of privileged scaffolds.[4–8] Specifically, five-membered carbo- and heterocyclic frameworks are valuable targets of cyclization methodologies due to their prevalence in biologically relevant molecules.[9,10] Several intra- and intermolecular retrosynthetic strategies are employed for the assembly of five-membered frameworks. For example, intramolecular construction is enacted utilizing 5-*exo*-dig, 5-*exo*-trig, 5-*exo*-tet, or 5-*endo*-dig cyclizations developed by Baldwin (Figure 1a),[11,12] while intermolecular assembly is divided into (2+2+1)-, (3+2)-, and (4+1)-cyclization disconnects (Figure 1b).[7,13,14] Years of research have been dedicated to advancing (2+2+1)- and (3+2)-methodologies, from their initial discovery to various modifications allowing for stereoelectronic flexibility and vast substrate tolerance. However, the (4+1)-disconnect is relatively underutilized when compared to the latter two cyclization strategies.[14]

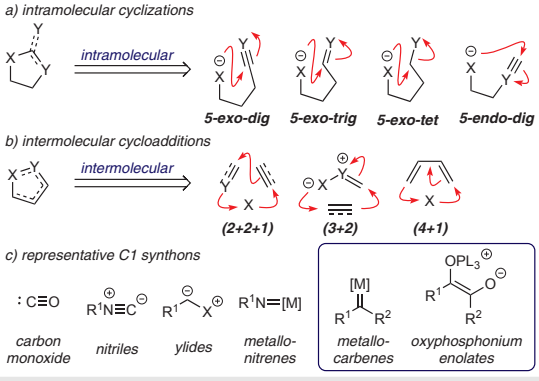

Figure 1 Cyclization strategies for 5-membered ring construction: (a) intramolecular cyclization retrosynthetic disconnects; (b) intermolecular cycloaddition retrosynthetic disconnects; (c) selected C1 synthons in (4+1)-cycloadditions.

A major challenge in (4+1)-cyclization methodology is the identification of an appropriate C1 synthon that exhibits biphilicity, allowing for initial bond formation and subsequent ring closure. This challenge is exemplified in cheletropic reactions, where five-membered frameworks are assembled in a concerted fashion, but only due to specific orbital requirements of the one-atom component. Compounds such as carbon monoxide, isocyanides, ylides,

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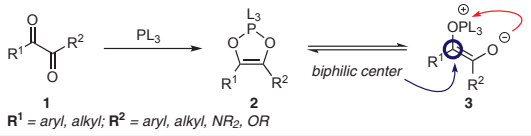
metallonitrenes, metallocarbenes, and oxyphosphonium enolates are several examples of one-atom synthons used pervasively in organic synthesis (Figure 1c). Our contributions to the evolution of (4+1)-cycloaddition-based technologies by exploiting the utility of oxyphosphonium enolates and metallocarbenes as C1 synthons in the presence of various four-atom components for the construction of privileged molecules including 2,3-dihydrobenzofurans, 2,3-dihydroindoles, oxazolones, cyclopentenones, and pyrrolones are discussed herein.[15–19]

2 (4+1)-Cyclizations Employing Kukhtin–Ramirez-Like Reactivity

The addition of trivalent phosphorus to 1,2-dicarbonyls, originally reported by Kukhtin and Ramirez independently, has proven viable for the construction of C–C and C–O bonds.[20] Recently, the Radosevich group has pioneered a resurgence in Kukhtin–Ramirez-like reactivity, developing methodologies catalyzed through exploitation of P^{III}–P^{V} redox cycling.[21] The generic Kukhtin–Ramirez reactivity relies on the oxyphilic nature of trivalent phosphorus and the favorable thermodynamic formation of pentavalent phosphine oxide. The addition of PL_3 to 1,2-dicarbonyl **1** results in the formation of oxyphospholene **2** which establishes a solvent/temperature-dependent equilibrium with oxyphosphonium enolate **3**, with the latter exhibiting biphilicity, reacting with both electrophilic and nucleophilic reagents (Scheme 1). Furthermore, through the perturbation of the ligands (L) bound to phosphorus the reactivity of **3** is highly influenced, thus able to catalyze a variety of reactions.[15–17,20,21] Through exploitation of the inherent biphilicity of intermediate **3**, our laboratory has reported several methods utilizing four-atom components for the construction of privileged scaffolds *via* nucleophilic 1,2- or 1,4-addition followed by ring closure and liberation of $O{=}PL_3$ as the thermodynamic driving force.[22]



1 2 3

R^1 = aryl, alkyl; R^2 = aryl, alkyl, NR_2, OR

Scheme 1 Reactivity of 1,2-dicarbonyls in the presence of trivalent phosphorus

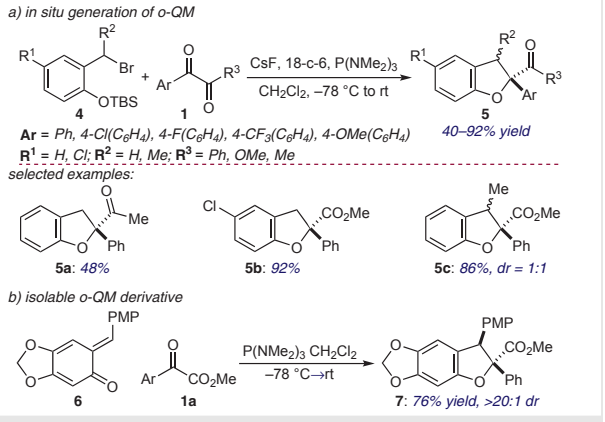
Biographical Sketches

Zachary D. Tucker was born in Cincinnati, Ohio (USA) in 1994. He received his BS degree in chemistry from Bellarmine University, Louisville, Kentucky in 2016, graduating magna cum laude. As an undergraduate, Zachary studied under the supervision of Prof. Amanda J. Krzysiak, researching the synthesis of chalcone and chalconoid derivatives for the development of cytotoxic agents and anticancer activity of the β-phenylacrylophenone framework. Presently, Zachary is a PhD candidate in the Department of Chemistry and Biochemistry at the University of Notre Dame, studying under the supervision of Prof. Brandon L. Ashfeld. His current research has involved the development of methodologies for the synthesis and functionalization of nitrogen-containing heterocycles via transition-metal-stabilized carbene intermediates. In addition to method development, his research has entailed target-directed synthesis. Notably, the total synthesis of indole alkaloid natural products and ionic liquid materials bearing unique biological/physical properties. Zachary has also examined the physiochemical properties of ionic liquids via variable temperature spectroscopy and their subsequent applications.

Professor Brandon L. Ashfeld is a native of Minnesota and received his BS degree in chemistry from the University of Minnesota–Twin Cities (USA) in 1998 while working in the laboratories of Professor Thomas R. Hoye. He subsequently began his graduate studies at the University of Texas at Austin and received his PhD under the supervision of Professor Stephen F. Martin in 2004. From there, he moved to Stanford University and joined the laboratories of Professor Barry M. Trost as a National Institutes of Health Ruth L. Kirschstein postdoctoral fellow. In the fall of 2007 he joined the faculty in the Department of Chemistry and Biochemistry at the University of Notre Dame. His research interests include the 1) development of new transition-metal-catalyzed multicomponent couplings for the assembly of highly substituted carbon centers, 2) exploitation of carbenoid/nitrenoid reactivity to facilitate new C–C and C–N bond-forming molecular rearrangements, 3) synthesis of small molecules system as novel brain-penetrant kinase inhibitors toward the discovery of new treatments for central nervous (CNS) disorders, and 4) the design and development of ionic liquid frameworks that provide insight into the fundamentals behind phase-separation behavior.

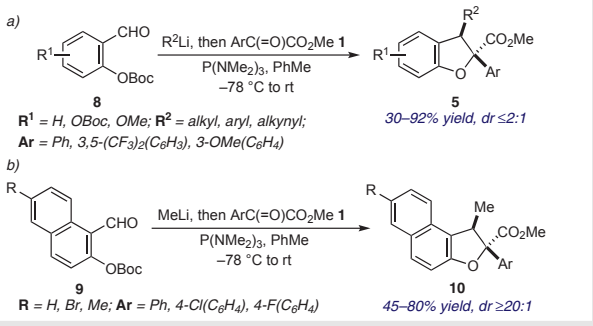
2.1 *o*-Quinone Methides as Four-Atom Synthons for the Assembly of 2,3-Dihydrobenzofurans

In 2016 our laboratory disclosed a (4+1)-cyclization between *o*-quinone methides (*o*-QMs) and oxyphosphonium enolates, proceeding through the treatment of silyl ethers **4**[23,24] with CsF and 18-crown-6 in the presence of α-keto esters **1** and $P(NMe_2)_3$ affording dihydrobenzofurans **5** in 40–92% yield (Scheme 2a).[15] We discovered that structural perturbations of the α-keto esters were well tolerated, and included: electron-rich, electron-poor, and halogenated aryl substituents (40–88%). Similarly, symmetrical and unsymmetrical 1,2-diketones provided the desired cycloadducts with the latter providing **5a** as a single regioisomer in 48% yield. Substitution at R^1 of the silyl ether with chlorine yielded **5b** in 92% yield, and benzylic substitution led to 86% yield of 2,3-dihydrobenzofuran **5c** albeit in 1:1 *dr*. Furthermore, isolable *o*-QM **6** in the absence of CsF and 18-crown-6 was tolerated and provided tricycle **7** in 76% yield as a single diastereomer (Scheme 2b), exhibiting the effect of benzylic substitution on the diastereochemical outcome.



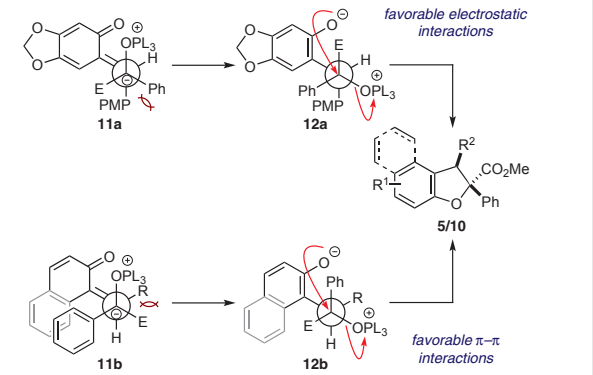
Scheme 2 (a) 2,3-Dihydrobenzofuran **5** assembly employing *o*-silyloxy benzyl bromides **4** and selected examples **5a–c**; (b) (4+1)-cyclization of isolable *o*-quinone methide **6** providing tricycle **7**.

Attempts to expand this methodology to substituted benzyl bromides for the synthesis of disubstituted 2,3-dihydrobenzofurans proved incompatible under CsF/18-crown-6 catalyzed conditions. Therefore, inspired by the work of Pettus and co-workers, we turned our attention to the generation of *o*-QMs *via* the addition of organometallic reagents to Boc-protected salicylaldehydes **8**. Whereby the desired *o*-QM intermediate is formed *via* a nucleophilic addition to the carbonyl, triggering a sequential 1,5-acyl migration/β-elimination allowing for *in situ* generation (Scheme 3a).[23,25] The addition of organolithium reagents followed by **1** and $P(NMe_2)_3$ provided 2,3-substituted dihydrobenzofurans **5** in 30–92% yield with diastereoselectivities ≤ 2:1 in favor of the *syn*-isomer. Consistent with our previous results, electron-poor aryl α-keto esters resulted in higher yields (80% yield) than their electron-rich counterparts (35% yield). Utilizing 2-naphthyl-derived salicylaldehydes **9** resulted in an increase in diastereoselectivity (dr >20:1) with yields ranging from 45–80% of cycloadduct **10** (Scheme 3b). Our observed diastereoselectivities are proposed to originate from an electrostatic interaction between the *o*-QM oxygen and phosphonium cation, while minimization of gauche interactions resulting in the larger aryl group orienting away from the *o*-QM benzenoid ring *via* open transition state **11a** (Scheme 4). Upon C–C bond formation and liberation of phosphine oxide from the *anti*-conformer **12a,** the *syn*-diastereomer **5** is obtained. In contrast, 2-naphthyl substitution leads to the *syn*-isomer due to favorable π–π interactions in transition state **11b**.

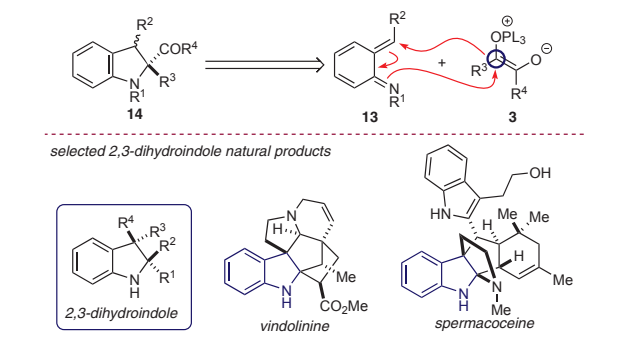


Scheme 3 (a) (4+1)-Cyclization of *o*-QM generated from salicaldehydes **8** in the presence of organolithium reagents and α-keto esters **1** to provide dihydrobenzofurans **5**; (b) highly diastereoselective formation of dihydrobenzofurans **10** *via* 2-naphthyl salicylaldehydes **9**.

Bond formation followed by rotation about the newly formed C–C bond places the phosphonium cation *anti*-periplanar to the phenoxide in **12b**. Similarly, liberation of $O{=}PL_3$ *via* nucleophilic attack by the phenoxide anion gives way to the corresponding *syn*-diastereomer **10**.



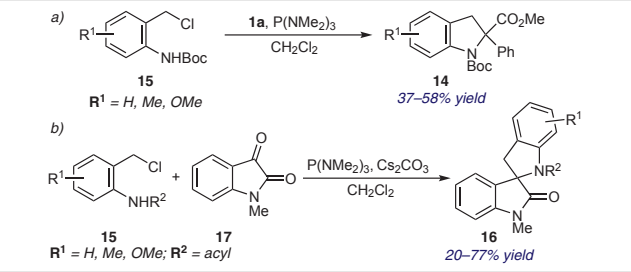
Scheme 4 Proposed transition states **11a**,**b** and **12a**,**b** rationalizing the observed diastereoselectivity *via* favorable electrostatic interactions or π–π interactions providing *syn*-isomers **5**/**10**



Scheme 5 Aza-*o*-QM retrosynthetic disconnect for the construction of **14** and selected examples of biologically relevant 2,3-dihydroindole natural products

2.2 Aza-Quinone Methides as Four-Atom Synthons for the Assembly of 2,3-Dihydroindoles

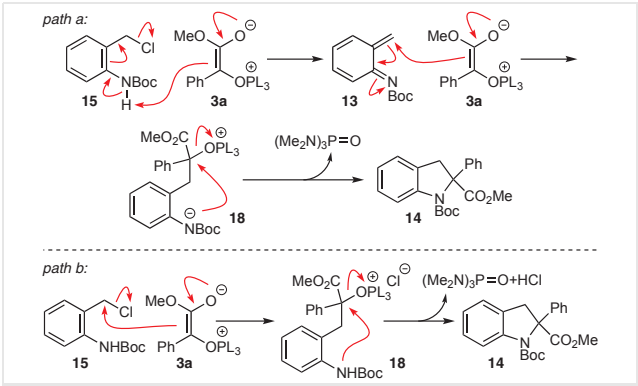
Analogously we expanded the (4+1)-cyclization methodology utilizing oxyphosphonium enolates for the construction of *N*-heterocyclic frameworks. Through the utilization of aza-*ortho*-quinone methides (aza-*o*-QM) **13**[26–28] as four-atom synthons, while employing Kukhtin–Ramirez conditions, we reported the construction of 2,3-dihydroindoles **14** (Scheme 5).[16] The assembly of **14** was accomplished utilizing 2-aminobenzyl chlorides **15**, as aza-*o*-QM precursors, in the presence of two equivalents of α-keto ester **1a** and $P(NMe_2)_3$ providing the desired cycloadducts in yields ranging from 37–90% (Scheme 6a). Substitution of **15** with methyl or methoxy at C5 provided the desired cycloadduct **14** albeit in 37% and 58% yield, respectively. While, *N*-acyl anilines bearing halogens at C4 or C5 failed to undergo the desired cycloaddition. However, we expanded this methodology to isatin derivatives, which served as the C1 synthon, allowing for the formation of spirooxindoles **16**. Through treatment of **15** with Cs_2CO_3, $P(NMe_2)_3$, and isatin **17** the corresponding cycloadducts could be obtained in 20–77% yield (Scheme 6b).



Scheme 6 Construction of 2,3-dihydroindoles **14** and spirooxindoles **16** *via* trivalent phosphorous reagents and diketones

Our group discovered that the addition of Cs_2CO_3 was essential for aza-*o*-QM generation, as the pK_a of the enolate of *N*-alkyl oxindoles is significantly lower in comparison to α-aryl formyl enolates generated in the construction of **14**, in which one equivalent of oxyphosphonium enolate served as a sacrificial base. Substitution of **15** at C5 and C6 with methyl and methoxy groups provided the desired spirooxindoles in yields ranging from 20–51%. Unfortunately, functionalization of **17** failed to provide the desired cycloadduct.

We speculated that the formation of 2,3-dihydroindoles **14** and spirooxindoles **16** involved an initial deprotonation of 2-aminobenzyl chloride **15** by one equivalent of oxyphosphonium enolate **3a** followed by elimination of chloride yielding aza-*o*-QM **13a** (Scheme 7, path a). Conjugate addition of a second equivalent of **3a** provides zwitterion **18** that upon liberation of $O{=}P(NMe_2)_3$ provides the corresponding cycloadduct.[20,26] However, an alternative mechanism involving initial displacement of chloride by **3a** followed by deprotonation *via* the second equivalent of the oxyphosphonium enolate yielding zwitterion **18** prior to ring closure cannot be discounted (path b).



Scheme 7 Proposed mechanisms for the (4+1)-cyclization of **15** and **3a**

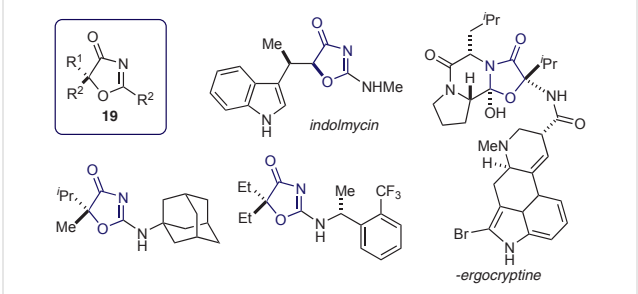
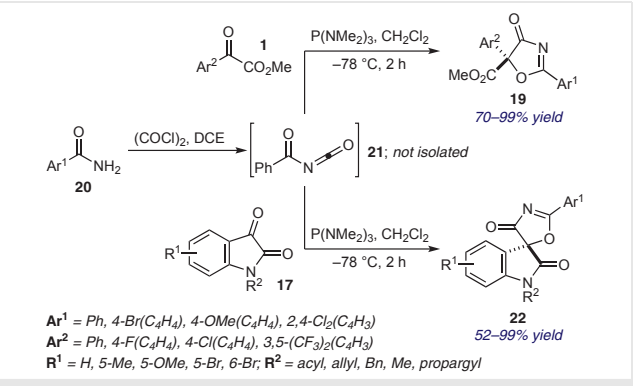


Figure 2 The 3-oxazolone framework and selected biologically active alkaloids bearing the heterocyclic framework

2.3 Aroyl Isocyanates as Four-Atom Synthons for the Assembly of Oxazolines

Our laboratory subsequently utilized Kukhtin–Ramirez reactivity for a (4+1)-cyclization disconnect to access the 3-oxazolone heterocyclic framework **19**, a structural motif found extensively in compounds exhibiting positive biological activity (Figure 2).[29] Prior to this report, arguably the most prominent approach toward oxazolone construction relied on the intramolecular *O*-alkylation of α-halo imides, which are notably susceptible to undesired reactivity hindering the selective formation of **19**.[30]

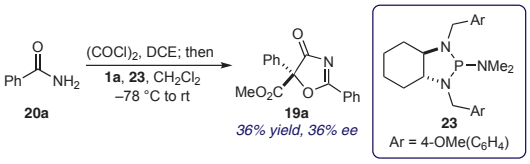
We realized through the utilization of **3** in conjunction with aroyl-isocyanates the synthesis of **19**, bearing C5-substitution, was feasible in good to excellent yields.[17] The synthesis of **19** was enacted *via* treatment of benzamides **20** with oxalyl chloride generating the corresponding isocyanates **21**. The crude isocyanates were then treated with a combination of α-keto esters **1** and $P(NMe_2)_3$ at cryogenic temperatures resulting in the formation of the desired cycloadduct in yields up to 99% yield (Scheme 8).



Scheme 8 Synthesis of C5-substituted oxazolones **19** and spirooxazolones **22**

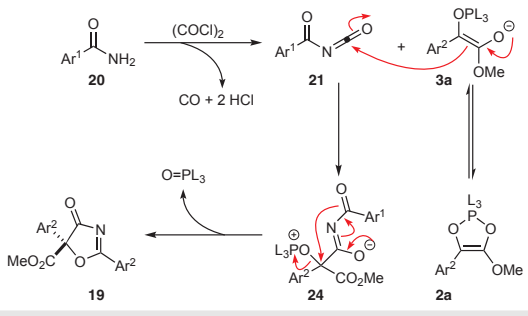
Furthermore, our group discovered that replacement of **1** with isatin derivatives **17** provided access to the corresponding spirooxindole adducts **22** in similar yields (up to 99%), exhibiting the robust nature of the (4+1)-cyclization approach to 3-oxazolones. Aryl substitution of the benzamide precursors included electron-donating groups and halogens, which were well tolerated in yields ranging from 71–99%. Similarly, halogen and trifluoromethyl substitution on the aryl moiety of **1** provided the desired oxazolones in 70–99% yield. We found that expansion of this strategy for the construction of spirooxindole oxazolones **22** was equally effective. *N*-Functionalization as well as aryl substitution including alkyl, halogen, and electron-donating groups at C5 and C6 of the oxindole framework were well tolerated in 52–99% yield. Electron-withdrawing perturbations on the benzamide exhibited a stronger influence on the outcome of the (4+1)-cycloaddition, exemplified by 4-bromo functionalization (55% yield) and the presence of electron-donating 4-methoxy substitution (64% yield). Additionally, *ortho*-aryl substitution of the benzamide led to trace oxazolone formation, we presume due to an increase in steric encumbrance either in the addition of **3** to **21** or upon the subsequent cyclization.

Next, we turned out attention to the role of the trivalent phosphorus reagent in the C–C and C–O bond-forming events of the (4+1)-cycloaddition and examined the asymmetric formation of **19a** through the utilization of an optically enriched trivalent phosphorus reagent.[31] Replacement of $P(NMe_2)_3$ with chiral phosphoramine **23** led to the generation of **19a**, from benzamide **20a** and keto ester **1a**, in 36% yield and 36% *ee* (Scheme 9). This modest level of enantioinduction indicates that **23** is likely present during formation of the stereogenic center at C5 of **19a**.



Scheme 9 Synthesis of optically enriched 3-oxazalone **19a** *via* the introduction of a chiral phosphoramine reagent **23**

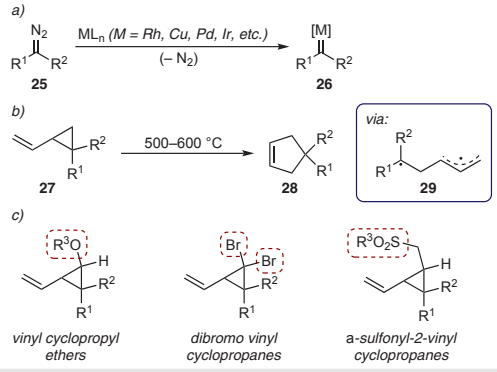
A plausible mechanism for oxazolone formation involves initial formation of isocyanate **21** and the establishment of an equilibrium between oxyphospholene **2a** and oxyphosphonium enolate **3a** upon exposure of α-keto ester **1a** to $P(NMe_2)_3$ (Scheme 10).[15–17,20,21] We propose addition of the nucleophilic enolate **3a** to aroyl-isocyanate **21** first yields zwitterionic intermediate **24**. Subsequent ring closure *via* intramolecular displacement of $O{=}P(NMe_2)_3$ by the imide anion then provides the desired oxazolone **19**. Although a mechanism in which disassociation of $O{=}P(NMe_2)_3$ generates a stabilized carbocation followed by cyclization *via* quenching of the cation cannot be dismissed. However, the moderate enantioinduction observed in the formation of **19a** would indicate that dissociation and carbocation formation is not the dominate pathway.



Scheme 10 Proposed mechanism for the formation of 3-oxazolones **19** through 1,2-addition of **3a** to **21** followed by $O{=}PL_3$ liberation of **24**

3 (4+1)-Cyclizations Employing a Cyclopropanation/Ring-Expansion Sequence

Diazo compounds **25** have exhibited a rich history as C1 synthons serving as ylides and/or precursors to carbenes upon perturbation with light or heat.[32] Additionally, when treated with the appropriate transition metal, diazo compounds form amphiphilic metallocarbene reagents **26** capable of a wide range of transformations including cyclopropanations, C–H insertions, and 1,3-dipolar cycloadditions (Scheme 11a).[33,34] Of these transformations, cyclopropanations are of great interest due to their prevalence in pharmaceuticals, biologically relevant molecules, as well as reagents for organic synthesis.[35,36] The thermal ring expansion of vinyl cyclopropanes **27** is a powerful strategy for the formation of five-membered carbocycles **28**, however, the high temperatures (500–600 °C) in addition to the tentative diradical intermediate **29** limit the efficacy of rendering the rearrangement stereo- and/or chemoselective (Scheme 11b).[37] In response, anion-accelerated variations utilizing substrates such as vinyl cyclopropyl ethers, dibromo vinylcyclopropanes, and α-sulfonyl-2-vinylcyclopropanes have lowered the thermal barrier of ring expansion allowing the rearrangement to proceed at cryogenic temperatures (Scheme 11c). However, due to prerequisite functionalization/multistep preparation to facilitate the desired reaction, the aforementioned substrates often suffer from functional group incompatibilities with base- and redox-sensitive substrates.[38]

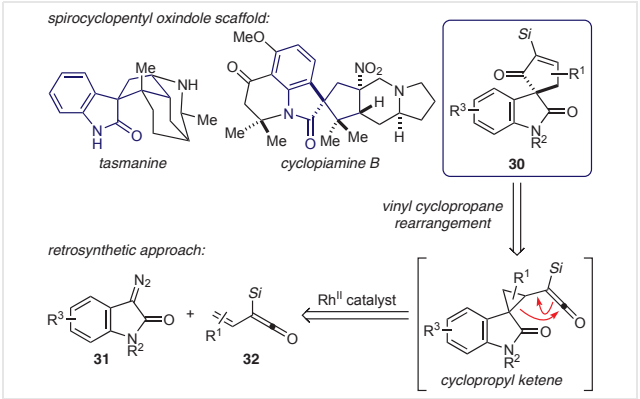


Scheme 11 (a) Diazo compounds and catalysts which facilitate metallocarbene formation; (b) thermal rearrangement of vinyl cyclopropanes **27** to cyclopentenes **28** *via* diradical **29**; (c) previously reported vinyl cyclopropane derivatives capable of rearranging at cryogenic temperatures.

Therefore, methods which provide the desired five-membered carbo- or heterocycle under milder conditions are attractive. Inspired by reports by of Danheiser[39] and Rigby[40] the utilization of vinyl ketenes and vinyl isocyanates as four-atom synthons in conjunction with Rh^{II}-metallocarbenes was reported by our laboratory as a viable retrosynthetic disconnect to afford formal (4+1)-cyclizations.[18,19,41] Through the cyclopropanation/vinyl cyclopropyl rearrangement of cyclopropyl vinyl ketenes/isocyanates *via* 1,3-carbon migration aided by the orthogonal cumulene π-system we realized the synthesis of spirooxindole cyclopentenones and pyrrolones.[18,19,41]

3.1 Vinyl Ketenes as Four-Atom Components for the Synthesis of Spirooxindole Cyclopentenones

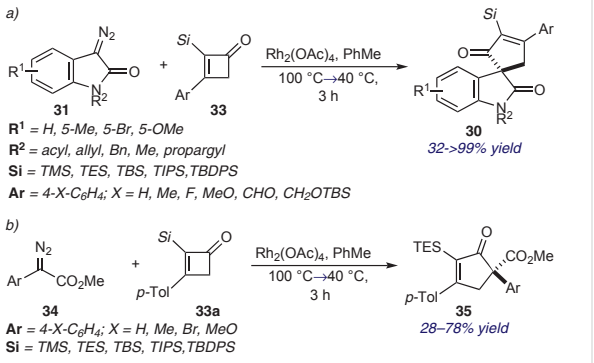
The spirooxindole cyclopentyl framework **30**, a privileged scaffold found in many biologically active oxindole alkaloids (i.e., tasmanine and cyclopiamine B), was targeted and synthesized by our group *via* a (4+1)-cyclization strategy.[42,43] Through employment of donor–acceptor diazo compounds derived from isatins **31**, serving as precursors to metallocarbene C1 synthons, the synthesis of spirooxindoles was recognized utilizing a Rh^{II}-catalyzed cyclopropanation/vinyl cyclopropyl ring expansion of vinyl ketenes **32** (Scheme 12).



Scheme 12 Retrosynthetic analysis of spirooxindoles **30** *via* a formal (4+1)-cyclization strategy arising from the cyclopropanation/vinyl cyclopropyl rearrangement between diazo compounds **31** and vinyl ketenes **32**

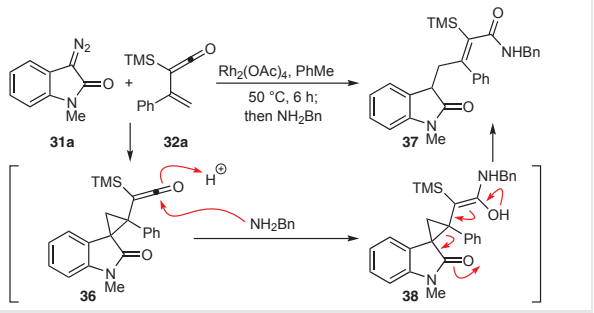
Through employment of α-silyl vinyl ketenes generated in situ *via* the thermal ring expansion of cyclobutenone **33a** (Ar = Ph, Si = TMS)[39] followed by treatment with 5 mol% $Rh_2(OAc)_4$ and diazooxindole **31a** (R^1 = H, R^2 = Me) at 40 °C we discovered cyclopentenone spirooxindole **30a** could be obtained in 91% yield (Scheme 13a). Substitution of **31**, in general, proved tolerable to *N*-acyl, benzyl, allyl, and propargyl functionalization providing the formal (4+1)-cycloadducts **30** in good to excellent yields (60–94%). Similarly, methyl and bromide substitution at C5 of the oxindole arene provided **30** in 77% and 99% yield, respectively. However, incorporation of a strong electron-donating methoxy group at the C5 position resulted in a diminished yield of 36% of the formal cycloadduct. It was realized that modification of silyl group of the **33** (Si = TES, TIPS, TBS, TBDPS) provided the desired oxindole in good to excellent yields ranging from 66–99%. Similarly, upon introduction of elec-

tron-donating groups and halogens on the aryl moiety of **33** cycloadduct **30** was obtained in 74–99% yield. Unfortunately, introduction of *para*-formyl and *ortho*-methyl substitution led to diminished yields of the corresponding spirooxidoles in 55% and 32% yield, respectively. We also extended this (4+1)-cyclization strategy to aryl diazoacetate **34** providing cyclopentenones **35** albeit in slightly depressed yields (28–78%) (Scheme 13b).



Scheme 13 (a) Substrate tolerance of spirooxindoles **30** in the formal (4+1)-cyclization; (b) expansion of the formal (4+1)-cyclization for the synthesis of cyclopentenones **35**.

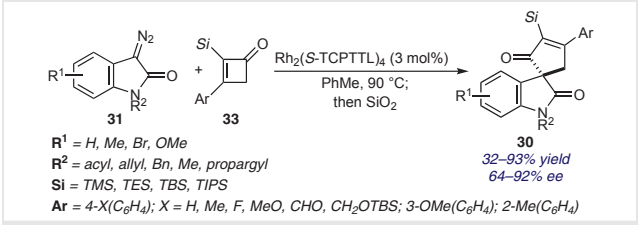
Our laboratory then enlisted a nucleophilic trapping experiment to probe the validity of the proposed cyclopropyl ketene intermediate **36** (Scheme 14). Introduction of $BnNH_2$ to the reaction following consumption of **31a** provided the corresponding amide **37** in 34% yield. We rationalized the formation of **37** by nucleophilic attack of **36** at the ketene carbon by $BnNH_2$ to yield enol **38**, which upon a π-assisted cyclopropyl ring opening followed by tautomerization provides **37**. Furthermore, we monitored the formation of cyclopropane **36** and subsequent ring expansion to **30a** *via* ^{1}HNMR spectroscopy. Additionally, **36** was isolated and characterized by X-ray crystallography and subsequently shown to convert into **30** under the optimized reaction conditions.[18,41]



Scheme 14 Confirmation of cyclopropane **36** *via* a nucleophilic trapping experiment utilizing benzyl amine as the sequestering agent

3.2 Enantioselective Construction of Spirooxindole Cyclopentenones *via* a 1,3-Carbon Shift of Cyclopropyl Ketenes

Confirmation of intermediate **36** in the synthesis of **31** inspired the development of an asymmetric (4+1)-cyclization exploiting an enantioselective cyclopropanation followed by 1,3-carbon migration. The synthesis of enantioenriched spirooxindoles was examined through employment of chiral carboxylate/amidate Rh^{II} catalysts, disclosed by Davies and Doyle, for enantioselective cyclopropanations and C–H insertions.[44] Our laboratory achieved the asymmetric transformation through utilization of Rh_2(*S*-TCPTTL)$_4$ in the presence of diazooxindoles **31** and vinyl ketenes derived from cyclobutenones **33**. Following asymmetric cyclopropanation, the addition of SiO_2 provided the corresponding cycloadducts **30** with yields and enantiomeric excesses up to 93% and 92%, respectively (Scheme 15).



Scheme 15 Enantioselective construction of spirooxindoles **32** *via* asymmetric cyclopropanation followed by 1,3-carbon migration

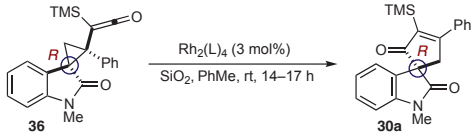
Evaluation of the structural diversity across diazooxindole **31** exhibited moderate yields (43–75%) and high enantiomeric excess (84–86% *ee*) when the arene moiety was substituted with electron-rich substituents at C5, C6, and C7, while alkyl and halogen substitution at C5 provided the cycloadduct in 93% yield, 90% *ee* and 90% yield, 77% *ee*, respectively. Additionally, functionalization of the nitrogen with *N*-acyl, benzyl, allyl, and propargyl proved viable providing **30** yields ranging from 68–91% and enantiomeric excesses of 72–91%. Variations of the α-silyl group on **33** did not impact the enantioselectivity in a negative fashion, however, yields tended to decrease with the increased size (TES > TBS > TIPS). Conversely, substitution of the aryl moiety with election-rich and electron-poor functional groups resulted in low to moderate yields (32–85%) and moderate to high *ee* (64–88%), with *ortho* substituents resulting in the lowest yield and enantiomeric excess (32% yield, 64% *ee*). It is worth noting that our group observed modest improvements in yield and enantioselectivity for several substrates when the reaction was performed at 4 °C over 48 h, which we attest to the influence of electronic perturbations on the 1,3-stereoselective quaternary carbon migration.

The reaction of **31a** and the vinyl ketene derived from **33a** at depressed temperatures provided cyclopropyl ketene **36** which we observed as a single diastereomer in 95% *ee*. The stereochemical outcome *en route* to cycloadduct **30a**

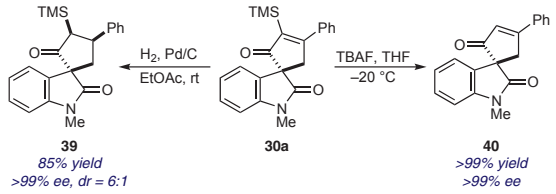
from cyclopropyl intermediate **36** was monitored and discovered to rearrange upon addition of SiO_2 providing the cycloadduct in 73% yield and 90% *ee*. Furthermore, analysis of cyclopropyl ketene **36** *via* X-ray crystallography revealed a *syn*-relationship of the oxindole arene and ketene across the cyclopropane in an *R* configuration at the C3-oxindole quaternary center. Upon our analysis of the X-ray crystal structure obtained for enantioenriched **30a** and cyclopropyl ketene **36** we discovered the outcome was a net stereoretentive migration at the C3-oxindole.

Next, we turned our attention to determining the mechanistic role/influence of a chiral Rh^{II} catalyst in optical enrichment *via* several control experiments (Table 1). Treatment of racemic **36** with Rh_2(*S*-TCPTTL)$_4$ led to no optical enrichment of **30a** (Table 1, entry 1). Additionally, treatment of enantioenriched **36** with $Rh_2(OAc)_4$ led to an enantioenriched cycloadduct **30a**, and upon omission of the catalyst a similar outcome was observed leading to the conclusion that the Rh^{II} catalyst installs the stereochemical information during the cyclopropanation event and is not involved in ring expansion (Table 1, entries 2 and 3). Additionally, our laboratory was successful in enacting several synthetic modifications of **30a** including reduction of the alkene functionality to provide cyclopentanone **39** and protodesilylation yielding cyclopentenone **40**. In both cases the reaction proceeded in high yield and retained the stereochemical information installed during the formal (4+1)-cyclization between **31** and **33** (Scheme 16).

Table 1 Control Experiments Determining the Role of the Chiral Rh^{II} Catalyst



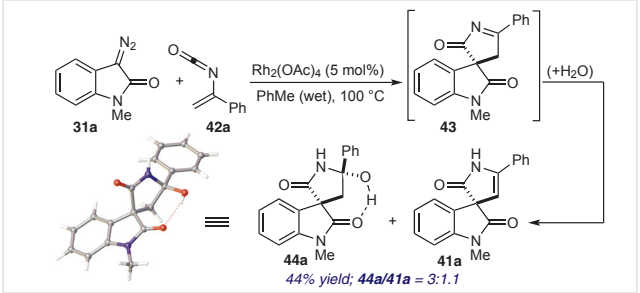
Entry	**36** *ee* (%)	L	Yield (%)	**31a** *ee* (%)
1	0	*S*-TCPTTL	>99	0
2	94	OAc	>99	84
3	94	no catalyst	>99	86



Scheme 16 Functionalization of enantioenriched spirooxindole **30a** to provide derivatized spirooxindole products **39** and **40**

3.3 Vinyl Isocyanates as Four-Atom Components for the Synthesis of Spirooxidole Pyrrolones

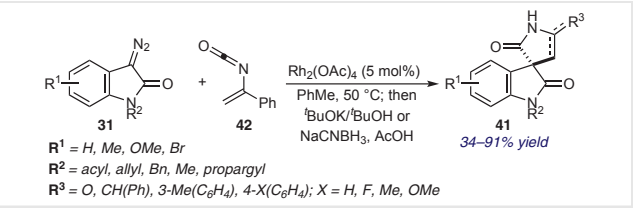
Additionally, our efforts led to a complimentary Rh^{II} method for the synthesis of spirooxindole pyrrolone **41a** through the vinyl cyclopropyl ring-expansion sequence between diazooxindole **31a** and vinyl isocyanate **42a**.[45,46] Initial attempts to afford the (4+1)-cyclization were met with difficulty due to the instability of intermediary acyl imine **43** (Scheme 17). However, we discovered that introduction of advantageous water *via* wet PhMe provided a mixture of acyl ene-amide **41a** and hemiaminal **44a** in a 3:1.1 ratio in a combined yield of 44%,[19] where cycloadduct **44a** was isolated as a single diastereomer confirmed by X-ray crystallography. Interestingly, upon addition of water (1.0 equiv) **31a** was degraded to *N*-methyl isatin, illustrating a delicate balance in the concentration of trapping agent employed.



Scheme 17 Initial discovery of (4+1)-cyclization between diazooxindole **32a** and vinyl isocyanate **42a** providing spirooxindoles **44a** and **41a**

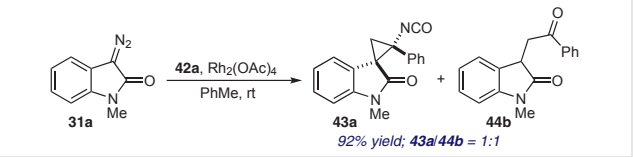
We then turned our attention to the (4+1)-cyclization between vinyl isocyanates **42** and diazooxindoles **31**, optimizing the selective formation of **41**. This outcome was achieved through a combination of **42** and $Rh_2(OAc)_4$, in conjunction with diazooxindoles **31**, followed by sequential addition of *t*-BuOH/*t*-BuOK yielding **41** in yields up to 91%. Evaluation of functional group compatibility proved tolerable to substitution of the diazooxindole in good to excellent yields of the cycloadduct (Scheme 18), with protection of *N*-acyl and benzyl providing the desired spirooxindole in 80–84% yield. Additionally, *N*-allyl and propargyl substrates performed in 77–79% yield without competitive alkene/alkyne cycloaddition. It was realized that functionalization at R^1 with electron-donating groups as well as halogens was tolerated on C5–7 in yields ranging from 53–76%. While, variation of the olefin moiety on vinyl isocyanate **42** provided similar yields (64–89% yield), however, with an inverse trend compared to the diazooxindole, with electron-withdrawing groups providing higher yields (≤82%). Furthermore, highlighting the stereoelectronic influence on penultimate 1,3-carbon migration we observed in the previous study. Unfortunately, tri- and tetrasubstituted **42** failed to provide the corresponding cycloadduct **41** in great-

er than trace quantities. However, we discovered that when a silyl enol ether moiety was substituted for the vinyl functionality the corresponding spirooxindole succinamide was obtained, highlighting the substrate tolerance of the aforementioned (4+1)-cycloaddition, providing access to another class of biologically relevant scaffolds.



Scheme 18 Substrate tolerance of **31** and **42** for the synthesis of spiropyrrolone oxindoles **40**

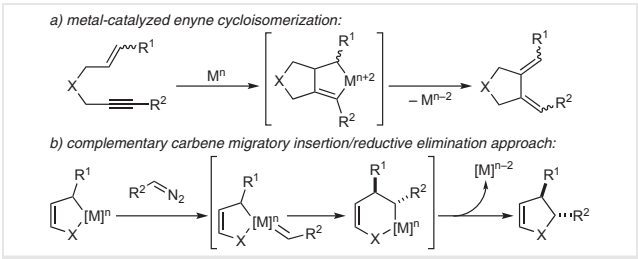
Furthermore, reductive conditions employing $NaCNBH_3$, in replacement of *t*-BuOH/*t*-BuOK, as the trapping agent allowed for the isolation of a spirooxindole lactam in 80% yield as a 1.2:1 mixture of diastereomers. We obtained mechanistic insight into the formal (4+1)-cycloaddition, through isolation of the presumptive spirooxindole cyclopropyl isocyanate **43**. Performing the Rh^{II}-catalyzed cyclopropanation of diazooxindole **31a** and vinyl isocyanate **42a** (R^3 = Ph) at room temperature was sufficient in halting the subsequent ring expansion enabling isolation of cyclopropane **43a** as a single diastereomer in a 1:1 mixture consisting of ketone **44b** in 92% combined yield (Scheme 19); where ketone **44b** arises presumably from advantageous water reacting with **43a** during purification.



Scheme 19 Validation of a cyclopropyl isocyanate intermediate **43a** and degradation to ketone **44b** *via* depression of reaction temperature

4 Pd-Catalyzed (4+1)-Cyclizations through Carbene Migratory Insertion/Reductive Elimination Processes

The success of cycloadditions occurring through an initial cyclopropanation/1,3-carbon migration of vinyl ketenes and/or vinyl isocyanates employing Davies' chiral Rh^{II}-carboxylate complex inspired our laboratory to examine underutilized transition metals as potential catalysts for (4+1)-cyclizations. The Wang and Van Vranken groups have revealed the utility of Pd carbenes in a variety of different cross-couplings with aryl/alkyl halides,[47] boronic acids,[48] and nitrogen/carbon nucleophiles[49] in which the key mechanistic step involves a migratory insertion as the critical C–C bond-forming event. This alteration in reaction profile offers a unique approach to (4+1)-cyclizations accessing heterocycles through the exploitation of a migratory insertion/reductive elimination cascade reminiscent of Pd-catalyzed enyne and diene cycloisomerizations (Scheme 20a).[50] Unfortunately, a significant impediment to expanding Pd–carbene chemistry arises in the difficulty in diverting favorable β-hydride elimination(s). However, through the incorporation of internal nucleophiles, β-elimination has proven unfavorable, promoting the extrusion of a Pd^{II} catalyst through reductive elimination yielding a new C–C, C–N bond (Scheme 20b).

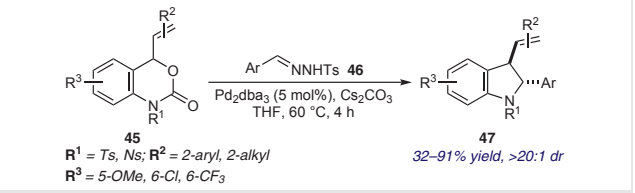


Scheme 20 (a) Previous enyne cyclization strategy for the construction of five-membered frameworks; (b) complimentary (4+1)-cyclization strategy *via* carbene migratory insertion/reductive elimination cascade.

4.1 Diverting β-Hydride Elimination of Pd^{II}-Allyl Carbene Complexes for the Assembly of Disubstituted Indolines

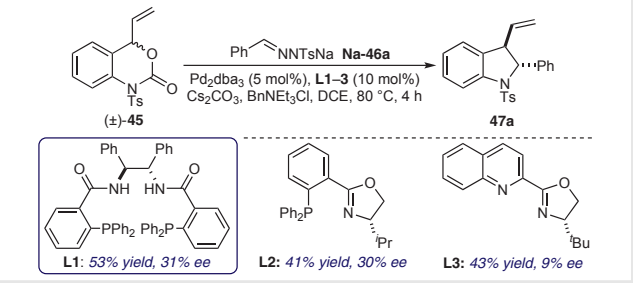
We realized a Pd-catalyzed (4+1)-cycloaddition, whereby β-hydride elimination was circumvented, through the utilization of vinyl benzoxazinones **45** with *N*-tosylhydrazones **46** under virtually ligandless conditions with Pd_2dba_3 and Cs_2CO_3 in THF providing substituted 2,3-dihydroindoles **47** in 32–91% yield as single diastereomers.[51] It is noteworthy that upon introduction of ligands the yields of the reaction significantly decrease, presumably due to saturation of the Pd center. Evaluation of the architectural limitations of vinyl benzoxazinone **45** proved tolerable to olefin substitution with R^2 alkyl and aryl substitution at C2 (90–91% yield; Scheme 21). However, this methodology proved sensitive to alkene functionalization for either mono- or disubstitution, at the terminal position failing, to provide the desired cycloadduct. Additionally, our efforts in benzylic functionalization were not tolerated under the reaction conditions. Nevertheless, *N*-substitution with sulfonyl protecting groups provided **47** in yields ranging from 52–87%. Functionalization of the arene was well tolerated, providing the 5-chloro, 5-CF_3, and 4-methoxy functionalized product in 82%, 57%, and 52%, respectively. Substitution of the aryl hydrazones **46** with resonance electron-donating groups provided **47** in 51–71% yield. While electron-withdrawing functionalities provided the cycloadduct in low to moderate yields (39–55%). Alkyl and halogen

substitution underwent the cyclization in 32–61% yields, with *ortho* substitution leading to depressed yields. Furthermore, we expanded this methodology to direct alkenyl substitution providing the (4+1)-cyclized product in 72% yield. It is noteworthy that when utilizing the aforementioned (4+1)-cyclization we observed >20:1 dr for all substrates in favor of the *anti*-diastereomer bolstering the diastereoselectivity of the reaction.



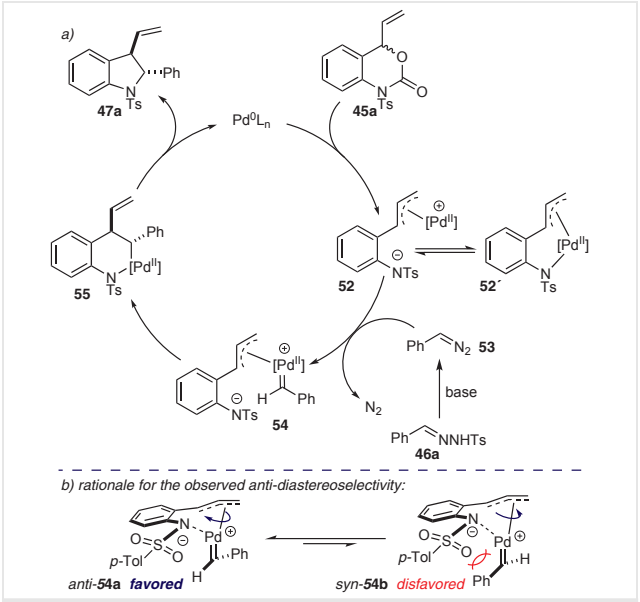
Scheme 21 A (4+1)-cyclization providing dihydroindoles **47** *via* carbene migratory insertion and suppression of β-hydride elimination

We then turned our attention to optically enriched cycloadducts *via* a dynamic kinetic asymmetric transformation (DyKAT). Under slightly modified conditions, utilizing sodium sulfonate **Na-46a**, Pd_2dba_3, stilbene diamine ligand **L1**, Cs_2CO_3, and $BnNEt_3Cl$, **47a** was obtained in 53% yield and 31% *ee* (Scheme 22), while a variety of ligands (**L2** and **L3**) were tested and all failed to improve the yield or optical enrichment of **47a**.



Scheme 22 Dynamic kinetic asymmetric transformation of **45** into **47a** and selected ligands screened for enantioinduction

In consensus with the reports by Wang and Van Vranken, the proposed mechanism for the formation of **47** is displayed in Scheme 23a.[47a,48c,52] We proposed an initial oxidative decarboxylation of **45a** *via* Pd^0 provides π-allyl Pd^{II} complex **52**, which exists in equilibrium with metallocycle **52′**.[53] Desulfonylation of hydrazone **46a** followed by decomposition of the diazo compound **53** yields Pd-allyl carbene **54**.[54] Though a diastereoselective migratory insertion the six-membered palladacycle **55** is generated, which upon reductive elimination provides cycloadduct **47a**. However, we cannot discount an outer-sphere mechanism involving attack on the π-allyl ligand by diazo compound **53**.[53b] The observed diastereoselectivity is proposed to arise from minimization of steric interactions between the aryl substituent on the Pd-stabilized carbene and the *N*-sulfonyl group of intermediate **54** (Scheme 23b).



Scheme 23 (a) Proposed mechanism for the Pd-catalyzed formal (4+1)-cyclization; (b) plausible origin of diastereoselectivity for *anti*-**54**.

Presuming the stereodetermining step is C–C formation *via* migratory insertion of the carbene to the π-allyl ligand of **54** leading to the favored isomer through intermediate *anti*-**54a**. Conversely, intermediate *syn*-**54b** would provide the unobserved stereoisomeric dihydroindole. The favored *anti*-**54a** orients the hydrogen of the carbene in a *syn*-relationship to the *N*-sulfonyl group minimizing the steric interactions present in *syn*-**54b**. While a dynamic equilibrium process *via* bond rotation between *anti*-**54b** is proposed to account for our exceptional levels of diastereoselectivity in the (4+1)-cyclization.

5 Summary

This Account has summarized the growing efforts in (4+1)-cyclization methodologies and the possibilities of this underutilized retrosynthetic disconnect. Through this technology our laboratory has realized the synthesis of privilege scaffolds including 2,3-dihydrobenzofurans, 2,3-dihydroindoles, 3-oxazolones, cyclopentenones, and pyrrolones. The heterocycles 2,3-dihydrobenzofurans, 2,3-dihydroindoles and oxazolones were constructed employing Kukhtin–Ramirez-like reactivity utilizing trivalent phosphine as an organocatalyst. The 1,2- or 1,4-addition of oxyphosphonium enolates derived from 1,2-dicarbonyls to *o*-QMs/aza-*o*-QM/aroyl isocyanates was shown to generate zwitterionic intermediates bearing internal nucleophiles capable of C–N/C–O bond formation, which were achieved due to thermodynamically favorable intramolecular displacement of phosphine oxide affording the penultimate cyclization. The spirooxindole frameworks were synthesized *via* vinyl cyclo-

propyl/cyclopentene rearrangements utilizing donor–acceptor Rh^{II}-metallocarbenes in the presence of vinyl ketenes and vinyl isocyanates, respectively. Furthermore, we disclosed the synthesis of enantioenriched spirooxindole cyclopentenones *via* a stereoretentive 1,3-carbon migration. The aforementioned methodologies have presented the viability of reducing the kinetic barrier of vinyl cyclopropane/cyclopentane rearrangements through the introduction of an orthogonal π-system, which, present in cumulenes/heterocumulenes, are capable of facilitating the key 1,3-carbon migration under impressively mild conditions with high degrees of stereo- and chemoselectivity. Finally, our laboratory discovered a highly diastereoselective synthesis of 2,3-disubstituted dihydroindoles utilizing Pd^{II}-metallocarbenes. Through an underutilized C–C bond-forming migratory insertion of Pd^{II}-allyl carbene complexes followed by C–N bond formation *via* reductive elimination the formal (4+1)-cyclization was realized. Furthermore, the reported Pd-metallocarbene chemistry exemplifies an expansion of the field where upon suppression of β-hydride elimination valuable bond-forming events are achieved.

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