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Dual Catalysis in Rhodium(II) Carbenoid Chemistry

Anae I. Bain[+],[a] Kiran Chinthapally[+],[a] Arianne C. Hunter[+],[a] and Indrajeet Sharma*[a]

Dual catalysis represents an alternative archetype in carbene chemistry that surpasses traditional single catalyst systems. By employing dual catalyst systems, one can improve the efficiency of existing reactions and enable new chemical transformations. Reactions involving dual synergistic catalysis are increasingly valuable as they offer convenient strategies for synthesizing challenging quaternary carbon centers and bioactive core structures. This review article focuses on trapping diazo-derived, rhodium (II) zwitterionic intermediates with varying electrophiles such as Michael acceptors, alkynes, π-allyl Pd(II) complexes, and the Nicholas intermediate.

1. Introduction

Simultaneously engaging two catalysts to initiate a chemical reaction can offer unique opportunities for the rapid construction of molecular complexity.[1] In particular, dual synergistic catalysis, a mode of catalysis where two catalytic cycles cooperatively work to enable new bond formation, has become a unique tool in reaction design.[2] Dual catalysis is emerging as a more efficient and complementary approach to traditional mono-catalytic systems,[3] where only one substrate is catalytically activated and altered. Dual synergistic catalysis involves two catalysts that independently activate two separate substrates. This concurrent activation creates two reactive species that can rapidly react to form a new bond.[2] This differs from other multicatalyst systems, such as double activation catalysts, where two catalysts work cooperatively to activate a single substrate[2,4] or cascade/relay catalyst systems that require the systematic activation of a single substrate.[5] Often, these systems are more efficient than traditional single catalysts and enable new transformations not possible in monocatalytic systems.[2,6]

Dual catalysis has been far less explored due to the difficulty of identifying two catalysts with compatible reactivities and turnover pathways.[7] Likewise, the metals involved must be redox compatible to avoid catalyst deactivation. In rhodium carbenoid dual catalysis systems (Figure 1), the role of rhodium is primarily to decompose the diazo species, forming the electrophilic rhodium carbenoid. Once formed, a substrate activated by the second catalyst can react with the carbenoid, often in a highly diastereo- and enantioselective manner.

Diazo-derived metal carbenes have generated considerable recognition in the chemical community.[8] Rh(II) carbenoids are particularly significant as they are capable of performing novel transformations such as cyclopropanations,[9]

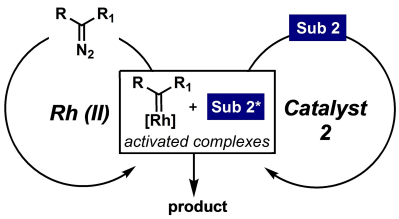

Figure 1. Conceptual visual of dual synergistic catalysis in rhodium carbenoid chemistry.

cyclopropenations,[10] insertion reactions (C–H, N–H, O–H, S–H, B–H),[11] trifluoromethylations,[12] dipolar additions,[13] cascades,[8j] and rearrangement reactions.[14] Rh(II) carbenoids can participate in a wide range of transformations due to their convenient generation, relative stability, controlled reactivity in typical catalytic reactions, and redox compatibility with various transition metals.[15] These characteristics make Rh(II) carbenoids ideal substrates for dual catalysis. Rh(II) carbenoids generated from the decomposition of diazo compounds are electrophilic in nature and can undergo reactions with protic nucleophiles (O–H, N–H, S–H, C–H) to generate activated zwitterionic intermediates.[13,16] This zwitterionic intermediate has the propensity to undergo one of two distinct pathways; i) protodemetallation to form the corresponding insertion product, or ii) trapping by an activated electrophile to create a new bond (Figure 2).

Following protodemetallation, often, the insertion product cannot undergo the secondary transformation when exposed to the second catalyst. This phenomenon highlights the necessity of a synergistic dual catalysis system.[17] The major challenge in synergistic catalysis in rhodium carbenoid chemistry is stabilizing the reactive zwitterionic intermediate to avoid undesired protodemetallation.

This review provides a non-comprehensive survey of recent advances in trapping zwitterionic intermediates derived from Rh(II) carbenoids with various activated electrophilic species. Specifically, we have highlighted the recent advances of trapping Rh(II) carbenoids with i) Michael acceptors, ii) activated alkynes, and iii) π-allyl Pd(II) complexes, among other electrophiles. This review will focus on dual metal-catalyzed reactions

[a] A. I. Bain,[+] Dr. K. Chinthapally,[+] Dr. A. C. Hunter,[+] Prof. I. Sharma
Department of Chemistry and Biochemistry, University of Oklahoma
101 Stephenson Parkway, Norman, OK-73019, USA
E-mail: indrajeetsharma.com
E-mail: isharma@ou.edu

[+] Anae I. Bain, Kiran Chinthapally, and Arianne C. Hunter, all contributed equally as first author.

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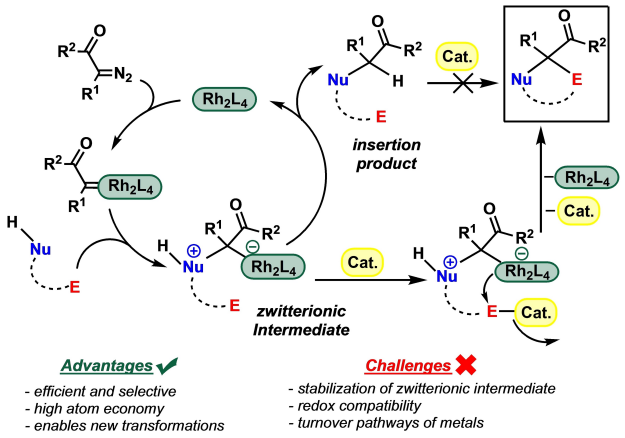


Figure 2. A mechanistic overview of dual catalysis in rhodium(II) carbene chemistry.

while also encompassing recent rhodium/organocatalytic transformations within these parameters not previously reviewed. Although there are several reviews on cooperative and synergistic catalysis[5a,6,18a,b–d] and rhodium carbenoids,[19] no single review focuses on the synergism of bimetallic, Rh(II)-mediated reactions. As such, we have accumulated recent literature to highlight the resourcefulness of these transformations.

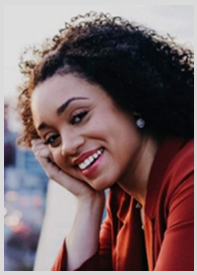
2. Trapping Zwitterionic Intermediates with Michael Acceptors

Chemists have used the Michael reaction for decades as an efficient method to synthesize functionalized sp^3 carbon centers in a single step.[20] The Michael reaction involves the addition of a nucleophile to an α,β-unsaturated carbonyl, cyano, or nitro group. This conjugate addition serves as an efficient and mild protocol for practical C–C bond formation.[21] These reactions typically exhibit high atom economy as well as high diastereo- and enantioselectivities when a chiral catalyst is employed. These qualities make catalytically-activated Michael acceptors ideal substrates to participate in multicomponent reactions with Rh(II) carbenoids in catalytic cascades.

In 2018, Feng *et al.* used a Rh(II)/Sc(III) catalytic system for the synthesis of chiral indoline derivatives through the intramolecular trapping of zwitterionic ammonium intermediates derived from α-diazoketones (Figure 3).[22] To initiate their studies, the authors screened various Lewis acids and ligands derived from L-proline, L-ramipril, and L-pipecolic acid in combination with $Rh_2(OAc)_4$. The authors identified $Rh_2(OAc)_4$

Anae Bain was born in Nassau, Bahamas. She received her B.S. from Taylor University in May 2017, under the guidance of Dr. Dan Hammond. There, her research surrounded examining hydrocarbon content in freshwater algae species. Following her graduation, she moved to Norman, Oklahoma, where she joined the Sharma Research Group at the University of Oklahoma under the direction of Indrajeet Sharma in the Spring of 2018. Currently, her work focuses on carbene-mediated methodology development, specifically targeting spirocyclic and carbohydrate-based motifs.

Dr. Kiran Chinthapally obtained his Ph.D. in 2015 from IIT Hyderabad for his work in the studies directed towards the synthesis of biologically active molecules under the guidance of Professor Sundarababu Baskaran. After his Ph.D., Kiran moved to the University of Oklahoma as a postdoctoral research associate in the laboratory of Dr. Indrajeet Sharma. In Dr. Sharma's lab, his research focused on the carbene-initiated synthesis of medium-sized heterocycles. Currently, he is working as a postdoctoral associate at the University of Notre Dame under Dr. Brian Blagg.



Dr. Arianne Hunter obtained her B.A. in Chemistry at Dartmouth College in 2014 under Dr. Gordon Gribble. In the Fall of 2014, Arianne joined the laboratory of Dr. Indrajeet Sharma at the University of Oklahoma, where she was a fully-funded SMART Department of Defense Scholar and Nancy L. Mergler Dissertation Completion Fellow. In Dr. Sharma's laboratory, her research was focused on developing carbene cascade spirocyclizations and annulations for the efficient synthesis of underexploited scaffolds in drug discovery. Currently, she is working as a Forensic Chemist at the U.S. Army Criminal Investigation Laboratory.

Dr. Indrajeet Sharma obtained his M.Sc. degree from IIT Kharagpur in 2006, where he worked with Professor Dipakranjan Mal studying the Hauser Annulation reaction to synthesize anthraquinones. He then began his Ph.D. studies in glycopeptide chemistry with Professor David Crich at the University of Illinois at Chicago. He then moved with him to Wayne State University in 2007, where he completed his degree in 2011. After a postdoctoral position at Memorial Sloan-Kettering Cancer Center with Professor Derek S. Tan, Dr. Sharma began his independent career at The University of Oklahoma in 2014. His research focuses on the development of new synthetic methods based on metal carbene chemistry and their applications in total synthesis and drug discovery.

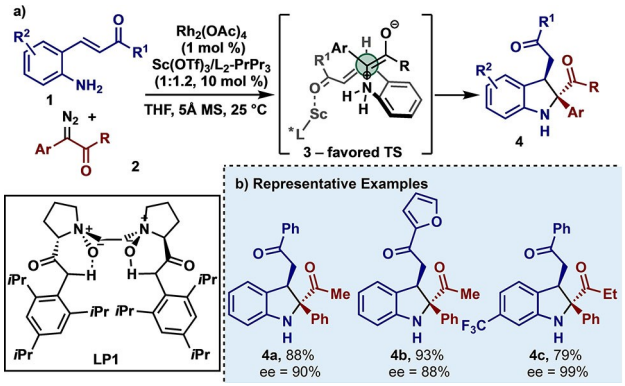


Figure 3. a) Rh(II)/Sc(III) catalyzed asymmetric trapping of Michael acceptors for the synthesis of functionalized indolines; b) Representative Substrate Scope.

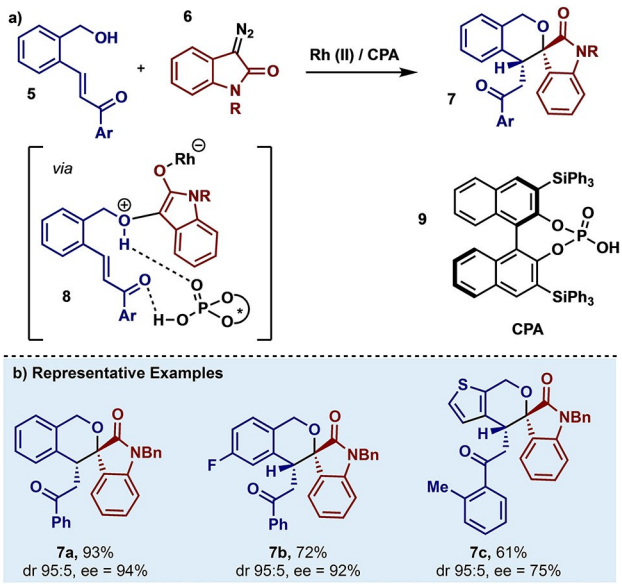


Figure 4. a) Rh(II)/CPA catalyzed reactions of diazo oxindoles and *o*-hydroxymethyl chalcones; b) Representative Substrate Scope.

and $Sc(OTf)_3$ in the presence of L-proline derived ligand **LP1** as the ideal conditions for the desired transformation. Once the optimized conditions were identified, the authors investigated the overall applicability of the reaction. A variety of 2-aminophenyl-substituted enones were explored. The parent substrate **4a** was synthesized in 88% yield with good enantioselectivity. Additionally, furan-substituted enone underwent the desired transformation to produce **4b** in a 93% yield. Lastly, changing the alkyl substituent from methyl to ethyl decreased the yield of **4c** to 79%. However, the enantioselectivity was increased significantly to 99%, presumably due to steric crowding in transition state **3**.

The N–H insertion product was exposed to standard conditions to verify whether the transformation occurs sequentially; however, the desired indole was not formed. This observation corroborates that this transformation indeed occurs via a synergistic pathway.

In 2020, Hu *et al.* reported a rhodium/chiral phosphoric acid co-catalyzed enantioselective intramolecular Michael-type trapping of oxonium ylides to construct chiral spirochroman-3,3-dioxindole derivatives (Figure 4).[23] The authors concluded their optimization studies with the identification of $Rh_2(OAc)_4$ and chiral phosphoric acid **9** as the optimal co-catalysts. With these conditions, the authors then synthesized a variety of enantioenriched oxabicyclic dibenzooxacines in good yields with high enantio- and diastereoselectivities. Both electron-withdrawing and donating substituents on the aryl ring were compatible with reaction conditions. As such, the related products were synthesized in high yields (up to 93%) with excellent enantioselectivities (up to 94%). Notably, the thiofuran-chalcone derivative was also well-tolerated to afford the novel spiro[indolinethienopyran]-2-one **7c** in good yield (61%) with 75% ee. Moreover, the reaction was also performed at a gram-scale with low catalyst loading (0.1 mol% $Rh_2(OAc)_4$ and 1.0 mol% of chiral binol phosphoric acid).

Several control experiments were conducted to verify this system's possible mechanistic pathway. In one such study, the O–H insertion product was exposed to the parent conditions. However, this failed to deliver the desired scaffold. Additionally, when the parent substrates were exposed to the Brønsted acid alone, the desired dibenzooxacines were not observed. These results indicate the necessity of a dual catalyst system to permit the desired transformation.

In 2018, Hu *et al.* reported a Rh(II)/Sc(III) co-catalyzed three-component reaction of diazo compounds with thiophenols and enones (Figure 5).[24] Various sulfur-substituted ketones were synthesized with this strategy in moderate to high yields with good diastereoselectivities. This transformation is thought to proceed through a sulfonium zwitterionic intermediate (**16**/**17**) generated *in situ* from the rhodium carbenoid **15** and thiophe-

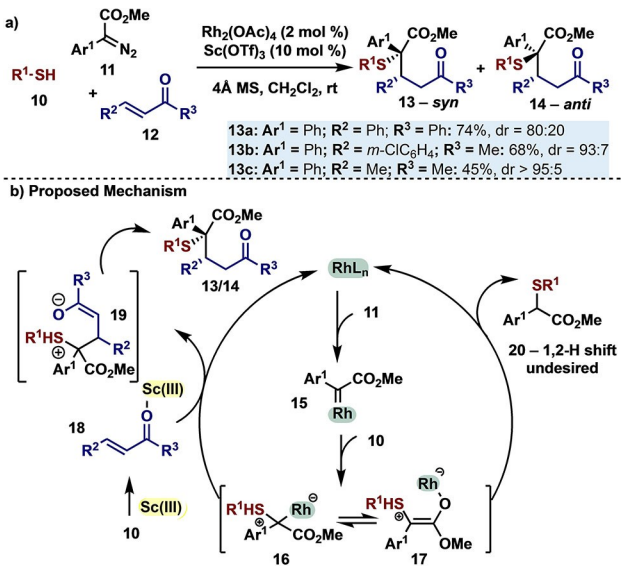


Figure 5. a) Rh(II)/Sc(III) catalyzed trapping of Michael acceptors for the synthesis of γ-sulfur substituted ketones; b) Proposed Mechanism.

nol **10**. The protic sulfonium zwitterionic intermediate is immediately trapped by the electrophilic enone that is cooperatively activated by Sc(III) to give the desired three-component adduct **13/14** via a Michael-type addition.

Once the optimized conditions were identified, the authors investigated the overall applicability of the three-component reaction (Figure 5a). The parent substrate **13 a** was produced in a 74% yield with a moderate stereoselectivity. However, substituting the alkenyl aryl ring of the enone with a *meta*-chloro substituent significantly increased the diastereoselectivity (**13 b**). Other electron-deficient and electron-rich substituents on the aryl ring of the alkenyl terminal of the enone provided the desired three-component products in decent yields with good diastereoselectivities. When a methyl or ester group was present at the β-position of the unsaturated ketone, the reaction also proceeded, albeit in a slightly decreased yield. Moreover, various *para*-substituted thiophenols were examined, and the desired three-component adducts were obtained in good yields with high diastereoselectivities. Further, different substituted aryl diazoacetates were used, and all provided the desired adducts in high efficiency regardless of electronic character.

When completing control experiments, the authors exposed the S–H insertion product to chalcone **12**. However, the three-component adduct was not formed. This indicated that the transformation likely proceeds through an *in situ* Michael-type sulfonium ylide trapping pathway as opposed to a stepwise S–H insertion/Michael addition.

In 2020, Qian *et al.* optimized a Rh(II)/phosphoric acid-catalyzed three-component reaction for the formation of azonaphthalenes (Figure 6).[25] To optimize this strategy, the authors treated diazoacetophenone **22**, azonaphthalene **23** and benzyl alcohol with $Rh_2(OAc)_4$ and phosphoric acid **28**. Initial optimization studies only furnished a mixture of regioisomers for the *N*-addition adduct. Further studies disclosed the need for a sterically hindered aryl ring on the azonaphthalene system, such as a 2,4,6-trichloro substitution to form the desired annulated product. Mechanistically, this reaction is initiated by the capture of oxonium intermediate **26**, via an sp^2 C–H insertion, as opposed to an *N*-addition. This is followed by a rearomatization/cyclization sequence to furnish the desired azonaphthalene **25**.

Once optimal conditions were identified, the authors explored a substrate scope. The parent substrate **25 a** was synthesized in a 70% yield. Electron donating (**25 d, 25 f**) and electron-withdrawing (**25 b, 25 e**) analogues were also synthesized in moderate yields. Lastly, the sterically hindered ^{t}Bu analogue (**25 c**) was synthesized in a moderate yield.

Gong *et al.* reported a Rh(II)/urea catalyzed enantioselective semipinacol rearrangement/Michael addition cascade (Figure 7).[26] This work was the first report of a rhodium/chiral urea dual catalysis system. Reaction optimization led to the identification of $Rh_2(OAc)_4$ and squaramide **35** as the optimal co-catalysts to facilitate their desired transformation. Mechanistically, the authors hypothesized that following a Rh(II)-catalyzed diazo decomposition, Rh-carbenoid **32** would undergo a semipinacol rearrangement to afford intermediate **33**. Rhodium catalyst regeneration would then supply product **34**, which would *in situ* undergo an enantioselective Michael addition.

Once optimization studies were completed, the authors investigated the generality of this protocol for diazo alcohols **29**. The parent substrate **31 a** was synthesized in an 81% yield and excellent enantioselectivity. However, a 1:1 mixture of diastereomers was formed with these conditions. Additional substitution α- to the diazo hydroxyl group slightly improved diastereoselectivity, as seen in the propargyl analogue, **31 b**. The authors then employed this methodology to synthesize quaternary stereogenic centers by employing tertiary diazo alcohols. The desired ring-expansion products were well tolerated, and various ring sizes were synthesized in yields up to 99% in excellent diastereoselectivities and enantioselectivities (**31 c**–**31 f**).

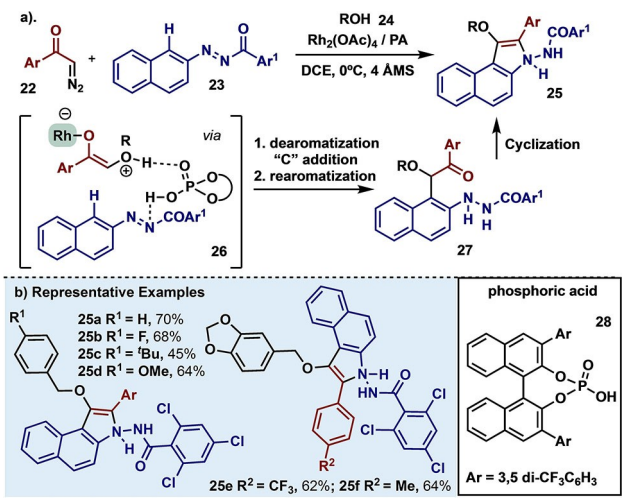


Figure 6. a) Rh(II)/phosphoric acid catalyzed oxonium ylide trapping; b) Representative Substrate Scope.

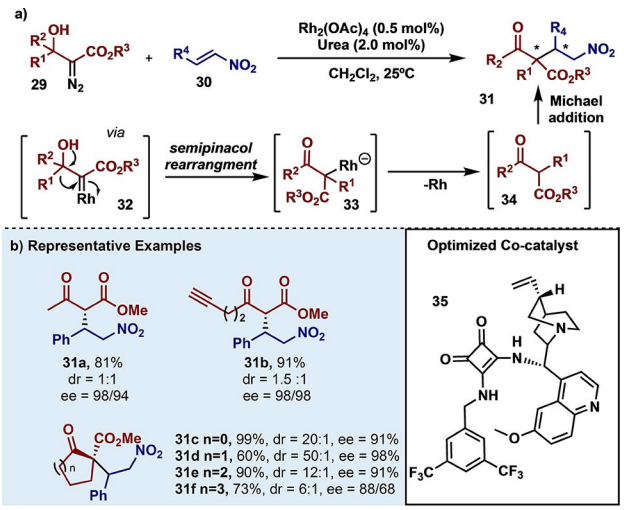


Figure 7. a) Rh(II)/urea catalyzed asymmetric trapping of Michael acceptors; b) Representative Substrate Scope.

3. Trapping Zwitterionic Intermediates with Activated Alkynes

Historically, Conia-ene cyclizations consist of a thermally induced intramolecular cyclization of an enolizable carbonyl with an olefinic or propargyl moiety. The Conia-ene reaction is a widely utilized synthetic transformation that can be used for the construction of carbon-containing rings.[27] Implementation of a metal catalyst allows for further activation of the π-system, thereby decreasing the activation energy necessary for the desired cyclization. This activation allows for milder reaction conditions and shorter reaction times. Pioneering strategies for metal-catalyzed Conia-ene reactions were developed by Toste,[28] and the reaction has since been expanded to encompass diazo-mediated reactions.

Hatakeyama *et al.* proposed a Rh(II)/Zn(II) catalyzed [4 + 1] cycloaddition protocol to access substituted tetrahydrofurans in 2014 (Figure 8).[29] To optimize reaction conditions, the authors subjected but-3-yn-1-ol and acceptor/acceptor diazo **37** to 1 mol% of $Rh_2(esp)_2$ and various Lewis acids. Both precious metal and Earth-abundant metal salts were screened, and the authors identified $ZnCl_2$ as the most favorable co-catalyst. Mechanistically, an O–H insertion into the rhodium carbenoid leads to the formation of an oxonium zwitterionic intermediate. This charged intermediate then undergoes an additional zinc-catalyzed Conia-ene cyclization. While the initial O–H insertion is robust, the subsequent Conia-ene cyclization is sluggish and requires long reaction times or refluxing conditions to furnish the desired product and avoid the undesired 1,2 proton transfer.

Once the authors identified optimal conditions, they pursued a substrate scope to determine the reaction's limitations. As such, a variety of substituted tetrahydrofurans were synthesized in good yields (**38 a**–**38 c**). While the desired reaction proceeds in good yields, the authors noted that their conditions did not elicit any sizeable diastereoselectivity.

When non-terminal propargyl alcohols are employed, the authors note exclusive *E*-selectivity, as seen in **38 d**. The authors unsuccessfully attempted to extend this methodology to access both tetrahydropyrans and oxetanes. However, only the insertion product was observed when pentynols were exposed to the optimized conditions to synthesize six-membered rings. Equally, when propargyl alcohol was exposed to the parent conditions, the oxetane was isolated in meager yields. Additionally, when the C1 position is geminally substituted, the authors note that diazo **37** can participate in a competitive cyclopropenation reaction with the propargyl group.

More recently, in 2020, Frover and co-workers developed a Rh(II)/Zn(II) strategy to access pyrroloindoles (Figure 9).[30] This protocol incorporates an sp^2 C–H functionalization/Conia-ene cascade of *N*-propargylindoles. Optimization studies revealed that a combinatory $Rh_2(OAc)_4/ZnBr_2$ cocktail best furnished the desired scaffolds. With conditions optimized, the authors then sought to develop a substrate scope to identify their method's limitations. The parent substrate **41 a** was synthesized in a moderate yield (64%). Likewise, C5 and C6 substitutions were generally well tolerated (**41 b-41 i**) and high-yielding. Halide-substituted analogues (**41 b**–**41 c**, **41 h**–**41 i**) were well tolerated and synthesized in good yields (up to 82%), as well as aryl substituents (**41 d**). Electron-donating analogues were also prepared in good yields (**41 f**–**41 h**). Their substrate scope highlighted this system's low tolerance for electron-deficient indoles. This is highlighted in the sharp decrease in yields seen in **41 e** and **41 m**. Next, various acceptor/acceptor diazos **40** were prepared and subjected to the optimized conditions (**41 j**–**41 l**). Methyl (**41 j**) and ethyl (**41 k**) ester pyrroloindoles were synthesized in moderate yields, while the bis(2,2,2-trifluoroethyl) malonate analogue (**41 i**) was synthesized in a 76% yield.

The group conducted several control experiments to gain additional insight and found that the reaction could be reproduced in a one-pot, stepwise fashion, albeit in diminished yields. Additionally, the sp^2 C–H insertion product could be isolated and exposed to $ZnBr_2$ to furnish the desired pyrroloindoles. These observations provide evidence of a relay catalysis strategy.

Rhodium carbenoids can be trapped by an appropriate ambiphilic synthon containing both a protic nucleophile and electrophile. Alkynols, alkynoic acids, and aminoalkynes are all examples of appropriate 'traps.' Sharma *et al.* have reported several studies of rhodium carbenoid trapping with various substrates to access a diverse library of functionalized spirocores and quaternary centers.[31] The following examples will highlight their relevant published work.

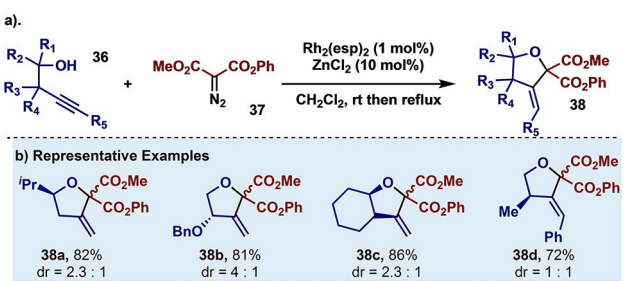


Figure 8. a) Rh/Zn co-catalyzed [4 + 1] cycloadditions of homopropargyl alcohols and acceptor/acceptor diazos; b) Representative Substrate Scope.

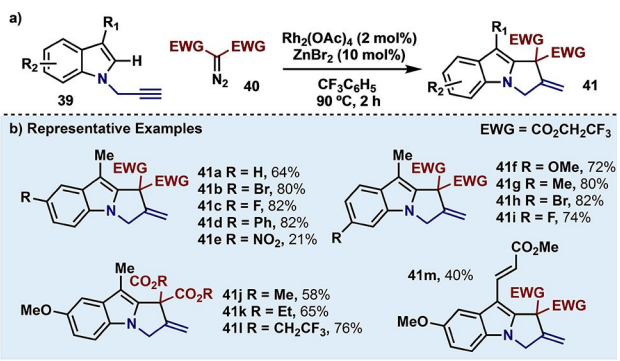


Figure 9. a) Rh(II)/Zn(II) catalyzed sp^2 C–H functionalization/Conia-ene strategy for the synthesis of pyrroloindoles; b) Representative Substrate Scope.

After identification of $Rh_2(esp)_2$ as an ideal catalyst for carboxylic acid O–H insertion into acceptor/acceptor diazos in 2016,[32] the group expanded upon this work to develop an O–H insertion/Conia-ene cascade to synthesize γ-butyrolactones[31c]

Inspired by the Au(I) catalyzed Conia-ene cyclization developed by Toste,[33] the authors identified a Rh(II)/Au(I) dual catalyst system to facilitate the insertion/Conia-ene tandem reaction. When O–H insertion product **44** was exposed to a combinatory AgOTf/PPh_3AuCl system, the authors observed the formation of the desired γ-butyrolactone at room temperature within 2 hours. With this observation, they hypothesized that a synergistic Rh(II)/AgOTf/PPh_3AuCl system would facilitate an O–H insertion/Conia-ene cascade from starting materials **42** and **43**. They observed the instantaneous formation of the desired γ-butyrolactone when precursors **42** and **43** were exposed to $Rh_2(esp)_2$ and the cationic PPh_3AuOTf (Figure 10a).

With optimized conditions, the authors then developed a substrate scope (Figure 10b). The parent compound **45a** was synthesized in an 83% yield. To probe the diastereoselectivity of the conditions, phenyl-substituted analogue **45b** was synthesized as a single diastereomer. Likewise, the authors note that these conditions tolerate both acceptor/acceptor and acceptor/donor diazos (**45c,45d**). It is significant to note that when the authors attempted to premix the corresponding pentynoic acid with AgOTf/PPh_3AuCl, this resulted in the self-lactonization of the acid, highlighting the specificity of the reaction conditions.

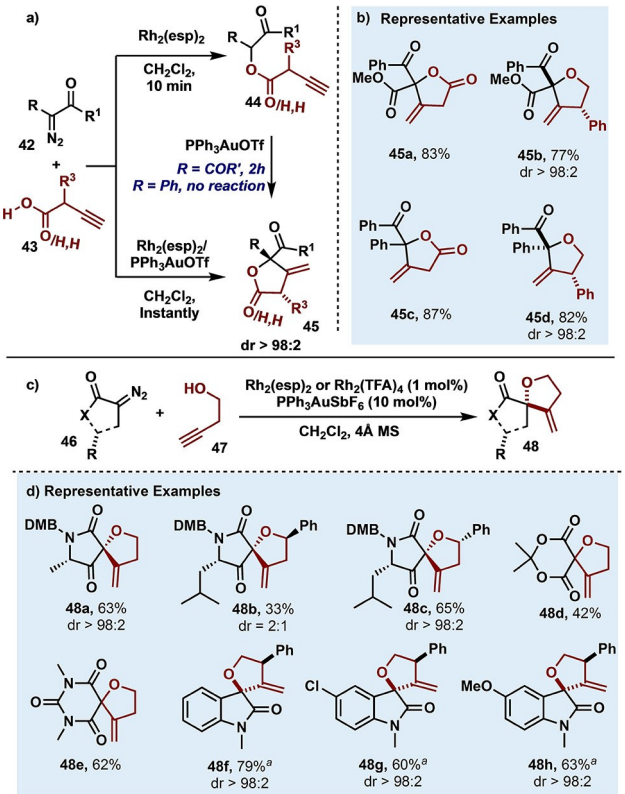


Figure 10. a) Rh(II)/Au(I) catalyzed O–H insertion/Conia-ene cascade for the synthesis of γ-butyrolactones and tetrahydrofurans; b) Representative Substrate Scope; c) Rh(II)/Au(I) catalyzed O–H insertion/Conia-ene cascade for the synthesis of spiroethers; d) Representative Substrate Scope.

In 2018, the group further expanded this methodology to access a diverse array of spiroethers (Figure 10c).[31b] Initially, the authors attempted to apply their previously identified $Rh_2(esp)_2$/PPh_3AuOTf system; however, the resulting transformation was low yielding. The reoptimized conditions for the formation of spiroethers now included $AgSbF_6$ as opposed to AgOTf to generate cationic gold. With optimized conditions identified, the authors synthesized a diverse set of spiroethers, including pseurotins, spiro-Meldrum's acids, spirobarbituates, and spirooxindoles.

The parent spirocycle **48a** was synthesized with high stereoselectivity in a moderate yield (63%). When an enantiopure 3-butynol derivative whose stereochemistry did not match the stereochemistry of the diazo was subjected to the optimized conditions, the reaction was found to be slow, low yielding and less diastereoselective (**48b**). In contrast, when the opposite enantiomer was used, the reaction proceeded efficiently in a higher yield with high diastereoselectivity (**48c**).

Further exploring the applicability of the reaction, the authors studied other acceptor/acceptor diazos that were obtained from Meldrum's acid and barbituric acid. The diazo derivative of Meldrum's acid provided the desired spiroether **48d** in a 42% yield due to the molecular instability of spiro-Meldrum's acid substrates in the presence of Lewis acids. The diazo derivative of barbituric acid also provided the desired sprioether **48e** in a 62% yield.

Next, the authors attempted to apply their optimized conditions to cyclic donor/acceptor isatin diazos. However, the reaction was low yielding and afforded the insertion product exclusively. After further optimization, a combinatory $Rh_2(TFA)_4$/PPh_3AuOTf system furnished the desired spirooxindole **48f** in a good yield as a single diastereomer. Additionally, both electron-poor and electron-rich isatin diazos tolerated these conditions in moderate yields (**48g**–**48h**).

For further mechanistic understanding, the authors conducted deuterium labeling experiments on barbituric acid diazo **46a** and isatin diazo **46b** (Figure 11a). When the substrates were exposed to optimized conditions, deuterium scrambling was not observed in either case. Additionally, the stereochemistry of the deuterium was confirmed as *syn* to the carbonyl functionality via ^1H NMR experiments. This observation was consistent with previous observations of Toste *et al.*[33] The lack of deuterium scrambling and the isolation of a single regioisomer of the deuterated spiroethers suggests the key intermediate involves a gold-alkyne π-coordinated complex.

Additionally, the authors subjected a non-terminal homopropargylic acid **43a** to the optimized reaction conditions (Figure 11b). Under these conditions, no Conia-ene cascade was observed; however, an unexpected [3.1.0]-fused bicyclic ring system **50** was obtained as a single diastereomer. The authors hypothesized that this product forms through cyclopropanation of the resulting unsaturated furanone produced during premixing the carboxylic acid with the catalyst cocktail via a 5-*endo*-dig self-lactonization. Lastly, additional insights into the reaction mechanism were obtained through ^1H and ^{13}C NMR

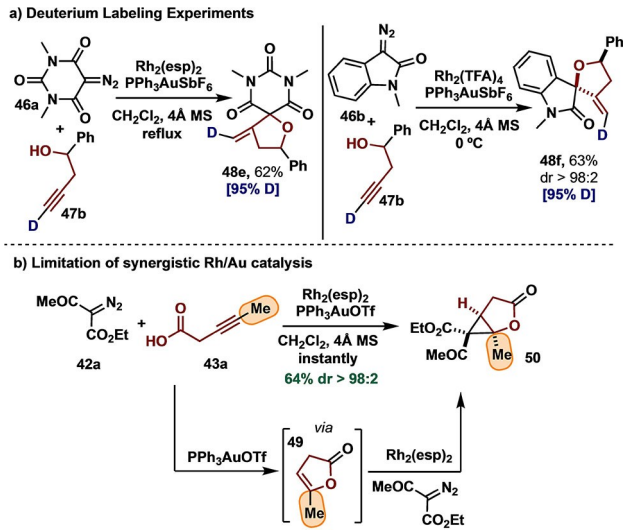


Figure 11. a) Mechanistic insights through deuterium labeling studies; b) Attempted application to non-terminal alkynes.

experiments. When 3-butynoic acid was mixed with stoichiometric amounts of $Rh_2(esp)_2$ and PPh_3AuOTf in CD_2Cl_2, there was an observed loss of the alkyne proton signal in ^1H NMR and a shift in the alkyne-carbon peaks in ^{13}C NMR, suggesting the formation of a gold-acetylide as an active intermediate which is in dynamic equilibrium with a gold-π-complex.[34]

In 2018, the same group expanded their X–H insertion/Conia-ene methodology to trap aminoalkynes with Rh(II) carbenoids (Figure 12).[31d] Using their previously identified $Rh_2(esp)_2/PPh_3AuSbF_6$ conditions, the authors were able to synthesize a variety of *N*-heterocycles, including spiropyrrolidines and spiroindolines. When cyclic donor/acceptor diazos derived from 2-tetralone and phenanthren-9(10*H*)-one were exposed to aniline **52** and the optimized catalytic system, the desired spiropyrrolidines were isolated in moderate yields

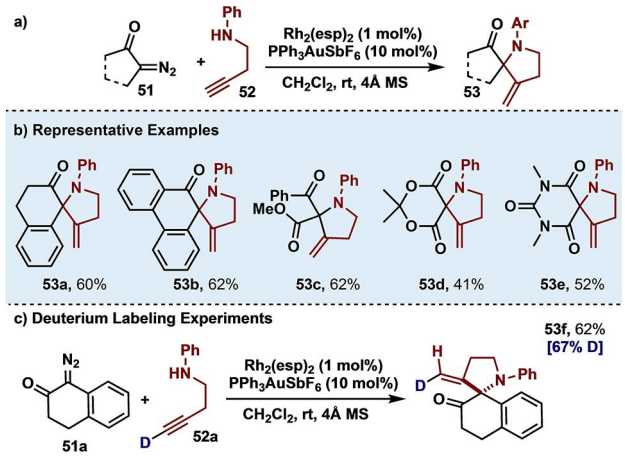


Figure 12. a) Rh(II)/Au(I) catalyzed N–H insertion/Conia-ene cascade for the synthesis of spiropyrollidines; b) Representative substrate scope; c) Mechanistic insights through deuterium-labeling studies.

(**53 a**–**53 b**). Utilization of more stable acceptor/acceptor diazos required higher reaction temperatures; however, the corresponding azacycles were synthesized in moderate yields (**53 c**–**53 e**).

The authors conducted deuterium labeling experiments for mechanistic elucidation, as depicted in Figure 12c. 2-Tetralone diazo **51 a** and deuterated aminoalkyne **52 a** were exposed to the optimized reaction conditions, and the desired product **53 f** was obtained in 62% yield with 67% deuterium incorporation. This observation of deuterium scrambling was inconsistent with previous studies reported by the group and results reported by Toste.[33] The authors proposed that this is due to the active gold-acetylide and the alkyne π-complex existing in dynamic equilibrium.

A generalization of the work by the Sharma group mentioned within this section can be summarized by the mechanism depicted in Figure 13. Specifically, Rh(II) decomposes diazo **54** to form Rh-carbenoid **55**. Carbenoid **55** can undergo a heteroatom insertion to provide an ylide intermediate that can tautomerize to furnish the rhodienolate species **56**. Gold-activation of the propargyl group can induce a subsequent Conia-ene cyclization to furnish the desired cyclized product **58**. Alternatively, rhodienolate **56** can participate in a 1,2 proton transfer to yield the insertion product **57**.

The stepwise mechanism involving rhodium enolate **56** also justifies the lack of enantioinduction observed with chiral rhodium salts. Additionally, the authors note that no Conia-ene cyclization is observed with monocarbonyl diazos (pKa ~ 20), as they predominately exist in their ketone form. Dicarbonyl systems, however, typically exist in the enol-form due to their lower pKa (~ 12).

To synthesize carbon-based spirocycles, Sharma and coworkers optimized an intramolecular sp^2 C–H functionalization strategy to synthesize diverse 5-,6-, and 7-membered spirocarbocyclic systems (Figure 14a).[31d] Initially, the authors attempted to synthesize [5,5] spirooxindole systems from the corresponding keto-amido diazos; however, when they subjected the appropriate diazo precursor to their previous Rh/Au conditions, they observed an undesired exo-glycal due to the disfavored 5-enolendo-*exo*-dig cyclization. They then extended the carbon

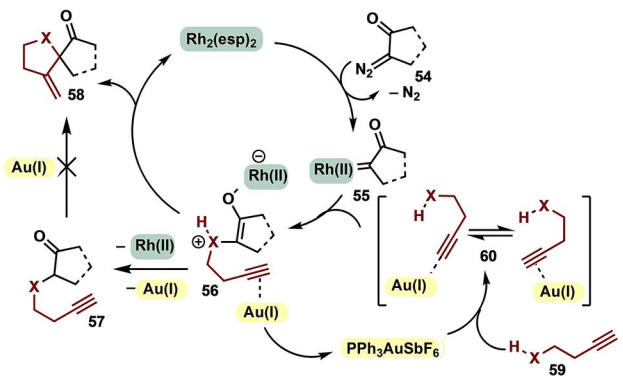


Figure 13. A generalized mechanism for Rh(II)/Au(I) catalyzed X–H insertion/Conia-ene cascade.

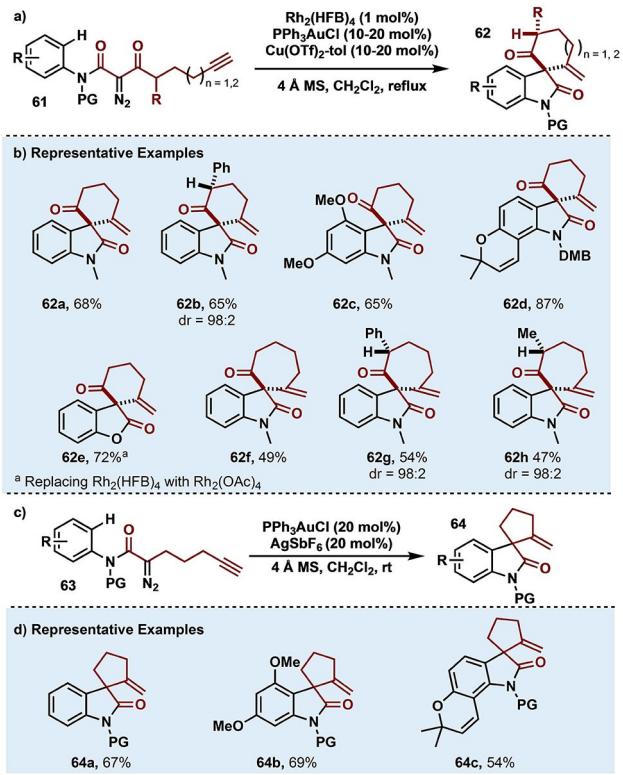


Figure 14. a) Rh/Au/Cu catalyzed sp^2 C–H functionalization/Conia-ene cascade for the synthesis of spirocarbocycles; b) Representative Substrate Scope; c) Au-catalyzed approach for the synthesis of 5-membered spirooxindoles; d) Substrate Scope.

skeleton of the diazo precursor to successfully access 6- and 7-membered spirocycles. Mechanistically, this transformation proceeds through an initial sp^2 C–H insertion into the rhodium-carbenoid, followed by an additional Conia-ene cyclization. A variety of Lewis acids were screened to optimize reaction conditions, and a combinatory PPh_3AuCl/CuOTf system was found to be the best reaction condition. Rhodium salts were then screened. $Rh_2(HFB)_4$, a highly electron-deficient dirhodium catalyst, was found to give the most efficient transformation.

With optimized conditions realized, the authors then pursued a substrate scope to examine the generality of the reaction conditions. The parent 6-membered substrate **62a** was synthesized in a 68% yield. To probe diastereoselectivity, a phenyl substituted diazo was exposed to the optimized conditions to furnish **62b** smoothly in 65% yield with excellent diastereoselectivity (98:2). Electron-donating aryl substituents were well tolerated by these reaction conditions (**62c**). Likewise, benzopyran (**62d**) and γ-lactone (**62e**) analogues were also synthesized in good yields. The synthesis for 7-membered spirooxindoles required increased loading of CuOTf and PPh_3AuCl to 20 mol%. The parent 7-membered substrate **62f** was synthesized in a 49% yield. Likewise, phenyl and methyl-substituted carbocycles were also synthesized in moderate yields (**62f, 62g**) with high diastereoselectivity.

To synthesize [5,5] spiro-systems, the authors utilized monocarbonyl diazos **63** (Figure 14c). As diazos bearing only one electron-withdrawing moiety are less stable than acceptor/acceptor diazos, the authors hypothesized that these diazos could be decomposed without rhodium. As expected, when diazos **63** were subjected to cationic gold, the authors observed the desired 5-membered spirooxindoles. The parent compound **64a** was synthesized in a 67% yield. Likewise, electron-donating analogue **64b** was synthesized in a 69% yield. Finally, benzopyran fused system **64c** was synthesized in a 54% yield.

4. Trapping zwitterionic intermediates with π-allyl-Pd(II) complexes

Transition metal-catalyzed allylic alkylation is a powerful tool for carbon–carbon bond formation and has been widely applied towards the synthesis of several important bioactive molecules.[35] Early in his career, Tsuji *et al.* demonstrated that π-allyl palladium complexes, bound in an η^3 fashion, could be trapped with a carbanion, providing a new route to C–C bond formation.[35] Later, the Trost group reported the first enantioselective allylic substitution with a "soft" carbon nucleophile.[36] Recently, chemists have been inspired by this work and began to use Pd(II)-π-allyl complexes as trapping sources for Rh(II)-catalyzed insertion reactions.

In 2017, Ji *et al.* reported the Rh(II)/Pd(0) dual catalyzed cross couplings of *o*-alkoxy substituted α-diazo-β-ketoesters and allyl benzoates to synthesize functionalized dihydrofuran-3-ones.[37] To initiate their studies, the authors screened various Rh(II) and Pd(II) salts and found that $Rh_2(^tBuCO_2)_4$ and $[PdCl(allyl)]_2$ in the presence of Xantphos was optimal for the desired transformation (Figure 15).

Mechanistically, this transformation proceeds through a Rh(II) catalyzed decomposition of α-diazo-β-ketoester **65** to produce Rh(II) associated alkylic-oxonium zwitterion **68**. Simultaneously, a π-allyl Pd(II) species **69** is generated from the Pd(0)-catalyzed oxidative addition of the allyl carboxylate. The zwitterionic intermediate **68** and Pd(II) π-allyl species **69** then cooperatively react to alkylate oxonium zwitterion **70**. This prompts an elimination of both catalysts to provide the desired benzofuranone **67**. Control, stepwise, and crossover experiments conducted by the authors provide evidence for the existence of a Rh(II)/Pd(II)-associated intermediate, validating the synergistic nature of this transformation.

The authors first examined different aryl substituted diazos **65**, which were generally well tolerated (**67a**–**67e**). The authors then examined various substituted allyl carboxylates to probe the palladium-mediated segment of the mechanism. Substituting the allyl carboxylate with a phenyl group had no noticeable effect on the reaction (**67f**). However, when the reaction was conducted with an *E/Z* mixture of the sterically demanding *o*-bromide aryl allyl benzoate, only the *Z* isomer of the desired product **67g** was obtained in a 40% yield. In contrast, an *E/Z* mixture of the *p*-bromo aryl allyl benzoate produced an *E/Z* mixture of the desired product **67h** in a 87% yield.

Using the same conditions, the authors then synthesized a variety of 2,3-disubstituted benzofurans (Figure 16). The elec-

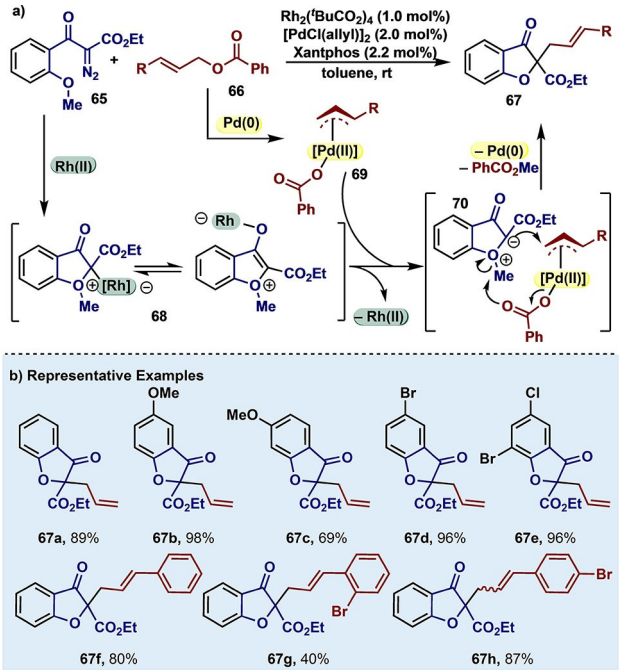


Figure 15. a) Rh(II)/Pd(0) catalyzed asymmetric coupling of diazos with allyl benzoates for the synthesis of dihydrofuran-3-ones; b) Representative Substrate Scope.

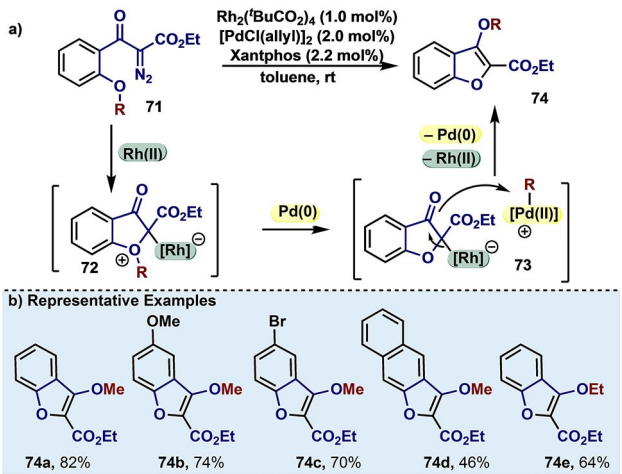


Figure 16. a) Rh(II)/Pd(0) catalyzed asymmetric coupling of diazos with allyl benzoates for the synthesis of benzofurans; b) Representative Substrate Scope.

tronically neutral α-diazo-β-ketoester furnished the parent benzofuran **74a** in a 82% yield. Electron-rich and electron-deficient diazos behaved similarly, indicating that the electronic character of the Rh(II) carbenoid had no significant effect on the efficiency of the reaction (**74b**–**74c**). However, the naphthyl-substituted α-diazo-β-ketoester (**74d**) was synthesized in a moderate 46% yield, indicating steric interference. Lastly, when an ethyl group was used instead of methyl for the inserting alkoxy group, the yield decreased to 64% (**74e**). This is presumably due to the propensity of β-hydride elimination in the ethyl palladium complex.

Similar to the aforementioned work, in 2018 Lee *et al.* successfully extended Rh(II)/Pd(0) dual catalysis to a one-pot synthesis of α-quaternary, chiral β-lactams from α-diazo-β-ketoamides and allyl carboxylates (Figure 17).[38] To initiate their studies, the authors screened several chiral Rh(II) and Pd(II) salts and selected Rh_2[(*S*)-*tert*-PTTL]$_4$ and $Pd_2(dba)_3$/*rac*-BINAP as the optimal catalytic conditions.

The authors believe this transformation proceeds through a Rh(II)-catalyzed decomposition of diazoketoamide **75** to facilitate an enantioselective intramolecular C–H functionalization to form β-lactam **78**. Simultaneously, a π-allyl Pd(II) species **79** is generated from the Pd(0)-catalyzed oxidative addition into an allyl carboxylate **76**. These two species proceed to cooperatively react to allylate the C–H functionalization product. When the C–H functionalization product was isolated and exposed to the Pd-catalyzed allylic alkylation conditions in a stepwise fashion, the allylated β-lactam was formed, verifying that this reaction proceeds through a relay, where β-lactam **78** serves as an intermediate.

Both electron-donating and electron-withdrawing groups at *meta* or *para* positions of the phenyl ring on the α-diazo-β-ketoamide **75** proceeded smoothly and provided the corresponding α-quaternary allylated chiral β-lactams in good yields with high diastereo- and enantioselectivities (**80b, 80d**–**80e**). Likewise, *ortho* substituents on the phenyl ring of the α-diazo-β-ketoamide, such as *o*-methyl and *o*-trifluoromethyl, showed low reactivity, poor to moderate yields, and low stereoselectivities (**80a, 80c**). The authors propose that this observation may be attributed to increased steric hindrance. Furthermore, the reaction of various substituents on the phenyl ring of the allylic coupling partner **76** proceeded smoothly. However, *ortho*

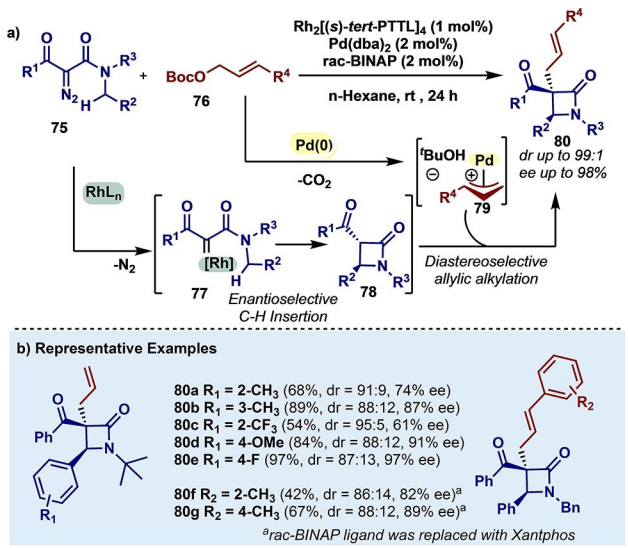


Figure 17. a) Rh(II)/Pd(0) catalyzed asymmetric coupling of diazoketoamides and allyl carboxylates for the synthesis of α-quaternary chiral β-lactams; b) Representative Substrate Scope.

substituents on the cinnamyl carbonates lead to a decreased yield due to steric hindrance of the π-allyl Pd(II) complex.

Chen *et al.* extended the scope of Rh(II)/Pd(0) dual catalysis by developing a protocol for the one-pot synthesis of C_3-quaternary allylic oxindoles from *N*-aryl-α-diazo-β-ketoamides and functionalized allyl carbonates (Figure 18).[39] This binary catalyst system is facilitated by a Rh(II) catalyzed intramolecular aryl C–H insertion, followed by a Pd(0)-catalyzed allylation sequence.

Using slightly varied conditions of $Rh_2(^tBuCO_2)_4$ and $[PdCl(allyl)]_2$ in the presence of Xantphos, the authors synthesized a variety of C_3-quaternary allylic oxindoles. Various *N*-aryl-α-diazo-β-ketoamides **(82c–82i)** bearing different substituents on the *N*-aryl ring were investigated using allyl *tert*-butyl carbonate as a coupling partner. These reactions were not significantly affected by the electronic or steric factors of the substituents. To further explore the substrate scope, an array of functionalized allyl *tert*-butyl carbonates were reacted with *N*-aryl-α-diazo-β-ketoamides. Various 3-phenyl-substituted allyl carbonates were subjected to the optimized conditions to furnish the corresponding oxindoles (**82j–82q**) in good yields up to 96%. Likewise, 3-phenyl-substituted allyl carbonates bearing both electron-rich (**82k–82m**) and electron-withdrawing groups (**82n–82q**) on the phenyl ring can be readily employed. However, the reaction was noticeably affected by the position of the substituents. Similarly, the thiophenyl substituted oxindole **82r** was also successfully synthesized in moderate yield (64%).

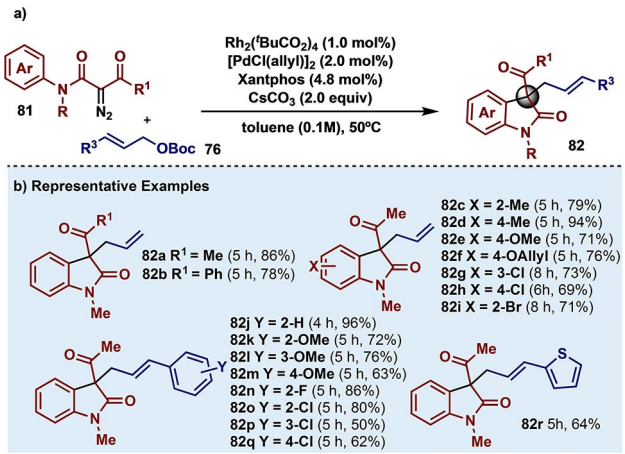


Figure 18. a) Rh(II)/Pd(0) catalyzed synthesis of C_3-quaternary allylic oxindoles; b) Representative Substrate Scope.

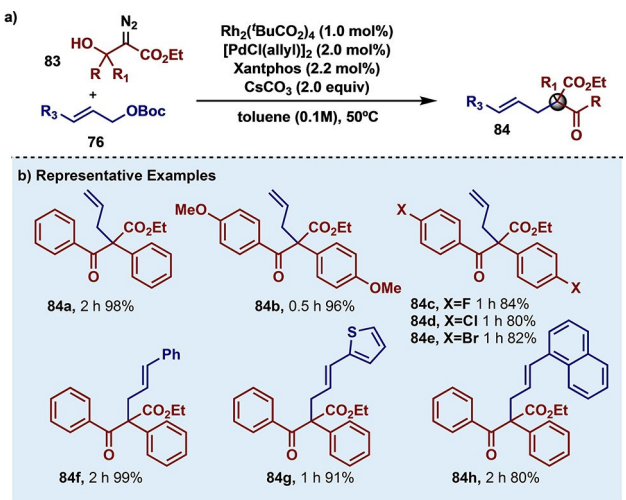


Figure 19. a) Rh(II)/Pd(0) catalyzed synthesis of α-quaternary-β-keto-esters; b) Representative Substrate Scope.

In 2020, the same group developed a Rh(II)/Pd(0) catalyzed approach for the synthesis of α-quaternary-β-keto-esters (Figure 19).[40] By utilizing their previously disclosed conditions, the group was able to access functionalized quaternary carbons via the two-step cascade sequence. Mechanistically, this approach features a Rh(II) induced [1,2]-sigmatropic rearrangement of α-diazo tertiary alcohols, followed by a Pd(0)-catalyzed allylic alkylation.

Once conditions were further optimized, the authors first investigated various α-diazo tertiary alcohols (**84a–84e**). The parent substrate (**84a**) was synthesized in 2 hours in a 98% yield. Likewise, electron-donating diazos (**84b**) were well tolerated. Notably, halogen-substituted diazos (**84c–84e**) were also well tolerated by the bimetallic system, thus providing the opportunity for further coupling reactions. A variety of allyl *tert*-butyl carbonates **76** were also investigated. Both phenyl (**84f**) and thiophene (**84g**) analogues were well tolerated, as well as 1-naphthyl substituted allyl carbonate (**84h**) in excellent yields (up to 99%).

Lee and co-workers were also able to apply this bimetallic system to the first report of a chemo- and stereoselective coupling between π-allyl Pd(II) complexes and α-imino Rh(II) carbenoids (Figure 20).[41] To initiate their studies, the authors screened various Rh(II) and Pd(II) salts and found that $Rh_2(^tBuCO_2)_4$ and $Pd_2(dba)_3$ in the presence of Xantphos ligand was optimal for the cooperative transformation. With their optimized reaction conditions, the authors screened a variety of allyl carboxylates. The transformation accommodated different allyl benzoates, and the parent substrate **87a** was synthesized in an 86% yield. The authors observed that the reaction was sensitive to the electronics of the benzoate. Electron-rich *para*-methoxy allyl benzoate gave the desired product **87b** in a 76% yield, while the electron-deficient *para*-nitro allyl benzoate produced the desired product **87c** in a 44% yield. The reaction also accommodated allyl acetate, producing **87d** in a 70% yield.

Next, the authors screened various triazoles under the optimized reaction conditions. The triazole containing an *ortho*-methyl substituent did not react under the optimized conditions; however, when the reaction was heated to 70 °C, the desired product **87e** was produced in a 84% yield. In contrast, the less sterically demanding *para*-methyl substituted triazole reacted efficiently under the optimized conditions to give **87f** in a 89% yield. There was also a prominent electronic effect seen in these triazole substrates. Electron-rich *para*-methoxy triazole gave the desired product **87g** in a 81% yield. In contrast, the electron-deficient *para*-cyano triazole required

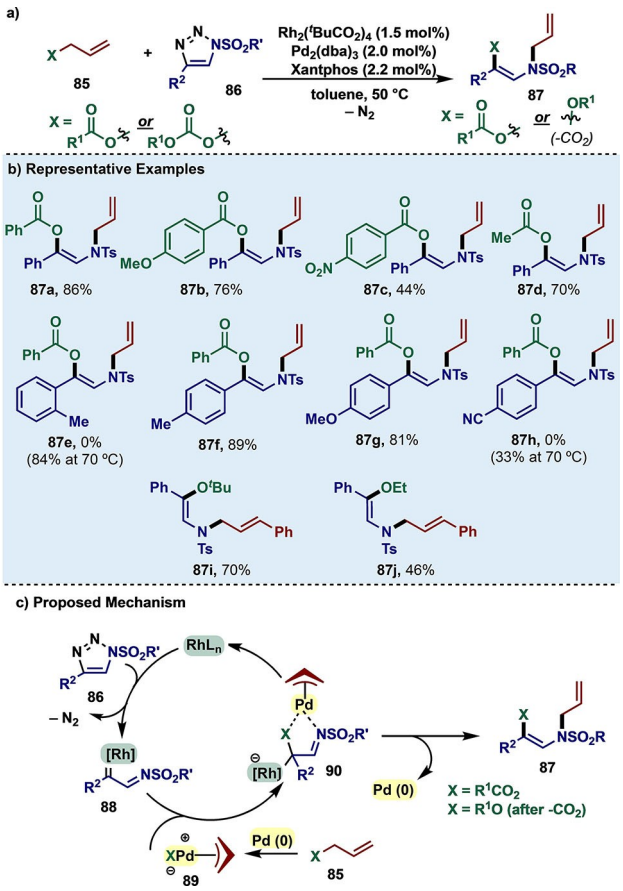


Figure 20. a) Rh(II)/Pd(0) catalyzed coupling of triazoles and allyl carboxylates/carbonates for the synthesis of *N*-allylated vinyl ethers/acetates; b) Representative Substrate Scope; c) Proposed Mechanism.

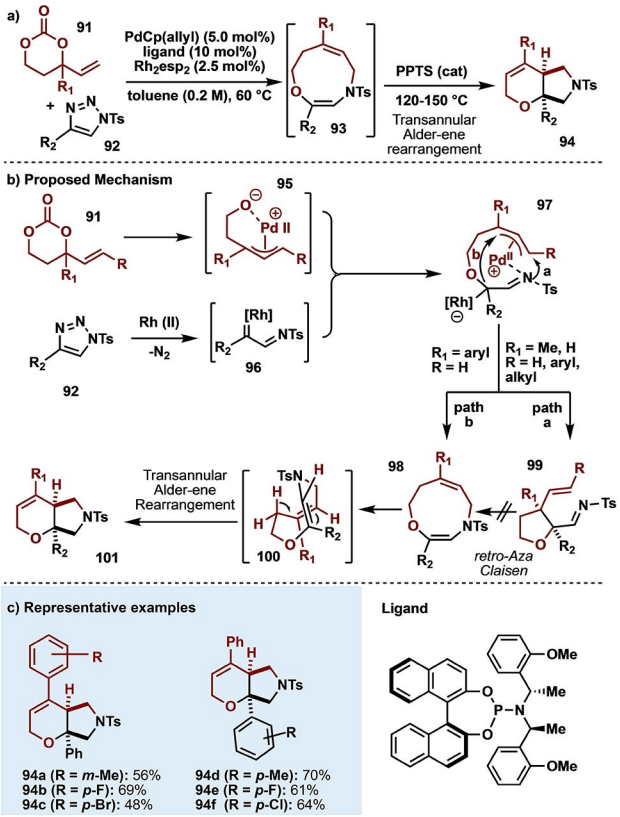


Figure 21. a) Rh(II)/Pd(0) catalyzed [6 + 3] coupling strategy; b) Proposed Mechanism; c) Representative Substrate Scope.

increased reaction temperatures to provide the desired compound **87 h** in a 33 % yield.

Lastly, the authors investigated different carbonates, which can undergo a decarboxylation event to afford vinyl ethers. *Tert*-butyl carbonate delivered the desired compound **87 i** in a 70 % yield. In comparison, ethyl-carbonate furnished the desired compound **87 j** in a decreased 47 % yield, highlighting an effect of *tert*-butoxide *vs.* ethoxide anion stability.

Using observations acquired from the application of their optimized conditions to a wide substrate scope, the authors were able to propose a mechanism for the transformation. The Pd(0) and Rh(II) catalysts selectively activate their respective substrates to form a π-allyl Pd(II) complex **89** and an α-imino Rh(II) carbenoid **88**. The Rh(II) carbenoid intercepts the Pd(II) species to form intermediate **90**, which undergoes *N*-allylation to furnish a variety of *N*-allylated carboxylates/ethers **87**.

Recently, in 2021 the same group reported a novel Pd(0)/Rh(II) dual catalytic strategy to facilitate [6 + 3] cycloadditions between vinylpropylene carbonates (VPCs) **91** and *N*-sulfonyl-1,2,3-triazoles **92** to furnish monocyclic 1,4-oxazonines **94** (Figure 21).[42] The catalytically generated 1,6-zwitterionic π-allyl Pd(II) complex **95** and 1,3-dipole-equivalent α-imino Rh(II) carbenoid **96** react to facilitate a [6 + 3] dipolar cycloaddition to form nine-membered N,O-heterocyclic dienes **93**. Dienes **93** can undergo a transannular Alder-ene rearrangement in the same pot to afford the *cis*-fused [4.3.0] bicycles **94**.

After thorough optimization studies, the authors established PdCp(allyl)/$Rh_2(esp)_2$ in toluene were ideal for facilitating the desired cycloadditions. With these optimized conditions, the authors synthesized a variety of nine-membered N,O-heterocyclic dienes **93**. Without isolation, these compounds were then subjected to catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) and elevated temperatures to induce a transannular Alder-ene rearrangement to afford the *cis*-fused [4.3.0] bicyclic compounds (**94 a**–**94 f**) in moderate to good yields (48 %–70 %).

Lastly, in 2021 Chen and co-workers described a cooperative Rh(II)/Pd(0) strategy to access substituted 3(2*H*)-furanones (Figure 22).[43] Exposure of α-diazo-δ-keto-esters **102** and allyl benzoate **76** to the group's previously identified Rh/Pd conditions[37,39–41] cleanly furnished the desired furanones in toluene. This bimetallic system displayed high chemo-, regio-, and stereoselectivities across a wide range of functionalities. Both electron-donating (**103 a**) and electron-withdrawing (**103 e**,**103 f**) aryl substituents were tolerated extremely well, as well as halide substitutions (**103 b**–**103 d**). Likewise, both furan and thiofuran aryl substitutions were well tolerated by the bimetallic system (**103 g**,**103 h**).

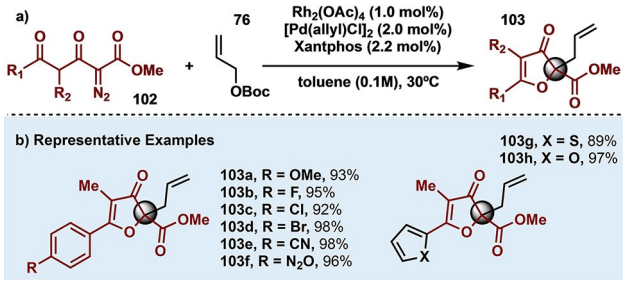


Figure 22. a) Rh(II)/Pd(0) catalyzed synthesis of highly substituted 3(2H)-furanones with C2-quaternary centers; b) Representative Substrate Scope.

5. Miscellaneous Examples

Feng *et al.* reported a Rh(II)/chiral *N,N'*-dioxide-indium (III) system to realize a tandem insertion/enantioselective Claisen rearrangement of *N*-sulfonyl-1,2,3-triazoles with allyl alcohol derivatives to access various γ-oxo-β-amino esters **106** (Figure 23).[44]

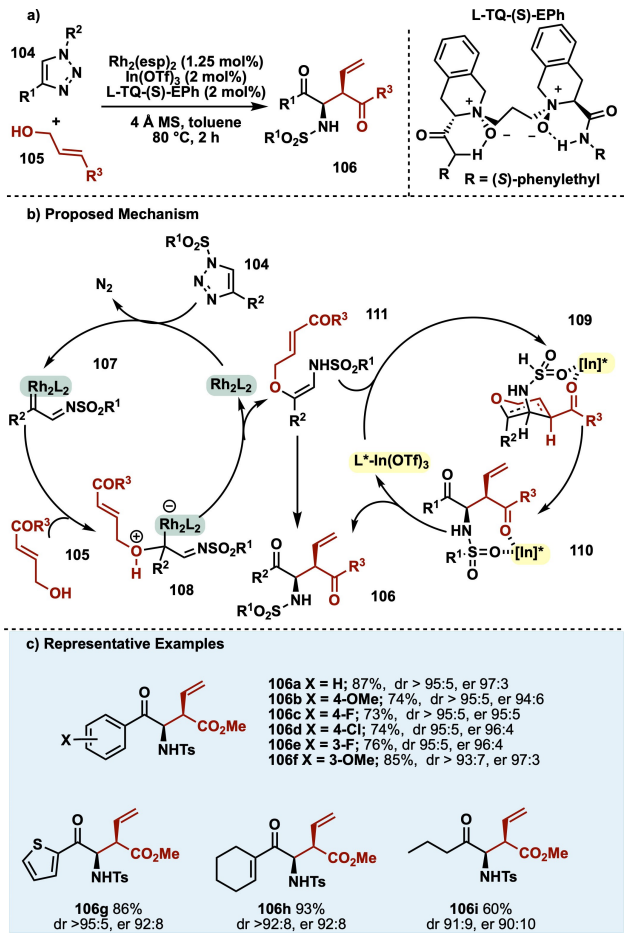


Figure 23. a) Rhodium(II)/Indium(III) catalyzed protocol for O–H insertion/asymmetric Claisen rearrangement; b) Proposed Mechanism; c) Representative Substrate Scope.

Mechanistically, the authors hypothesize that the readily formed allylic vinylic ether **111** could be efficiently bound and activated by chiral Lewis acid complexes, enabling an enantioselective [3,3]-sigmatropic rearrangement (Figure 23b). To optimize reaction conditions, the authors screened $Rh_2(esp)_2$ with various metal salts and *N,N'*-dioxide ligands. They then identified $Rh_2(esp)_2$, $In(OTf)_3$, and the (*S*)-phenylethanamine derived chiral *N,N'*-dioxide L-TQ-(*S*)-EPh ligand as the ideal reagents.

With optimized reaction conditions, the authors synthesized a variety of γ-oxo-β-amino esters. Electronically diverse, 1-tosyl-substituted triazole aryl groups underwent the desired O–H insertion/[3,3]-sigmatropic rearrangement smoothly to yield the desired products in consistently excellent enantio- and diastereoselectivities (**106b**–**106f**). Moreover, 2-thiophenyl substituted 1,2,3-triazole also performed well, delivering the corresponding product **106g** in high yields and selectivities. Other 4-alkyl-1,2,3-triazoles were also compatible with reaction conditions, albeit with moderate reactivities and stereocontrol (**106h**–**106i**).

Likewise, Werz *et al.* reported a [3+3] annulation of carbonyl ylides and donor/acceptor cyclopropanes by developing a Rh/Lewis acid catalyzed protocol in 2019 (Figure 24).[45] Initially, the diazo undergoes a Rh(II) catalyzed decomposition to generate carbonyl ylides *in situ*. These ylides undergo a cycloaddition reaction with Lewis acid-activated donor-acceptor cyclopropanes to afford substituted pyran scaffolds. As the employed cyclopropanes are relatively inert, a synergistic catalyst system is necessary for activation. This protocol serves as a true example of synergistic catalysis, as these transformations would be infeasible with traditional monocatalyst systems.

Reaction optimization studies concluded with the identification of $Rh_2(OAc)_4$ and $Sc(OTf)_3$ doped with $Yb(OTf)_3$ as the ideal catalyst system and toluene as the optimized solvent. 9-Oxabicyclo[3.3.1]nonan-2-one cores (**114aa**–**114ea**) were synthesized readily in yields up to 93%. For the preparation of 10-membered systems, the authors report a modest adjustment to the previous conditions, namely a change in solvent and homologue of diazo **113**. Altering the solvent from toluene to dichloromethane furnished cyclononenoles in contrast to the expected cyclononanones, in high yields and excellent diastereoselectivities. The authors hypothesize that the striking differences in diastereoselectivities can be attributed to the solvent effect, influencing the reactivities of intermediates **118** and **119**. The respective carbonyl ylides derived from **113a** and **113b** differ in reactivity. Ylides derived from **113a** are conjugated; however, the ylides derived from **113b** lack this conjugation. Likewise, dichloromethane can stabilize the more sterically hindered intermediate **118**, thereby promoting higher diastereoselectivities. Once optimized, several 10-membered analogues were prepared (**115ab**–**115eb**), featuring high diastereoselectivities.

Schneider *et al.* reported the first cooperative, catalytic, enantioselective [4+3] cycloannulation of *ortho*-quinone methides (*o*-QMs) and carbonyl ylides to afford complex and enantiomerically enriched oxabicyclic dibenzooxacines with excellent yields and stereoselectivity (Figure 25).[46] In this

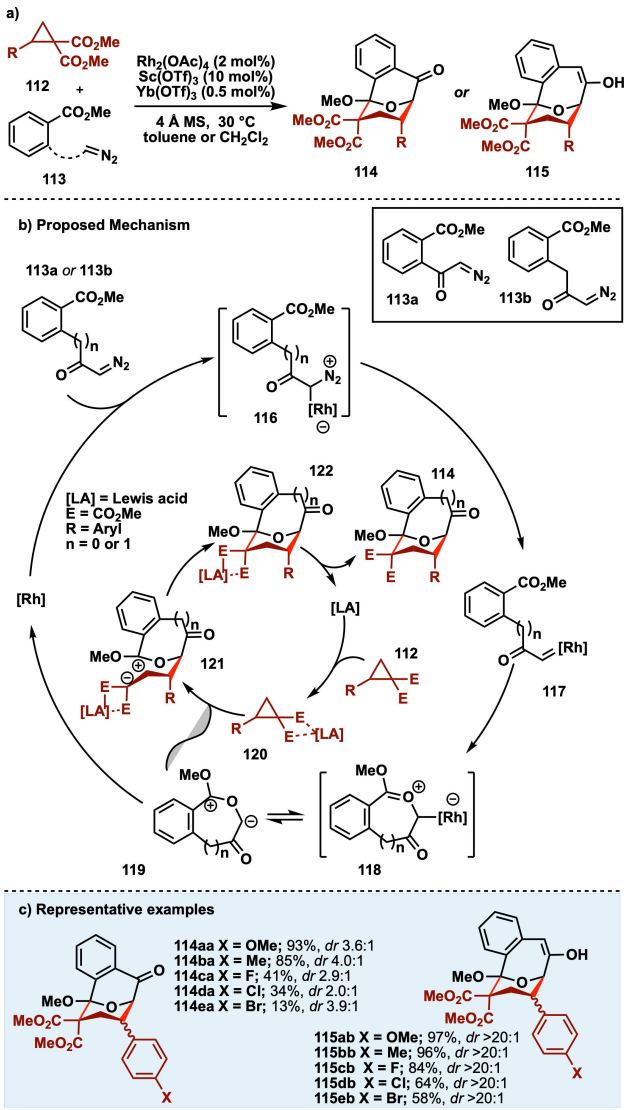


Figure 24. a) Synergistic Rh(II)/Lewis acid-catalyzed [3 + 3] annulation strategy; b) Proposed Mechanism; c) Representative Substrate Scope.

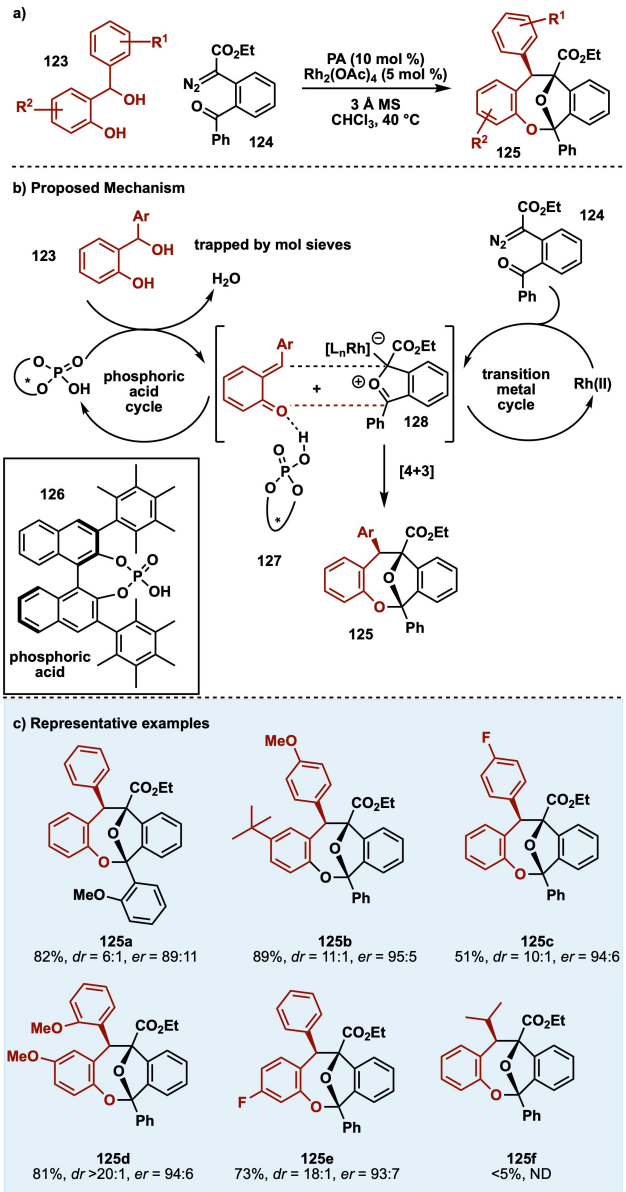


Figure 25. a) Rh(II)/PA catalyzed [4 + 3] cycloannulation of *ortho*-quinone methides; b) Proposed Mechanism; c) Representative Substrate Scope.

approach, rhodium and chiral phosphoric acid catalysts simultaneously generate transient intermediates **127** and **128**. These intermediates undergo a cycloaddition event to directly access complex functionalized oxa-bridged dibenzooxacines **125**.

The optimal conditions consisted of $Rh_2(OAc)_4$ in the presence of a chiral binol phosphoric acid **126** in chloroform at room temperature. The authors conducted several control experiments to gain mechanistic insights. These experiments highlighted the need for both catalysts as the substrates failed to react if either the phosphoric acid or $Rh_2(OAc)_4$ was not present, indicating the necessity of a dual catalytic system. Additionally, when *O*-methyl-protected benzyl alcohol was used in place of **123** and exposed to optimized conditions, the substrates failed to react, verifying that this reaction indeed proceeds via an *ortho*-quinone methide intermediate.

The authors synthesized a variety of enantioenriched oxabicyclic dibenzooxacines in good yields with the optimized reaction conditions. The diastereoselectivity appeared to be dependent on the electronic character of the aryl substituent, with electron-rich aryl groups (**125 b,125 d**) generally furnishing near-perfect selectivity.

Alternatively, electron-poor substituents (**125 c,125 e**) furnished products with diminished diastereoselectivity, albeit in excellent yields and up to 96:4 e.r. *Ortho*-substituted aryl groups had a detrimental effect on both the diastereo- and enantioselectivity, as shown for **125 a** (6:1 d.r., 89:11 e.r.), likely due to steric restraints. Unfortunately, the *i*Pr-substituted benzhydryl alcohol failed to deliver product **125 f** because the transient *o*-QM generated *in situ* from *i*Pr-substituted benzhydryl alcohol is too unstable to engage the transient carbonyl ylide in the cycloannulation event successfully.

Lastly, in 2020, Hu *et al.* reported a Rh(II)/Ag(I) catalyzed three-component reaction of propargylic alcohol-$Co_2(CO)_6$ complexes, diazo compounds, and primary alcohols to synthesize hexacarbonyl-complexed 3,3-disubstituted oxindoles (Figure 26).[47] This work involves trapping Rh(II)-derived oxonium ylides with Ag(I)-generated Nicholas intermediates, showcasing a synergistic Rh/Ag system.

The Nicholas reaction involves a Lewis-acid catalyzed dehydration of dicobalt octacarbonyl-stabilized propargyl alcohols.[48] The Lewis acid facilitates the leaving of a 2° or 3° hydroxyl group, revealing a dicobalt octacarbonyl-stabilized propargylic carbocation. An appropriate nucleophile can attack this stabilized carbocation, i.e. the Nicholas intermediate, to furnish the desired product. Nicholas intermediates are remarkably stable due to the significant delocalization of the cationic charge onto the $Co_2(CO)_6$ moiety. Once completed, the propargyl group can be de-complexed to furnish the free alkyne.

The author's optimization studies revealed a synergistic $Rh_2(OAc)_4/AgBF_4$ system as the optimal catalysts; however, no significant diastereoselectivity was achieved. Likewise, the authors attempted to induce enantioselectivity through chiral Rh(II) salts and chiral ligand/$AgBF_4$ systems. However, no such selectivity was realized. Once a suitable system was identified, a subsequent substrate scope was prepared. Initially, various dicobalt hexacarbonyl-complexed propargyl alcohols were investigated. Cyclopentenyl (**132a**), cyclohexenyl (**132b**), and cycloheptnyl (**132c**) TMS-propargyl analogues were synthesized in good yields. Likewise, aromatic propargyl alcohols (**132e**,**132f**) were investigated for this transformation.

Mechanistically, the generation of the oxindole rhodium carbenoid **130**, leads to the formation of the zwitterionic rhodienolate **133**. Enolate **133** can attack onto the silver-generated Nicholas intermediate, carbocation **134**. A subsequent S_N1/S_N1' attack on the carbocation results in the formation of the desired multicomponent adduct. Control experiments indicated that both Rh(II) and Ag(I) were indispensable for this transformation as a single catalyst system was not sufficient for the formation of the desired product.

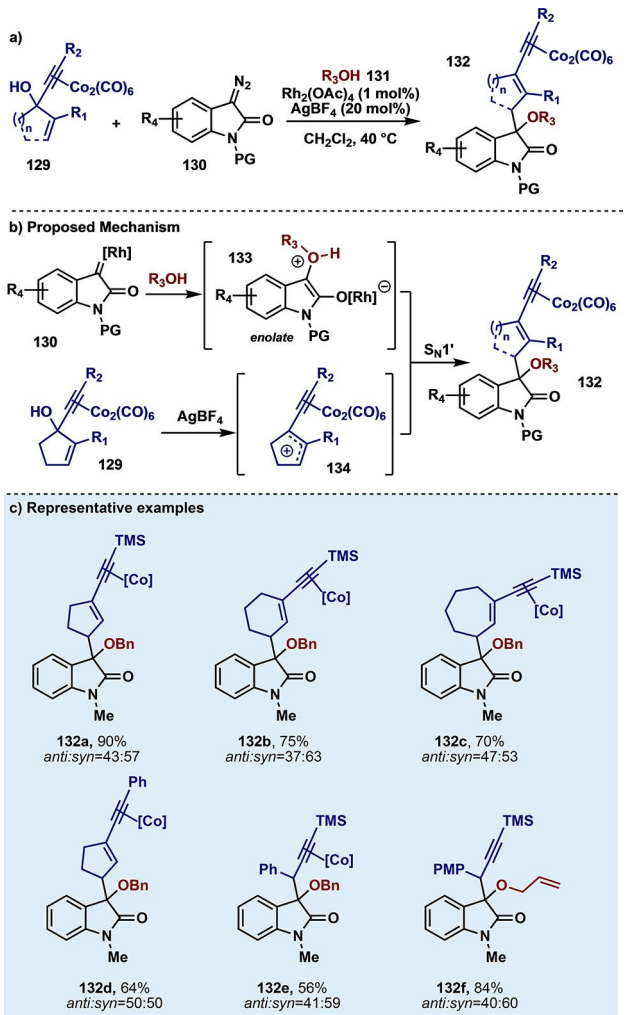


Figure 26. a) Rh(II)/Ag(I) catalyzed multicomponent reaction of propargylic alcohol-$Co_2(CO)_6$ complexes; b) Proposed Mechanism; c) Representative Substrate Scope.

7. Outlook and Conclusions

Dual catalysis has emerged as a promising tool in organic synthesis for the fast and efficient construction of new bonds. This strategy employs readily available starting materials and enables new chemical transformations to provide products with high levels of three-dimensionality and stereoselectivity. Despite the advancements mentioned in this review, the use of dual catalysis in carbene chemistry is still in its infancy. Limitations such as i) the ability to efficiently stabilize reactive metal-bound zwitterionic intermediates and ii) the identification of compatible substrates and catalysts remain to be solved. Therefore, thorough mechanistic and computational insights are needed to comprehend these transformations to enable new transformations. Moving forward, there is much knowledge to be uncovered involving metal carbenes participating in dual catalysis. We encourage the scientific community to bring this field to its ultimate potential.

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Conflict of Interest

There are no conflicts to declare.

Keywords: Carbenoid · Diazo compounds · Dual catalysis · Rhodium · Zwitterions

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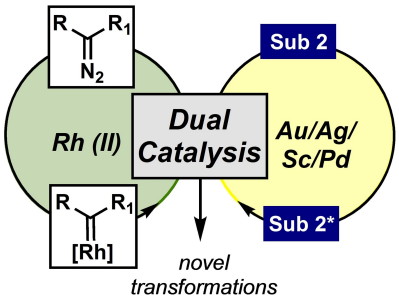
REVIEW

This review describes the recent developments of dual catalysis in rhodium (II) carbenoid chemistry, where rhodium is cooperatively working with a second transition metal (Sc/Pd/Ag/Au) or organocatalyst. The redox compatibility, turnover pathways, and the generation of unique rhodium-bound zwitterionic intermediates make rhodium an attractive partner for dual catalysis reactions to enable new transformations.



*A. I. Bain, Dr. K. Chinthapally, Dr. A. C. Hunter, Prof. I. Sharma**

Special Issue