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C–H Insertion Reactions of Donor/Donor Carbenes: Inception, Investigation, and Insights

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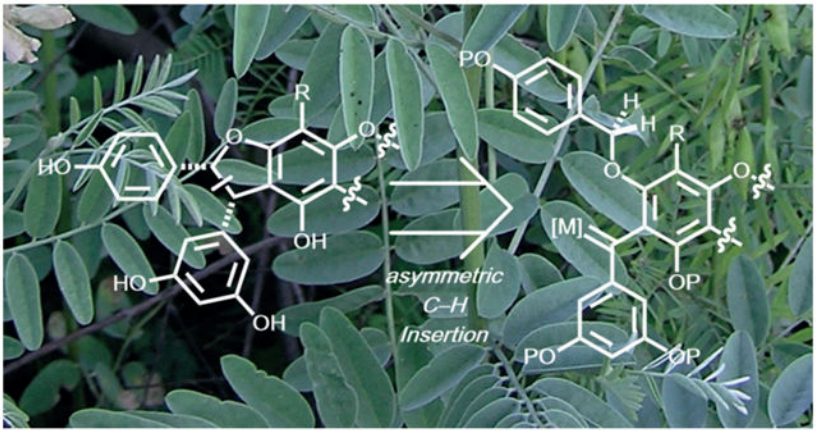
Abstract

Insertion reactions of donor/donor carbenes have emerged from obscurity to become a versatile method for the synthesis of a variety of cyclic structures with excellent control of diastereo- and enantioselectivity. This Account describes the origin of this project as part of a natural product synthesis and the ensuing decade of reaction development that has resulted in new asymmetric methods as well as intriguing tangential observations.

Graphical Abstract



Keywords

C–H insertion; carbenes; rhodium; asymmetric catalysis

Introduction

The synthesis of organic molecules has been a constant driver for my enthusiasm in science ever since I first started my research career in 1992 as an undergraduate in the laboratory of Prof. Clayton Heathcock (UC Berkeley). Proceeding from there to what was a small company at the time (Gilead Sciences) and on to graduate school at UC Irvine led me to become one of the first students to join the laboratory of Prof. Keith Woerpel (now at New York University). While seeing firsthand the stress a new professor goes through, I also saw

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the fun of both teaching and working with students in new areas of science. After graduating, I headed off to a postdoctoral stay with Prof. David Evans (now emeritus, Harvard University) and, I assumed, a faculty position shortly thereafter.

Life had other plans for me that would have a dramatic impact on my professional path and, indirectly, lead to the project discussed in this Account. While at UC Irvine, I met my future spouse (Prof. Annaliese Franz, UC Davis), who was also focused on a career in academics. After we lived apart for the entirety of my postdoc and I failed to get a job that would align with our plans, she secured a postdoctoral position with Prof. Stuart Schreiber (Harvard University). I neither wanted to do a second postdoc nor take a position in industry that I would have to leave to return to academics. As luck would have it, there had been a recent departure from the fellows program at the Institute for Chemistry and Chemical Biology (ICCB) at Harvard Medical School, jointly directed by Profs. Stuart Schreiber and Timothy Mitchison. Unbeknownst to me at the time, the ICCB would later split and the portion involving Prof. Schreiber's lab and the fellows engaged in chemistry would become part of the nascent Broad Institute of Harvard and MIT. I accepted the position, which came with scientific autonomy and the ability to build a small research group with postdocs and undergraduate researchers. In addition to pursuing my own ideas, I would be on the same floor as a high-throughput screening facility and would have the opportunity to interact with dozens of scientists exploring libraries of small molecules for the ability to modulate their biological system of interest. Although similar positions are more common in biomedical research, this type of intermediate position was nearly unknown among organic chemists. That said, the five years I spent at the ICCB and Broad Institute from 2002 to 2007 were transformative in my appreciation for how organic synthesis could contribute broadly to biomedical research.

Inception

While working on several projects aimed at making libraries of complex heterocycles for screening, I also started collaborating on a project examining FtsZ, which is a bacterial homologue of eukaryotic tubulin, as a new target for antibiotics. The latter project prompted me to think more about other sources for compounds that could kill bacteria and I was inspired by a review article on plant-based antimicrobial natural products.[1] One group of compounds described in that review, the alopecurones (isolated from Sophora alopecuroides, pictured in the graphical abstract), caught my eye (Figure 1).[2] Although they combine common structural motifs, including a flavanone core, isoprenoid substituents, and a portion derived from resveratrol, the structures were unique. In addition, these compounds had very high antimicrobial activity against many strains of methicillin-resistant Staphylococcus aureus (MRSA). While these compounds did not look like they would be good starting points for drugs, their unique structures and origin (a medicinal plant rather than a microorganism) suggested that they could reveal new information in the fight against resistant infections.

We started with a bit of a 'background check'. Having seen some natural product studies end in tragedy, namely with a mis-assigned structure or irreproducible biology, we wanted to secure some natural material for additional studies. Dr. Yuchen Tang, a Mandarin-speaking

postdoc in my lab, offered to work with a vendor of traditional Chinese medicinal (TCM) products in Boston to get some of the plant material. He was told that harvesting the root material had been banned, but that we could still get clippings that included some root at the base of the stems. Another postdoc, Dr. Marcos González-Lopéz, then followed the advice of a local natural product expert, Prof. Jon Clardy (Harvard Medical School), for how to proceed. After securing the plant material and borrowing a ball mill, Marcos was able to grind, extract and tentatively confirm the structure of alopecurone C. Collaborative studies with a company developing a new profiling technique for antibiotic mechanism of action confirmed the antimicrobial activity and hinted at a potentially interesting mechanism of action (unpublished). Marcos elected to start a campaign to synthesize alopecurone C with the idea that we could then make new probes to examine its mechanism of action and possibly discover a more potent and more drug-like variant.

Marcos and I had many productive discussions on how to approach this densely substituted target, starting in 2006. We considered the possibility of using an enzyme provided by Prof. Joseph Noel (Salk Institute) to prepare large quantities of the flavanone core. As a first step, Marcos also successfully prepared a diazo compound to use in a rhodium-catalyzed C–H insertion reaction to form the pyran ring of the flavanone with an eye toward controlling absolute stereochemistry (Scheme 1). This basic transformation was one that I had first seen in department seminars at UC Irvine from Profs. Michael Doyle (University of Texas, San Antonio) and Huw Davies (Emory University) and later applied to the preparation of an intermediate I needed at the time for my dissertation research.[3,4] Treatment of 4 with $Rh_2(OAc)_4$ led to a high yield of the five-membered ring product 6 through a Stevens-like rearrangement, an observation that we later realized had been made over a decade earlier for an identical substrate.[5] Marcos moved with me to UC Davis, where he made significant progress on an unrelated target (viriditoxin).[6] During this time he secured a fellowship to support his work on the alopecurones, which proved crucial for him to devote more time and energy to the project. During these unsuccessful studies, Marcos's appointment ended and he made plans to move on to his next position.

Shortly before leaving, Marcos came to my office and said that he had a completely new way to approach the core of the alopecurones based on C–H insertion (Scheme 2). He drew out the transformation and indicated that he had (unsurprisingly) already started making a model substrate. This C–H insertion would be different from most others in that the carbene would not have any electron-withdrawing groups attached to it. A survey of the literature revealed that these 'donor/donor' carbenes were almost wholly unexplored.[7] Although most carbenes are made using diazo-transfer processes, Marcos indicated that he was going to oxidize a hydrazone. He used the large-scale prep reported by Mathias Brewer[8] and then executed the reaction using inverse addition of this compound to a solution of catalyst using a syringe pump. Much to our delight, the product was formed in high (for a first try) yield and with some level of diastereoselectivity in favor of the cis isomer based on comparison of the ^1H-^1H coupling constants to related compounds. After this Eureka! moment, Marcos left for his new position and the project stalled with little funding while I devoted all of my efforts to the main projects in the lab while preparing to submit my package for tenure promotion.

Method Development

The project languished for a while until it was taken up by a new postdoctoral researcher in the group, Dr. (now Prof.) Cristian Soldi (Universidade Federal de Santa Catarina, Brazil). Cristian initially set about preparing the complex substrate needed to make alopecurone C. When this effort stalled, we decided to take a closer look at the scope of the C–H insertion reaction first demonstrated by Marcos. Cristian made a series of important discoveries in a short period of time (Scheme 3). First, he used an old reaction employing MnO_2 to replace the Swern conditions for hydrazone oxidation. This proved to be fast, high-yielding, and requiring no further purification once the MnO_2 was removed by filtration. Next, he simply added the rhodium catalyst to the solution of substrate and observed rapid C–H insertion with few by-products and no loss in conversion when compared to inverse addition. Finally, we agreed that it would be absolutely amazing if one could simply add MnO_2 and rhodium catalyst to the hydrazone and get to the benzodihydrofuran without isolating the diazo intermediate. This process worked and seemed to be highly efficient even when there was no effort to exclude oxygen or water. Eureka! moment #2 and counting…

With good reactivity in hand, we next tackled stereochemistry. A variety of achiral rhodium catalysts worked in high yield, albeit with little variation in diastereoselectivity. We then investigated chiral catalysts with the hope of finding one that controlled both relative and absolute stereoinduction. Prof. Doyle was kind enough to send us a sample of one of his catalysts (**10**), and we also examined two catalysts (**12**, **14**) reported by Davies (Scheme 4). Doyle's catalyst, which was originally developed for highly electrophilic carbenes, showed no reaction. Commercially available Rh_2(*S*-DOSP)$_4$ (**12**) was highly active and yielded the product with excellent diastereoselectivity and modest enantioselectivity. The third catalyst that was used, Rh_2(*R*-PTAD)$_4$ (**14**, also commercially available) provided the product with nearly perfect yield, diastereoselectivity and enantioselectivity! Eureka #3! As a point of contrast, we had another project in the group for which we tried dozens of catalysts, each requiring three to five steps to make, that never produced one publishable enantioselective reaction, mirroring an experience I had as a postdoctoral researcher.

This C–H insertion reaction worked well for a variety of substrates (Scheme 5).[9] The reactivity toward carbenes can be approximated by the stability of the cation that would result if hydride were abstracted from the center undergoing insertion. Benzyl ethers universally worked well, as did allyl ethers, including cis and trans alkenes, which showed no erosion of configuration. Alkyl ethers worked the least well, enabling us to examine conditions for optimizing the conversion. A solvent screen revealed that acetonitrile improved the yield significantly with only slight erosion of selectivity. This was a testament to the vastly lower electrophilicity of these carbenes relative to those studied previously, in which nonpolar solvents are required for good catalyst activity. We later noted that we could add water to the acetonitrile and see no loss in yield! Finally, we examined propargyl substrates, which gave frustratingly low yields and low enantioselectivity in spite of their propensity to give high diastereoselectivity. A range of different catalysts, kindly provided to us by Prof. Joseph Fox (University of Delaware), failed to improve the yield or enantioselectivity.

After this first paper, we examined this reaction in more depth and reached several important conclusions.[10] First, the one-pot conditions were sometimes lower-yielding than the 'two-pot' conditions in which the diazo intermediate is separated from the MnO_2 by filtration before adding catalyst. This was later traced to incomplete oxidation and led to our 'modified one-pot' conditions in which the oxidation is followed by TLC before adding catalyst. The presence of the MnO_2 was irrelevant, i.e., it was only the additional time for the oxidation that increased the yield! Second, we noted that the cinnamyl ether gave a little bit of cyclopropanation as a side product (Scheme 6). We demonstrated that this is not happening directly, but rather by uncatalyzed 1,3-dipolar cycloaddition (DPC) followed by nitrogen extrusion. This discovery was made while trying to improve this reaction with the two-pot process, which yielded the DPC product and cyclopropane at room temperature before the catalyst could be added. This process was competitive with rhodium-catalyzed insertion, leading to lower yields.

Finally, the phenylpropargyl ether gave no insertion product and was cleanly converted into something we could not identify at the time of the first paper when two-pot conditions were employed. A postdoctoral researcher, Dr. Edward Balmond reasoned (correctly) that it was the product of a DPC reaction and compared the NMR spectrum to that of a similar reaction.[11] When he tried to crystallize this product, he observed something altogether surprising: the DPC product had undergone a sigmatropic ring contraction (Scheme 7). While the ring contraction had no precedent at the time we discovered it, the basic reaction involving an acyclic shift, and dubbed the 'van Alphen-Hüttel rearrangement', had been described seven decades earlier[12–14] and a related ring expansion was well-established.[15] Moreover, the unique spirocyclic products were unknown in either the publication or patent literature. We examined the scope of this reaction and were excited to publish the first example of this intriguing ring-contraction when we were 'scooped' by another laboratory working on related chemistry.[16] They completed some of the exact same substrates and the main difference was the origin of the diazo intermediates, which were derived from the more common toluenesulfonyl hydrazones. You win some, you lose some. This project had involved enough winning that we proceeded with publication and moved on.[17]

While working on the C–H insertion processes, we recognized that we could also pursue insertion into O–H, N–H and possibly Si–H bonds, collectively referred to as X–H insertion. At the time we started this project there were few examples for donor/donor carbenes and many cases of Lewis acid-catalyzed etherification that probably proceed without carbene intermediates. While we have made some progress in this area, we recognized that uncatalyzed esterification via diazo compounds had some unmet needs (Scheme 8). Although diazomethane was once pervasive for esterification, it has fallen out of favor due to safety concerns for both the reagent itself and one of its common (mutagenic) precursors, namely methylnitronitrosoguanidine (MNNG). TMS-diazomethane is commercially available, yet still has drawbacks in both stability and toxicity. While hydrazone oxidation provides a nice entry into a wide variety of diazo compounds, the problem of azine formation, i.e., double condensation of two equivalents of aldehyde, limits this approach. The use of TBS hydrazones alleviates the azine problem, but requires an HF-based oxidant for diazo formation.[18] We developed a one-pot hydrazone-to-ester reaction and demonstrated that this reaction proceeds without the buildup of diazo intermediates.[19]

Our initial study of benzodihydrofuran synthesis formed the basis for exploring analogous substrates with widely varying reactivity (Scheme 9A). Moreover, the lack of success with X–H insertion suggested that this reaction would have wide functional group tolerance, unlike many reactions of more electrophilic carbenes. We demonstrated that C–H insertion was still very efficient and selective when oxygen was replaced with atoms that reduce reactivity (carbon) or introduce basicity (nitrogen) and/or nucleophilicity (sulfur).[20] In one case, a substrate has a benzylic alcohol, which neither interferes with C–H insertion nor undergoes oxidation at a competitive rate. We also observed a rapid reaction of substrate **30**, which initially appeared to be insertion into the vinyl C–H bond (Scheme 9B). This product was racemic, which suggested that the catalyst was not involved, and this was confirmed by excluding the catalyst (unpublished). We eventually assigned the product as **35**, resulting from a dearomatizing electrocyclization followed by hydride shift, a process observed previously.[21,22]

Having fully exploited five-membered ring synthesis, we sought to expand to six-membered rings (Scheme 10). Although this sounds like a modest intellectual leap, the latter reaction is rare for C–H insertion.[23] First, five-membered ring insertion is almost always kinetically favored when both options are available. Second, Stevens-like rearrangement is a constant risk if a heteroatom is placed four atoms away from the carbene, requiring C–H insertion to form a six-membered ring to be faster than nucleophilic attack to form a five-membered ring ylide. As we saw previously, Stevens rearrangement can dominate completely or, under the best of circumstances, erode the yield of C–H insertion. We were delighted to find that six-membered ring formation proceeds readily with diastereo- and enantio-selectivities that are, on average, superior to those observed for five-membered ring formation![24] The reaction works well for a wide variety of substrates, including propargyl ethers! In fact, when the hydrazone precursor was stirred with MnO_2, a rapid color change to the diazo intermediate was observed to persist for five days. This result confirms that the DPC pathway that plagued the five-membered ring precursor was slow enough at room temperature not to compete with rhodium-catalyzed insertion.

We also executed (one of?) the first known C–H insertion reactions to form six-membered ring nitrogen heterocycles. This latter result was particularly hard-fought. Several students worked on a variety of substrates and Leslie Nickerson in particular prepared a wide variety of precursors with differing levels of substitution and electron density on nitrogen. After about a year of failure, I contacted Prof. Fox and his collaborator Dr. Olga Demytrenko, who looked at all of our substrates computationally. They concluded that there were high energy barriers and or alternate pathways for all but **41a**, which was the last one we had undertaken (Scheme 11); they suggested this one had the highest probability of working. Although Leslie had synthesized the ketone precursor, hydrazone formation was not straightforward, so we had shelved this substrate when we abandoned the idea of making six-membered nitrogen heterocycles. Leslie dug it back out of the freezer, made the hydrazone, and found that it proceeded rapidly to a single stereoisomer! Two related substrates also worked reasonably well. We were not able to entirely escape the Stevens rearrangement pathway. N-Boc substrate **43** provided isoindoline product **46** in 50% yield. This reaction was examined computationally by Croix Laconsay (working in the laboratory of Prof. Dean Tantillo, UC

Davis), which demonstrates that the rhodium catalyst is probably expelled before the rearrangement step.

Conclusion

All told, the investigation of donor/donor carbenes over the last decade has been one of the more interesting developments of my scientific career. Although this project had its origin at the Broad Institute while I pondered the antimicrobial activity of a plant-derived natural product, the chemistry was 100% initiated and completed at my current institution, unlike the other two major projects on which I have worked. In addition, this project has involved enantioselective catalysis at its core, an area of organic synthesis in which I did not engage as a graduate student or to any great extent as a postdoctoral researcher. Finally, this project highlights the importance of 'seed' funding. It was supported by two consecutive international postdoctoral fellowships, a 'new directions' grant from the ACS Petroleum Research Fund and eventually an R01 from the National Institutes of Health. As for the synthesis of the alopecurones, we made a big push to work on alopecurone C at the outset of the project and then shelved it while we focused on methodological studies. Earlier this year, we revived the project and hope to complete one of these targets in the near future…stay tuned!

Acknowledgment

I have acknowledged many individual contributors to this project in the text of the document. I would like to specifically thank Leslie Nickerson, Benjamin Bergstrom and Lucas Souza for help in editing the figures and text of this document. Prof. Karl Scheidt (Northwestern University) is acknowledged for providing guidance and insight for this project and many others continuously since June of 1999 when we shared a bench in the Evans group. Prof. Joe Fox is acknowledged for providing advice on rhodium catalysis as well as samples of dozens of catalysts prepared in his research group.

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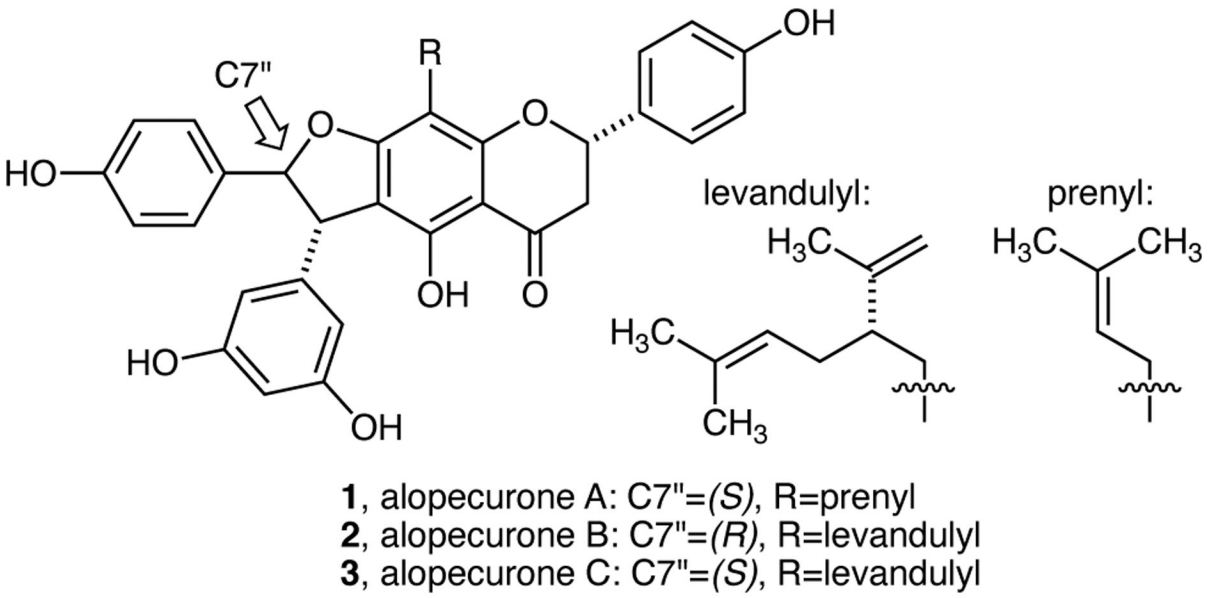
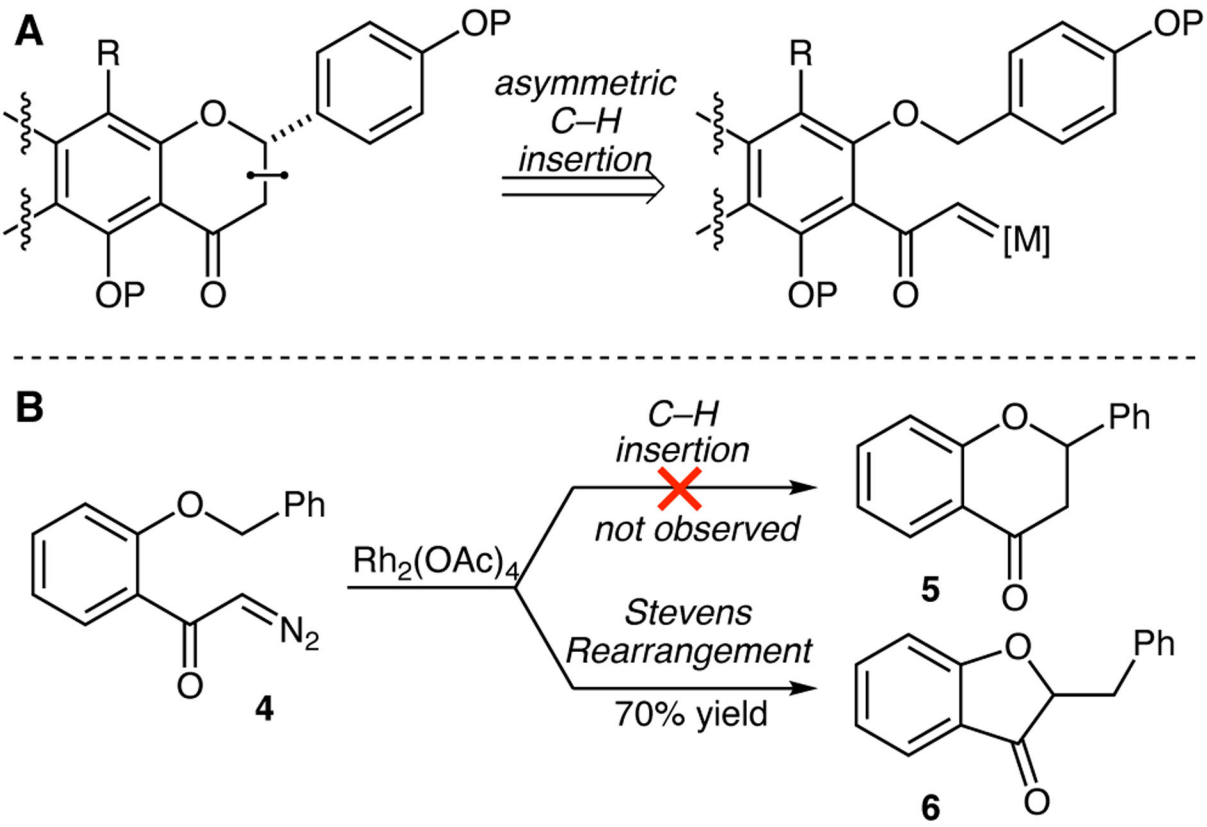
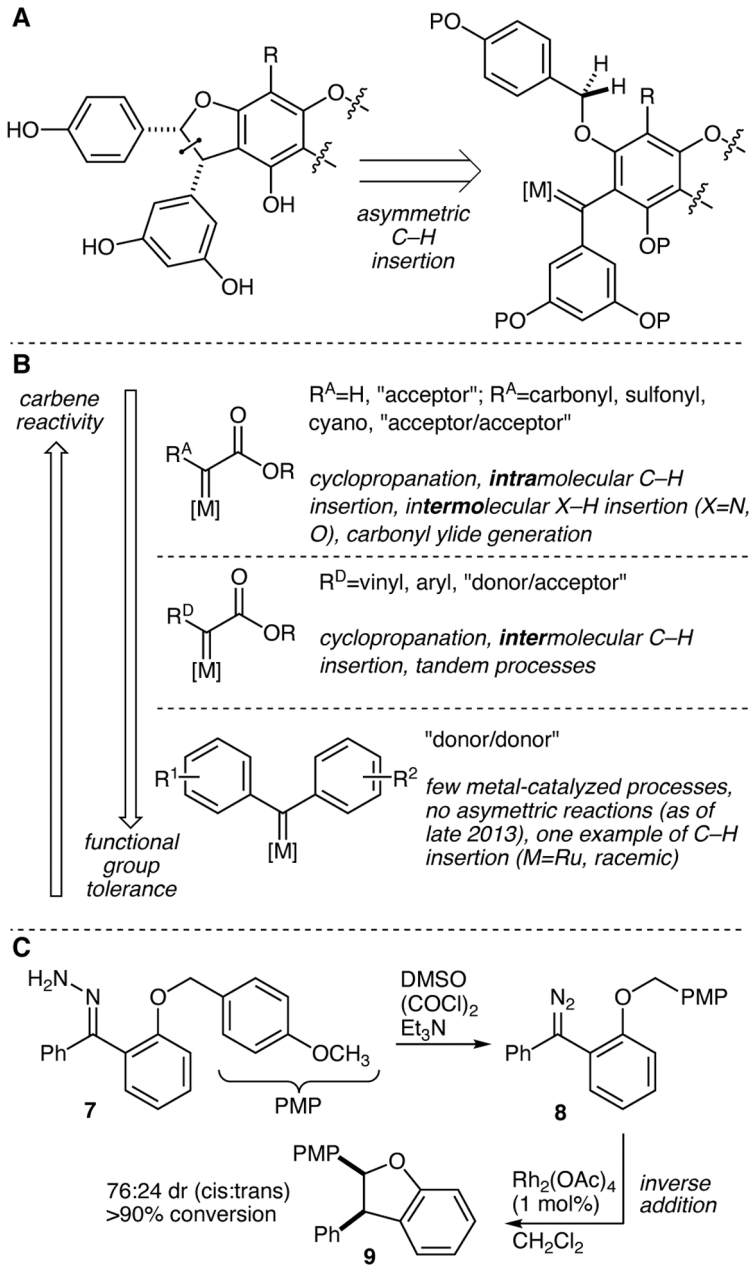


Figure 1.
Structure of alopecurones A–C



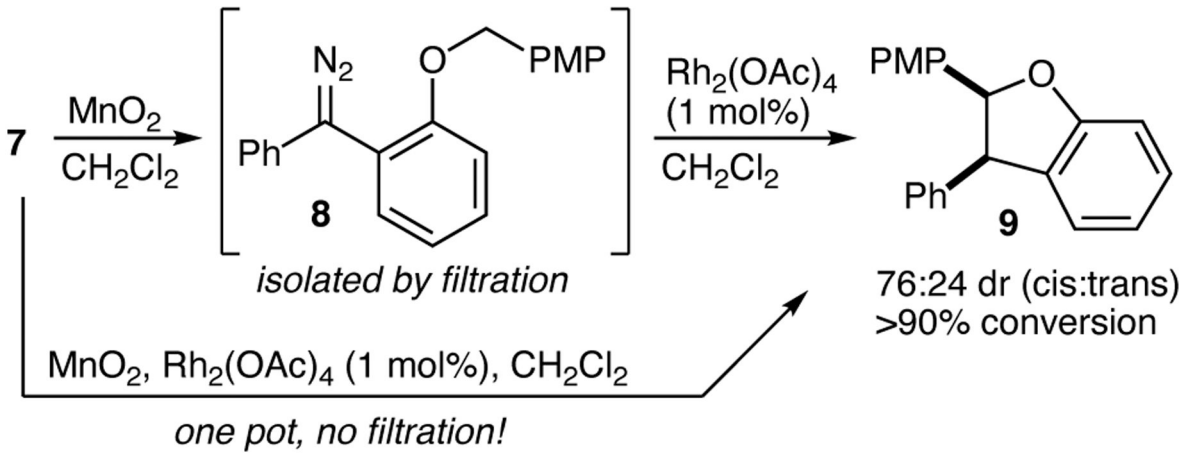
Scheme 1.

(A) Key disconnection in the retrosynthetic analysis of alopecurone C; (B) attempted C–H insertion.

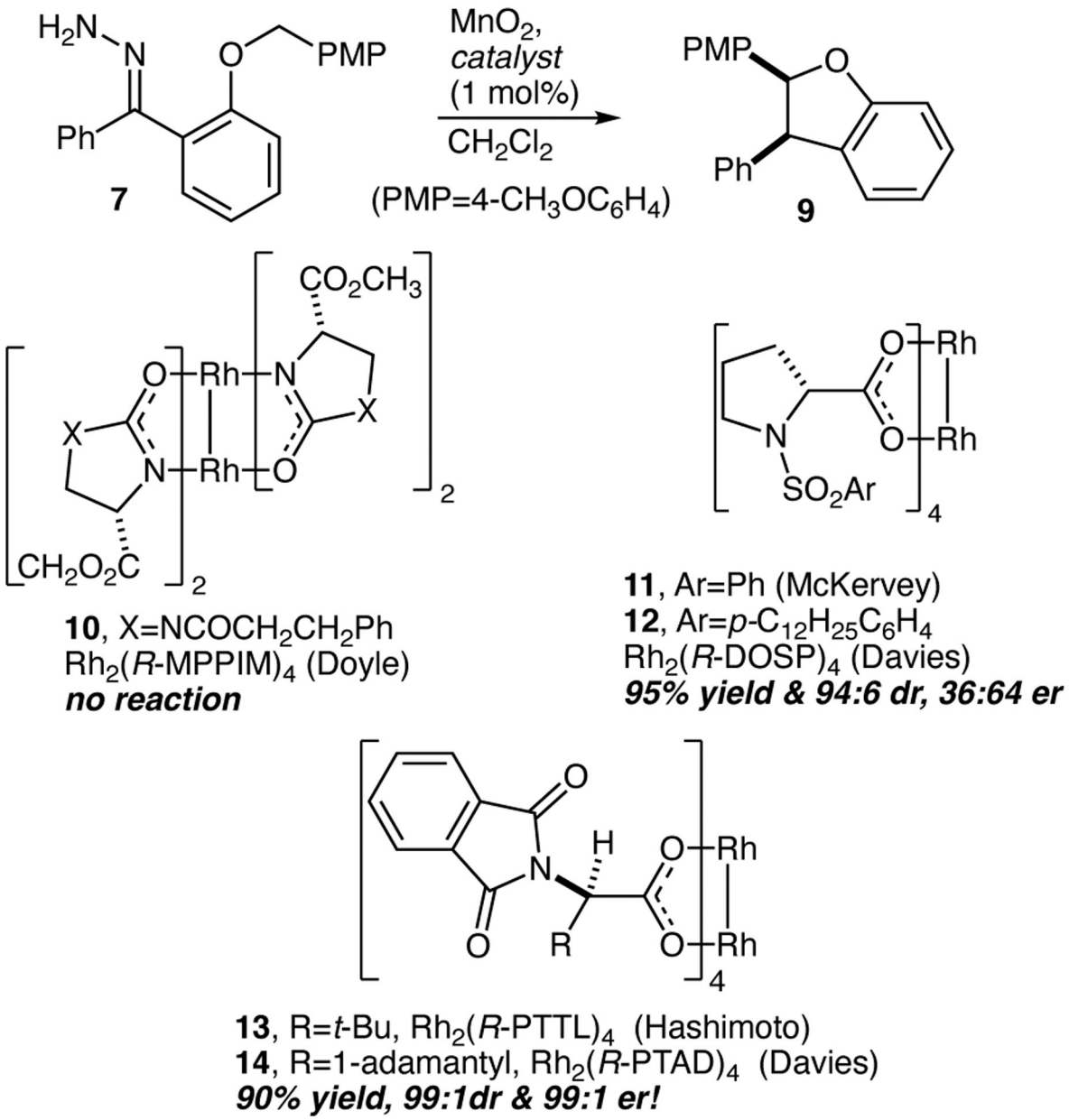


Scheme 2.

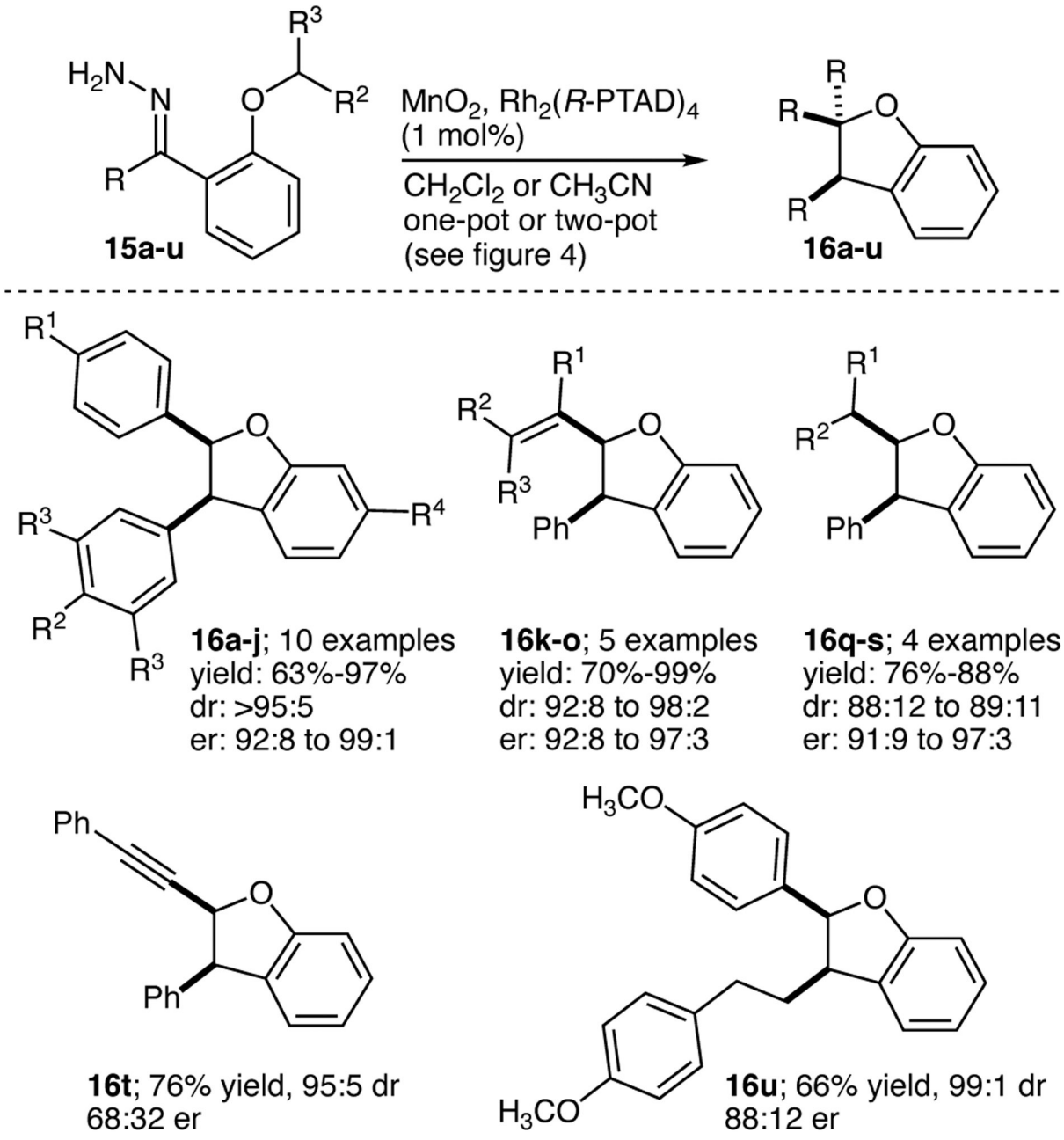
(A) Strategic bond disconnection for the synthesis of the common core of the alopecurones. (B) Summary of carbene reactivity; (C) Preliminary result for a donor/donor carbene.



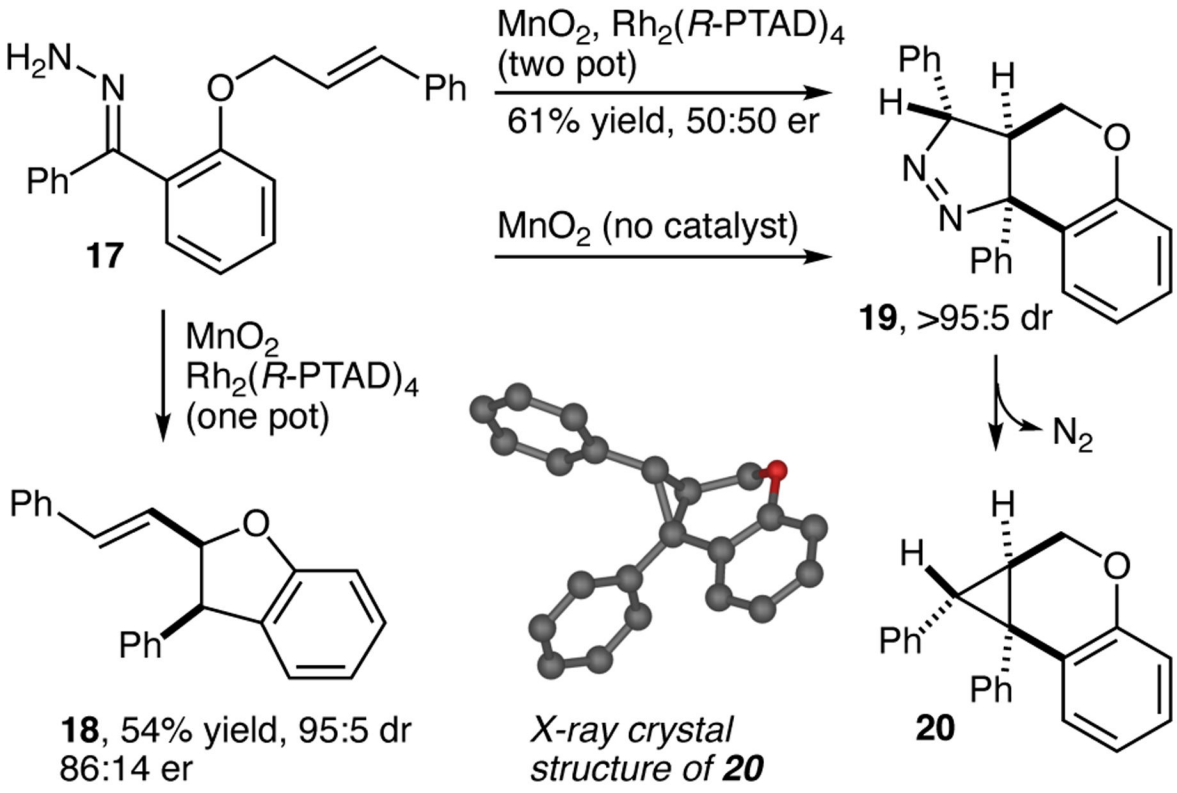
Scheme 3.
Discovery of the one-pot C–H insertion process



Scheme 4.
Preliminary results for C–H insertion with chiral Rh(II) catalysts

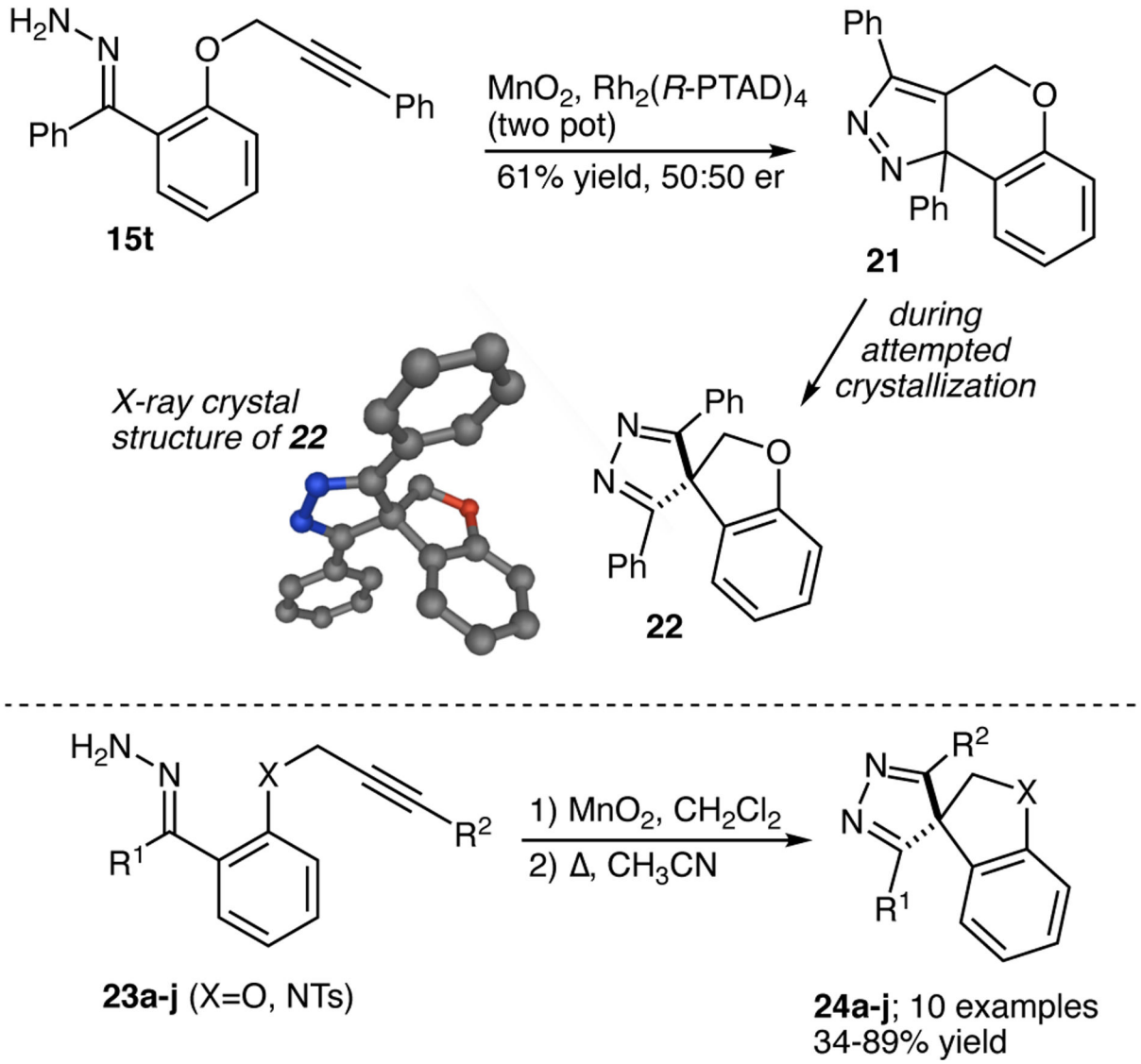


Scheme 5.
Substrate scope in the asymmetric synthesis of benzodihydrofurans

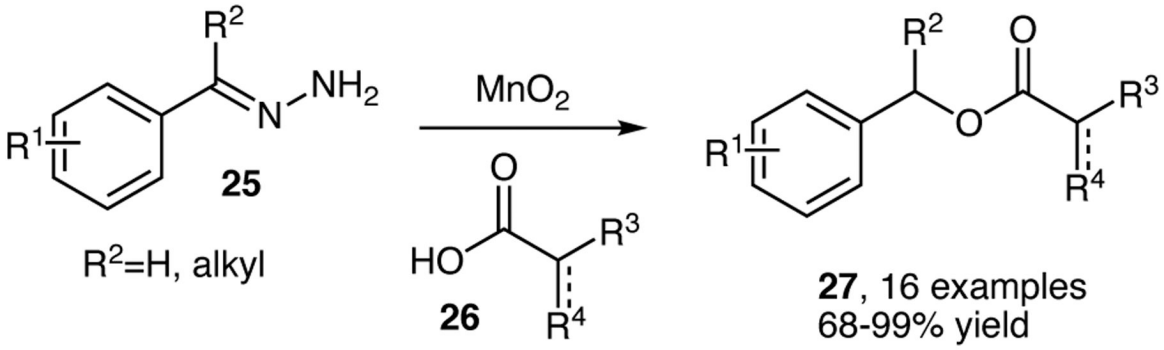


Scheme 6.

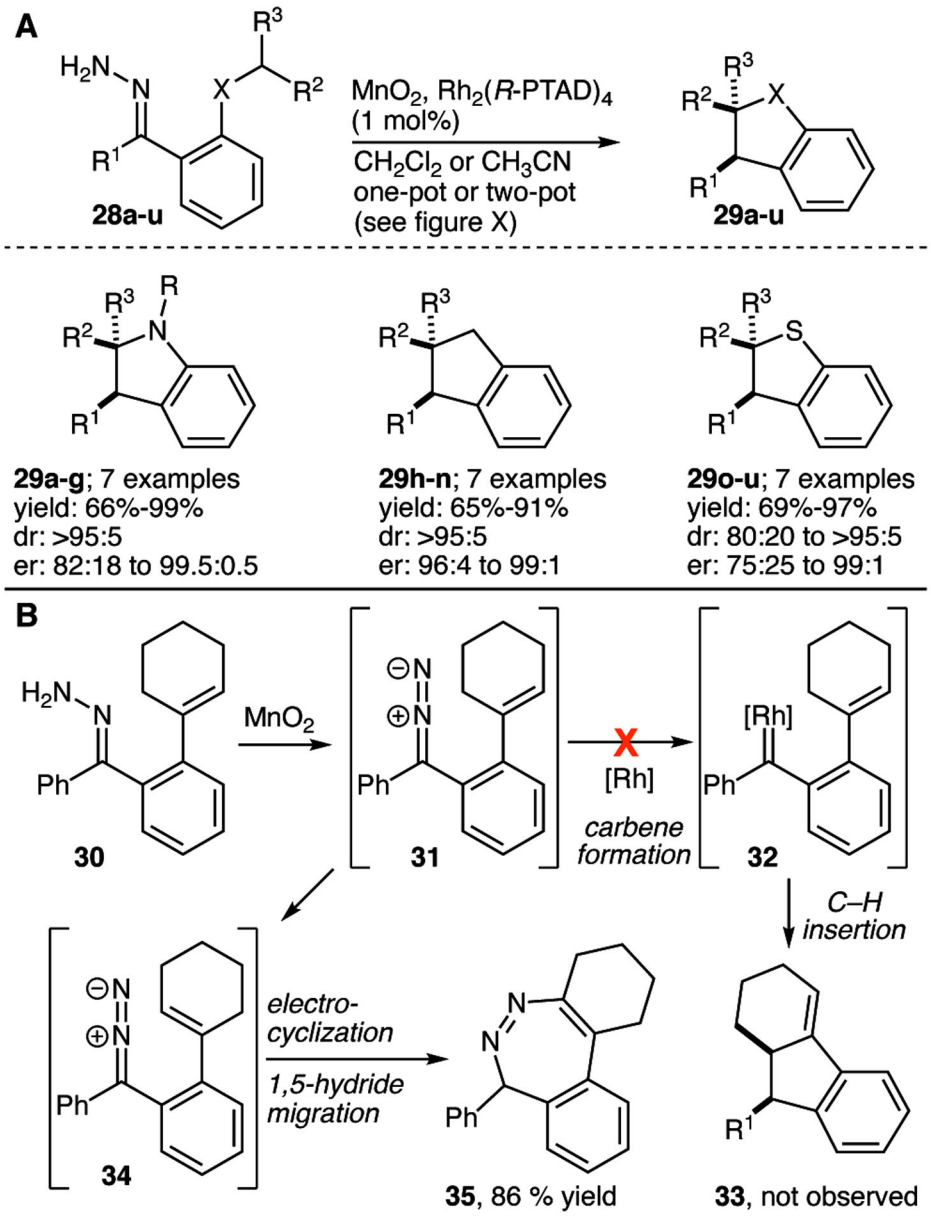
(A) Competing dipolar cycloaddition reaction of alkene substrate **17** resulting in lower yield of **18** and the eventual formation of a cyclopropane **20**



Scheme 7.
Reactions of propargyl ethers in the DPC-rearrangement pathway

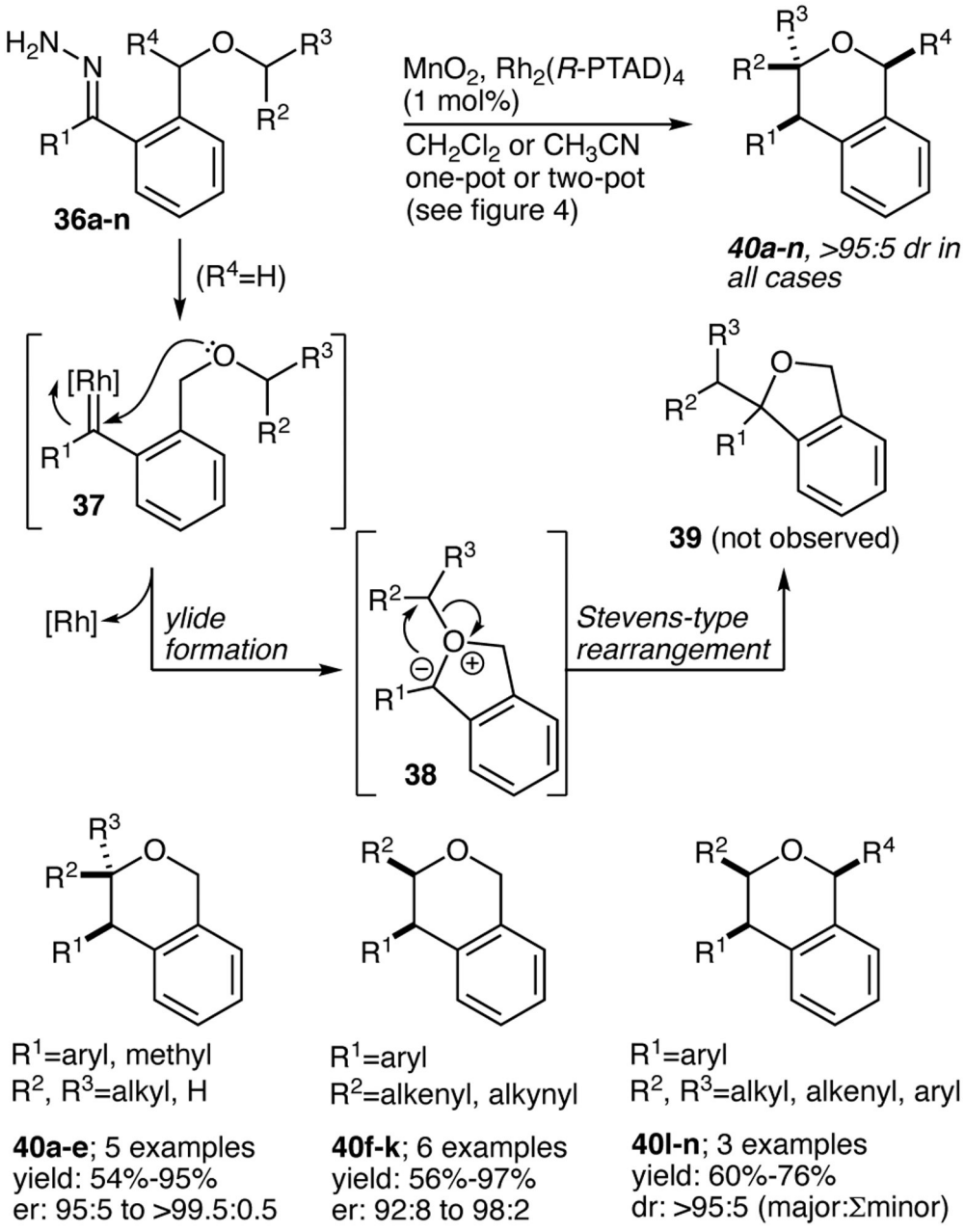


Scheme 8.
One pot esterifications using hydrazones and MnO_2

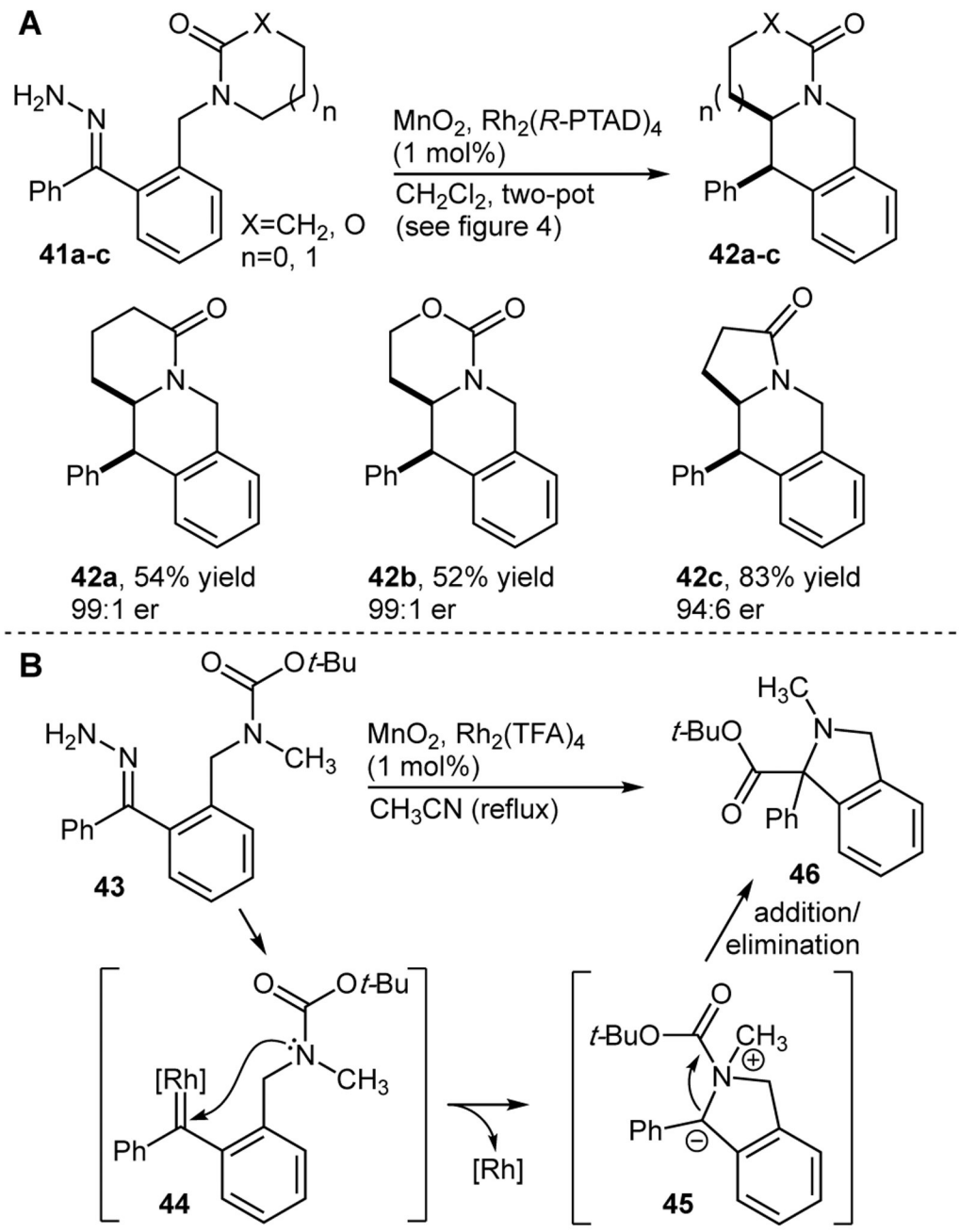


Scheme 9.

(A) Asymmetric synthesis of indanes, indolines and benzodihydrothiophenes by C–H insertion. (B) Rearrangement of an *ortho*-vinyl benzophenone hydrazone.



Scheme 10.
Asymmetric synthesis of isochromans by C–H insertion



Scheme 11.

(A) Asymmetric synthesis of tetrahydroisoquinolines by C–H insertion. (B) Stevens-type rearrangement of acyclic substrate **43**.