"Total Synthesis of Bioactive Natural Products by Palladium-Catalyzed Domino Cyclization of Allenes and Related Compounds"

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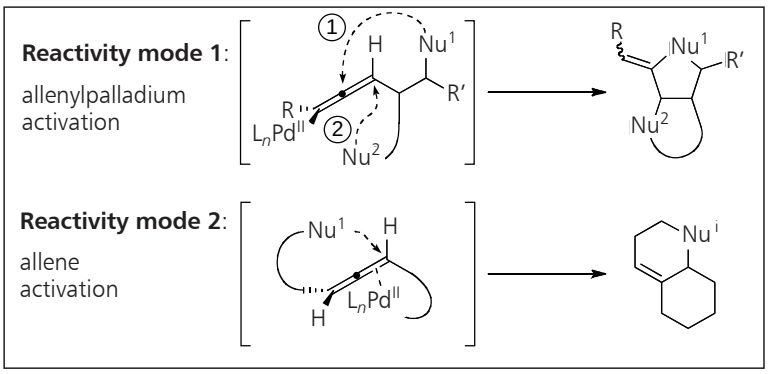
In the latest contribution to the "Springer Theses" series, which celebrate outstanding graduate research from the physical sciences, Shinsuke Inuki provides a detailed account of his PhD research, entitled "Total Synthesis of Bioactive Natural Products by Palladium-Catalyzed Domino Cyclization of Allenes and Related Compounds". Inuki carried out this work in the laboratory of Professor Hiroaki Ohno (Kyoto University, Japan), whose young research group has established a reputation in the field of late transition metal-catalysed 'cascade' organic reactions (also known as 'domino' reactions) involving alkynes and allenes. The target audience for the book includes practicing organic chemists with interests in synthesis, and those with specific interests in palladium-catalysed organic reactions, and as such is suited to graduate level and above.

As the title suggests, the book delves extensively into mechanistic aspects of palladium-catalysed allene chemistry, with a focus on two reaction types: intramolecular reactions of allenylpalladium(II) complexes with pendant nucleophiles, and intramolecular reactions of allenes activated by pendant palladium(II) species (**Scheme I**). The key feature of these processes is the ability of the palladium(II) catalyst to enhance the electrophilicity of the allene through coordination to the metal atom in its +2 oxidation state, thus triggering nucleophilic attack. Having established an understanding of each metal-catalysed bicyclisation, Inuki goes on to apply this chemistry to the synthesis of a number of bioactive alkaloid natural products. The overall aims of the work are firstly to extend the state of the art in palladium-activated allene chemistry through a



Scheme I. Palladium(II) activation of allenes towards nucleophilic attack

detailed investigation of the influence of substrate stereochemistry on the selectivity and outcome of these reactions, and secondly to demonstrate the utility of this chemistry in the efficient assembly of bioactive natural products. In both respects, the author has certainly succeeded, and delivers an entertaining and informative account of his graduate research.

For **Schemes I, II** and **V**:

Nu^1 = *O*,*N* nucleophiles, 1,3-dicarbonyl enolates

Nu^2 = *O*,*N* nucleophiles, alkenyl/aryl/alkynyl zinc or copper species

R, R′ = alkyl, aryl

L = mono or bidentate phosphine ligands

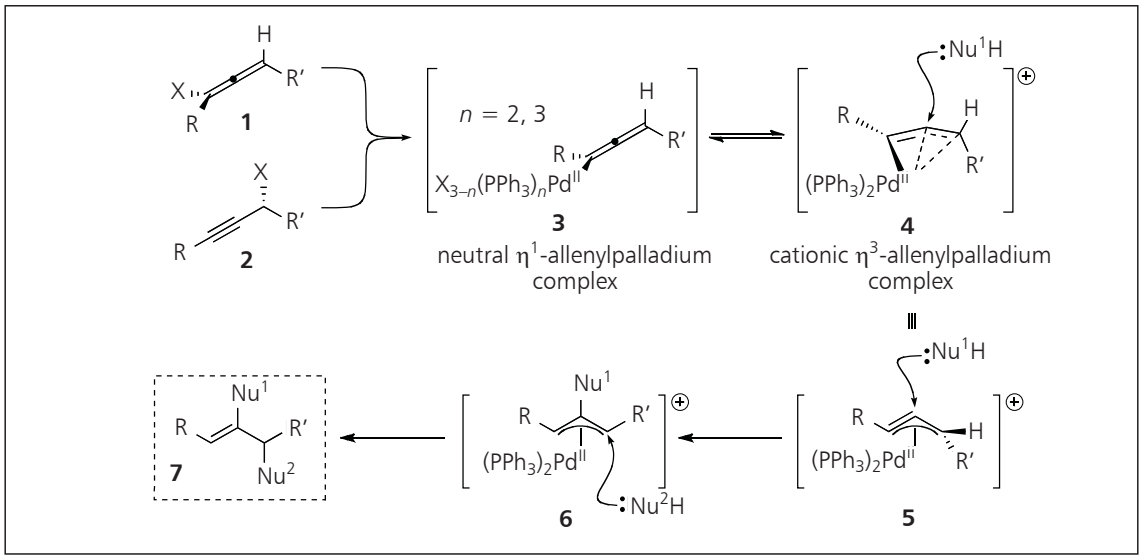
X = halide, carbonate, acetate

Cascade (or domino) reactions are of great appeal to organic chemists, as they allow the formation of multiple covalent bonds in a single step, and therefore the synthesis of relatively complex products from simple starting materials (1); for recent reviews, see (2, 3). In the context of this book, the palladium catalyst is able to mediate the formation of two covalent bonds through sequential nucleophilic attacks on an allene, thereby building stereochemistry-rich bicyclic products from acyclic starting materials. The book begins with a short review of this reactivity, including background work from the author's own group, and an outline of the topics covered in each chapter. This introductory section also contains an extensive selection of seminal and recent references which the reader may consult for further details of the discovery and evolution of this mode of palladium-catalysed reactivity.

Reactivity Mode 1: Reactions of Allenylpalladium(II) Complexes

The second and third chapters focus on investigations into the first mode of allene activation: the formation of allenylpalladium(II) complexes. These intermediates may be formed from oxidative addition into two distinct precursors: allenyl halides (**1**, **Scheme II**), and propargylic electrophiles **2**, which – on paper at least – deliver an equivalent neutral η^1-allenylpalladium intermediate **3** (4). Nucleophilic attack on these species is believed to be accelerated *via* formation of a non-linear cationic η^3-allenylpalladium complex **4** (5, 6), which is formed by coordination of the second allene double bond to the initially-formed η^1-allenylpalladium(II) species **3** following loss of an anionic ligand. There are multiple ways to represent complex **4**, including the recognition that **4** contains a π- and σ-coordinated palladium atom, and can therefore be represented as a kind of π-allyl complex **5** (the allyl complex being coplanar with the σ-framework of the molecule). What is clear and common to all representations is that this coordination causes an increase in strain at the central allene carbon through bending of the allene structure (C=C=C angle ~150°), which is relieved by nucleophilic attack with concurrent (or subsequent rapid) protonation to give an η^3-π-allylpalladium intermediate **6**. This latter palladium(II) complex is then susceptible to standard π-allyl nucleophilic addition chemistry, giving rise to the corresponding double addition product **7** – which in the case of this work is a bicyclic structure arising from the use of two tethered (i.e. intramolecular) nucleophiles. For a general review of nucleophilic cyclisations onto propargyl/allenylpalladium complexes, see (7).

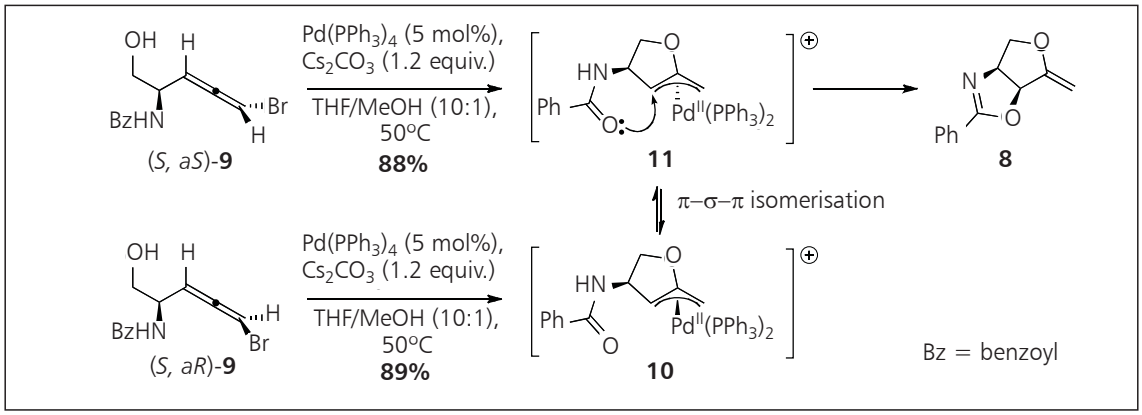
Inuki investigates both allenyl and propargyl electrophiles as sources of allenylpalladium(II)



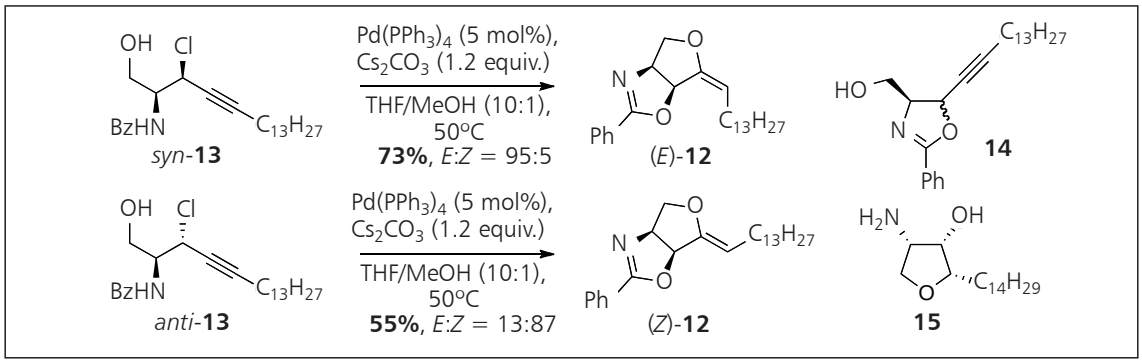
Scheme II. Generation of allenylpalladium(II) complexes and double addition reactions with nucleophiles

complexes, and in the second chapter begins with reactions of bromoallenes. Throughout his work, tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) serves as the palladium precatalyst, with a variety of bases and solvents being investigated for their influence on the stereo- and regioselectivity of the cyclisation events. Both are found to play an important role; for the bromoallenes, the combination of caesium carbonate (Cs_2CO_3) in a mixed tetrahydrofuran/methanol solvent system delivers a high yield of bicyclic product **8** (**Scheme III**). Interestingly, both diastereomers of bromoallene **9** delivered the same product **8** in comparable yield, reflecting the ability (and requirement for cyclisation) of the palladium(II) π-allyl intermediates **10** and **11** to interconvert *via* the usual π-σ-π mechanism.

In the third chapter, Inuki contrasts the bromoallene precursor to the η3-allenylpalladium intermediate with propargylic chlorides and carbonates (**Scheme IV**). The former react more efficiently under equivalent conditions to the bromoallenes, delivering the corresponding bicyclic products (*E*)-**12** or (*Z*)-**12** depending on which diastereomer of **13** is used as substrate. In these cases, some monocyclic byproducts **14** were isolated which correspond to a rarely observed direct propargylic substitution reaction,



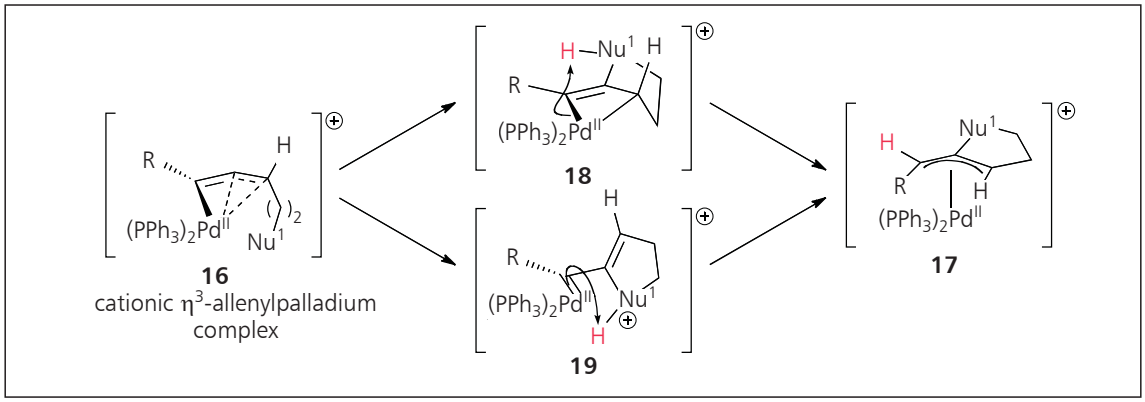
*Scheme III. Degeneracy in the bicyclisation of allenes (S, aS)-**9** and (S, aR)-**9** to oxazoline **8***



Scheme IV. Cyclisation of propargylic chlorides to bicyclic products: diastereomer-dependent stereoselectivity

also likely mediated by the palladium catalyst, arising from a choice of which of the two nucleophiles (hydroxyl or carbonyl) reacts in the initial cyclisation event. For a recent case where propargylic cyclisation predominates, see (8). The corresponding propargylic carbonates (not shown) show less reliance on the presence of a basic additive, but give slightly inferior yields and selectivities to the chlorides. The author concludes this chapter by successfully converting the cyclised products to the natural product jaspine B (pachastrissamine) **15** (9).

Throughout these two chapters, a more in-depth discussion of the precise mechanism of cyclisation could have been beneficial to the reader. Certainly, there remains controversy over the pathway of the conversion of the cationic η^3-allenylpalladium(II) intermediate **16** to the η^3-π-allylpalladium(II) complex **17** (**Scheme V**) – where this pathway could occur *via* a transient palladacyclobutene **18** (recent DFT calculations support the formation of the palladacyclobutene(II) intermediate, although its formation is distinctly less facile than the corresponding platinacyclobutene (10), see also (5, 6)) or a palladium carbenoid **19** (Tsuji has performed deuterium labelling studies which lend support to the carbenoid mechanism (11)), either of which are converted to **17** by inter- or intramolecular protonation (the latter is shown in **Scheme V**). Few workers in the field have comprehensively examined the influence of diastereomer stereochemistry on this process, and the significant body of results Inuki has gathered for these reactions may yet contain information which reveals or supports the exact mechanism of these cyclisations, due to the distribution and nature of the reaction products. The source of the allenylpalladium(II) intermediate may also be crucial, with oxidative addition into the bromoallene being perhaps more likely to lead to an η^3-intermediate than addition into a propargylic chloride, and certainly a propargylic carbonate.



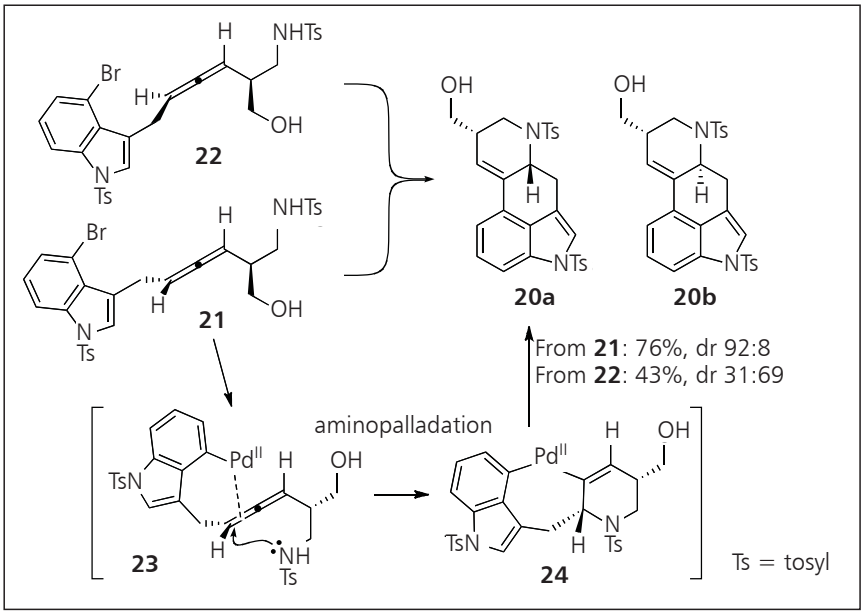
Scheme V. A mechanistic dichotomy: conversion of allenylpalladium(II) to allylpalladium(II) intermediates

Reactivity Mode 2: Palladium(II)-Promoted Reactions of Allenes

The fourth and fifth chapters of the book switch the focus of palladium-catalysed allene activation to a π-acid role for the metal. Now, arylpalladium(II) intermediates generated from oxidative addition into pendant aryl bromides are able to activate allenes towards intramolecular nucleophilic cyclisation. This reaction, illustrated in **Scheme VI**, leads to the formation of two rings in a single step, here corresponding to the carbon framework **20** of the lysergol ergot alkaloids. Chapter 4 establishes this reactivity using racemic allene substrates; in Chapter 5, this work is extended to enantio- and diastereomerically enriched substrates. The experimental observation in this work is that the cyclisation event proceeds in markedly contrasting yields and diastereoselectivities depending on the choice of allene diastereomer, with **21** giving significantly better results than **22**. Inuki provides some rationalisation for these outcomes based on possible reaction mechanisms. These likely involve a choice (or competition) between allene carbopalladation (to give a π-allyl intermediate through C–C bond formation at the central allene carbon, not shown) followed by aminocyclisation, or aminopalladation of the π-activated allene **23** to give an alkenylpalladium(II) intermediate **24** followed by reductive elimination, with the latter being the pathway favoured by Inuki. Although it remains unclear from the experimental results whether one or both of these pathways operate, synthetically useful levels of selectivity can be obtained. This chapter concludes with the application of this bicyclisation to the synthesis of three lysergic alkaloids (12).

Concluding Remarks

Overall, the book is well-written and provides plenty of food for thought for specialists in palladium(II) chemistry, as many aspects of palladium-activated allene reactivity are explored, but not totally solved, in the course of this work. Being a thesis, the book also benefits from a comprehensive experimental section at the end of each chapter. This section will prove most valuable to practising chemists in this field, particularly in detailing the conditions employed for the key palladium-catalysed cascade cyclisations. In total, the book reflects the high quality experimental skills of the author, and provides a useful handbook for the synthetic organometallic chemist. Whilst the audience for such theses is always likely to be somewhat specialised, the concise but clear nature of the book retains the interest of the reader, and gives insight into the subtleties and many reaction pathways of palladium-activated allene chemistry.



Scheme VI. Allene activation through palladium(II) complexation/ aminopalladation

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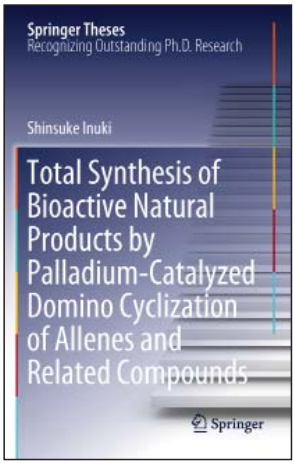
The Reviewer

Ed Anderson is a Lecturer in Chemistry at the University of Oxford, UK. His interests in platinum group metals are centred on palladium-catalysed organic reactions, with a particular focus on organopalladium chemistry involving allenes and alkynes, cascade reactions involving carbopalladation processes, and palladium-catalysed reactions of ynamides. His research in these areas ranges from methodology and mechanism to applications in organic synthesis.



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