FEATURE ARTICLE

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Synthesis and applications of rhodacyclopentanones derived from C–C bond activation

Megan H. Shaw and John F. Bower*

Rhodacyclopentanones, an "sp³-rich" class of metallacycle, underpin an emerging range of catalytic methodologies for the direct generation of complex scaffolds. This review highlights strategies for accessing rhodacyclopentanones (and related species) by C–C bond activation of cyclobutanones or cyclopropanes. The scope and mechanism of methodologies that exploit these activation modes is outlined.

Introduction

Synthetic strategies that provide chiral "sp³ rich" molecular scaffolds are highly desirable to medicinal chemists.[1] To address this, numerous research groups have focused on the development of protocols to activate and functionalise "traditionally inert" C(sp³)–H bonds.[2] While progress in this area has been rapid, the realisation of complementary processes that exploit the activation of C–C bonds, which are also found in almost all organic molecules, has proven more challenging.[3] However, as highlighted in this article, recent advances in C–C bond activation have led to catalytic protocols that provide direct access to challenging chiral ring systems, thereby illustrating the potential for this activation mode to access underexplored chemical space.

Key challenges for developing methodology based on C–C bond activation are (a) the high activation barrier for metal insertion into C–C bonds (*cf.* C–H bonds)[4] and (b) control of regioselectivity in the C–C bond oxidative addition step. A common strategy for overcoming the barrier to oxidative addition is to use highly strained 3- and 4-membered cyclic systems for catalysis initiation; here, relief of ring strain drives insertion of the metal catalyst. Alternatively, coordination of the metal catalyst to an appropriate directing group can

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John F. Bower

Fellowship and commenced his independent career at the University of Bristol. Bower's research has been recognized by a number of awards, including the 2013 Royal Society of Chemistry Harrison-Meldola Memorial Prize and the 2015 Royal Society of Chemistry Hickinbottom Award.

enhance both the rate of oxidative addition and the regioselectivity of this step.[5] Although chelation-assisted metal insertion has been exploited for the activation of both strained and unstrained C–C bonds,[3,5,6] protocols involving strained systems are far more extensive.

Rhodacyclopentanones provide a versatile catalysis platform for an emerging range of C–C bond activation triggered methodologies. Although the first report of an isolable rhodacyclopentanone complex dates back to the 1960s,[7] the reactivity of these Rh(III)-metallacycles has only been exploited in reaction design within the last 20 years. In this context, rhodacyclopentanones represent an "sp^3-rich" class of metallacyclic intermediate that is capable of delivering an array of complex molecular scaffolds. In particular, rhodacyclopentanones participate efficiently in cycloaddition reactions with various π-unsaturated components. Recently, there have been significant and impressive developments in cycloaddition methodologies of this type. Herein, strategies for accessing rhodacyclopentanones (and related species) will be highlighted, and the scope and mechanism of representative synthetic methodologies will be discussed. Note that hydroacylative and oxidative coupling approaches to rhodacyclopentanones are not covered in this Feature Article.[8]

Synthesis of rhodacyclopentanones

Rhodacyclopentanones can be generated catalytically by C–C bond activation of either cyclobutanone or cyclopropane precursors (Scheme 1). In the former case, Rh(I)-catalysts preferentially undergo oxidative addition into the acyl–C(sp^3) bond of cyclobutanones to deliver rhodacyclopentanones. For cyclopropanes, generation of the Rh(III)-metallacycle requires migratory insertion of a CO ligand, thereby necessitating the use of a carbonylative atmosphere for catalytic transformations. In both cases, insertion of the Rh(I)-catalyst into substituted ring systems can potentially deliver a number of regioisomeric rhodacyclopentanones. The selectivity of C–C bond activation can be influenced by both steric and electronic factors, with chelation-assisted metal insertion often enabling precise control of regioselectivity.
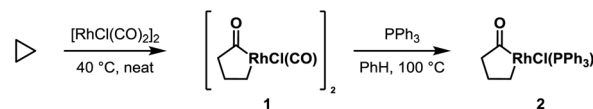
In 1968, Wilkinson and co-workers reported that exposure of cyclopropane to a CO-ligated Rh(I)-catalyst resulted in ring expansion to deliver dimeric rhodacyclopentanone 1 (Scheme 2A).[7] Upon treatment with PPh$_3$, the CO and bridging Cl ligands were displaced and monomeric phosphine-bound rhodacyclopentanone 2 was generated. Subsequently, McQuillin and Powell examined the effect of cyclopropane substitution on the regioselectivity of rhodacyclopentanone formation (Scheme 2B).[9]
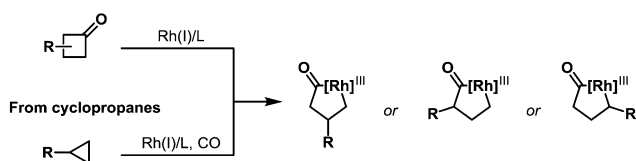
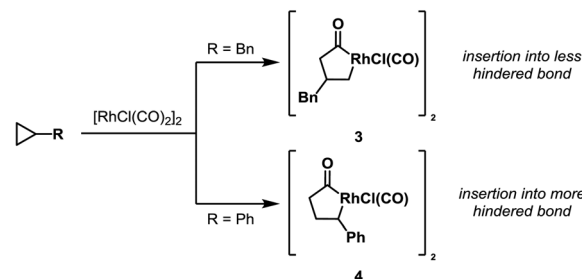**Scheme 1** Generation of rhodacyclopentanones from cyclobutanones or cyclopropanes.

Scheme 2 Stoichiometric Rh(I)-mediated ring expansions of cyclopropanes to generate rhodacyclopentanones.

Exposure of benzyl cyclopropane to $[RhCl(CO)_2]_2$ resulted in Rh-insertion into the less hindered C–C bond to deliver rhodacycle 3. In contrast, phenyl cyclopropane afforded dimeric rhodacycle 4, derived from insertion into the more hindered cyclopropane C–C bond, demonstrating that electronic activation can override steric factors. Stoichiometric carbonylative ring expansions of other cyclopropane-containing structures, such as quadricyclene,[10] 3,5-dehydronoriceane,[11] and dibenzosemibullvalene,[12] to rhodacyclopentanones have also been reported.

In 2013, our group reported a strategy for accessing amino-rhodacyclopentanones from carbamate-substituted amino-cyclopropanes.[13] Here, the carbonyl directing/protecting group of 5 directs metal insertion into the more hindered cyclopropane C–C bond and, in addition, directs migratory insertion of the CO ligand to deliver amino-rhodacyclopentanone 6 selectively (Scheme 3A). Exposure of carbamate-substituted cyclopropane 7 to $[RhCl(CO)_2]_2$ resulted in regioselective formation of dimeric rhodacycle 8, the structure of which was confirmed by X-ray diffraction; this was the first X-ray crystal structure of a rhodacyclopentanone complex derived from carbonylative cyclopropane ring expansion.[14] Note that earlier studies by Chirik and co-workers had shown that strongly coordinating phosphinites can direct Rh(I)-catalysts into the more hindered C–C bond of tethered cyclopropanes, albeit under non-carbonylative conditions.[15]

As mentioned previously, Wilkinson and co-workers reported that exposure of dimeric rhodacycle 1 to excess PPh$_3$ delivered complex 2 with two phosphine ligands bound to the Rh-centre (Scheme 2A).[7] In contrast, treatment of rhodacycle 8 with excess PPh$_3$ delivered monomeric complex 9 bound to a single phosphine ligand, such that coordination of the directing group is maintained (Scheme 3B).[16] Formation of monomeric cationic Rh(III)-complex 10 was accomplished by treatment of 8 with $P(3,5-(CF_3)_2C_6H_3)_3$ and AgOTf.[17] Subsequently, a series of dimeric rhodacyclopentanone complexes (11a–c) containing different carbonyl protecting/directing groups were synthesised, with the stretching frequency of the CO ligand *trans* to the directing group allowing quantification of its donor strength (Scheme 3C).

A) Directed generation of amino-rhodacyclopentanones:
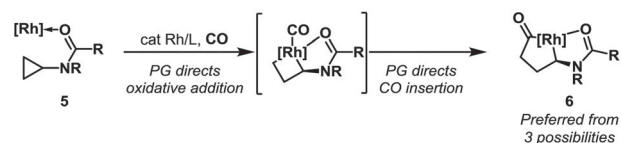
B) Synthesis of rhodacyclopentanone complexes from aminocyclopropanes:
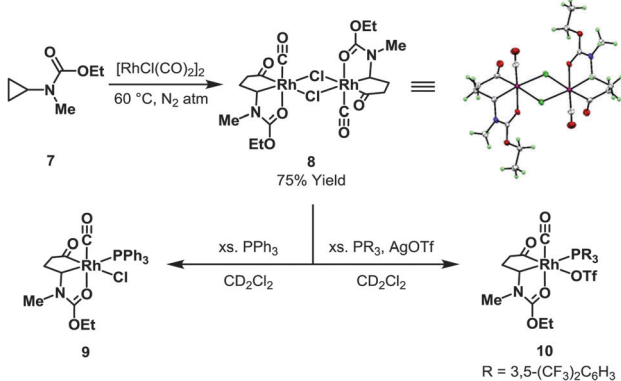
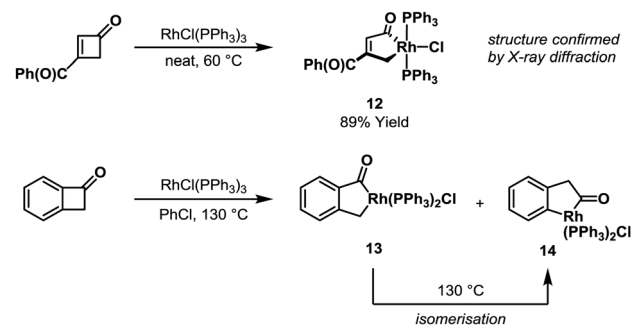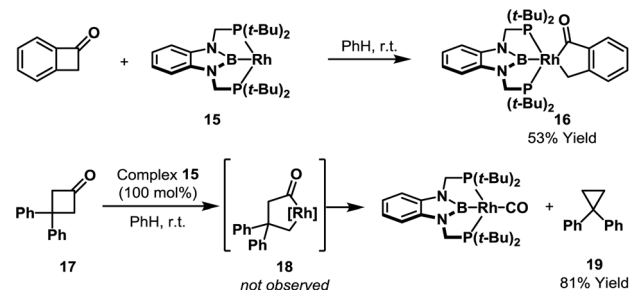C) Relative donor strengths of different *N*-directing groups

R	υ(CO) / cm^{-1}	
11a, Ph	2045.6	*Weakest donor ligand*
11b, OBn	2043.8	
11c, NMe$_2$	2022.5	*Strongest donor ligand*

Scheme 3 Synthesis and evaluation of carbonyl-protected amino-rhodacyclopentanone complexes.

A) Formation of rhodacyclopentenone and rhodaindanone complexes

B) Comparison of the stability of rhodaindanone **16** and rhodacyclopentanone **18**

Scheme 4 Stoichiometric Rh(ı)-mediated ring expansions of benzocyclobutenone and cyclobutenones.

The following ranking was determined: urea ≫ carbamate > amide, and this data was used to guide subsequent methodology development.[16,17]

Stoichiometric reactions between cyclobutanones and Rh(ı)-complexes to deliver isolable rhodacyclopentanones have not been achieved. However, insertion of Rh(ı)-catalysts into cyclobutenones and benzocyclobutenone, to deliver rhodacyclopentenones and rhodaindanones respectively, was reported by Liebeskind and co-workers in 1992 (Scheme 4A).[18] In contrast with (η^5-C$_9$H$_7$)Co(PPh$_3$)$_2$, which delivered η^4-vinylketene complexes, RhCl(PPh$_3$)$_3$ underwent insertion into substituted cyclobutenones to deliver stable rhodacyclopentenone complexes; the structure of rhodacycle **12** was confirmed by X-ray diffraction. Exposure of benzocyclobutenone to Wilkinson's catalyst delivered a mixture of rhodaindanones **13** and **14**, resulting from activation of the acyl–C(sp^3) bond and acyl–C(sp^2) bond, respectively. Upon heating, conversion of **13** to **14** was observed, which indicates that rhodaindanone **14** arises *via* isomerisation of kinetically favoured rhodaindanone **13**. Subsequent computational studies support isomerisation by way of a retrocarbonylation–recarbonylation mechanism.[19] Recently, Murakami and co-workers reported an X-ray crystal structure of rhodaindanone **16** (Scheme 4B).[20] By utilising the bulky electron-rich Rh-catalyst **15**, insertion into benzocyclobutenone proceeded at room temperature to deliver a single rhodaindanone regioisomer **16**. Attempts to isolate an analogous intermediate derived from cyclobutanone **17** were unsuccessful, with the

putative rhodacyclopentanone **18** undergoing rapid decarbonylation to cyclopropane **19**.

Reactivity of rhodacyclopentanones: decarbonylative transformations

In 1994, Murakami and Ito reported the first example of Rh-mediated C–C bond activation of cyclobutanones.[21] Here, stoichiometric Wilkinson's catalyst was employed to effect decarbonylation of cyclobutanone **20** to cyclopropane **23** in 99% yield (Scheme 5A). Oxidative addition of the Rh(ı)-catalyst into the less hindered acyl–C(sp^3) bond of **20** delivers rhodacyclopentanone **21**, which extrudes CO prior to reductive elimination of **22** to yield cyclopropane **23**. The requirement for stoichiometric RhCl(PPh$_3$)$_3$ was postulated to result from the formation of catalytically inactive CO-ligated Rh(ı)-complex **24**. The ring contraction of larger cyclic ketones was also reported, although in these cases the efficiency was significantly reduced (cyclobutanone: 41 h, 99% yield *vs.* cyclopentanone: 8 days, 57% yield).

In a subsequent report, Murakami and Ito demonstrated that decarbonylation of cyclobutanones could be rendered catalytic by utilising chelating or electron-deficient monodentate ligands on the Rh-catalyst (Scheme 5B).[22] Cyclopropane and alkene decarbonylation products were both observed and the product selectivity could be controlled by judicious choice of ligand. Alkene products, derived from β-hydride elimination and reductive elimination of the intermediate rhodacyclobutane (*cf.* **22**), were favoured by the use of wide bite angle ligands (*e.g.* dppp and dppb) with a neutral Rh(ı)-catalyst. Alternatively, by employing AsPh$_3$, an electron-deficient monodentate ligand,
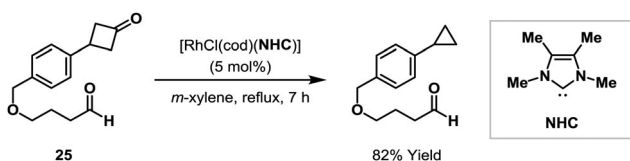
A) Stoichiometric decarbonylation of cyclobutanones
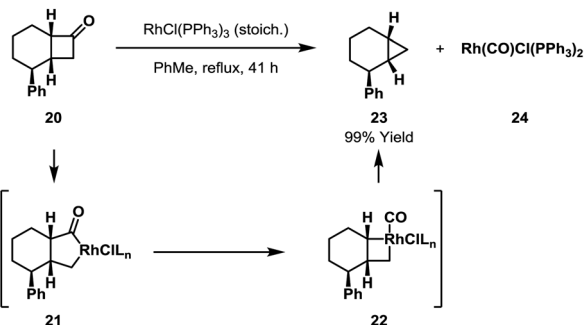
B) Catalytic decarbonylation of cyclobutanones
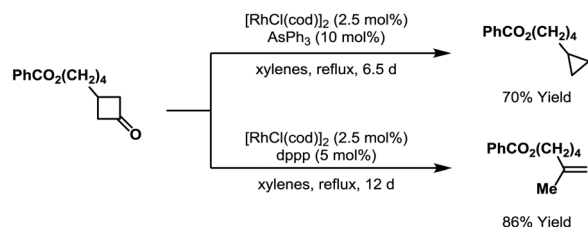
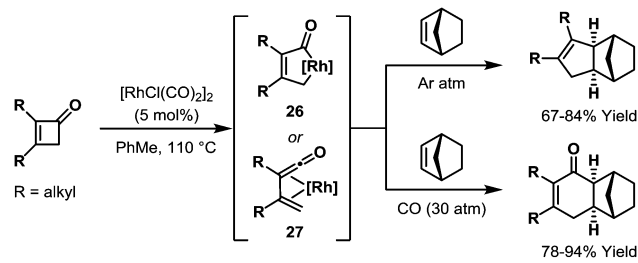**Scheme 5** Rh(I)-mediated decarbonylation of cyclobutanones.

Scheme 6 Selective decarbonylation of a cyclobutanone in the presence of an aldehyde.

the selectivity of the reaction could be switched to favour formation of the cyclopropane product.

Murakami and co-workers highlighted the importance of ligand choice in Rh-mediated C–C bond activation protocols by demonstrating that an NHC-ligated Rh(I)-catalyst could selectively decarbonylate cyclobutanones in the presence of aldehydes (Scheme 6).[23] Transition metal-catalysed activation of aldehydic C–H bonds has been demonstrated to be a relatively facile process[24] and other phosphine-ligated Rh(I)-catalysts exhibited either no selectivity or selectivity towards the aldehyde in the decarbonylation of substrate **25**. As previously discussed, Murakami and co-workers later reported that Rh-catalyst **15** inserts into cyclobutanones at room temperature to deliver cyclopropane products (see Scheme 4B).[20] Related decarbonylation reactions typically require high temperatures (*cf.* Scheme 5, 110–140 °C), however the highly electron-donating ligand system of **15** promotes C–C bond activation under relatively mild reaction conditions.

Multicomponent decarbonylative transformations involving rhodacyclopentanone intermediates have not been reported, however, protocols involving related rhodacyclopentenones and rhodaindanones have been developed. In 2004, Mitsudo, Kondo and co-workers described direct and decarbonylative cycloadditions of alkyl-substituted cyclobutenones and 2-norbornene upon exposure to [RhCl(CO)$_2$]$_2$ (Scheme 7).[25] For both transformations,

Scheme 7 Direct and decarbonylative cycloadditions of cyclobutenones.

one feasible mechanistic pathway involves insertion of the Rh(I)-catalyst into the acyl–C(sp^3) bond of the cyclobutenone to generate rhodacyclopentenone intermediate **26** directly. An alternate possibility involves rhodacyclopentenone formation *via* initial ring opening of the cyclobutenone to vinyl ketene intermediate **27**.

Recently, Dong and co-workers showed that rhodainda-nones **28**, generated from benzocyclobutenones, undergo intra-molecular decarbonylative cycloadditions with tethered alkynes to deliver fused indane ring systems in moderate to good yields (Scheme 8A).[26] Subsequent studies revealed that intramolecular decarbonylative couplings of benzocyclobutenones with tethered trisubstituted alkenes (**29**) proceed *via* a mechanistically distinct pathway to deliver spirocyclic products **33** (Scheme 8B).[27] In the proposed mechanism, initial C–C bond activation of benzocyclo-butenone **29** delivers the expected rhodaindanone intermediate **30** (*cf.* **28**), which engages the alkene to deliver rhodacycle **31**. At this stage, β-hydride elimination occurs to give acyl–Rh-hydride species **32** and, upon decarbonylation and reductive elimination, spirocyclic product **33** is formed. In some cases, isomerisation

A) Decarbonylative cycloadditions of benzocyclobutenones and alkynes
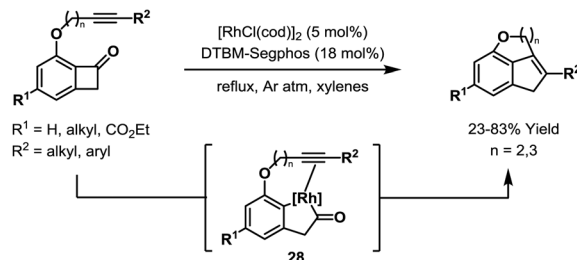
B) Decarbonylative spirocyclisation of benzocyclobutenones and alkenes
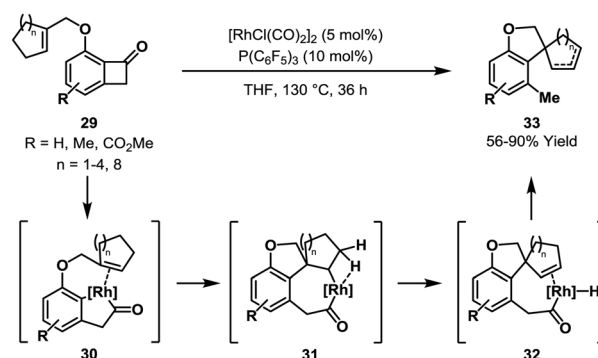
Scheme 8 Decarbonylative transformations involving rhodaindanones.

of the product alkene was observed and experimental mechanistic studies suggested that the two products are generated *via* independent reaction pathways, rather than by post-reaction isomerisation. Subsequent computational studies implicated acyl–Rh-hydride complex **32** as a key intermediate in the alkene isomerisation pathway.[28]
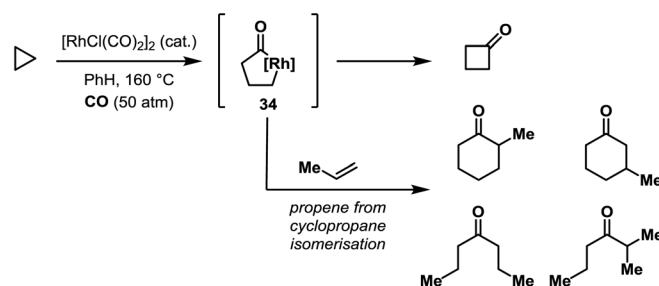
Reactivity of rhodacyclopentanones: carbonylative ring expansions of cyclopropanes

Carbonylative ring expansions of simple cyclopropanes to rhodacyclopentanones using stoichiometric Rh(ɪ)-complexes were reported over 40 years ago,[7,9] however, until recently, there were few reports of catalytic ring expansions based on this activation mode. In contrast, there have been numerous reports of cycloadditions involving cyclopropane derivatives activated by internal or adjacent unsaturation, such as alkylidene cyclopropanes, vinyl cyclopropanes and cyclopropenes (Scheme 9). For transformations utilising alkylidene cyclopropanes as a three-carbon component, the alkylidene carbon generally contributes to the three-carbon unit in the new ring system (*vs.* the cyclopropane delivering all three carbons).[29] Accordingly, carbonylative cycloadditions of alkylidene cyclopropanes do not proceed *via* the formation of a rhodacyclopentanone intermediate (Scheme 9A).[30] Vinyl cyclopropanes have been shown to undergo carbonylative couplings with tethered π-unsaturates, however, the vinyl cyclopropane is typically incorporated as a five-carbon unit.[31] Yu *et al.* reported (3+1+2) carbonylative cycloadditions that utilise the vinyl cyclopropane moiety as a three-carbon unit but a rhodacyclopentanone intermediate was not implicated in the mechanistic pathway (Scheme 9B).[32] In 2010, Wang and co-workers demonstrated that cyclopropenes were competent coupling partners for carbonylative (3+1+2) cycloadditions with tethered alkenes and alkynes (Scheme 9C).[33] The increased ring strain of cyclopropenes (*vs.* cyclopropanes) renders them highly reactive towards metal insertion[34,35] and the ring expansion protocol was proposed to proceed *via* a rhodacyclopentenone intermediate.
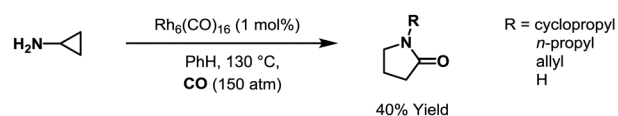
Two component ring expansions of cyclopropanes

The catalytic carbonylative ring expansion of unsubstituted cyclopropane was reported by Uchida and co-workers in


Scheme 10 Carbonylative ring expansions of cyclopropane and aminocyclopropane.

1980 (Scheme 10A).[36] Under forcing reaction conditions, exposure of cyclopropane to [RhCl(CO)$_2$]$_2$ afforded a mixture of cyclic and acyclic ketones in low yield (<5% yield for each product). In addition, formation of propene was observed and this likely derives from β-hydride elimination of a rhodacyclobutane intermediate (*cf.* Scheme 5B). The simplest ring expansion product, cyclobutanone, results from reductive elimination of rhodacyclopentanone **34**. The higher order ketone products are proposed to form *via* migratory insertion of propene into rhodacyclopentanone **34**, however, the source of reductant for the acyclic ketone products was not identified. Under similarly forcing reaction conditions, Iqbal reported a Rh-catalysed C–C bond activation of aminocyclopropane to deliver a mixture of *N*-substituted γ-lactams in moderate yield.[37] Although not proposed, it is not unreasonable to implicate the intermediacy of a rhodacyclopentanone in this process.

Murakami and co-workers demonstrated that spiropentanes exhibit enhanced reactivity towards C–C bond activation, presumably due to the increased ring strain of the spirocyclic system. Rh-catalysed carbonylative ring expansions of spiropentanes **35** delivered cyclopentenones **38** in high yields (Scheme 11).[38] The proposed mechanism involves oxidative addition of a Rh(ɪ)-catalyst into the least hindered C–C bond
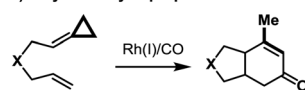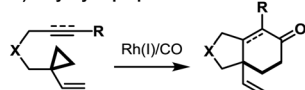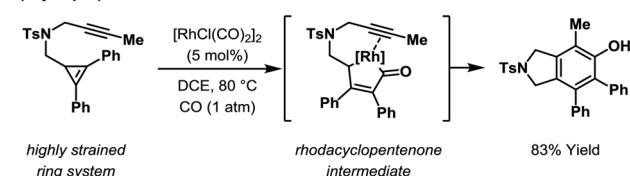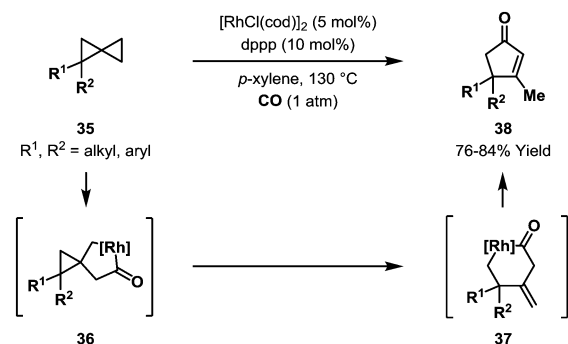

Scheme 9 Reactivity of activated cyclopropane derivatives in Rh-catalysed cycloadditions.


Scheme 11 Carbonylative rearrangements of spiropentanes.

of **35**, followed by migratory insertion of a CO ligand to furnish rhodacyclopentanone **36**. Regioselective β-carbon elimination affords 6-membered rhodacycle **37**, which can undergo reductive elimination and isomerisation to provide cyclopentenone **38**. The regioselectivity of β-carbon elimination was diminished when mono-substituted spiropentanes were employed and, consequently, mixtures of isomeric cyclopentenone products were obtained (see Scheme 23B). Notably, C–C bond activation of alkyl-substituted cyclopropanes was not observed under the same reaction conditions.

Three component ring expansions of cyclopropanes

Intramolecular cycloadditions between catalytically generated rhodacyclopentanones and π-unsaturates have enabled access to complex carbocyclic and heterocyclic scaffolds. Within this area, processes involving the carbonylative generation of rhodacyclopentanones (*i.e.* Rh + CO + cyclopropane) remain challenging. Narasaka and Koga reported the formation of bicyclic cyclohexenones (*e.g.* **39**) and phenols (*e.g.* **40**) from cyclopropanes bearing a tethered alkyne (Scheme 12).[39] This carbonylative cycloaddition was proposed to proceed *via* rhodacyclopentanone intermediate **41**, which derives from insertion of the Rh(ɪ)-catalyst into the more hindered C–C bond of the cyclopropane. In this process, oxidative addition of the Rh(ɪ)-catalyst may be directed by the alkyne. The yield of carbocyclic products **39** and **40** improved under elevated pressures of CO (43% yield at 1 atm *vs.* 63% yield at 4 atm) as the formation of by-products (*e.g.* alkenes) derived from non-carbonylative pathways was disfavoured. Substitution on the alkyne tether and cyclopropane ring was tolerated and the substituted cyclohexenones were obtained in moderate yield.

In 2013, our group demonstrated that regioselective generation of amino-rhodacyclopentanones from aminocyclopropanes can be achieved by utilising an *N*-protecting group directed C–C bond activation strategy (see Scheme 3).[13] The ability to access these metallacyclic intermediates in an efficient and selective manner provides a catalytic platform for the synthesis of chiral *N*-heterocyclic scaffolds. Carbonylative (3+1+2) cycloadditions involving aminocyclopropanes, CO and alkynes to deliver *N*-heterobicyclic enones were investigated as a proof-of-principle transformation. As shown in Scheme 13, the proposed mechanism involves the directed carbonylative ring expansion of **42** to deliver rhodacyclopentanone **43**. Directing group dissociation
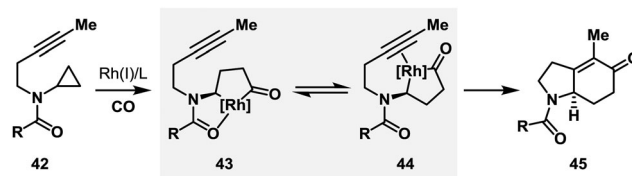

Scheme 13 Multicomponent carbonylative ring expansions of aminocyclopropanes.

(to **44**), migratory insertion of the alkyne and C–C bond reductive elimination then affords the desired N-heterocycle **45**.

Preliminary studies highlighted the importance of selecting an appropriate *N*-directing group as it must (a) compete with the alkyne for coordination of the catalyst at the stage of **42** but (b) be labile enough to allow alkyne coordination at the stage of rhodacycle **43**. As previously discussed, stoichiometric studies demonstrated that amide, carbamate and urea directing groups were all capable of delivering the desired rhodacycle, however, for the outlined cycloaddition, considerably higher efficiencies were observed when the most strongly donating dimethylurea directing group was employed (*vs.* amide or carbamate variants, see Scheme 3C). These results indicate that a strong directing group is required to outcompete the alkyne for coordination of the Rh(ɪ)-catalyst prior to oxidative addition.

Under optimised reaction conditions, employing a neutral Rh(ɪ)-catalyst, urea-substituted aminocyclopropanes **46** were converted to N-heterobicyclic enones **47** in moderate to good yield (Scheme 14).[13] Aryl- and alkyl-substituted alkynes participated to deliver the desired N-heterocycles (**47a–d**). In addition, products of greater stereochemical complexity were accessed by employing substrates with substitution on the alkyne tether. In these cases, increased cyclisation efficiencies were observed to deliver **47c–d** with moderate levels of diastereoselectivity.

Further investigations revealed that cationic Rh(ɪ)-systems provide higher yields and enhanced reaction rates for challenging cycloadditions.[16] However, in order to achieve this beneficial effect coordinating solvents are required to stabilise the Rh-catalyst, with benzonitrile identified as the optimal choice.[40] As shown in Scheme 15, by using a cationic Rh(ɪ)-system, significantly improved reaction efficiencies were observed for terminal alkynes and those with electron-deficient or heteroaromatic substituents.
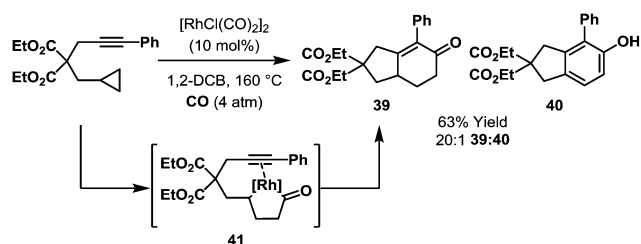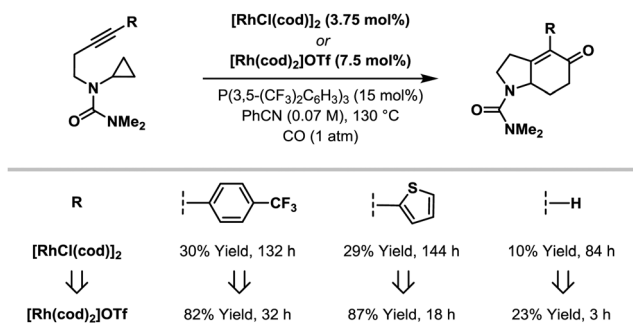

Scheme 12 (3+1+2) cycloaddition involving a cyclopropane, carbon monoxide and an alkyne.
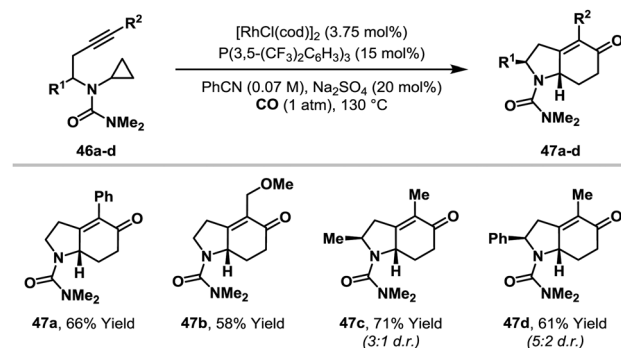
Scheme 14 Urea-directed (3+1+2) cycloadditions between aminocyclopropanes, CO and tethered alkynes.

Scheme 15 Comparison of "neutral" and "cationic" conditions for (3+1+2) cycloadditions involving functionalised alkynes.

Subsequent studies established that synthetically flexible directing groups could be used to generate heterocycles with higher "sp³-content". Indeed, Cbz-directed (3+1+2) cycloadditions involving aminocyclopropanes, CO and alkenes afforded stereochemically complex N-heterocycles (i.e. **49**) in an efficient manner (Cbz = carboxybenzyl).[17] In preliminary work, it was found that a neutral Rh(ı)-system provided high yield and diastereoselectivity for the cyclisation of **48a** to **49a** (Scheme 16A). However, for substrates with substitution on the alkene tether (e.g. **48b**, R = Ph) little diastereocontrol with respect to the R substituent was observed (3:2 d.r.), even though high trans-diastereoselectivity at the ring junction was maintained. This result was not surprising because if carbonyl-directed oxidative addition is the diastereo-determining step, then high diastereocontrol requires the R substituent to bias Rh-insertion into one

of the two proximal diastereotopic cyclopropane C–C bonds, an aspect which at the outset appeared challenging. To circumvent this, a strategy that achieves high levels of diastereocontrol via reversible rhodacyclopentanone formation was established, as depicted in Scheme 16B. Here, non-diastereoselective oxidative addition into cyclopropane **48**, leads to diastereomeric rhodacyclic π-complexes **50a** and **50b**. At this stage, because these structures are bicyclic, the steric effects of the R¹ and R² substituents are magnified such that the rate of alkene insertion (k_1 and k_2) from **50a** and **50b** is different. Consequently, in a scenario where rhodacyclopentanone formation is rapid and reversible, product diastereoselectivity should be principally dependent on the relative rates of alkene insertion (k_1 vs. k_2).

The realisation of the strategy outlined in Scheme 16B was achieved by switching to a cationic Rh(ı)-system. Here, an additional vacant coordination site on the catalyst may enhance reversibility by facilitating retro-carbonylation from **50a/b**. Due to the instability of cationic Rh(ı)-systems, optimisation was highly challenging. However, it was eventually found that the use of [Rh(cod)₂]OTf, in conjunction with a coordinating additive (isobutyramide), enabled highly diastereoselective cyclisation of substrate **48b** (79% yield, 8:1:1 d.r.) (Scheme 17). Under these reaction conditions, a broad array of substrates with alkyl and aryl substituents at R¹ and/or R² cyclised in good yield and with excellent diastereoselectivity. Note that even cyclopropane substituents are tolerated (as in **49c**).

Exchange studies supported the "reversibility" proposition outlined in Scheme 16B (Scheme 18).[17] Model cationic rhodacyclopentanone complex **10a**, which possesses a methyl carbamate directing group, was exposed to stoichiometric quantities of ethyl carbamate protected cyclopropane **7b** under a CO atmosphere. This resulted in partial exchange to deliver rhodacycle **10b** and cyclopropane **7a**. An inverse experiment, utilising complex **10b**, delivered analogous results. Complex **10a** was also shown to be catalytically competent for the conversion of **48a** to **49a**. These studies demonstrated that reversible rhodacyclopentanone formation can occur under carbonylative conditions.
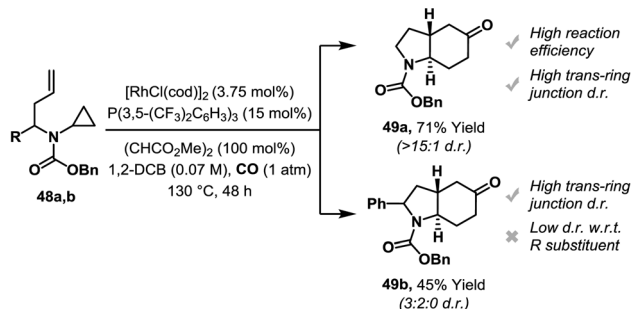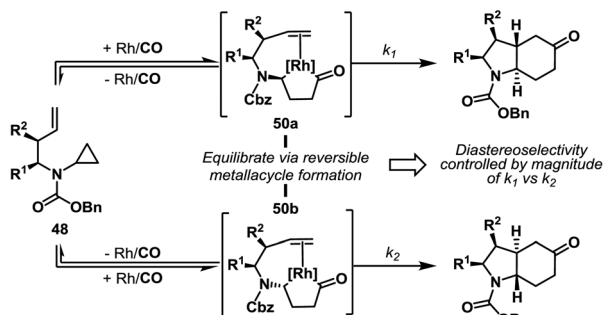
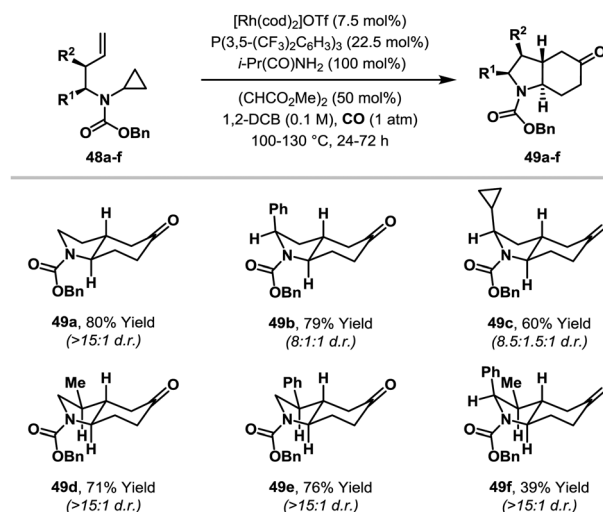**Scheme 16** (3+1+2) carbonylative cycloadditions between aminocyclopropanes and tethered alkenes, and a strategy for achieving high diastereoselectivity.

Scheme 17 Diastereoselective (3+1+2) cycloadditions between aminocyclopropanes, CO and tethered alkenes.
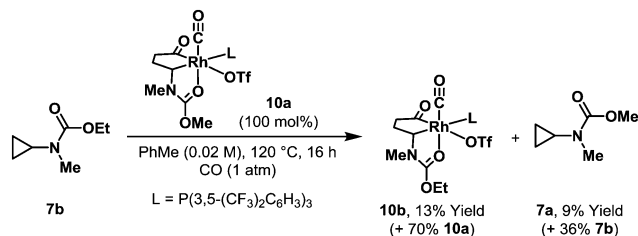
**Scheme 18** Stoichiometric reversibility studies.

Catalytic carbonylative ring expansions of cyclopropanes are particularly attractive as substituted (and enantioenriched) cyclopropanes can be readily synthesised using existing technologies.[41] Exposure of *trans*-1,2-disubstituted cyclopropane **51** to optimised reaction conditions afforded adduct **52** in good yield. **52** derives from regioselective Rh-insertion into the less hindered proximal C–C bond of the cyclopropane (bond **a**) and complete transfer of the cyclopropane stereochemistry was observed (Scheme 19). In contrast, *cis*-1,2-disubstituted cyclopropane **51** generated solely regioisomer **53**, which derives from Rh-insertion into the more hindered proximal C–C bond (bond **b**). Stoichiometric experiments confirmed, in both cases, that product regioselectivity reflects the regiochemical preference of rhodacyclopentanone formation.[17,42]

Amino-rhodacyclopentanones can also be utilised as intermediates in mechanistically distinct cycloaddition-fragmentation processes. Using this approach, a direct and modular entry to azocanes **57** from *N*-cyclopropylacrylamides **54** was developed, *via* a formal (7+1) cycloaddition-tautomerisation sequence (Scheme 20).[42] Amide-directed C–C bond activation of **54** delivers rhodacyclopentanone **55**, and, from here, migratory insertion of the alkene affords rhodabicycle **56**. At this point, instead of C–C reductive elimination (*cf.* Scheme 13), β-hydride elimination of C7–H and C–H reductive elimination affords azocane **57**. This latter step is highly regioselective and products derived from β-hydride elimination *via* C4–H are not generated. Deuterium labelling studies support the proposed mechanism.

The scope of the azocane methodology is outlined in Scheme 21. Under "conditions A", 1,1-disubstituted alkenes cyclised efficiently to afford R²-substituted azocanes, however, 1,2-disubstituted alkenes were not well tolerated (*e.g.* **57d**, 10% yield). Note that the azocane products are highly strained, possessing an unusual twisted enamide (see X-ray crystal structure, Scheme 20). Cycloadditions involving
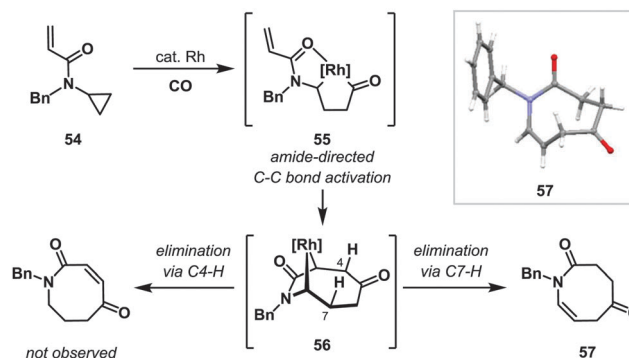

**Scheme 20** Rh-catalysed cycloaddition-fragmentation for the synthesis of azocanes.
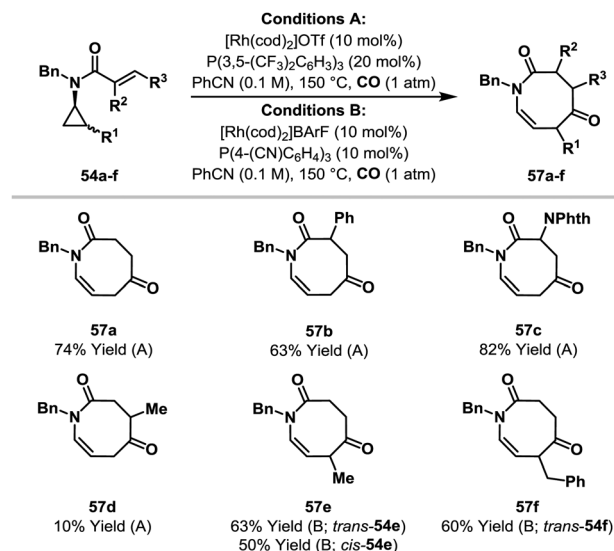
Scheme 21 Rh-catalysed carbonylative cycloadditions of *N*-cyclopropylacrylamides to deliver substituted azocanes.

1,2-disubstituted aminocyclopropanes required alternate conditions ("conditions B"), but proceeded smoothly. Interestingly, both *cis*-**54e** and *trans*-**54e** afforded the same Me-substituted azocane **57e**. Adduct **57e** arises from insertion of Rh and CO into the more hindered proximal C–C bond of **54e**. This result was expected for *cis*-**54e** as it mirrored C–C bond activation regioselectivities observed in earlier work (see Scheme 19). However, the conversion of *trans*-**54e** to **57e** was inconsistent with stoichiometric studies and earlier work where *trans*-1,2-disubstituted cyclopropanes delivered products derived solely from Rh-insertion into the less hindered proximal C–C bond.

The exchange studies in Scheme 18 show that rhodacyclopentanone formation is reversible using cationic Rh(I)-systems under a CO atmosphere. This observation underpins a mechanism that accounts for the regioselectivity of cyclisations of *trans*-1,2-disubstituted cyclopropanes to azocanes (Scheme 22). Insertion of Rh and CO can occur into bond **a** or **b** of **54e** to generate either rhodacyclopentanone **58a** or **58b**. The former pathway is favoured on steric grounds, but, following migratory insertion of the alkene into the acyl–Rh bond, *syn*-β-hydride
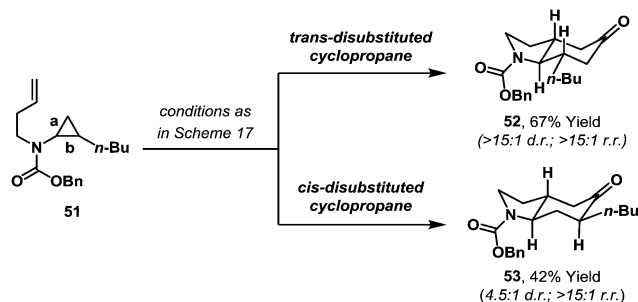
Scheme 19 Cycloadditions of *trans*- and *cis*-1,2-disubstituted cyclopropanes.
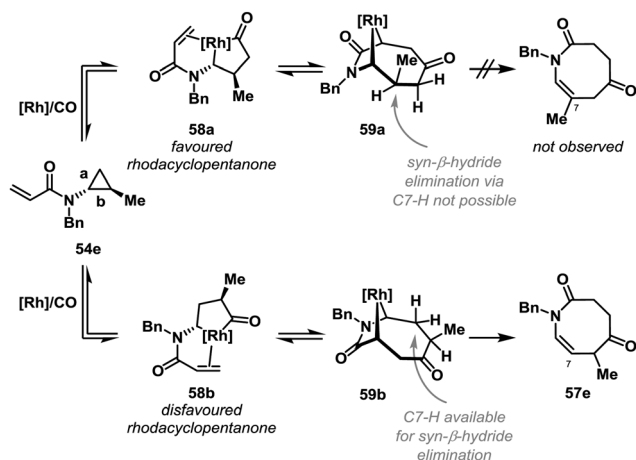
Scheme 22 Mechanistic rationale for the regioselectivity of cycloadditions involving *trans*-disubstituted aminocyclopropanes.
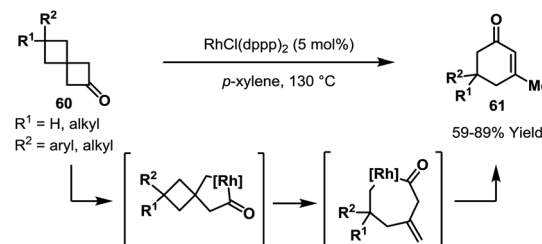
elimination *via* C7–H of **59a** is not possible. If the alkene insertion step is also reversible, then cyclopropane **54e** can be regenerated, and equilibration to regioisomeric metallacycle **59b** is possible. Here, *syn*-β-hydride elimination *via* C7–H can occur to deliver the observed regioisomer of the product. An alternate possibility is that alkene insertion into **58a** is slower than into **58b**, such that it is the facility of this step (rather than the β-hydride elimination step) that controls product regiochemistry.

Reactivity of rhodacyclopentanones: ring expansions of cyclobutanones
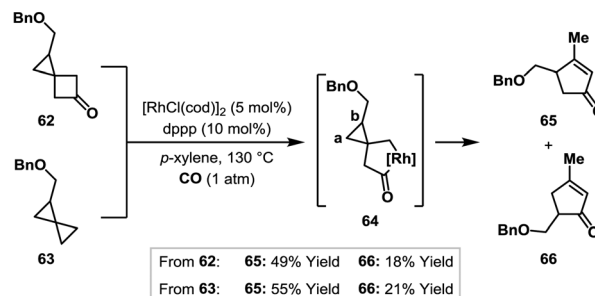
Catalytic activation of cyclobutanone C–C bonds was first reported by Murakami and co-workers in 1994.[21] Since this seminal publication, a variety of synthetic transformations have been developed that involve rhodacyclopentanones generated *via* Rh-insertion into cyclobutanones. In particular, cycloadditions with 2π-unsaturates have gained considerable attention as complex molecular scaffolds can be readily accessed using this approach. Additionally, protocols have been developed involving subsequent nucleophilic trapping or β-carbon/β-oxygen elimination steps. Oxidative addition of Rh(I)-catalysts into cyclobutanones generally occurs at the weaker acyl–C(sp^3) bond rather than the comparatively stronger C(sp^3)–C(sp^3) bond (see Scheme 26 for an exception to this rule). In the absence of coordinating functionality, Rh-insertion into unsymmetrical cyclobutanones occurs at the less hindered acyl–C(sp^3) bond.[22] However, directed oxidative addition of Rh(I)-catalysts into the more hindered acyl–C(sp^3) bond has been demonstrated in a number of multi-component ring expansion protocols.

In their initial report, Murakami and Ito showed that activation of the cyclobutanone acyl–C(sp^3) bond could be combined with hydrogenolysis of the resultant rhodacyclopentanone to deliver alcohols.[21,22] In subsequent studies, two different modes of C–C bond activation – cyclobutanone C–C bond oxidative addition and β-carbon elimination – were used in sequence to generate cyclohexenones **61** from spirocyclic cyclobutanones **60** (Scheme 23A).[43]
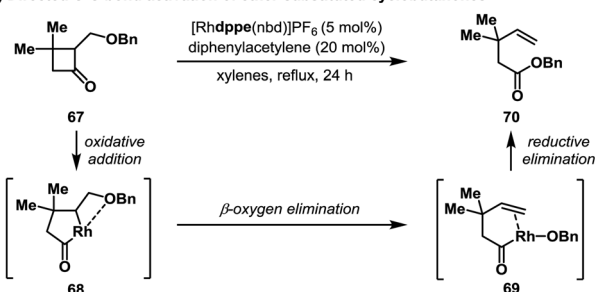

Scheme 23 Ring expansions of spirocyclic cyclobutanones and spiropentanes.

Notably, upon exposure to carbonylative conditions, spirocyclic cyclobutanone **62** and spiropentane **63** delivered identical mixtures of regioisomeric cyclopentenone products (**65** and **66**), thereby indicating that a common rhodacyclopentanone intermediate (**64**) can be generated from either starting material (Scheme 23B).[38] The formation of two isomeric cyclopentenone products was observed because, upon generation of rhodacyclopentanone **64**, subsequent β-carbon elimination can proceed through migration of either cyclopropane carbon **a** or **b**. The major product derives from migration of the less hindered cyclopropane carbon **a** (*cf.* Scheme 11). Prior to these studies, Liebeskind and co-workers reported a Rh-catalysed ring expansion of cyclobutenones with a pendant cyclopropane ring to deliver 7-membered cyclic ketones and this rearrangement likely proceeds *via* a similar oxidative addition/β-carbon elimination mechanism.[44]
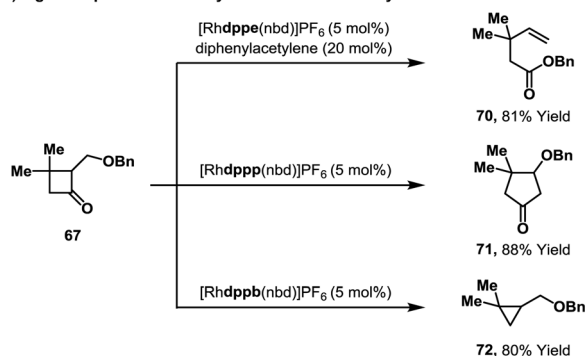
Murakami and Ito demonstrated that cyclobutanone C–C bond activation could also be used in conjunction with β-oxygen elimination to provide access to novel reaction manifolds.[45] When ether-substituted cyclobutanone **67** was exposed to the cationic Rh(I)-catalyst system outlined in Scheme 24A, formation of acyclic ester **70** was observed. **70** derives from Rh-insertion into the more hindered cyclobutanone C–C bond, which indicates that the pendant ether can coordinate and direct oxidative addition. In the proposed mechanism, β-oxygen elimination of rhodacyclopentanone **68** delivers alkene **69** and subsequent acyl–O reductive elimination can then proceed to afford the observed ester **70**. Interestingly, the bite angle of the bidentate phosphine ligand had a significant impact on the reaction pathway (Scheme 24B). Selective formation of cyclopentanone **71** was observed when a wider bite angle ligand, dppp (91°), was employed in place of dppe (85°).[46] Increasing the bite angle of the ligand further, to
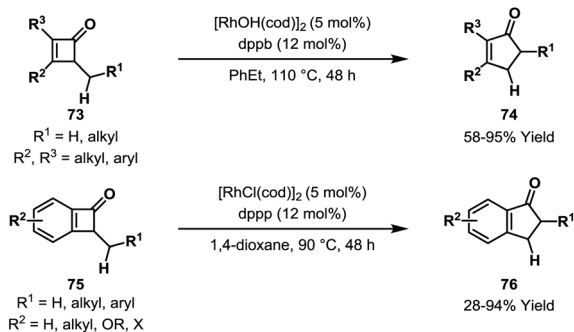
Scheme 24 Rh-catalysed reactions of ether-substituted cyclobutanone **67** and one-carbon ring expansions of cyclobutenones/benzocyclobutenones.

Scheme 25 Synthesis of cyclic lactones *via* ring expansion of phenol-substituted cyclobutanones.

dppb (98°), resulted in selective decarbonylation of rhodacyclo-pentanone **68** to afford cyclopropane **72**. For the dppp catalyst system it was postulated that, instead of reductive elimination at the stage of complex **69**, 6-*endo* migratory insertion of the alkene into the Rh–O bond occurs to deliver cyclopentanone **71** upon reductive elimination. Recent studies by Dong and co-workers demonstrated that related one-carbon ring expansions of cyclobutenones **73** and benzocyclobutenones **75** afford the homologated cyclopentenone and 1-indanone products (**74** and **76**) in moderate to good yield (Scheme 24C).[47] Mechanistic studies supported a similar reaction pathway to that proposed for the formation of **71**, wherein β-hydride elimination occurs (rather than β-oxygen elimination, *cf.* Scheme 24A) prior to alkene migratory insertion and reductive elimination.

In a subsequent study, Murakami and Ito established that pendant phenols could also direct insertion of Rh(I)-catalysts into the more hindered C–C bond of cyclobutanones (Scheme 25).[48] Distinct reactivity was observed in the oxidative ring expansions

of phenol-substituted cyclobutanones **77** and **80**. When R = H, directed oxidative addition of the Rh(I)-catalyst into the more hindered cyclobutanone C–C bond **a** delivers rhodacycle **78**. Subsequent nucleophilic trapping with the phenol OH, followed by β-hydride elimination and reductive elimination, affords 7-membered cyclic lactone **79**. However, when R = Me, the additional steric hindrance around the proximal acyl–C(sp³) bond prevents directed Rh-insertion from occurring. Consequently, insertion takes places at the less hindered bond **b** to afford ultimately 5-membered cyclic lactone **82** (*via* **81**). Directed ring expansion of **77** proceeded at 100 °C but, at this temperature, no reaction was observed for cyclobutanone **80** and the reaction temperature had to be raised to 140 °C to enable efficient formation of lactone **82**. The difference in reactivity between cyclobutanones **77** and **80** highlights the powerful impact directing group assistance can have on C–C bond activation protocols.

In 2002, Murakami reported the first examples of alkene insertion into cyclobutanone-derived rhodacyclopentanones (Scheme 26).[49] Cyclobutanone **83**, substituted with an appropriately positioned alkene, underwent an intramolecular (4+2) cycloaddition to afford bicyclic ketone **84**. The ring expansion is proposed to proceed *via* Rh(I)-insertion into the acyl–C(sp³) bond **a**, followed by alkene insertion and reductive elimination. As previously observed (see Scheme 24), the bite angle of the bidentate phosphine ligand had a substantial impact on the outcome of the reaction. Employing dppe (in place of dppp) resulted in formation of α,β-unsaturated ketone **85**, which
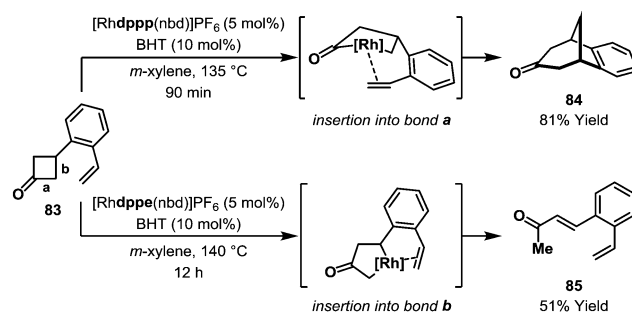

**Scheme 26** Ligand-dependent insertion of Rh(I)-complexes into cyclo-butanone C–C bonds.

derives from insertion of the Rh(I)-catalyst into the normally unreactive C(sp³)–C(sp³) bond **b** of the cyclobutanone. It was postulated that alkene-directed oxidative addition facilitated this unusual reactivity and, in support of this hypothesis, it was observed that extension of the alkene tether prevented Rh-insertion into bond **b**.

Recently, Cramer and co-workers reported enantioselective Rh-catalysed ring expansions of cyclobutanones, utilising substrates similar to those reported by Murakami (*cf.* **83**, see Scheme 26).[50,51] An additional substituent (R¹) was incorporated at the 3-position of the cyclobutanone ring (**86**) and, consequently, cyclisation delivered complex unsymmetrical bicyclic ketones **87**. Cramer demonstrated that chiral bisphosphine-ligated zwitterionic Rh(I)-complexes provided significantly enhanced efficiencies in comparison with phosphine-ligated cationic Rh(I)-complexes, however, only moderate enantioselectivities were obtained (42–87% ee).[50] In a subsequent publication, a neutral DTBM-Segphos-ligated Rh(I)-catalyst system was disclosed which delivered bicyclic ketones **87** in good to excellent yields and with high levels of enantiocontrol (Scheme 27).[51] In this transformation, oxidative addition of the Rh(I)-catalyst into the cyclobutanone acyl–C(sp³) bond is the enantiodetermining step. Bicyclic lactones **89** were synthesised in a highly enantioselective manner by extending the cycloaddition strategy to cyclobutanones bearing tethered carbonyl groups.[52] High yields were obtained when aldehyde substrates (**88**, R² = H) were exposed to the optimised reaction conditions and, interestingly, this Rh(I)-catalyst system exhibited complete selectivity for C–C bond activation over insertion into the aldehydic C–H bond. Only activated or relatively unhindered ketones participated and, when sterically bulky ketones were employed, decarbonylation of the cyclobutanone starting material was observed.

Murakami and co-workers reported that placement of a styryl group at the 2-position of cyclobutanone, rather than the 3-position (*cf.* Scheme 26), resulted in formation of eight-membered carbocycles **92** and **93** (Scheme 28).[53] In the proposed mechanism, the pendant alkene directs Rh-insertion to the more hindered acyl–C(sp³) bond of cyclobutanone **90** and migratory insertion of the alkene into the acyl–Rh bond delivers **91**. At this point, there are two possible pathways for β-hydride elimination, from
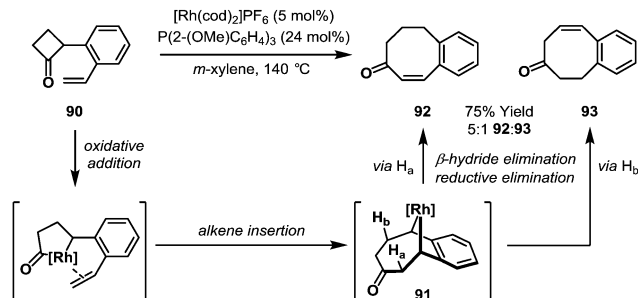
**Scheme 28** Rh-catalysed cycloaddition–fragmentation to deliver eight-membered carbocycles.
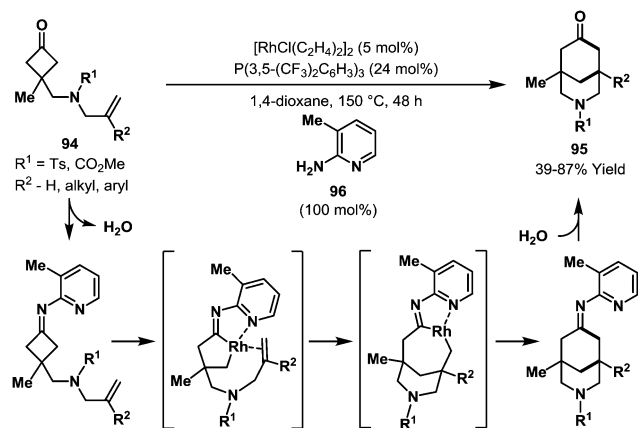
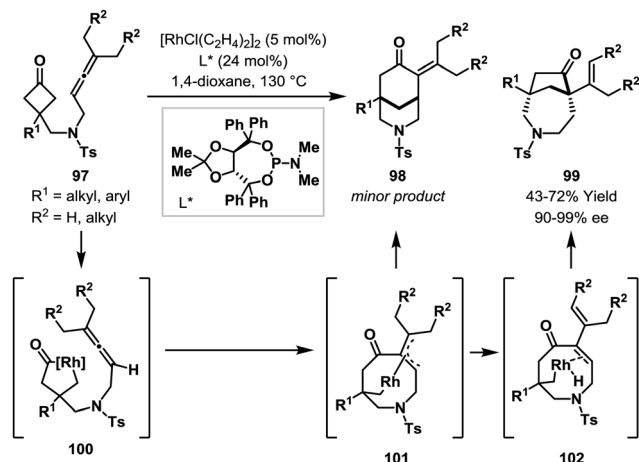**Scheme 29** (4+2) cycloadditions of cyclobutanones *via* a temporary directing group strategy.

Hₐ or H_b, with the major product arising from β-hydride elimination *via* Hₐ to give conjugated enone **92**.

In 2014, the Dong group reported Rh(I)-catalysed (4+2) cycloadditions of cyclobutanones **94** to N-heterobicyclic ketones **95** by utilising a temporary directing group strategy (Scheme 29).[54] Previous reports by Jun and co-workers demonstrated that 2-amino-3-methylpyridine **96** can be used to facilitate Rh-mediated C–C bond activation of unstrained ketones.[5c,d] In these protocols, pyridine **96** is postulated to condense with the ketone starting material and direct insertion into the proximal C–C bond through coordination of the pyridyl moiety to the Rh-catalyst. For the transformation outlined in Scheme 29, it was proposed that **96** (a) directs Rh-insertion into the α-bond of the generated imine and (b) acts as a protecting group to prevent detrimental decarbonylative side reactions from occurring. Under optimised reaction conditions, a variety of cyclobutanone substrates containing mono- and 1,1-disubstituted alkenes cyclised in moderate to good yield. In support of the proposed role of pyridine **96** as a protecting group, it was observed that, in the absence of **96**, only decarbonylated side products were formed.

In subsequent work, the Dong group endeavoured to expand this (4+2) cycloaddition protocol to cyclobutanones **97** containing a tethered allene.[55] However, interestingly, the (4+2) cycloaddition product **98** was only formed in small quantities and N-heterobicyclic ketone **99** was the major product isolated (Scheme 30).
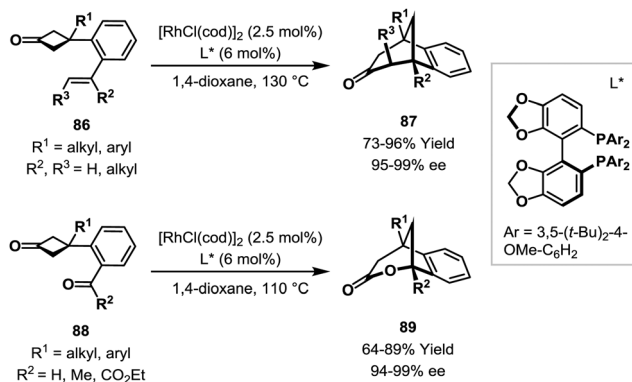
Scheme 27 Enantioselective cycloadditions of rhodacyclopentanones with pendant alkenes or aldehydes/ketones.

Scheme 30 (4+1) cycloadditions of cyclobutanones with tethered allenes.

Evaluation of the reaction scope, utilising an electron-deficient achiral phosphine ligand, showed generally high selectivity for the [4.2.1] bicycle **99** over the [3.3.1] adduct **98**. Subsequently, an enantioselective variant of the reaction was developed and, using a TADDOL-derived phosphoramidite ligand (L*), high enantioselectivities and moderate to good yields were obtained for bicyclic products **99**. The proposed mechanism for this transformation starts with generation of rhodacyclopentanone **100**, followed by migratory insertion of the allene to give π-allyl complex **101**. From intermediate **101**, reductive elimination would result in formation of the minor product **98**. Alternatively, β-hydride elimination delivers enone **102** and, after re-insertion of the alkene and reductive elimination, this pathway affords the observed product **99**. Deuterium labelling studies supported the proposed mechanism.

As previously mentioned, seminal work by Liebeskind and co-workers demonstrated that related rhodaindanone complexes could be generated via C–C bond activation of benzocyclobutenones (see Scheme 4A).[18] Recently, the Dong group has developed new methodologies that enable rapid access to complex chiral tricyclic scaffolds via the catalytic generation and trapping of rhodaindanones with various 2π-unsaturates (Scheme 31). The first example of this "cut and sew" strategy involved intramolecular coupling of rhodaindanones with mono- or di-substituted alkenes to deliver tricyclic products **103**.[56] An enantioselective variant of this reaction was developed and,

subsequently, this methodology was extended to cycloadditions involving trisubstituted alkenes.[57,58] Intramolecular cycloadditions with alkynes and oximes have also been developed and these protocols provide rapid access to phenols **104** and cyclic lactams **105**, respectively.[26,59]

Conclusions

This Feature Article highlights the synthesis and reactivity of rhodacyclopentanones (and related species) derived from C–C bond activation. Predominant methodologies access these reactive intermediates by oxidative addition of Rh(I)-catalysts into cyclobutanones or cyclopropanes. The former approach avoids the requirement of a CO atmosphere, whereas the latter method takes advantage of readily available and stereodefined cyclopropane precursors. For both strategies, C–C oxidative addition regioselectivity can often be controlled using directing groups. In several methodologies the directing group (e.g. phenol, alkyne) inserts into the incipient metallacycle to provide the target product. An alternate, and perhaps more powerful approach, uses N-protecting groups or temporary directing groups to control the C–C activation step. The rhodacyclopentanone intermediates can engage a wide range of π-unsaturates (e.g. alkynes, alkenes, aldehydes) or nucleophiles (e.g. phenols) to provide the target product.

Future development of the area will require an expansion of the range of components (e.g. π-unsaturates, nucleophiles) that rhodacyclopentanones can react with. Additionally, intermolecular rhodacyclopentanone-based cycloaddition methodologies remain a challenging yet tantalising prospect. Here, fine-tuning of the Rh-centre provides an avenue to control enantio-, diastereo- and/or regioselectivity. This versatility will likely underpin a flexible framework for developing methodologies that generate "sp³-rich" scaffolds in a direct and atom-economical manner. Such processes would be highly attractive to medicinal chemists for the generation of skeletally diverse compound libraries.

Acknowledgements

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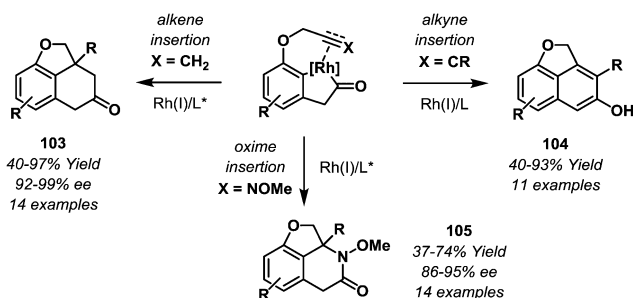
Scheme 31 Rh-catalysed cycloadditions involving rhodaindanones.

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