Formation of carbocycles through sequential carborhodation triggered by addition of organoborons

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This article highlights recent developments in the formation of carbocycles *via* multiple carborhodation steps triggered by the rhodium-catalysed intermolecular addition of organoborons. Various types of cascade reactions have been developed to demonstrate that multiple carborhodation steps can precede potentially competing processes such as protonolysis.

Introduction

The development of new reactions that construct organic frameworks through carbon–carbon bond formation continues to be a prime issue in synthetic organic chemistry. Transition metal-catalysed carbon–carbon bond forming reactions using conventional main-group organometallic compounds have significantly expanded the manifold of tools available to address this challenge. Organoboronic acids and esters are relatively non-toxic, easily accessible, mostly stable toward air and water, and hence, are often used as the organometallic compound of convenience in transition metal-catalysed carbon–carbon bond forming reactions.[1] In particular, the palladium-catalysed cross-coupling reaction of organoboronic acids has found wide applications in industrial processes as well as in laboratory syntheses.[2] Miyaura *et al.* reported in 1997 that arylboronic acids underwent conjugate addition to α,β-unsaturated ketones in the presence of a rhodium catalyst.[3] Since then, interest in the rhodium(I)-catalysed addition of organoboron species to unsaturated functionalities has grown dramatically as its utility for the carbon–carbon bond formation has become increasingly clear.[4] An organorhodium(I) species generated from organoborons by transmetalation is reactive enough to add intermolecularly to relatively polar unsaturated functionalities such as carbonyl,[5] imino,[6] and cyano[7] groups as well as to less polar alkynes[8] and alkenes.[9] In most of these reactions, the formal oxidation state of rhodium remains +1 throughout the catalytic cycle. A catalytically active Rh(I)OR species is often generated by protonolysis of an intermediate organorhodium(I) species with a proton source such as water. In this regard, rhodium-catalysed carbon–carbon bond forming reactions differ from most palladium-catalysed systems, in which a Pd(II)/Pd(0) redox process is operative.

On the other hand, cascade reactions which consist of multiple carbometallation steps provide powerful methods for the construction of structurally complex molecules in an efficient and atom-economical manner.[10] In recent years, the use of rhodium(I)-catalysed addition of organoborons in cascade reactions has increased significantly, as a complement to well-studied and valuable palladium-catalysed cascade

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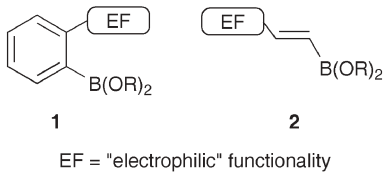
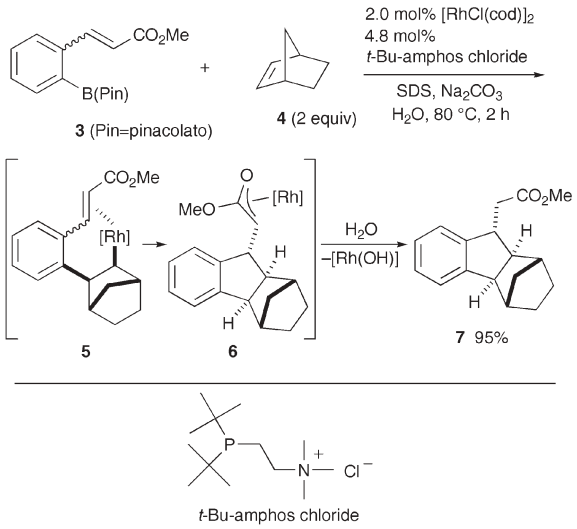


Chart 1



Scheme 1

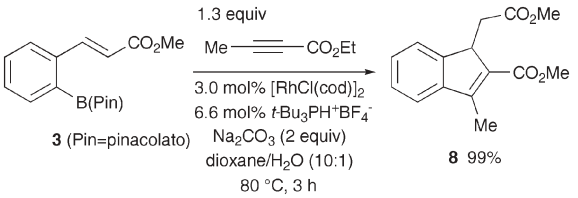
sequences.[11] These studies demonstrated that an organorhodium(I) species could undergo multiple carborhodation steps successively in preference to potentially competing processes including protonolysis and β-hydride elimination. This article highlights recent results on the formation of carbocycles through sequential carborhodation triggered by the rhodium-catalysed intermolecular addition of organoborons.

Addition of ambiphilic bifunctional organoborons to alkynes or strained alkenes

Although a carbon–boron linkage is potentially nucleophilic, it is stable enough to be incorporated in a molecule together with an "electrophilic" functionality (EF),† giving rise to ambiphilic bifunctional organoboron reagents such as **1** and **2** (Chart 1). Molecules such as **1** and **2**, which are comprised of both a carbon–boron linkage which can be transmetallated to an organorhodium(I) species and an electrophilic functionality which can eventually accept an organorhodium(I) species at a later stage, make very attractive reagents for rhodium-catalysed cascade reactions.

Arylboronic ester **3** bearing an electron-deficient olefin at the *ortho* position reacts with strained alkenes such as norbornene (**4**) in the presence of a rhodium/phosphine catalyst to afford the fused indane **7** with high diastereoselectivity (Scheme 1).[12] The catalytic cycle is initiated by transmetalation of the hydroxorhodium(I) with arylboronic ester **3** to generate the arylrhodium(I) species. Then, the

† Unsaturated functionalities to which an organorhodium species can add are described as "electrophilic" functionality in this article.



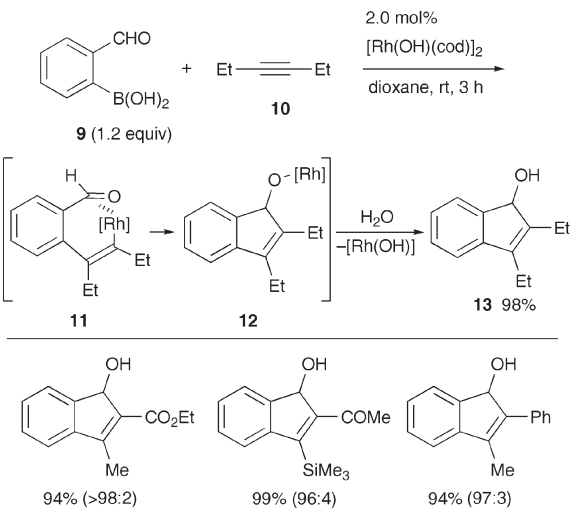
Scheme 2

arylrhodium(I) species adds to the carbon–carbon double bond in a *syn* fashion from the *exo* face. In the resultant norbornylrhodium(I) species **5**, the pendent alkene coordinates to rhodium. Subsequent carborhodation in a 5-*exo*-trig mode generates the (oxa-π-allyl)rhodium(I) **6**, which is easily protodemetallated by water. The product **7** is released with regeneration of the hydroxorhodium(I) catalyst.

The use of alkynes instead of norbornene as coupling partners gives indene derivatives such as **8** (Scheme 2).[13]

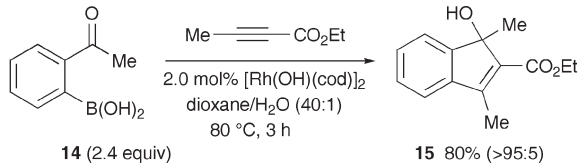
An indene skeleton is also produced by the rhodium-catalysed annulation of 2-acylphenylboronic acids with alkynes (Scheme 3).[14,15] For example, 2-formylphenylboronic acid (**9**) reacted with hex-3-yne (**10**) in the presence of $[Rh(OH)(cod)]_2$ in dioxane at room temperature to afford 1*H*-inden-1-ol **13** in 98% yield. High regioselectivities were observed with unsymmetrically disubstituted alkynes. Initially, the arylrhodium(I) species generated by transmetalation with **9** adds to the carbon–carbon triple bond in a *syn* fashion. Then, the resulting β-styrylrhodium(I) species **11** undergoes intramolecular addition to the aldehydic carbonyl group in a 5-*exo*-trig mode to form the rhodium(I) alkoxide **12**. Protonolysis produces 1*H*-inden-1-ols with regeneration of the hydroxorhodium(I) catalyst.

The carbonyl groups of ketones are less reactive toward an organorhodium(I) species than an aldehydic carbonyl group.[5] Hence, more forcing conditions were required for an analogous reaction of 2-acetylphenylboronic acid (**14**) (Scheme 4). Addition of a small amount of water promotes the reaction to give a good yield of 1-methyl-1*H*-inden-1-ol **15**.



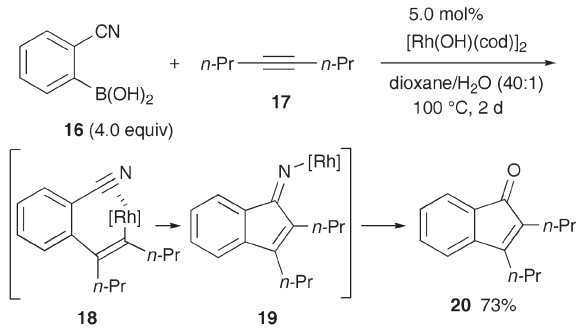
The regioisomer ratios given in parentheses.

Scheme 3



The regioisomer ratio given in parenthesis.

Scheme 4

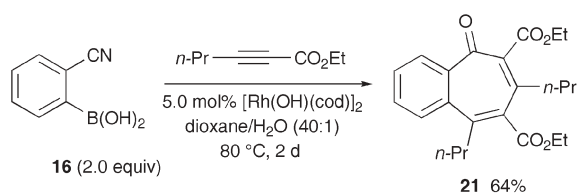


Scheme 5

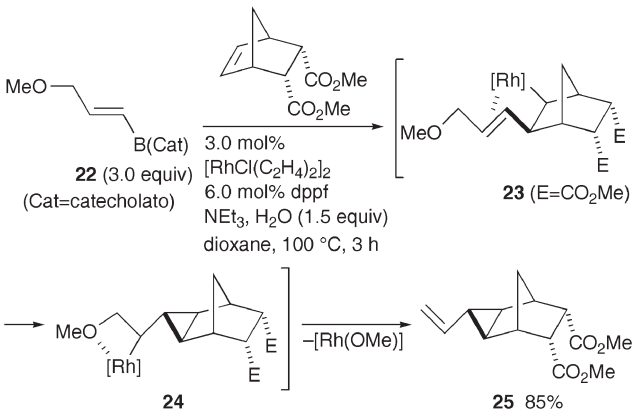
2-Cyanophenylboronic acid (**16**) also acts as an ambiphilic bifunctional reagent (Scheme 5).[16] An intramolecular arrangement increases the ease with which an organorhodium(I) intermediate adds to a cyano group.[7] Reaction of **16** with oct-4-yne (**17**) at 100 °C afforded indenone **20** in 73% yield. In this case, the β-styrylrhodium(I) **18** resulting from addition of the arylrhodium(I) species to the carbon–carbon triple bond undergoes an intramolecular 1,2-addition to the cyano group in a 5-*exo*-dig mode to furnish the *N*-rhodium(I) imine **19**. The arylrhodium(I) species is regenerated either by direct transmetalation of this adduct with **16** or *via* intervention of a hydrolysis step giving hydroxorhodium(I) prior to transmetalation.

Interestingly, when ethyl hex-2-ynoate was employed as the alkyne under similar reaction conditions, seven-membered ring benzotropone **21** was obtained as the major product (64%) instead of the five-membered ring indenone (Scheme 6). This product results from a second intermolecular carborhodation onto ethyl hex-2-ynoate rather than a 5-*exo*-dig cyclisation occuring with the initially formed β-styrylrhodium(I) intermediate. Finally, 7-*exo*-dig ring closure to the cyano group takes place. The steric constraint imposed on the linear cyano substituent may be responsible for the difference observed in the reactions of acetylenic esters with **9**, **14** and **16**.

When both nucleophilic and electrophilic functionalities are attached to a same carbon, that carbon possesses carbenoid character. Alkenylboronic ester **22** bearing a methoxy group at the allylic position presents an analogous ambiphilic



Scheme 6



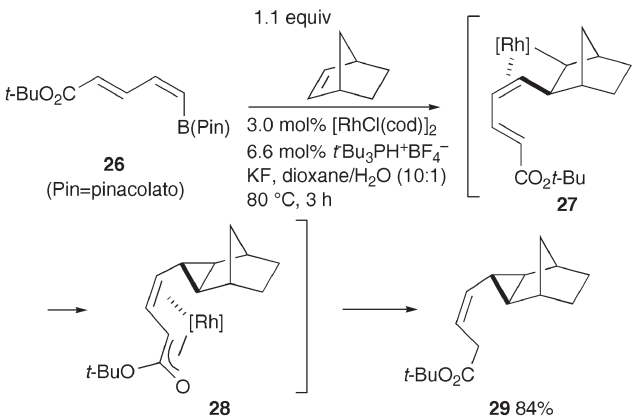
Scheme 7

compound with carbenoid character (Scheme 7).[17,18] Reaction of **22** with a norbornene derivative afforded vinylcyclopropane product **25** in 85% yield. The addition of the alkenylrhodium(I) species onto the strained carbon–carbon double bond from the *exo* face gives the norbornylrhodium(I) intermediate **23**. Then, ensuing carborhodation back to the allylic double bond in a 3-*exo*-trig mode leads to the stereoselective formation of the alkylrhodium(I) intermediate **24**. Finally, β-oxygen elimination with the methoxy group affords the product **25** and catalytically active methoxorhodium(I).

A similar rhodium-catalysed vinylcyclopropanation of strained alkenes is also achieved by the use of dienylboronic ester **26** bearing an extended conjugation (Scheme 8).[19] A rare 1,6-addition occurs with the norbornylrhodium(I) intermediate **27** to produce (oxa-π-allyl)rhodium(I) **28**. The conformation of **28** is locked by internal coordination of the carbon–carbon double bond and protonolysis produces vinylcyclopropane derivatives **29** stereoselectively with *Z* geometry.

Addition of organoborons to acceptors containing two or more "electrophilic" functionalities

When an acceptor molecule contains two or more "electrophilic" functionalities,† the primary electrophilic functionality (EF[1] in Chart 2), which is more reactive toward an organorhodium(I) intermediate than the others, provides the



Scheme 8

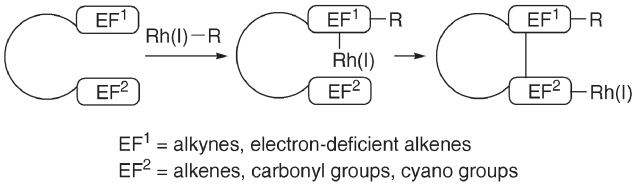


Chart 2

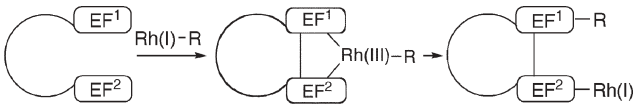


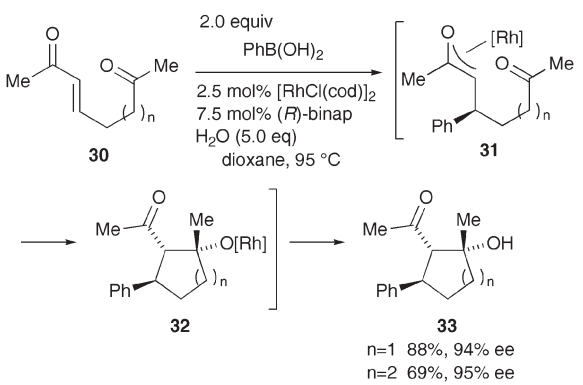
Chart 3

entry point for incorporation of an active carbon–rhodium linkage by way of initial intermolecular carborhodation. The second carborhodation onto the subordinate electrophilic functionality (EF^2) is then triggered to form a cyclic skeleton. Relatively more reactive electrophilic functionalities which can act as the primary reaction point include ordinary alkynes and electron-deficient alkenes activated by carbonyl groups. Typical subordinate, less reactive, electrophilic functionalities include alkenyl, carbonyl and cyano groups.

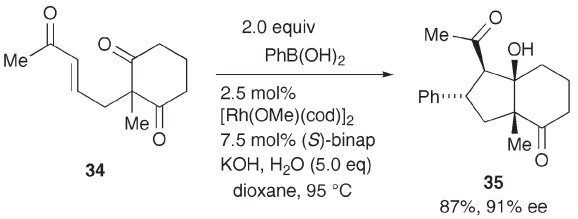
It should be noted that it is conceivable for the reactions of bifunctional acceptors to proceed through a different mechanism, for instance, one involving an oxidative cyclisation step (Chart 3).[20] Whereas a sequential stepwise mechanism is assumed in this article, such an alternative possibility should be taken into account in validating the mechanism.

Sequential enone/ketone addition

α,β-Unsaturated enones are more reactive toward an organorhodium(I) species than ordinary ketonic carbonyl groups. 1,4-Addition of phenylboronic acid to a conjugated enone having another ketonic carbonyl group results in the formation of an (oxa-π-allyl)rhodium(I) species, which then undergoes an intramolecular aldol addition at the ketonic carbonyl group. This sequence produces a cyclic aldol adduct with control of relative and absolute stereochemistries (Scheme 9).[21,22] For example, the reaction of keto-enone **30** with phenylboronic acid in the presence of a rhodium/(*R*)-binap catalyst gave the



Scheme 9



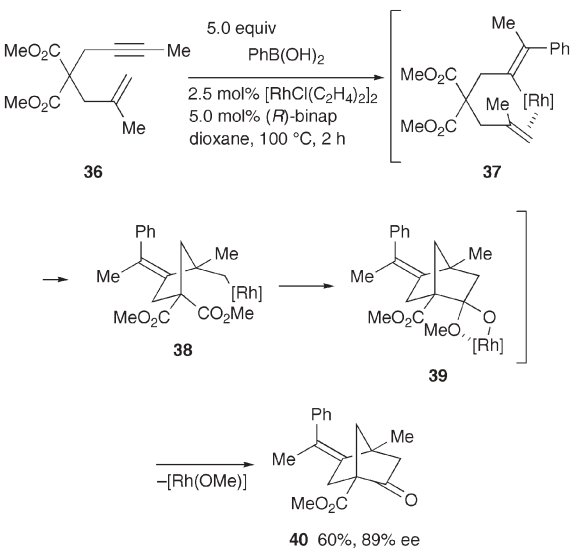
Scheme 10

five-membered ring aldol product **33** exclusively in 88% chemical yield and 94% enantiomeric excess.

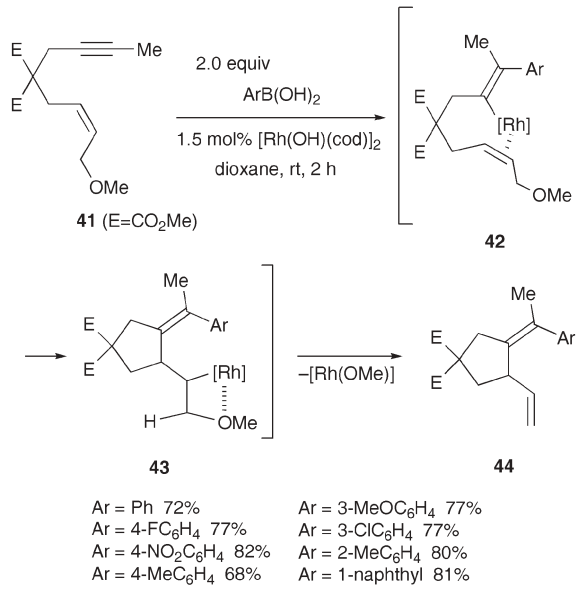
This method is applied to the desymmetrisation of diketo-enones, which results in the stereoselective formation of four contiguous stereogenic centers including a quaternary center (Scheme 10).[23]

Sequential alkyne/alkene addition

Arylrhodium(I) species undergo facile 1,2-addition across carbon–carbon triple bonds in an intermolecular sense to afford alkenylrhodium(I) intermediates, providing an entry point for cascade reactions. A cascade reaction of 1,6-enynes **36** possessing a methallyl moiety affords 2-norbornanones **40** (Scheme 11).[24] The reaction proceeds through three carborhodation steps. Initially, regioselective 1,2-addition of phenylrhodium(I) across the carbon–carbon triple bond gives the alkenylrhodium(I) intermediate **37**. Then, intramolecular carborhodation to the pendent methallyl moiety occurs in a 5-*exo*-trig mode, leading to the formation of (cyclopentylmethyl)rhodium(I) intermediate **38**. The enantiotopic face of the carbon–carbon double bond was selected (89% ee) when (*R*)-binap was used as a chiral ligand.[24b] The subsequent intramolecular acylation of **38** with the ester group on the tether *via* addition/elimination affords **40**, regenerating catalytically active methoxorhodium(I). It is notable that although organorhodium(I) species are not reactive enough to attack the carbonyl group of an ester intermolecularly, an intramolecular



Scheme 11

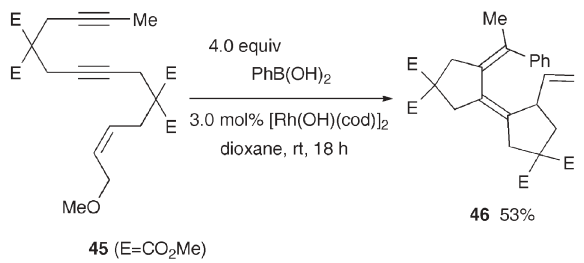


Scheme 12

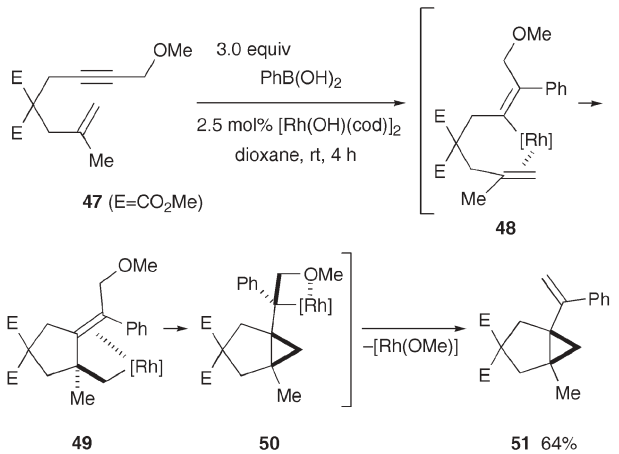
acylation with an ester group proceeds well as in the conversion of **38** to **40**.

The carborhodation cascade proceeds in a different way when the 1,6-enyne possesses a methoxy group at the allylic position as a leaving group as in **41** (Scheme 12).[25,26] The reaction is also initiated by the regioselective 1,2-addition of phenylrhodium(I) across the carbon–carbon triple bond, giving the alkenylrhodium(I) intermediate **42**. This is followed by intramolecular carborhodation onto the carbon–carbon double bond to afford organorhodium(I) intermediate **43**, which is related to **38** in Scheme 11. Intermediate **43** undergoes β-elimination with the methoxy group rather than acylation with an ester group, affording the product **44** and catalytically active methoxorhodium(I). It should be noted that with the organorhodium(I) intermediate **43**, β-oxygen elimination predominates over β-hydrogen elimination. This pathway is in sharp contrast with the palladium-catalysed Heck-type carbopalladation/cyclisation reaction of analogous 1,6-enyne substrates, wherein the related organopalladium(II) intermediate undergoes β-hydrogen elimination rather than β-oxygen elimination.[26b]

An analogous reaction can be conducted with diyne-ene **45** (Scheme 13). The desired cascade reaction occurred successfully to give the bicyclic triene **46** in 53% yield *via* multiple carborhodation steps and β-oxygen elimination as the termination step.



Scheme 13



Scheme 14

Another reaction pathway becomes feasible with 1,6-enynes such as **47** in which the methoxy group is shifted from the allylic position to the propargylic position (Scheme 14).[17,27] Organorhodium(I) intermediate **49** is formed through sequential addition to the carbon–carbon triple and then double bonds. Remarkably, rather than acylation with an ester, **49** undergoes 3-*exo*-trig ring closure onto the exo cyclic double bond despite the developing ring strain. β-Methoxy elimination occurs from the resultant cyclopropane intermediate **50** to produce the vinylcyclopropane **51** fused with a cyclopentane ring. It is conceivable that the three-membered ring closure is facilitated by incipient coordination of the methoxy group to rhodium. A good level of enantioselectivity (85% ee), which was similar to that observed with **40**, was induced when (*S*)-binap was used as the ligand.

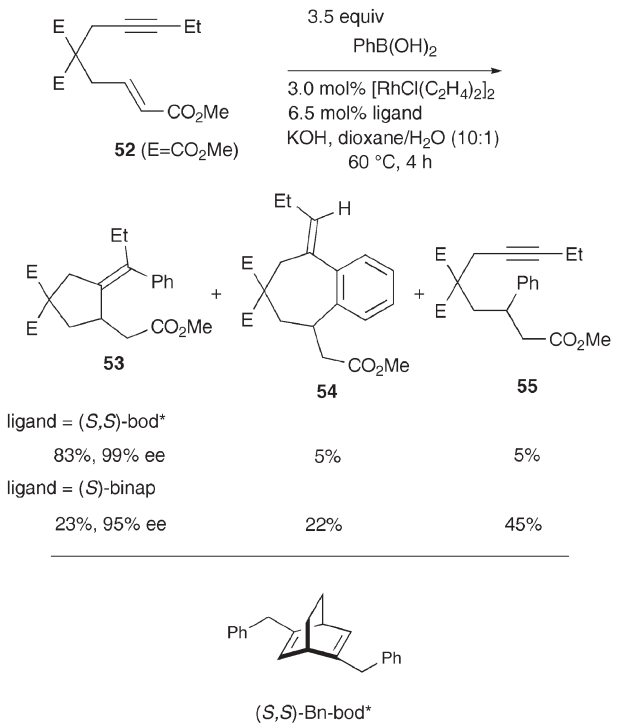
The diversity of reaction pathways observed with the 1,6-enynes **36**, **41** and **47** clearly suggests the breadth of reaction patterns possible for rhodium-catalysed cascade reactions.

Sequential alkyne/electron-deficient alkene addition

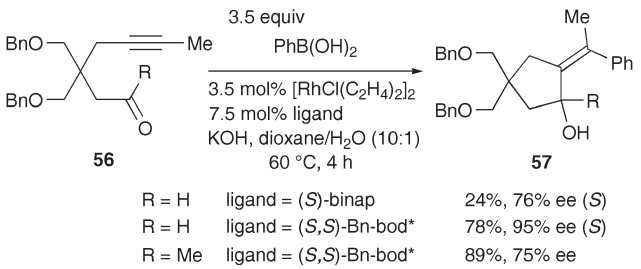
Both alkynes and electron-deficient alkenes react well with an arylrhodium(I) intermediate in an intermolecular fashion. In the case of alkynes bearing an α,β-unsaturated ester moiety, the primary electrophilic functionality changes depending on the ligand (Scheme 15).[28] When the chiral diene ligand,[29] (*S*,*S*)-Bn-bod* is used, initial 1,2-addition of phenylrhodium(I) occurs at the carbon–carbon triple bond. Conjugate addition of the resultant alkenylrhodium(I) to the α,β-unsaturated ester moiety follows in an enantioselective manner to afford the five-membered product **53** in 83% chemical yield and 99% enantiomeric excess. On the other hand, the use of (*S*)-binap as the ligand facilitates conjugate addition of phenylrhodium(I) such that **55** is obtained as the major product (45% yield) after protonolysis of the resultant (oxa-π-allyl)rhodium(I).

Sequential alkyne/carbonyl addition

In the reaction of formyl-alkynes with phenylboronic acid, the carbon–carbon triple bond is preferred over the carbonyl group for the initial addition of the intermediate phenylrhodium(I) (Scheme 16).[24a,30] 1,2-Addition across the



Scheme 15

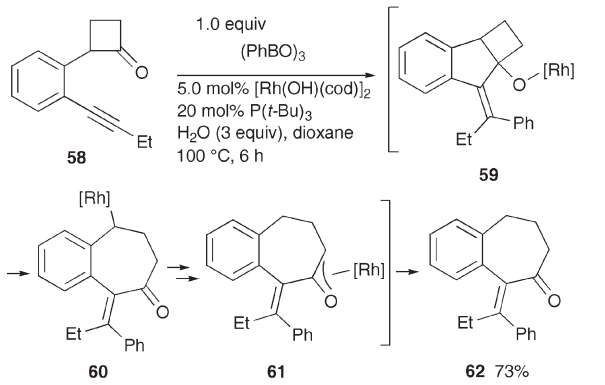


Scheme 16

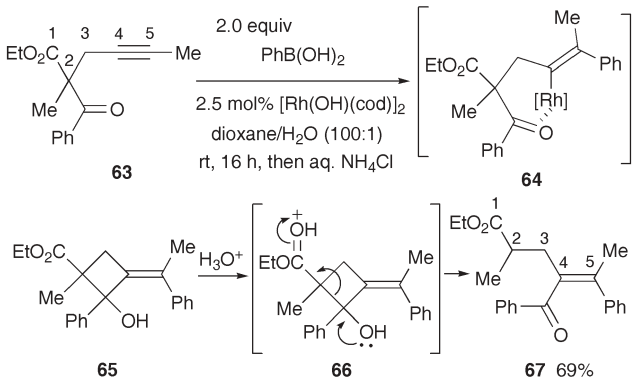
carbon–carbon triple bond is then followed by intramolecular addition to the carbonyl group in a 5-*exo*-trig mode to produce the corresponding cyclopentanols. A higher level of asymmetric induction as well as a better product yield was observed with the chiral diene ligand, (*S*,*S*)-Bn-bod*, than with (*S*)-binap.[24a] Keto-alkynes also undergo the sequential alkyne/carbonyl addition reaction.

When a cyclobutanone moiety is used as the subordinate electrophilic functionality, the second addition to the carbonyl group in a 5-*exo*-trig mode is followed by ring opening of rhodium cyclobutanolate **59** by β-carbon elimination. As a result, the four-membered ring ketone was expanded to the seven-membered ring ketone **62** (Scheme 17).[31]

In addition to the 5-*exo*-trig cyclisation, the 4-*exo*-trig mode is also feasible for the cyclisation step of a cascade reaction of keto-alkynes. When the keto-alkyne **63** reacts with phenylboronic acid in the presence of $[Rh(OH)(cod)]_2$ in dioxane at room temperature, the alkenylrhodium(I) intermediate **64** adds to the carbonyl group in a 4-*exo*-trig mode to form a four-membered ring despite the developing ring strain (Scheme 18).[32] Treatment of the cyclobutanol product having



Scheme 17



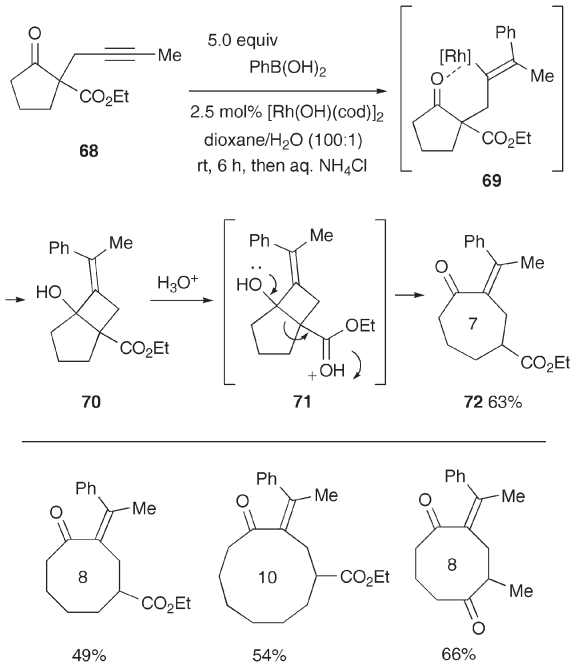
Scheme 18

an ester substituent with NH_4Cl induced a retro aldol reaction. The four-membered ring is opened and α,β-unsaturated ketone **67** is produced. In the overall sequence (**63** to **67**), the benzoyl group migrates from the 2-carbon onto the 4-carbon. The 1,3-acyl migration reaction of keto-alkynes consists of (i) phenylrhodation of a carbon–carbon triple bond, (ii) cyclisation in a 4-*exo*-trig mode, and (iii) ring opening by a retro-aldol reaction.

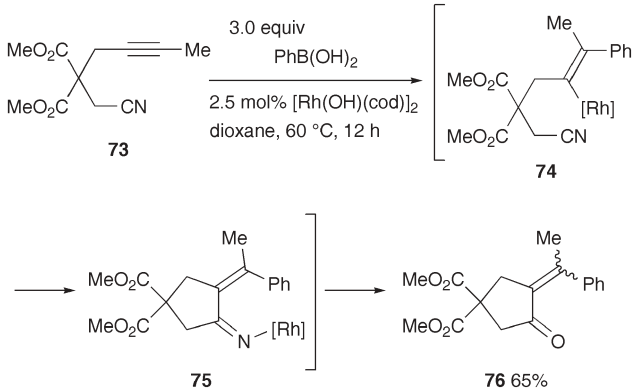
The 1,3-acyl migration reaction was further extended to a ring expansion reaction by the use of cyclic ketones having alkynyl side chains (Scheme 19). The original carbocyclic skeleton was expanded by two carbons. Substrates of five-, six- and eight-membered ring structures are expanded to the corresponding seven, eight and ten-membered ring products, respectively. Cyclic 1,3-diketones also undergo an analogous ring-expansion reaction.

Sequential alkyne/nitrile addition

Even a cyano group can act as the subordinate electrophilic functionality in a cascade process. Cyano-alkyne **73** reacted with phenylboronic acid in the presence of $[Rh(OH)(cod)]_2$ in dioxane at 60 °C to give arylated cyclisation product **76** in 65% yield as a mixture of *E* and *Z* isomers (36 : 64) (Scheme 20).[33] The alkenylrhodium(I) intermediate **74** adds to the cyano group in 5-*exo*-dig mode, as is the case with **18** in Scheme 5. The *N*-rhodium imine **75** is hydrolyzed to give α,β-unsaturated ketone **76**.



Scheme 19

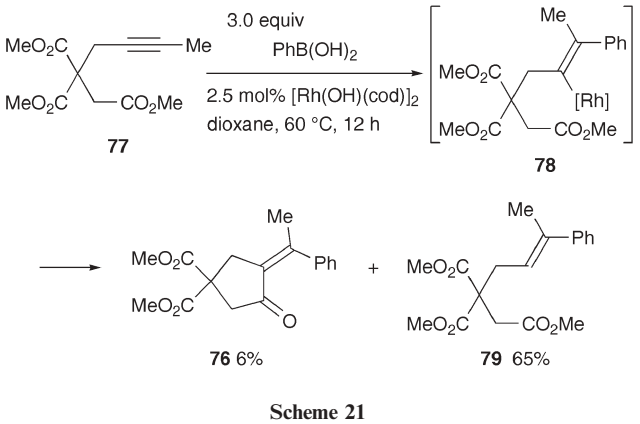


Scheme 20

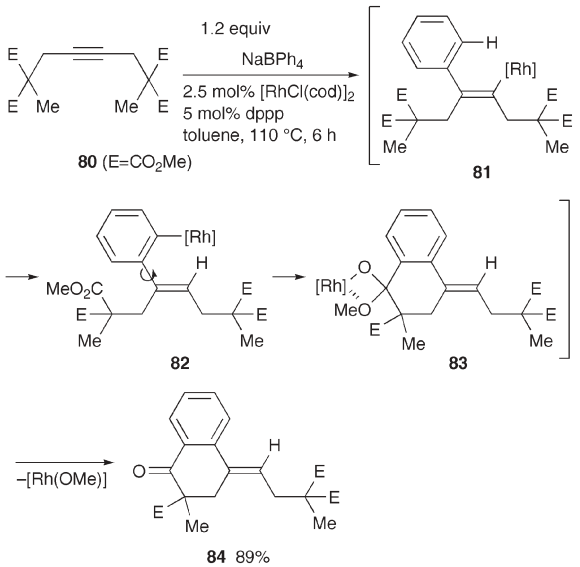
Comparison of the reactivity of the cyano group of **73** with that of the ester group of substrate **77** possessing an analogous structure is noteworthy. When alkynyl ester **77** was subjected to the identical reaction conditions, the cyclisation product **76** was obtained in only 6% yield. The major product **79**, isolated in 65% yield, resulted from protonation of the intermediate alkenylrhodium(I) species **78** (Scheme 21). These contrasting results demonstrate that the cyano group possesses a higher reactivity than an ester group toward the alkenylrhodium(I) species as the subordinate electrophilic functionality, although stereochemical factors may also influence the reactivities in this intramolecular case. It is remarkable that this reactivity order of cyano and ester groups is opposite that expected with organomagnesium reagents.[34]

Sequential alkyne addition/1,4-Rh shift/acylation with ester

When an alkyne flanked by malonic diester moieties (**80**) reacts with sodium tetraphenylborate under strictly anhydrous



Scheme 21



Scheme 22

conditions, a 1,4-Rh shift intervenes between two carbon–carbon bond forming steps to facilitate the six-membered ring formation (Scheme 22).[24b,35] Initially, phenylrhodium(I) adds across the carbon–carbon triple bond to give the alkenylrhodium(I) intermediate **81**. Then, 1,4-shift of rhodium takes place to form arylrhodium(I) intermediate **82**. Intramolecular acylation with the ester group affords α-tetralone derivative **84** with generation of a catalytically active methoxorhodium(I).

Conclusions

Rhodium-catalysed cascade reactions triggered by the addition of organoboron can result in a dramatic increase in molecular complexity in an atom-economical manner. The reactions included in this review article demonstrate that organorhodium(I) species can undergo multiple carborhodation reactions successively in preference to potentially competing processes including protonolysis and β-hydride elimination. Further studies in this area will disclose the utilities and breadth of the rhodium-catalysed cascade processes, which may present outcomes that are complementary to those obtained with palladium catalysts.

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