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Transition metal catalyzed [6 + 2] cycloadditions

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The [6 + 2] cycloaddition reactions are one of the important synthetic transformations to construct eight membered carbo-/heterocyclic systems. The present review is an attempt to update readers on transition metal catalyzed [6 + 2] cycloaddition reactions of various 6π -contributing substrates such as cycloheptatrienes (CHT), cyclooctatetraenes (COTT), allenals, vinylcyclobutanones, fulvene etc. employing rhodium, cobalt, titanium, copper, platinum, ruthenium, rhenium and diphenylprolinolsilyl ethers etc. as catalysts. The transition metal catalyzed [6 + 2] cycloaddition reactions with a variety of functionalized substrates provide straightforward access to eight membered cyclic and/or 5/8, 6/8 etc. condensed carbo-/heterocyclic molecules in moderate to good yields.

Introduction

Cycloaddition reactions are considered to be one of the most powerful methods for the construction of cyclic skeletons¹ with atom economy. There are ample reports on different variants of [4 + 2] and [3 + 2] cycloadditions which provide an easy access to a variety of five or six membered carbo-/heterocycles.^{2,3} However, the parallel methodologies such as [5 + 2],⁴ [6 + 2],⁵ [8 + 2]^{5b} etc. for the synthesis of seven, eight or ten membered carbo-/heterocycles are still uncommon in the literature. Eight-membered rings are found in a wide variety of natural products and are useful ring systems available in variety of drugs, drug leads, or biological probes.⁶ Taxol, the well-known natural product in this family, is now among the most potent anticancer drug in clinical use. In 2008, another member of this family, pleuromutilin was approved for use as an antibiotic by Food and Drug Administration (FDA)⁷ (Fig. 1). Several methods^{8–12} including ring-closing metathesis and Cope rearrangement have been reported for the synthesis of eight-membered carbocycles.¹³ However, the intolerance to substrate substituent in conventional procedures along with complexities observed in natural products makes these techniques ineffective and instigated the development of alternate protocols. Recent years have seen a significant upsurge in this direction with relatively few reports appearing on the synthesis of eight membered carbocycles using [6 + 2],¹⁴ and [4 + 2 + 2]¹¹ cycloaddition reactions. Concerted [6 + 2] cycloaddition reactions are forbidden thermally as per Woodward–Hoffmann rules, when the two reacting π -systems add in a suprafacial fashion. However, transition metal-catalyzed [6 + 2] cycloadditions constitute one such

protocol for the synthesis of monocyclic or condensed functionalized cyclooctadienes. The present review summarizes various reports on the transition metal catalyzed inter- and intra-molecular [6 + 2] cycloaddition reactions appeared in literature since 2000.¹⁴

Rhodium catalyzed [6 + 2] cycloadditions

Rhodium complexes plays a pivotal role in organic synthesis as major catalytic contributors to C–C bond formation reactions.¹⁵ A number of carbo-/heterocyclic systems have been generated employing rhodium complexes as efficient catalyst in a variety of cycloaddition/cyclization reaction¹⁶ Literature rationale suggests an inspiring advancement in this field and many research groups are extensively using rhodium complexes to efficiently conceive these reactions.¹⁷ Considering the importance of rhodium catalysed cycloadditions, there should have been a number of reports on generation of eight membered carbo-/heterocycles engaging rhodium complexes in [6 + 2] cycloadditions, however only a few reports are available which successfully comprehends [6 + 2] cycloadditions. Till now, different substrates such as cycloheptatriene, 2-vinylcyclobutanones, allenals, allenylcyclobutanes, cyclooctatrienes etc. have been reported as 6π -components in Rh(I) catalysed [6 +

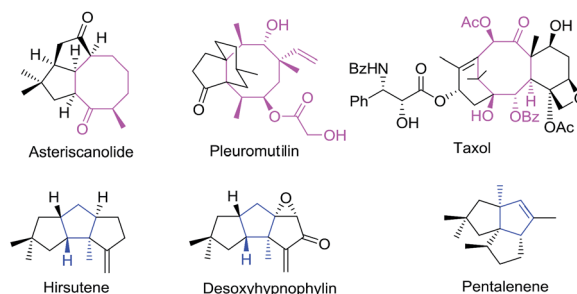


Fig. 1 Carbocycles in natural products.

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2] cycloadditions involving variety of alkene alkyne, allene as 2π -components to afford monocyclic/condensed eight membered carbocycles/heterocycles.

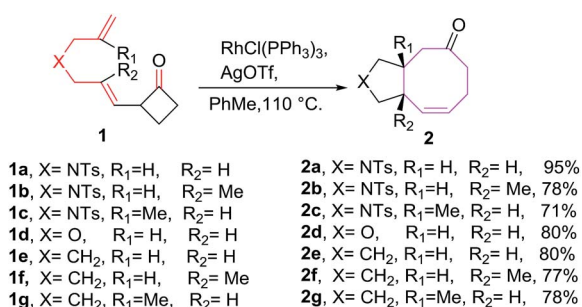
Rh(I) catalysed [6 + 2] cycloadditions of 2-vinylcyclobutanones

One of the earliest reports on Rh(I) catalyzed [6 + 2] cycloadditions of 2-vinylcyclobutanones as 6π -components is reported by Wender *et al.* It involves intramolecular [6 + 2] reactions of 2-vinylcyclobutanones **1a–h** with tethered alkenes for the construction of eight-membered-ring systems **2a–h**.¹⁸ The [6 + 2] reactions has diverse substrate compatibility and proceed for a variety of different tethers to produce *cis*-fused condensed cyclooctatrienes **2a–h** in excellent yields (Scheme 1).

The [6 + 2] cycloadditions involve initial formation of a five membered metallacycle **A**, which undergoes ring expansion to nine-membered metallacycle **B**, demetallation of **B** affords eight-membered condensed carbocycles *via* reductive eliminations (Fig. 2).

Rh(I)-catalyzed formal [6 + 2] cycloadditions of allenal

Sato *et al.* have developed an efficient methodology for the synthesis of fused bicyclic ketones **4**. It involves the Rh(I)-catalyzed intramolecular [6 + 2] cycloadditions of alkyne/alkene tethered allenal **3a–j** using Rh(I)-complex as catalyst. [Rh(I-Mes)(cod)]ClO₄ is an effective catalyst in these [6 + 2] cycloadditions.¹⁹ The use of other Rh(I) complexes as catalyst such as [Rh(IiPr)(cod)]ClO₄, [Rh(IPr)(cod)]ClO₄ and [Rh(IMes)(cod)]ClO₄ afford bicyclic ketones in lower yields and [Rh(dppe)]ClO₄ is



Scheme 1 Rh(I) catalysed [6 + 2] cycloaddition reactions of tethered alkenes with cyclobutanones.

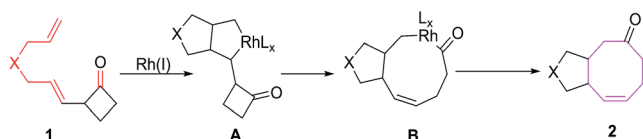


Fig. 2 Plausible mechanism for synthesis of eight-membered condensed carbocycles.

completely ineffective in conceiving [6 + 2] reactions. The [6 + 2] cycloadditions using RhCl(PPh₃)₃ afford bicyclic ketone **4** in relatively good yield (72%) but with longer time. The cyclizations of **3a** and **3b** having phenyl and TMS groups on the alkyne moiety provide **4a** and **4b** in 71% and 90% yields respectively. Substrate **3d–f** containing a heteroatom in the chain afforded corresponding heterocycles **4d–f** in good to excellent yields. Elongation of the tether between the alkyne and allene moieties by one carbon is well tolerated in the [6 + 2] cycloaddition reaction and afford 6/8 fused bicyclic ketone **4g** in 70% yield as evident by the conversion of **3g** to **4g**. The cyclizations of substrates **3h–i** having an tethered alkene also afford bicyclic ketones **4h–i** in a stereoselectively (Scheme 2).

The [6 + 2] cycloaddition of enantiomerically enriched (S)-**5** (94% ee) yields cyclic ketone (S)-**6** in high yields with reasonable transfer of chirality (86% ee) as shown in Scheme 3.¹⁹

The possible mechanism for the formation of **6** involves the oxidative addition of Rh(I) complex to the C–H bond of the aldehyde **5** followed by insertion of the C=C bond of the allene to give oxo-rhodacycle **C** which undergoes isomerization to oxo-rhodacycle **C** *via* π -allylrhodium intermediate **F**. Insertion of an alkyne or alkene into the Rh–C bond followed by reductive elimination yields bicyclic ketone **4/6** (Fig. 3).

Sato *et al.* have also explored the intermolecular [6 + 2] cycloadditions of 4-allenal **7** and alkyne **8**, for the synthesis of functionalised monocyclic cyclooctane derivatives **9**.²⁰ The intermolecular [6 + 2] cycloadditions suffer from unfavorable entropy disadvantage which resulted in decreased yield of the [6 + 2] cycloadducts with the isolation of side products **10** through hydroacylation of allenal **7**^{19c} and formation of **11** by trimerization of alkyne **8** (Scheme 4).

The [Rh(SIMes)(cod)]ClO₄ have been found to be efficient in conceiving intermolecular reactions with the selective formation of eight membered carbocycle **9** (68%). The [Rh(IMes)(cod)]ClO₄ as catalyst is non selective and afford mixture of eight

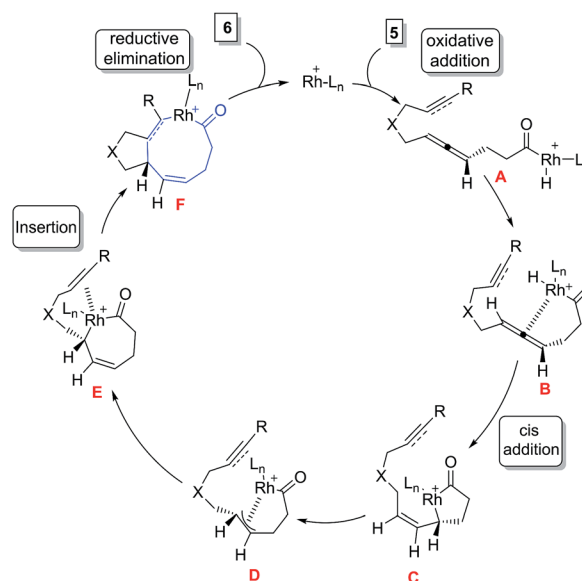
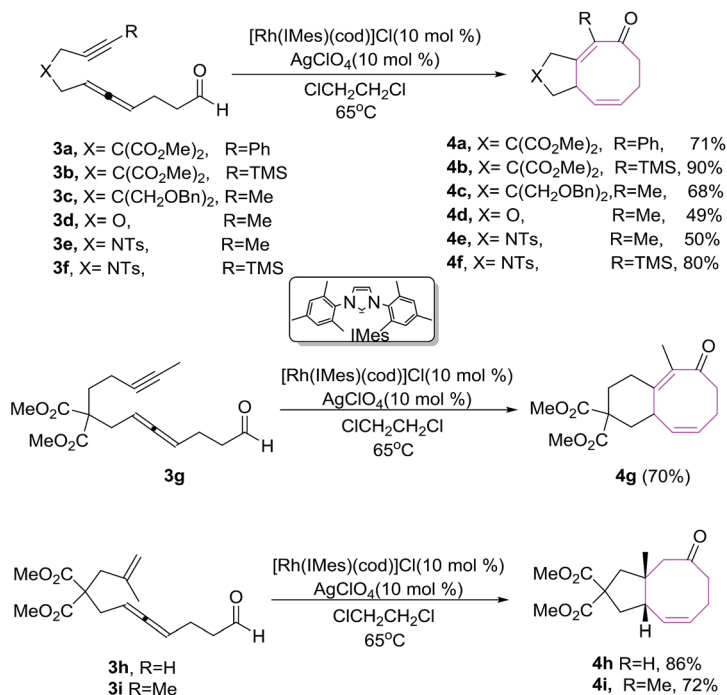
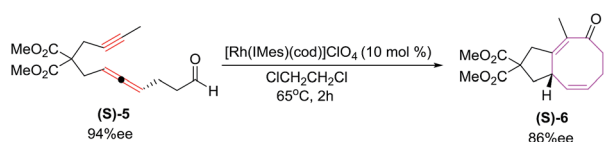


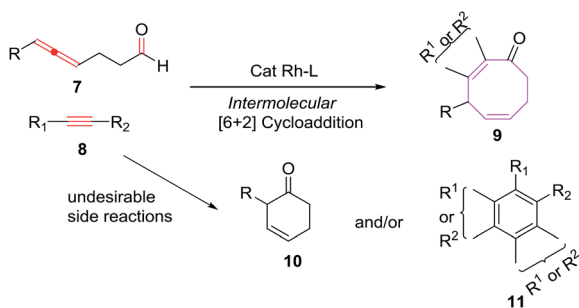
Fig. 3 Proposed mechanism for rhodium catalyzed [6 + 2] cycloaddition reactions of allenals.



Scheme 2 Rh(I)-catalyzed [6 + 2] cycloaddition of alkene tethered allenal.



Scheme 3 Rh(I)-catalyzed [6 + 2] cycloaddition of alkyne tethered allenal.



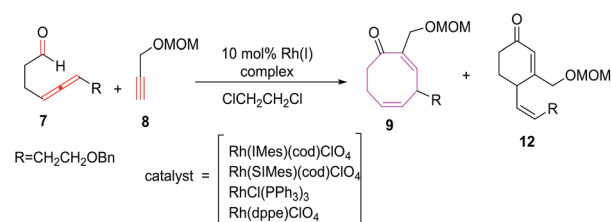
Scheme 4 Intermolecular [6 + 2] cycloadditions.

membered carbocycle **9** (61%) and six-membered carbocycle **12** (19%). Other tested catalysts such as [RhCl(PPh₃)₃] and [Rh(dppe)]ClO₄ do not promote the intermolecular [6 + 2] cycloaddition reactions (Scheme 5).

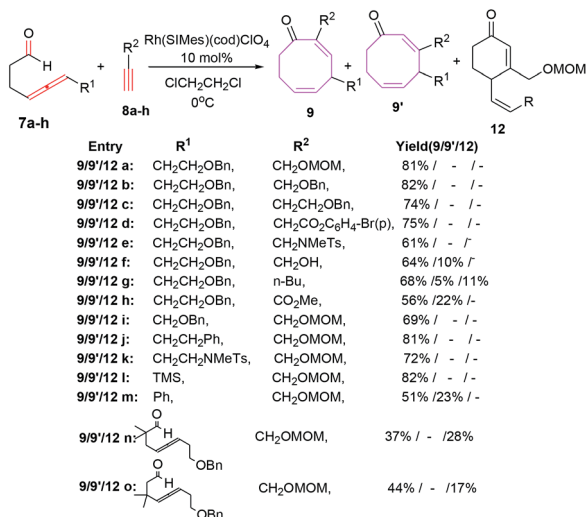
The intermolecular [6 + 2] cycloadditions of **7a** with various terminal alkynes possessing benzyloxy **8b–c**, benzoate **8d** and sulphonamide moiety **8e** have also been reported to proceed in a stereoselective manner affording eight membered carbocycles **9b–e** in high yields. The propargyl tethered alkyne moiety **8f**,

however, provide regiomer cyclooctadienone **9f** and **9f'** in yields of 64% and 10% respectively. Employing 1-hexyne have yielded a mixture of isomeric eight-membered rings **9g/9g'** in 68% and 5% yields along with six-membered carbocycles as side product **12g** (11%). Electron-withdrawing carboxylate functionality on alkyne nucleus **8h** have led to the regiomer cyclooctadienones **9h/9h'** in comparatively lower yields (56% & 22% respectively). 4-Allenal substituted with benzyloxy **7a–b**, benzyl **7c**, sulphonamide **7d** and TMS **7e** afford regioselective octa cyclic compounds **9a, i–l** in yields of 69%, 81%, 72% and 82% respectively. Phenyl substitution on allene however, retards the reaction rate and regioselectivity resulting in isolation of **9m/9m'** in 51% and 23% respectively.

The allenal **7g–h** possessing alkyl substitution between allene and aldehyde have resulted in increased formation of hydroacylation product **12n–o** in 28% and 17% yields along with intramolecular [6 + 2] cycloadducts **9n–o** in 37% and 44% yields respectively (Scheme 6).



Scheme 5 Intermolecular [6 + 2] cycloadditions using various Rh(I) complexes.



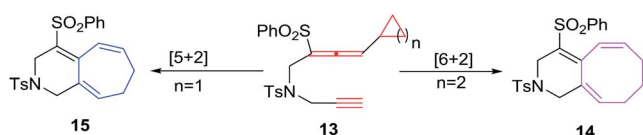
Scheme 6 Intermolecular [6 + 2] cycloadditions of allenyl and alkynes.

Rh(I) catalysed [6 + 2] cycloaddition reactions of allenylcyclobutanes

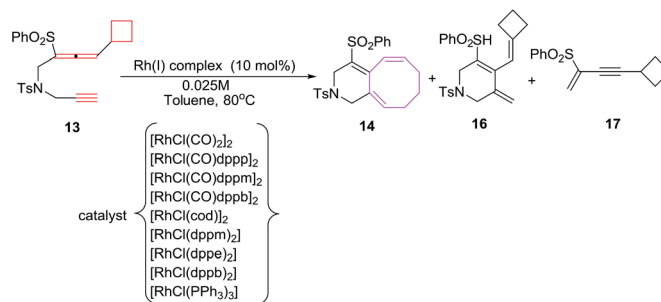
Mukai *et al.* have devised a cycloisomerisation methodology using rhodium(I) catalysed alkyne-allenyl unfunctionalised cyclopropane/butane **13** to afford bicyclic and compounds **15** and **14** through [5 + 2]²¹ and [6 + 2]²² cycloaddition respectively. The un-functionalized simple cyclobutane ring in [6 + 2] cycloadditions behaves as 6 π -component and afford an easy construction of the bicyclo[6.3.0]undecatrienes **14** in good yields (Scheme 7).

The [6 + 2] cycloaddition reactions are conceived by heating a solution of **13** in 1,2-dichloroethane at 80 °C in the presence of 10 mol% [RhCl(CO)₂] as catalyst to afford the desired bicyclo [6.4.0]dodecatriene **14** in 40% yield along with monocyclic side product **16** (52%). Replacement of catalyst to [RhCl(CO)dppp]₂ in toluene have witnessed a marked increase in yield of 6/8 bicyclic product **14** (80%). Other rhodium carbonyl catalysts are less effective in conceiving these [6 + 2] cycloadditions. Best results for [6 + 2] cycloaddition reactions are observed employing [RhCl(dppe)₂] as catalyst without carbon monoxide as ligand. A decrease in catalyst loading to 5 mol% have observed a lowering in reaction yield of **14**, however, using 5 mol% [RhCl(dppe)₂] in 0.1 M dioxane solvent at 80 °C have led to the formation of bicyclo[6.4.0]dodecatrienes **14** (87%) (Scheme 8).

The proposed mechanism involves the coordination of **13** with Rh(I) complex through allenal double bond, C–C bond of the strained cyclobutane ring and alkyne to produce intermediate **G**, which opens up immediately to rhodabicyclo[4.3.0]



Scheme 7 Rh(I) catalysed [6 + 2] reactions of unfunctionalised alkyne-allenyl cyclopropane/butane.



Scheme 8 Cycloadditions of alkyne-allenyl cyclobutane **13** in different Rh(I) complexes.

nonadiene intermediate **H** followed by π -carbon elimination of the strained cyclobutane ring of **H** leading to the formation of nine membered intermediate **I**, which undergoes reductive elimination leading to bicyclo[6.4.0]dodecatrienes **14**. However, π -hydride elimination instead of π -carbon elimination of **I** generates intermediate **J** which on reductive elimination yields monocyclic adduct **16**. Alternatively, rhodacycle intermediate **K**,^{23–25} produced from ring opening of strained cyclobutane ring intermediate **G**, undergoes insertion of C–Rh^{III} bond into the triple bond leading to the production of intermediate **I**²² (Fig. 4).

Rh(I) catalysed [6 + 2] cycloadditions of cyclooctatrienes

Conjugated cyclic trienes *viz.* cycloheptatrienes (CHT), cyclooctatrienes (COTT) *etc.* are excellent participants in [6 + 2] cycloadditions as the embedded trienes in the favored *cisoid* conformations acts as 6 π components with different alkenes, alkynes and dienes acting as 2 π component. The use of metal catalysts in these cycloaddition reactions have found an extensive place in literature. Metal catalysts such as titanium,²⁶ ruthenium,²⁷ molybdenum,²⁸ cobalt,²⁹ chromium³⁰ and iron³¹ complexes have been widely used to perceive such reactions.

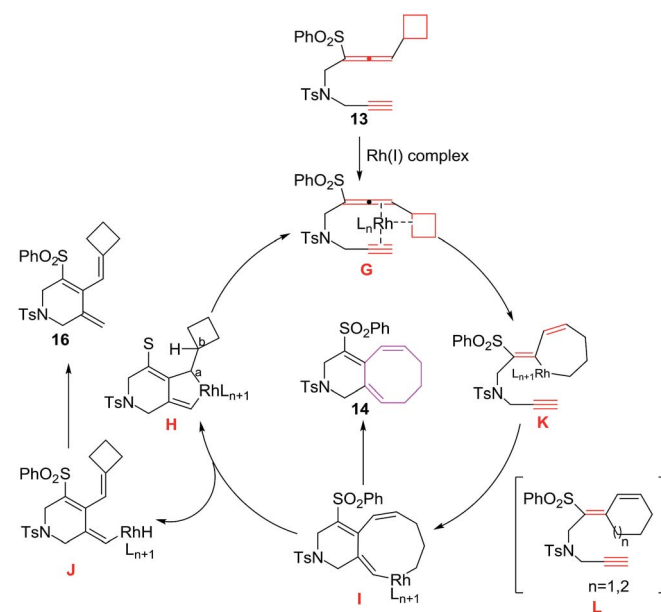


Fig. 4 Proposed mechanism for the formation of **14**.

Mach *et al.* have engaged Ziegler catalyst ($\text{TiCl}_4/\text{Et}_2\text{AlCl}$) in achieving these $[6 + 2]$ cycloadditions.³² Rigby *et al.* have employed carbonylchromium(0) complex bearing labile ligand to effectively achieve $[6 + 2]$ cycloadditions.^{10a-d} Buono *et al.* have recently established $[6 + 2]$ cycloadditions of CHT with terminal alkynes.³³ Also, cobalt(i) catalysed protocol has been applied to $[6 + 2]$ cycloadditions of COTT and internal and terminal alkynes³⁴ and CHT to substituted allenes.³⁵

Wang *et al.* have explored $[6 + 2]$ cycloadditions of cycloheptatriene **18** with internal alkynes **19** employing different rhodium(i) catalysts. The $[6 + 2]$ cycloadditions do not occur using PPh_3RhCl as catalyst at 60°C .³⁶ The $[6 + 2]$ cycloadditions at elevated temperature (120°C) witness the formation of cycloadduct (64%). Further increase in reaction temperature causes decrease in yield of **20** (53%). Introducing additives such as CuI ($10\text{ mol}\%$) which acts as phosphine cleavage reagent³⁷ have increased the yield of **20** (75%). Exchanging the catalyst to $[\text{Rh}(\text{COD})\text{Cl}]_2$ steers the reaction to better results (71%). Best results for $[6 + 2]$ cycloadditions (88%) are witnessed using $[\text{Rh}(\text{COD})\text{Cl}]_2$ as catalyst along with PPh_3 ($10\text{ mol}\%$) and CuI ($10\text{ mol}\%$) at 120°C . A number of terminal alkynes have been tried by Wang *et al.* The electron donating groups at *para* position of phenyl acetylene such as **19a**, **19c**, **19d** and **19f** have afforded better yields of $[6 + 2]$ cycloadducts (88% , 85% , 87% and 88% respectively). Conversely, electron withdrawing substituents on alkyne such as **19g-h**, **19i**, **19j**, **19k** resulted in lowering of reaction yields to 70% , 73% , 70% , 72% and 67% respectively demonstrating the importance of electron donating substituents. No substitution on alkyne nucleus **19b** have led to 81% isolation of **20b**. Introducing bulky groups as in **19l-n** have resulted in poor isolation of **20l-n** in 48% , 40% and 30% yields owing to the strong detrimental steric effect played by these groups (Scheme 9).

The mechanism for $[6 + 2]$ cycloadditions involves the initial conversion of catalytic precursor $[\text{Rh}(\text{COD})\text{Cl}]_2$ to $(\text{Ph}_3\text{P})\text{Rh}(\text{COD})\text{Cl}$ **N**, followed by exchange of COD ligand with CHT generating intermediate **O**. Replacement of PPh_3 with alkyne in the presence of CuI leads to intermediate **P** which immediately undergoes oxidative cyclometalation to intermediate **Q**. Addition of alkyne to **Q** produces σ, π -allyl complex **R** which undergoes reductive elimination through transition state **S** to

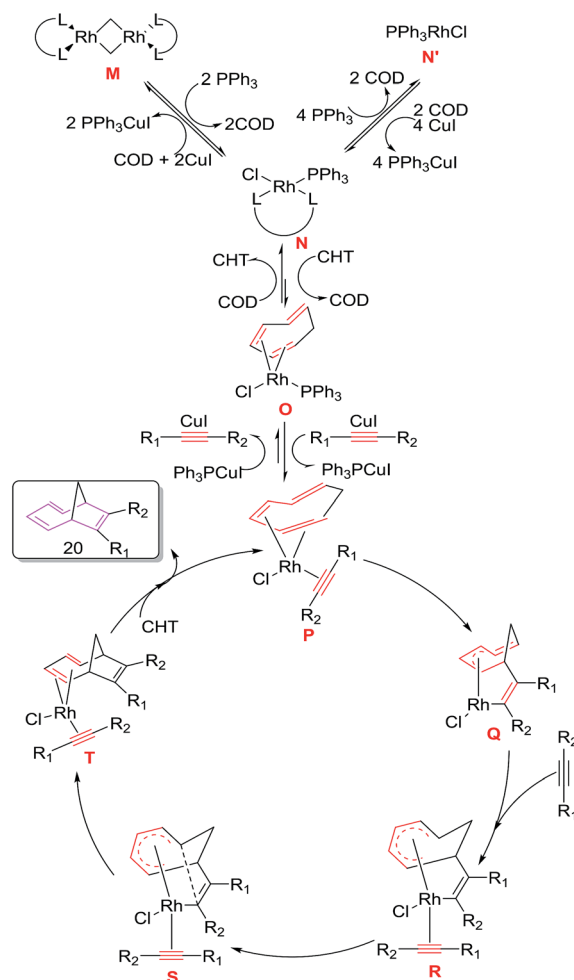


Fig. 5 Proposed Mechanism for rhodium catalysed $[6 + 2]$ cycloaddition reaction of CHT with internal alkyne.

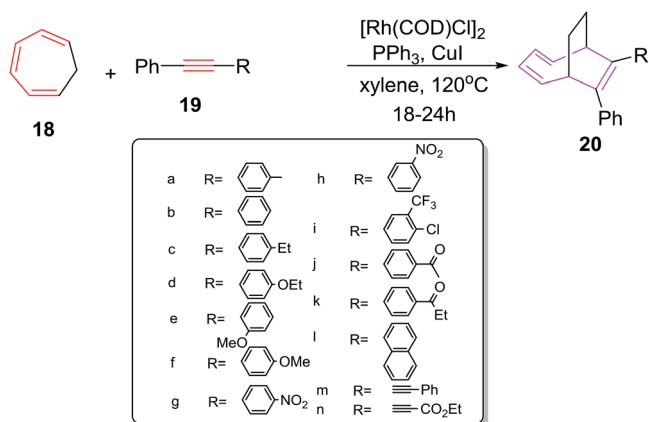
intermediate **T**. Ligand exchange of **T** with CHT delivers cycloadduct **20** and regenerates rhodium complex **P** to reenter the catalytic cycle. DFT calculations employing M06 function taking $\text{Rh}(\text{i})$ model as catalyst also confirms the proposed reaction mechanism with the observation of strong additive effect for the CuI in these $[6 + 2]$ reactions (Fig. 5).

Cobalt catalyzed $[6 + 2]$ cycloadditions

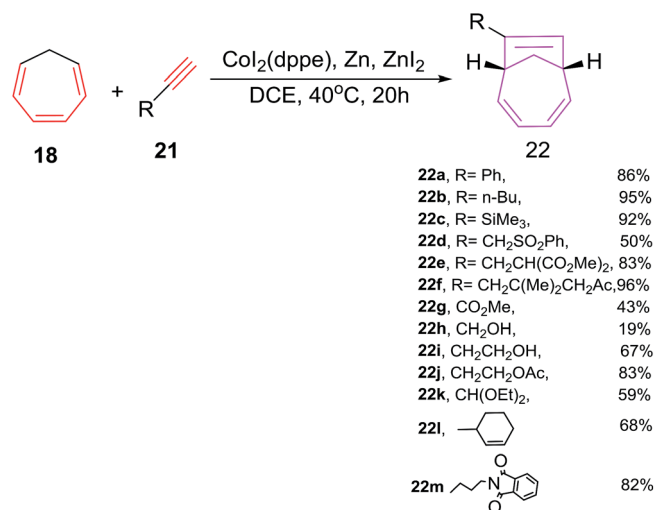
$\text{Co}(\text{i})$ complexes have been observed an excellent catalyst for $[6 + 2]$ cycloadditions of cycloheptatrienes, cyclooctatetraenes, dicobalt acetylene complexes as 6p-components with alkyne, allene enol silyl ethers as 2p-components to yield variety of monocyclic or condensed eight membered carbocycles. All the reported studies involve the intermolecular $[6 + 2]$ variants of these cycloadditions and $\text{Co}(\text{i})$ catalysed intramolecular $[6 + 2]$ cycloadditions are scarcely available in literature.

$[6 + 2]$ cycloadditions of cycloheptatriene (CHT) and alkynes

Buono *et al.* have reported the first cobalt(i) catalyzed $[6 + 2]$ cycloadditions of cycloheptatriene (CHT) **18** with alkynes **21** to afford 7-alkyl-bicyclo[4.2.1]nona-2,4,7-trienes **22** (Scheme 10).³⁸ Various cobalt(II) catalytic systems³⁹ have been tested for $[6 + 2]$



Scheme 9 $[6 + 2]$ cycloaddition of CHT with various alkynes.



Scheme 10 Cobalt(II) catalyzed [6 + 2] cycloaddition reactions of CHT with terminal alkynes.

cycloadditions. Best results are witnessed using cobalt(II)iodide/1,2-bis(diphenylphosphino)ethane (dppe) as catalyst, zinc metal as reducing agent, zinc iodide as a Lewis acid in 1 : 3 : 2 molar ratio in 1,2-dichloroethane as solvent. The catalytic combination of $\text{CoI}_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$ have also proven excellent tolerance to various functional groups such as nitrile, alcohol, imide, sulfone, ketone, ester, ketal or ethers substituted alkyne **21a–m** in their [6 + 2] cycloaddition reactions with CHT **18**. Alkynes having remotely substituted functional groups to the triple bond such as **21f**, **21j**, **21m** afford cycloadducts **22f**, **22j** and **22m** in excellent yields. The alkynes have substitution propargylic carbon **21d**, **21k** provide low yield of [6 + 2] cycloadducts. Electron poor alkynes such as methyl propiolate **21g** have afforded [6 + 2] cycloadduct **22g** with poor yield (21%) due to the preferential coordination of cobalt with **21g** initiating its cyclotrimerisation process. The efficacy of cobalt catalysed [6 + 2] cycloadditions are bettered using syringe pump controlled slow addition of the alkyne and lowering the catalyst loading (2.5 mol%) (Scheme 10).

A plausible mechanism involves the ZnI_2 reduction of CoI_2 by zinc metal to cationic $[\text{Co}(\text{I})\text{L}_2]^+$ complex which coordinates with alkyne **21** and CHT **18** followed by oxidative cyclometalation to produce cobalta-cyclopentene intermediate **U**. 1,5-migration of the C(sp³)–Co bond of **U** through consecutive σ, π -allyl complexes **V** and **W** leads to bicyclo cobalta-cycle **X** which on reductive elimination generates cycloadduct **22** and regenerates cationic intermediate $[\text{Co}(\text{I})\text{L}_2]^+$ to return to the catalytic cycle³⁸ (Fig. 6).

An enantioselective version of the [6 + 2] reactions has also been explored using phosphoramidite ligand as chirality inductors with improved yields and good enantioselectivity.

[6 + 2] cycloadditions of cycloheptatriene (CHT) and allene

Buono *et al.* have also reported cobalt catalyzed [6 + 2] cycloadditions of cycloheptatriene (CHT) **18** with variety of allenes **23** to afford bicyclic 7-bicyclo[4.2.1]nona-2,4-dienes **24** with an

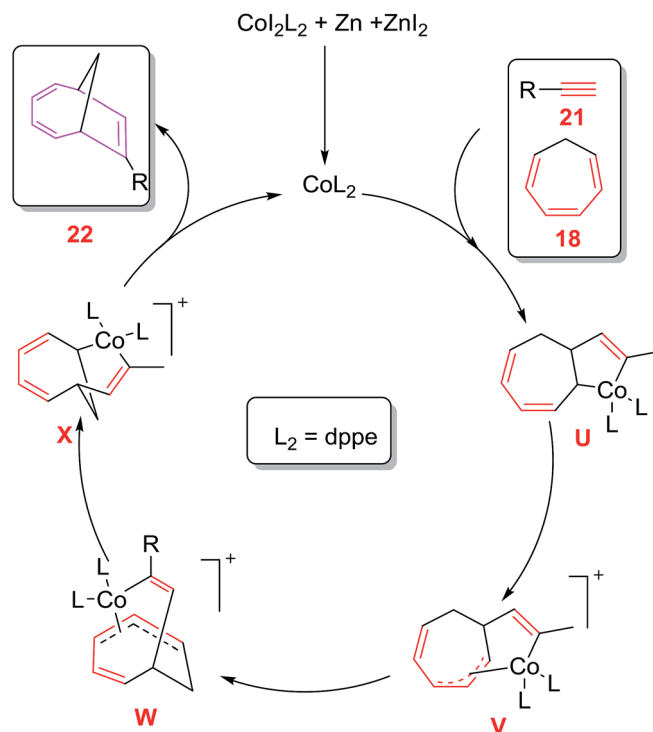
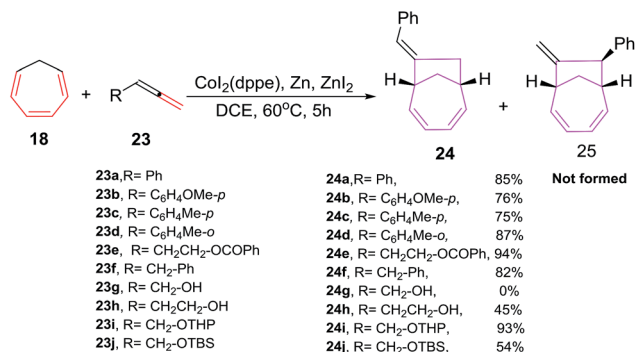


Fig. 6 Proposed Mechanism for cobalt catalysed [6 + 2] cycloadditions of CHT with terminal alkynes.

improved yield, enhanced regio- and geometrical selectivity (Scheme 11). The treatment of CHT **18** with phenylallene **23a** under $\text{CoI}_2(\text{dppe})/\text{Zn}$ powder/ ZnI_2 as catalytic system have resulted in an exclusive formation of *E*-isomer of 7-benzylidenebicyclo[4.2.1]nona-2,4-diene **24a** without the isolation of even traces of the other geometrical or regioisomer **25**. Zinc metal plays a pivotal role in these cycloaddition reactions, absence of which leads to non-isolation of [6 + 2] cycloadduct. Also, ligand plays an equally important role as bis(diphenylphosphino)methane (dppm) and 1,3 bis(diphenylphosphino)propane (dppp) were ineffective in conceiving these reactions. Optimal reaction conditions leading to best results in terms of yield of **24** is witnessed using $\text{CoI}_2(\text{dppe})$ catalytic system with Zn/ZnI_2 reducing agent in 1,2-dichloroethane as solvent.⁴⁰



Scheme 11 Cobalt catalyzed [6 + 2] reactions of CHT with substituted allenes.

The [6 + 2] cycloaddition reactions of monosubstituted allenes **23** are also studied using Co(II) complexed as catalysts. The methoxy or methyl substitution at *ortho*- or *para*- position of phenylallene **23a–d**, is well accepted and lead to the exclusive formation of *E*-isomers **24a–d** in good yields. [6 + 2] cycloadditions of benzylallene **23f** with CHT **18** also leads to the exclusive formation of *E*-7-benzylidenebicyclo[4.2.1]nona-2,4-diene **24f** in 82% yield. α -allenol **23g** and β -allenol **23h** are non reactive under these reaction conditions. With tetrahydropyranyl and benzoate protected α -allenols **23i** and **23e**, excellent yields of 93% and 94% are achieved for cycloadducts **24i** and **24e** respectively. Conversely, *tert*-butyl dimethylsilyl protected α -allenols **23j** leads to relatively low yields of [6 + 2] cycloadducts **24j** (54%) due to the degradation of allene during the catalytic cycle. The [6 + 2] cycloadditions of disubstituted allenes, require high temperature and greater reaction time to manage similar results both in terms of yield and selectivity⁴⁰ (Scheme 11).

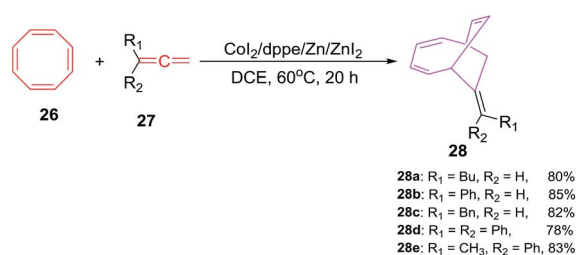
[6 + 2]-cycloadditions of cyclooctatetraene and terminal allenes

D'yakonov *et al.* have accomplished the Co(I) catalyzed [6 + 2]-cycloadditions of 1,3,5,7-cyclooctatetraene **26** (COTT) with functionalized terminal allenes **27a–e** in the presence of CoI₂/dppe/Zn/ZnI₂ catalytic system using 1,2-dichloroethane as solvent at 60 °C to afford (*E*)-bicyclo[4.2.2]deca-2,4,7-trienes **28a–e** in good yields (78–85%; Scheme 12).⁴¹ The reactions are gauged using varied reaction and catalytic system. It is observed that CoI₂ or ZnI₂ alone do not conceive the reactions even at elevated temperature (100 °C).

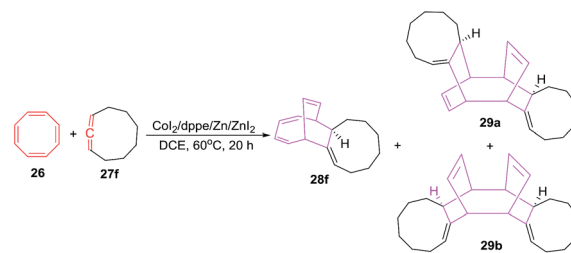
The [6 + 2] cycloadditions of COTT **26** with 1,2-cyclo-nonadiene **27f** under similar reaction conditions afford tricyclo[9.4.2.0]heptadeca-2,12,14,16-tetraene **28f** in 65% yield. Interestingly, the reactions also proceed further to produce regio- and stereomeric bis-adduct mixture **29a** and **29b** in total yield of 30%⁴¹ (Scheme 13).

[6 + 2] cycloadditions of cyclooctatetraene with alkynes

Buono *et al.* have also explored the cobalt-catalyzed [6 + 2] cycloadditions of cyclooctatetraene **26** with alkynes **30a–j** for the synthesis of monosubstituted bicyclo[4.2.2]-deca-2,4,7,9-tetraenes **31a–j** in fair to good yields (56–94%). The reaction of phenylethyne **30a** with COTT **26** using CoI₂(dppe) as catalyst/ligand and ZnI₂/Zn as Lewis acid/reducing agent couple in 1,2-



Scheme 12 Cobalt(II) catalyzed [6 + 2] cycloaddition reactions of COTT with terminal allenes.



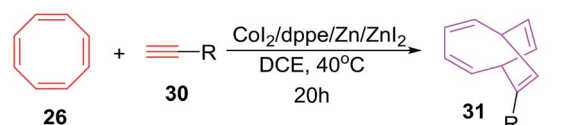
Scheme 13 Cobalt(II) catalyzed [6 + 2] cycloaddition reactions of COTT with cyclic allene.

dichloroethane at 40 °C have resulted in the isolation of 7-phenylbicyclo[4.2.2]deca-2,4,7,9-tetraene **31a** in 70% yield. Alternatively employing CoI₂(dppe), Bu₄NH₄/ZnI₂ catalytic system have led to the isolation of **31a** in 66% yield. The reaction protocol had proven to be of wide spread applicability as various functionalities on alkyne nucleus *viz.* ester, amide, nitrile, sulphonate, ketone, sulphones and trimethylsilyl are very well accepted as evident from moderate to good yields of [6 + 2] cycloadducts **31a–j** (56–94%; Scheme 14).⁴²

The [6 + 2] cycloadditions encountered similar success when COTT **26** is made to react with symmetrical alkynes **30k–l** for synthesis of cycloadducts **31k–l** in yields of 78% and 77% respectively. The [6 + 2] cycloadditions however have failed for diphenylethyne or 3-hexyne (Scheme 15).⁴²

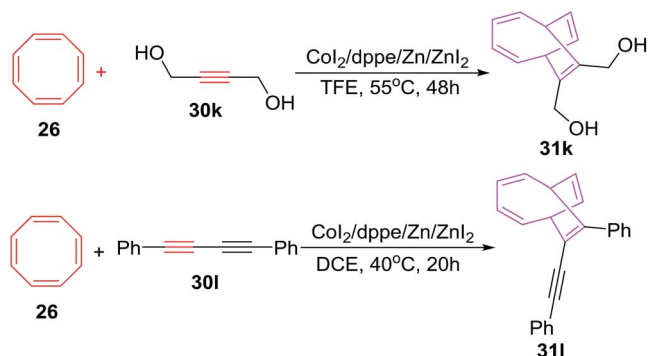
The cobalt-catalyzed cycloadditions of cyclooctatrienes (COT) **32** with various alkynes **30a–e** afford a mixture of desired [6 + 2] cycloadducts **33a–e** and tricyclic adduct **34a–e**. The absence of cycloadducts of type **35** and **36** from the product range rules out the possible [4 + 2] cycloaddition pathway for COTT **26** and COT **32** (Scheme 16).

The COT **32**/COTT **26** can exist in two isomeric forms namely monocyclic form **X** and 6 π bicyclic isomeric electrocycle **Y**. The [6 + 2] cycloaddition of terminal alkyne **30** to isomeric form **X** have resulted in the formation of desired cycloadduct **33**, whereas, [4 + 2] cycloaddition of **30** to bicyclic isomeric form **Y** have led to the isolation of cycloadduct **34**. The direct non participation of **X** in [4 + 2] cycloaddition with terminal alkyne **30** have resulted in non isolation of hypothetical products **35** and **36** (Fig. 7).

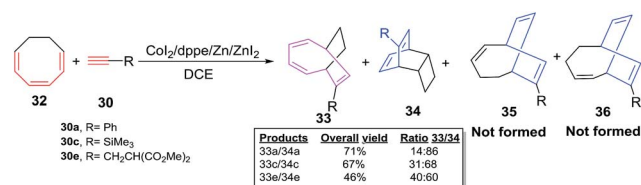


31a , Ph,	70%
31b , n-Bu,	61%
31c , SiMe ₃ ,	89%
31d , CH ₂ SO ₂ Ph,	71%
31e , CH ₂ CH(CO ₂ Me) ₂ ,	79%
31f , CH ₂ C(Me) ₂ CH ₂ Ac,	75%
31g , CH ₂ OH,	69%
31h , CH ₂ CH ₂ OH,	76%
31i , CH ₂ CH ₂ OAc,	56%
31j , CH ₂ CH ₂ OTs,	63%

Scheme 14 Cobalt-catalyzed [6 + 2] cycloadditions of cyclooctatetraene with terminal alkynes.



Scheme 15 Cobalt-catalyzed [6 + 2] cycloadditions of cyclooctatetraene with symmetrical alkynes.



Scheme 16 Cobalt-catalyzed [6 + 2] cycloadditions of cyclooctatriene (COT) with terminal alkynes.

Mechanistically, the reaction is expected to proceed through two pathways. Oxidative cyclometallation of **I** followed by its coordination to alkyne **30** generates cobaltacycle **VI** in the first path. Alkyne insertion to Co–C bond leads to cobaltabicyclic **V**, which on reductive elimination of cobalt affords cycloadduct **31/33** and regenerates active [CoL₂]⁺ to reenter the catalytic cycle. In the second path, oxidative cyclometallation of **II** leads to complex **III** which on 1,3-migration of Co–C(sp³) bond through σ-π-allyl complex forms cobaltabicyclic adduct **V**. Formation of [4 + 2] cycloadduct proceeds *via* sequential oxidative cyclometallation, alkyne insertion and reductive elimination of intermediate **VII** and **VIII** leading to product **34** (Fig. 8).⁴²

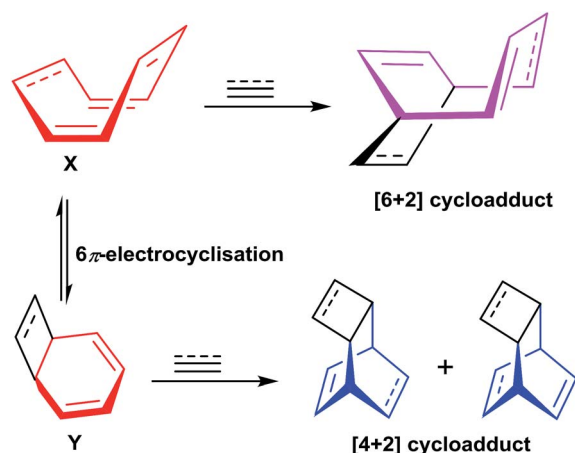


Fig. 7 Valence tautomeric forms of COT/COTT and their participation in cycloadditions with alkynes.

[6 + 2] cycloadditions of dicobalt acetylene complex with enol silyl ethers

Tanino *et al.* have developed methodology for the stereoselective synthesis of cyclooctanones **40** by formal [6 + 2] cycloadditions of a hexa carbonyl dicobalt acetylene complex **38** (6π component) with several enol silyl ethers 2π component **37** under the influence of EtAlCl₂.

The methodology holds special importance as no side product arising from intramolecular cyclisation/homo coupling of the cobalt complex is noticed which allowed equivalent mixing of reactants without employing high dilution synthesis (Scheme 17).⁴³

The reaction proceeds with the stereoselective formation of dicobalt acetylene complex **39** in good yields. Acyclic enol silyl ethers **37c**, **37d**, **37e** produce cycloadducts **39c**, **39d** and **39e** in 73% (88 : 12), 68% (*cis*) and 83% (86 : 14) yields respectively with the major product having *cis* arrangement of alkyl and silyloxy group. However, *trans* fused cyclooctanone **39f** is obtained as a single cycloadduct (81%) by employing cyclic enol silyl ether **37f**.^{43,44}

The [6 + 2] cycloadditions can be utilized to generate a model compound of taxane diterpenoid. The B–C ring system of taxane is constructed by employing [6 + 2] cycloaddition reaction of diacetylene dicobalt complex **38** with cyclic enol silyl ether **37f**.⁴⁵

Titanium(II) catalyzed [6 + 2] cycloadditions

Titanium complexes has successfully tested in [6 + 2] cycloadditions of variety of cycloheptatrienes, cyclooctatetraenes,

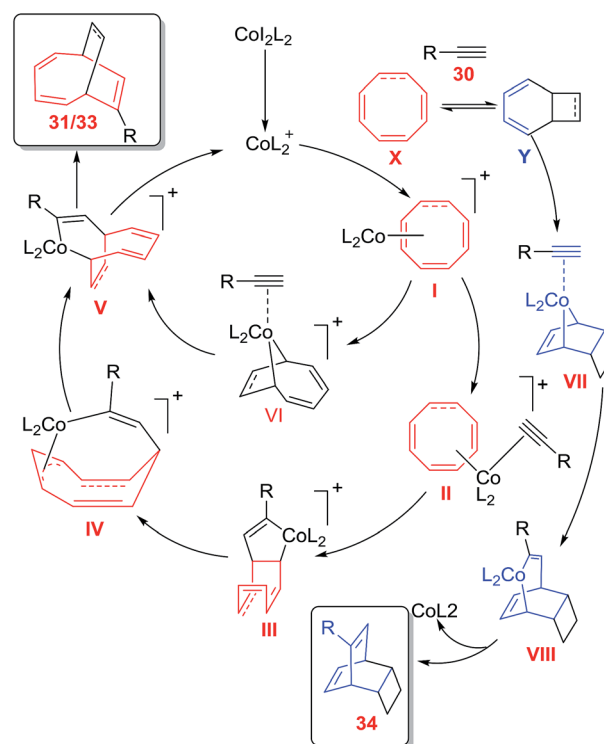
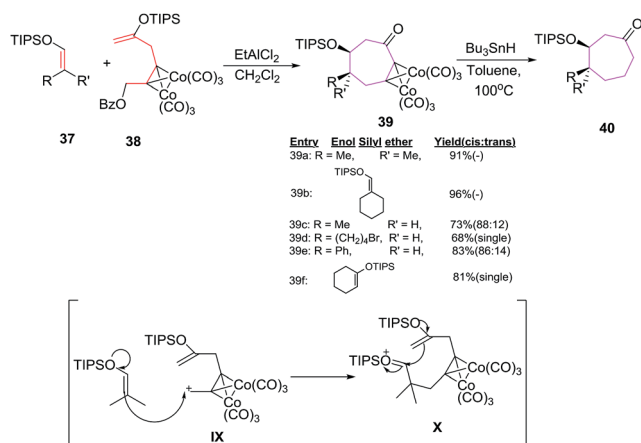


Fig. 8 Proposed mechanism for cobalt catalyzed cycloadditions of COTT 26/COT 32 with terminal alkynes 30.



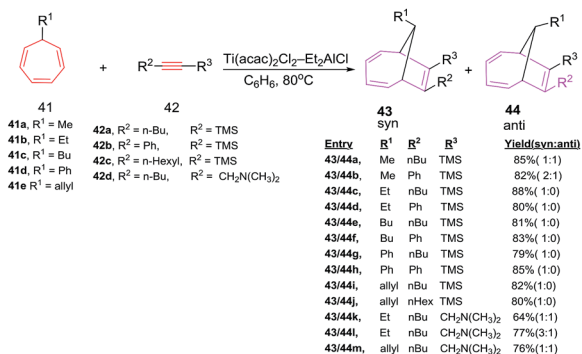
Scheme 17 [6 + 2] cycloadditions of various enol silyl ether with dicobalt acetylene complex.

bis(1,3,5-cycloheptatriene-7-yl)alkanes as 6 π -components with alkyne, 1,2-dienes, as 2 π -components to yield variety of monocyclic or condensed eight membered carbocycles. All the reported studies involve only intermolecular variants of [6 + 2] cycloadditions.

Titanium(II) catalyzed [6 + 2] cycloadditions of cycloheptatrienes with alkynes

D'yakonov *et al.* have explored the [6 + 2] cycloadditions of 7-alkyl(allyl,phenyl)-1,3,5-cycloheptatrienes **41** with alkynes **42** catalyzed by the two-component Ti(acac)₂Cl₂-Et₂AlCl system, resulting in the formation of substituted bicyclo[4.2.1]-nona-2,4,7-trienes **43/44** in excellent yields (up to 90%). The addition of alkyne **42** to the cycloheptatriene **41** (1 : 1) occurs in a stereoselective manner to afford predominantly *syn*-isomer. The [6 + 2] cycloadditions using alkyne **42** having ethyl-, butyl-, phenyl-, and allyl-substituted cycloheptatrienes **41b**, **41c**, **41d** and **41e** lead to cycloadducts **43e-j** *syn*-specificity (Scheme 18).⁴⁶

Symmetrical alkynes such as hex-3-yne, oct-4-yne and dec-5-yne are incompetent 2 π components in [6 + 2] cycloadditions and have shown competitive homo-cyclotrimerization. The [6 + 2] reactions afford bicyclic systems **43/44** using (i-PrO)₂TiCl₂



Scheme 18 Ti-catalyzed [6 + 2] cycloadditions of alkynes to 7-substituted 1,3,5-cycloheptatrienes.

and (t-BuO)₂TiCl₂ or TiCl₄ as catalysts.⁴⁶ The [6 + 2] reactions of 7-alkyl(allyl,phenyl)-1,3,5-cycloheptatrienes **41** with Si-containing alkynes **45** catalyzed by the Ti(acac)₂Cl₂/Et₂AlCl system, furnish substituted bicyclo[4.2.1]nona-2,4,7-trienes **46** in good yields (79–88%; Scheme 19).

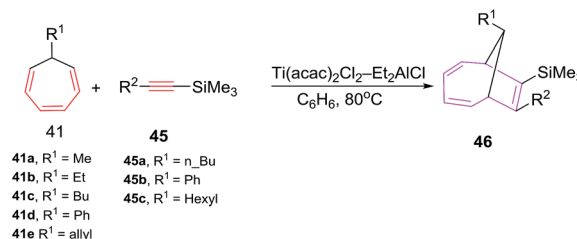
[6 + 2] cycloadditions of cycloheptatrienes with 1,2-dienes

D'yakonov *et al.* have also envisaged [6 + 2] cycloadditions of functionalized cycloheptatrienes **41** with allenes(1,2-dienes) **27** using Ti(acac)₂Cl₂-Et₂AlCl system as catalyst to generate predominantly endobicyclo[4.2.1]-nona-2,4-dienes **47a-f** in good yields.⁴⁷ The enhanced *syn* selectivity is largely attributed to the steric bulk at 7-position of CHT nucleus (Scheme 20).

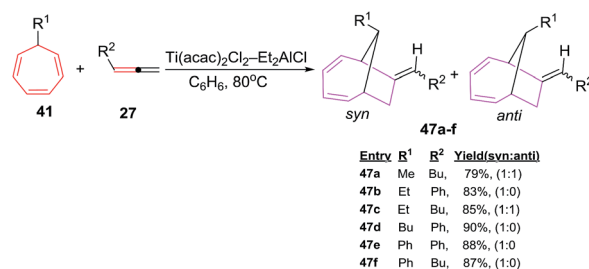
D'yakonov *et al.* have also studied [6 + 2] cycloadditions reactions using functionalized cycloheptatrienes **41** and 1,2-cyclonadiene **27f** to yield a mixture of *syn* and *anti* of isomeric tricyclo[9.4.1.0]-hexadeca-2,12,14-trienes **48a-d** (78–85%; Scheme 21).⁴⁷

[6 + 2] cycloadditions of bis(1,3,5-cycloheptatriene-7-yl)alkanes 47 and alkynes

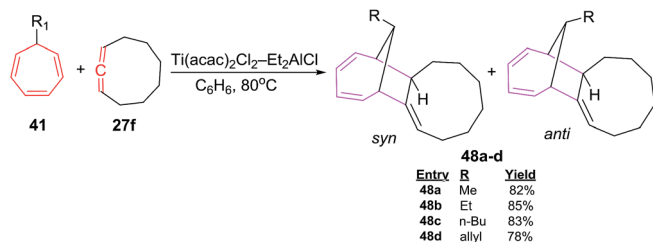
D'yakonov *et al.* have explored [6 + 2] cycloadditions of Si-containing alkynes **45** and bis(1,3,5-cycloheptatriene-7-yl)alkanes **49** using Ti(acac)₂Cl₂-Et₂AlCl as catalytic system, leading to selective formation of mono- and bis-adducts [9-[4-(2,4,6-cycloheptatrienyl)alkyl]-8-alkyl(phenyl)bicyclo[4.2.1]nona-2,4,7-triene-7-yl](trimethyl)silanes **50a-f** and bis(7-trimethylsilyl-8-alkyl(phenyl)bicyclo[4.2.1]nona-2,4,7-triene-7-yl)alkanes **51a-f** in 78–88% yields respectively. The cycloaddition reactions of alkynes **45** and bis(1,3,5-cycloheptatriene-7-yl)alkanes **49** are stereoselective, resulting in the isolation of *syn*-isomer. The high



Scheme 19 Ti-catalyzed [6 + 2] cycloadditions of silicon containing alkynes to 7-substituted 1,3,5-cycloheptatrienes (CHT).



Scheme 20 Ti-catalyzed [6 + 2] cycloadditions of 1,2-dienes to 7-substituted 1,3,5-cycloheptatrienes (CHT).

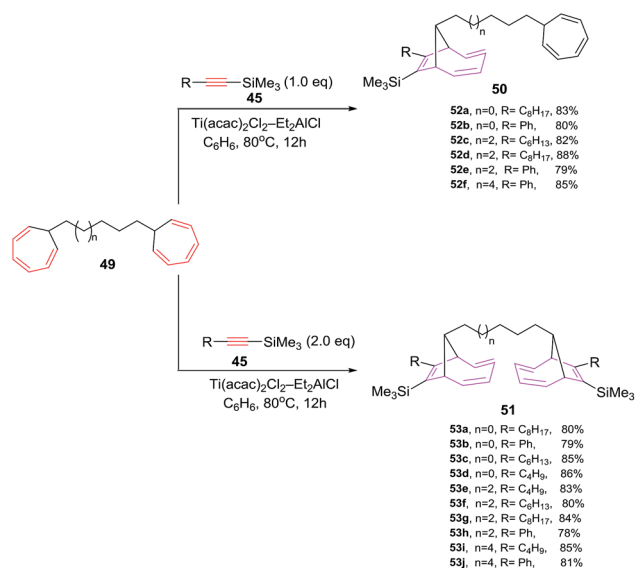


Scheme 21 Ti-catalyzed [6 + 2] cycloadditions of 1,2-cyclononadiene 7-substituted 1,3,5-cycloheptatrienes (CHT).

stereoselectivity is presumably attributable to steric factors associated with the bulky substituent at the bridging carbon atom in the initial bis(1,3,5-cycloheptatriene-7-yl)alkane **49**⁴⁸ (Scheme 22).

Platinum(II) catalyzed intramolecular [6 + 2] cycloadditions

Platinum(II) complexes have efficiently been explored in relatively less explored intramolecular variant of [6 + 2] cycloadditions to afford bicyclic cyclopentane fused bicyclo[4.2.1]nona-2,4,7-trienes. Tenaglia *et al.* have developed a facile, chemoselective and high yielding platinum-catalyzed (5 mol%) *en route* for intramolecular [6 + 2] cycloadditions of alkynes tethered to cycloheptatrienes **52a–k** at room-temperature to afford cyclopentane fused bicyclo[4.2.1]nona-2,4,7-trienes **53a–k** in good yields (66–99%). The cycloisomerizations of **52** with other metal complexes such as $[\text{RuCl}_2(\text{CO})_3]_2$ and AuCl_3 provide satisfactory results, whereas rhodium complexes are poor in catalysing these reactions. The best results are observed using PtCl_2 (5 mol%) as catalysts. The reactions are also analyzed in different solvents, such as THF (85%), acetone (91%), toluene (94%) are observed most promising solvent and cycloadditions in methanol, acetonitrile and DMF are unsuccessful. The [6 + 2] cycloaddition can tolerate variety of substitutions at



Scheme 22 Ti-catalyzed [6 + 2] cycloadditions of silicon containing alkynes with bis-1,3,5-cycloheptatrienes (CHT).

cycloheptatrienes such as CHT carrying acetal **52f**, ether **52d–e**, ester **52h–j**, sulfonate **52b**, cyclic carbonate **52g**, halide **52k** or nitrile substituents **52c** afford [6 + 2] cycloadducts in good yields. However, lengthening the tether by an additional carbon unit in **52** has a detrimental effect and no [6 + 2] cycloadduct is realised⁴⁹ (Scheme 23).

The CHT bearing internal alkynes **54a–e** have been observed reluctant participants in intramolecular [6 + 2] cycloadditions even at elevated reaction temperature (110 °C; Scheme 24).

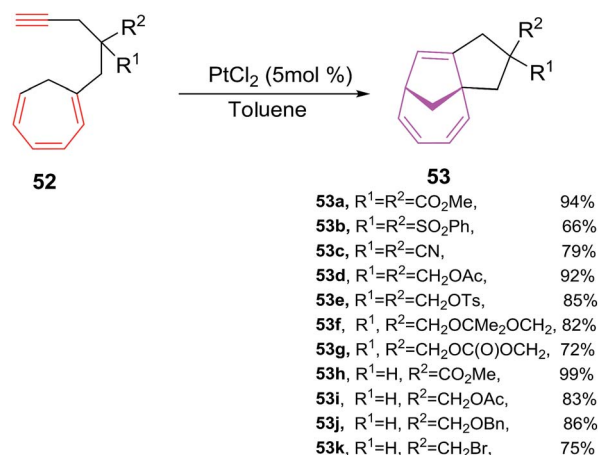
Alkyl **54a–b** and phenyl **54c** substituted trienyne are unreactive whereas, electron deficient **54d–e** afford [6 + 2] adducts **55d–e** albeit in low yields of 64% and 22% respectively.⁴⁹

The intramolecular [6 + 2] cycloisomerizations of trienyne **57a–g** bearing heteroatom in the tether yield [6 + 2] cycloadducts **58** along with the formation of side products such as dihydropyranes or tetrahydropyranes **59** via 1,2-hydrogen or alkyl migration, along with other products **60**, **61** and **62** as depicted in Scheme 25.⁴⁹

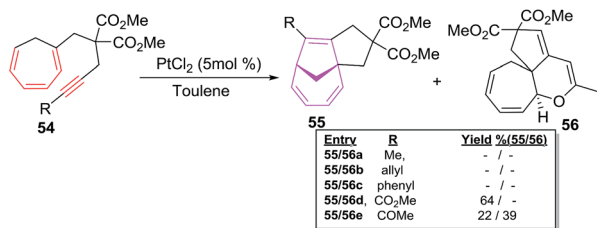
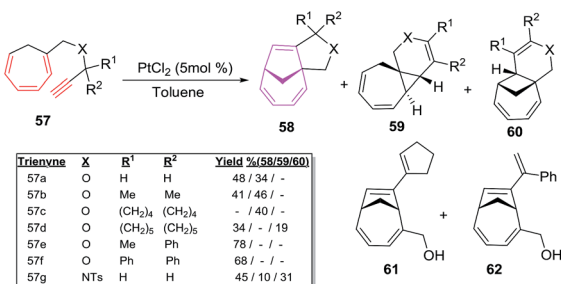
The proposed mechanism involves the *exo* cyclisations of **57** leading to pentadienyl cationic intermediate **IX** which through electronic redistribution affords [6 + 2] cycloadducts **58**. With trienyne bearing an acyl functionality, carbonyl group triggers the cyclisation of **57**, leading to dihydropyran **59**. Endocyclisation of **57** through zwitter ion **X** and platinumcarbene intermediate **XI** leads to product **59** presumably through a 1,2-hydrogen/alkyl shift followed by the elimination of metal ion. Formation of **60** is owed to the coordination of Pt^{2+} species to distant double bond of **59** followed by ring cleavage of the cyclopropane moiety. The tetrahydropyran ring opening of **58c/58e** driven by HCl (generated from PtCl_2) affords tertiary allylic carbocation yielding products **61** and **62** respectively⁴⁹ (Fig. 9).

Ruthenium(0) catalyzed [6 + 2] cycloadditions of cyclooctatriene (COT) with alkenes

Mitsudo *et al.* have envisaged [6 + 2] cycloaddition reactions of ruthenium(0) complex such as $\text{Ru}(\eta^4\text{-cod})(\eta^6\text{-cot})$ **63** with



Scheme 23 PtCl_2 -catalyzed [6 + 2] cycloadditions of alkynes tethered to cycloheptatrienes **54**.

Scheme 24 PtCl₂-catalyzed [6 + 2] cycloadditions of trienyynes 54a–e.Scheme 25 PtCl₂-catalyzed [6 + 2] cycloadditions of heteroatom tethered trienyynes 57a–g.

maleic anhydride **64a** or maleimides **64b–e** to generate a series of novel divalent ruthenacycles **65a–e**. The reaction proceeds by employing equivalent amounts of both reactants in *n*-hexane as solvent for 2 h to afford ruthenacycles **65a–e**⁵⁰ (Scheme 26).

Mitsudo *et al.* have also studied electron deficient alkenes such as dimethyl fumarate and dimethyl maleate in [6 + 2] cycloadditions to afford Ru(η^5 -cot)(η^2 -dimethyl fumarate).⁵¹ Employing *p*-benzoquinone in place of maleic anhydride produces an uncharacterizable mixture of products. *N,N*-Dimethylacrylamide and methyl vinyl ketone are ineffective in conceiving these reactions. Terminal alkynes on the other hand have afforded a zerovalent η^4, η^2 -bicyclodecatriene product.⁵² The proposed mechanism for the production of ruthenacycles **65** involves the change of coordination mode of COT ligand from **63** from 1-6- η^6 to 1-2:5-6- η^4 or 1-4- η^4 followed by **64** occupying

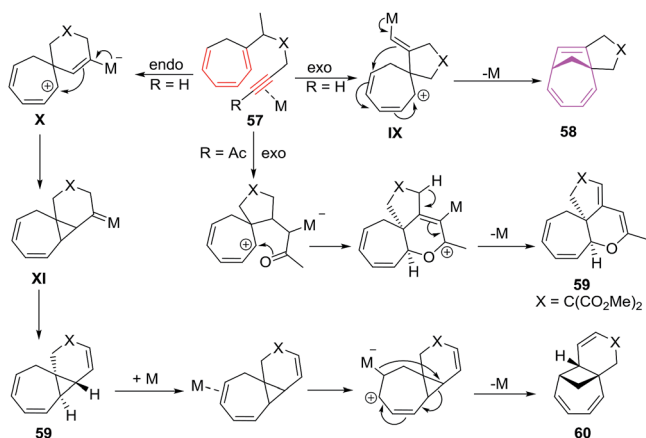


Fig. 9 Proposed mechanism for cycloisomerisations of trienyynes.

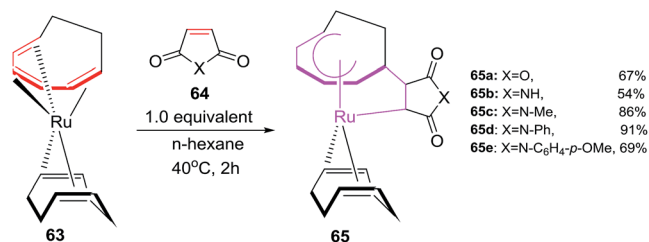
its vacant coordination site to either produce intermediate **XIIa** or **XIIIa**. The oxidative cyclisation of COT and **64** generates ruthenacycles intermediates **XIIb** and **XIIIb**, which re-coordinates of the C=C bond affording desired ruthenacycles **65** (Fig. 10).⁵⁰

The ruthenacycles **65a–e** react in a number of ways to create cyclooctyl complexes **66–70** respectively. The ruthenacycles **65d**, for example, on hydrogenation at 1 atm pressure affords *N*-phenylcyclooctylsucciniimide **66** in overall yields of 56%. The treatment of **65d** with HCl in Et₂O, however, have resulted in the formation of *N*-phenyl(3,5-cyclooctadien-1-yl)succiniimide **67** in 62% yield using mild reaction conditions. The ruthenacycle **65d** undergoes ring closure *via* reductive elimination at high temperature to afford tricyclic [6 + 2] cycloadduct **68**. Introduction additives such as PPh₃ promotes the production of **68** from **65d**, while 1,2-bis(diphenylphosphino)ethane (dppe) does not yield **68**, instead stable ruthenacycle **69** is formed (71%) presumably *via* ligand displacement between COD and dppe. The reaction of **65d** with CO in toluene at 1 atm pressure for 3 h have resulted in the isolation of tetracarbonyl ruthenacycle complex **70** in an overall yield of 76%. The reaction proceeds with full dissociation of COD ligand from **65d** followed with the insertion of three molecules of CO coordinated to Ru along with cycloheptadienyl hapticity change from the change η^5 to η^3 . The theoretical studies have also been carried to support the experimental results (Scheme 27).⁵⁰

Cu(II) catalysed [6 + 2] cycloaddition reactions

Dethe *et al.* have recently studied highly regio- and diastereoselective facile, one pot Lewis acid catalysed [6 + 2] cycloaddition reactions for the synthesis of highly substituted pyrrolo [1,2-*a*]indoles having three contiguous stereocenters. The reactions of indole alcohol **71a–d** with conjugated indole ester **72a–e** in the presence of 5 mol% Cu(OTf)₂ afford pyrroloindoles **73a–j** and **74a–j** in excellent overall yields of 85–92% with outstanding regio- and diastereoselectivity⁵³ (Scheme 28).

The ester moiety in case of **72** is crucial in controlling diastereoselectivity in these cycloadditions. Other Lewis acid catalysts such as TiCl₄, BF₃–Et₂O, FeCl₃, AlCl₃, Sn(OTf)₂ and Fe(OTf)₃ have resulted in poor diastereoselectivity of 11 : 1, 14 : 1, 4 : 1, 3 : 1, 7 : 1 and 6 : 1 for products **73/74**. The methodology has also been used for the construction of the fully functionalized tricyclic core of bioactive natural product yuremamine which has been isolated from the stem bark of

Scheme 26 Formation of ruthenacycles **67** *via* oxidative cyclisations.

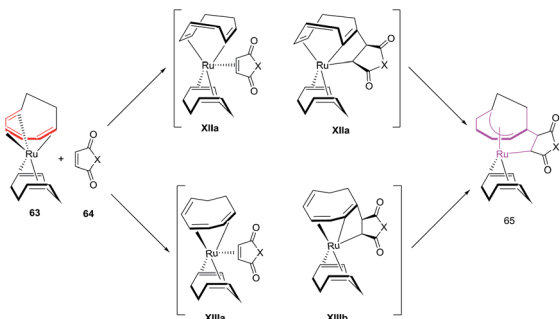
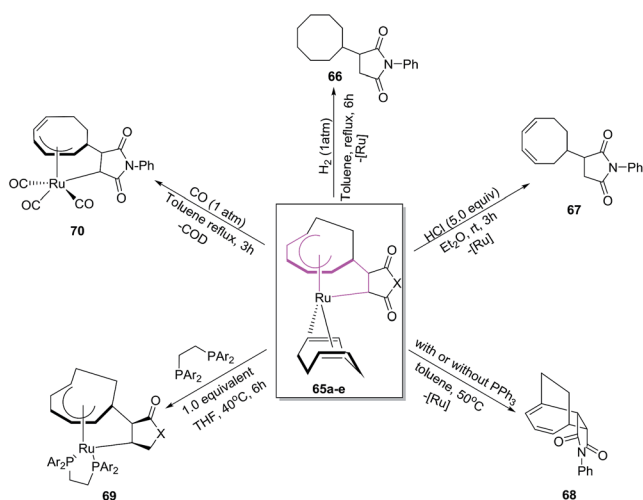


Fig. 10 Proposed mechanism for formation of ruthenacycles 65.



Scheme 27 Reactivity of ruthenacycle 65.

Mimosa hostilis having hallucinogenic and psychoactive effects⁵⁴ (Fig. 11).

Chromium catalysed [6 + 2] cycloaddition reactions

Chromium(0) complexes are also been tested in [6 + 2] cycloadditions and a single report on Cr(0) catalysed [6 + 2] cycloadditions is disclosed by Rigby *et al.* It involves the development of resin supported chromium(0) catalytic system and their use as catalyst in [6 + 2] cycloadditions of cycloheptatriene (CHT) with variety of alkenes. The resin based chromium catalyst

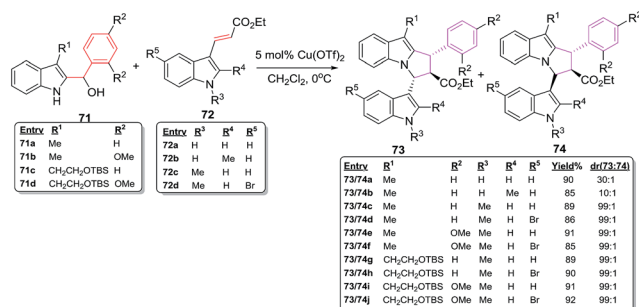
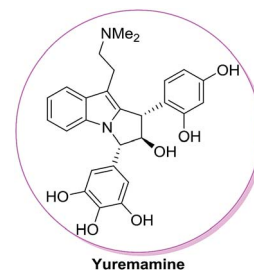
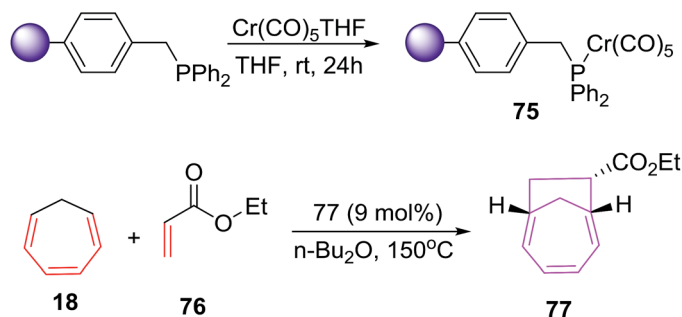
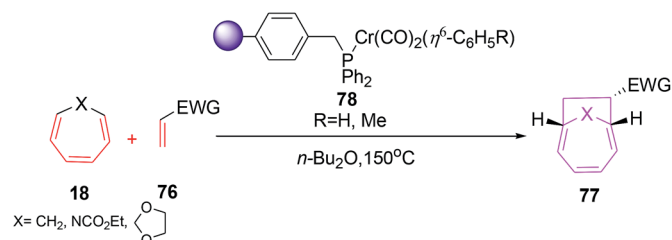
Scheme 28 Cu(OTf)₂ catalysed [6 + 2] cycloadditions reactions of 71 and 72.

Fig. 11 Structure of yuremamine.



Scheme 29 [6 + 2] cycloadditions of CHT with ethyl acrylate catalysed by solid supported chromium(0) complex.



Scheme 30 [6 + 2] cycloadditions of CHT with ethyl acrylate catalysed by solid supported chromium(0) complex.

prepared from chloromethylated polystyrene (PS-DVB) (Merri-field resin, 2% cross linked) 75 (9 mol%) catalyses the [6 + 2] cycloadditions of CHT 18 with excess ethyl acrylate 76 to afford bicyclo[4.2.1]nona-2,4-diene 77 in 59% yield. However, the catalytic system has a serious drawback of recyclability owing to thermal denaturation of the catalytic systems (Scheme 29).

Replacing chromium coordination sphere to $\eta^6\text{-C}_6\text{H}_5$ has marked effect on its multiple recyclability by simple filtration followed by washing with non polar solvents (Scheme 30).⁵⁵ The catalyst 78 affords [6 + 2] cycloadditions in excellent yield (64–92%) in the reactions of CHT 18 with various electron rich trienophiles.⁵⁶

Conclusion

In conclusion, the present review summarises transition metal catalysed [6 + 2] cycloaddition reactions that have appeared in literature since 2000. Various inter and intramolecular versions have been explored employing various substrates contributing

as 6π component promoted by different transition metal catalysts. The developed methodologies have provided a facile access to mono- and bicyclic carbo-/heterocyclic eight membered core structures which are otherwise difficult to achieve. Although, the developed protocols have provided an informal to functionalised ring systems, but, the true potential of $[6 + 2]$ cycloadditions still need to be scrutinized so as to access its regio and stereoselective versions under milder reaction conditions. Copper, ruthenium, chromium and platinum based complexes have made entry to the list of metals catalysed $[6 + 2]$ cycloadditions, but the detailed studies on such metals catalysed $[6 + 2]$ cycloaddition involving other prevalent substrates as 6π components still need to be explored. Moreover, the semicyclic variants of 6π components in transition metal catalysed still need to be studied. The studies on $[6 + 2]$ cycloadditions involving different heterodienophiles also need to be explored. Hence, $[6 + 2]$ cycloadditions have an enormous potential for the synthesis of eight membered monocyclic or fused heterocyclic systems.

The authors have tried to recapitulate most of the reports appearing within the stipulated time frame, nonetheless there will always be some experts missing for which we deeply apologize.

Conflicts of interest

There are no conflicts to declare.

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