REVIEW

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**), cyclooctatetrenes (**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 skeletons[1] 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][5,14] 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 reaction[16] 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-vinyl-cyclobutanones, allenals, allenylcyclobutanes, cyclooctatrienes *etc.* have been reported as 6π-components in Rh(I) catalysed [6 +
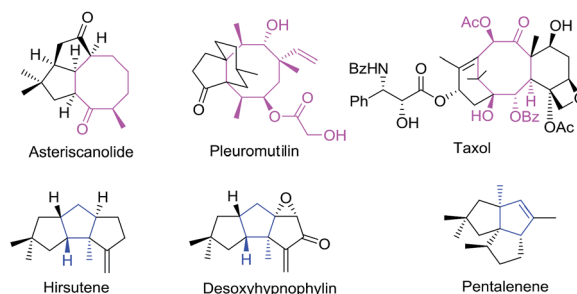
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Fig. 1 Carbocycles in natural products.

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

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

One of the earliest reports on Rh(ɪ) 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(ɪ)-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(ɪ)-catalyzed intramolecular [6 + 2] cycloadditions of alkyne/alkene tethered allenal **3a–j** using Rh(ɪ)-complex as catalyst. [Rh(I-Mes)(cod)]ClO$_4$ is an effective catalyst in these [6 + 2] cycloadditions.[19] The use of other Rh(ɪ) complexes as catalyst such as [Rh(IiPr)(cod)]ClO$_4$, [Rh(IPr)(cod)]ClO$_4$ and [Rh(IMes)(cod)]ClO$_4$ afford bicyclic ketones in lower yields and [Rh(dppe)]ClO$_4$ is

completely ineffective in conceiving [6 + 2] reactions. The [6 + 2] cycloadditions using RhCl(PPh$_3$)$_3$ 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(ɪ) 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**[10c] and formation of **11** by trimerization of alkyne **8** (Scheme 4).

The [Rh(SIMes)(cod)]ClO$_4$ have been found to be efficient in conceiving intermolecular reactions with the selective formation of eight membered carbocycle **9** (68%). The [Rh(IMes)(cod)]ClO$_4$ as catalyst is non selective and afford mixture of eight
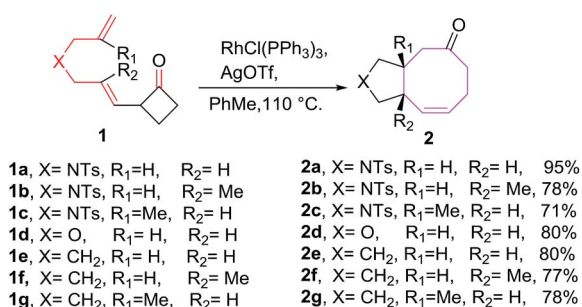
Scheme 1 Rh(ɪ) catalysed [6 + 2] cycloaddition reactions of tethered alkenes with cyclobutanones.
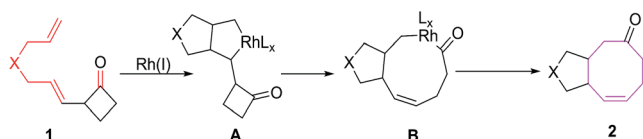

Fig. 2 Plausible mechanism for synthesis of eight-membered condensed carbocycles.
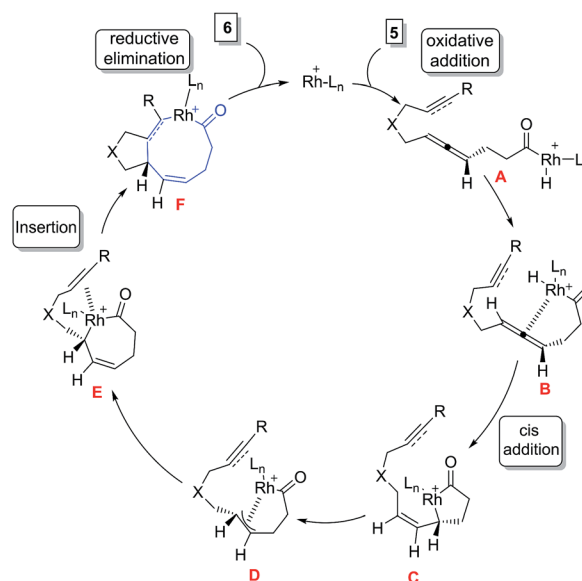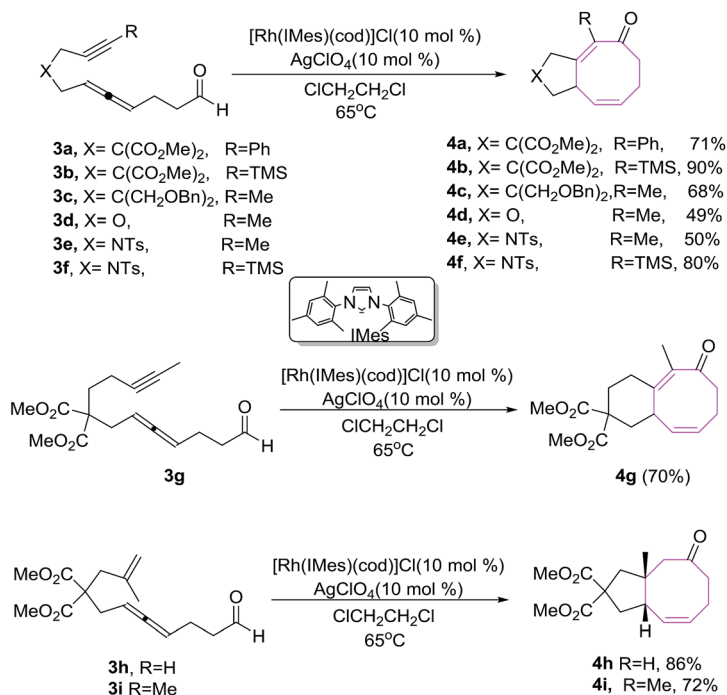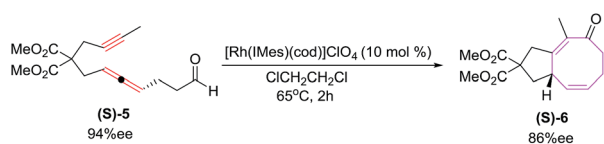

Fig. 3 Proposed mechanism for rhodium catalysed [6 + 2] cycloaddition reactions of allenals.
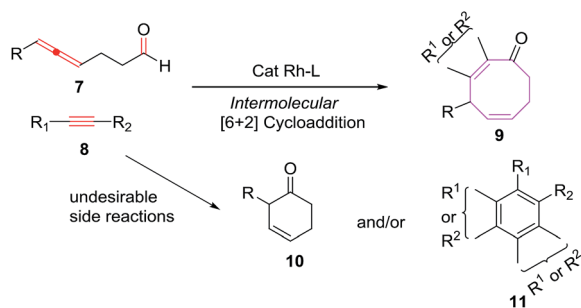
Scheme 2 Rh(I)-catalyzed [6 + 2] cycloaddition of alkene tethered allenal.

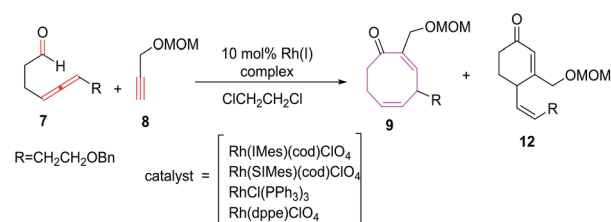**Scheme 3** Rh(I)-catalyzed [6 + 2] cycloaddition of alkyne tethered allenal.

Scheme 4 Intermolecular [6 + 2] cycloadditions.

however, provide regiomeric 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 regiomeric 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).

membered carbocycle **9** (61%) and six-membered carbocycle **12** (19%). Other tested catalysts such as [RhCl(PPh$_3$)$_3$] and [Rh(dppe)]ClO$_4$ 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**,
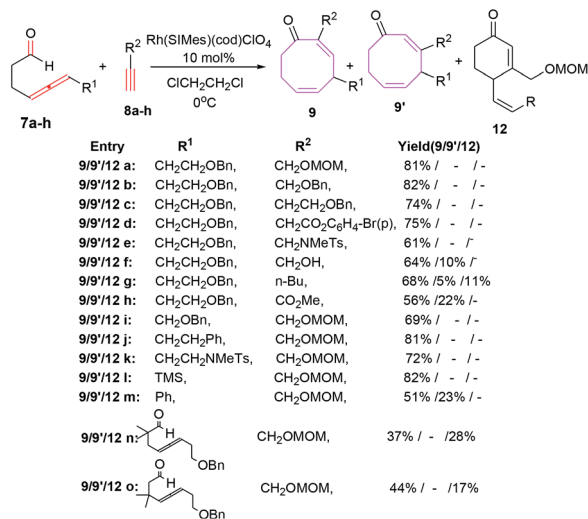
**Scheme 5** Intermolecular [6 + 2] cycloadditions using various Rh(I) complexes.

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

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

Mukai *et al.* have devised a cycloisomerisation methodology using rhodium(ɪ) 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 6π-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(ɪ) 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]
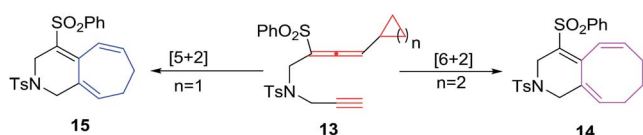
Scheme 7 Rh(ɪ) catalysed [6 + 2] reactions of unfunctionalised alkyne-allenyl cyclopropane/butane.
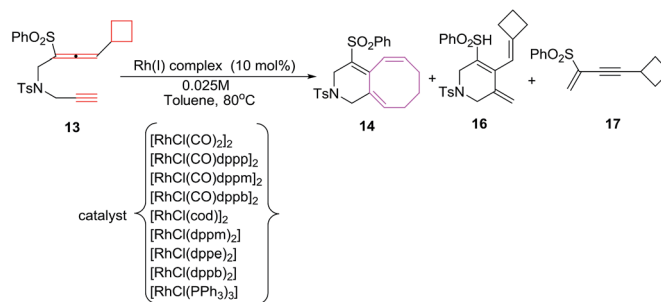
Scheme 8 Cycloadditions of alkyne-allenyl cyclobutane **13** in different Rh(ɪ) complexes.

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(ɪ) 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 confirmations 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] chromium[30] and iron[31] complexes have been widely used to perceive such reactions.
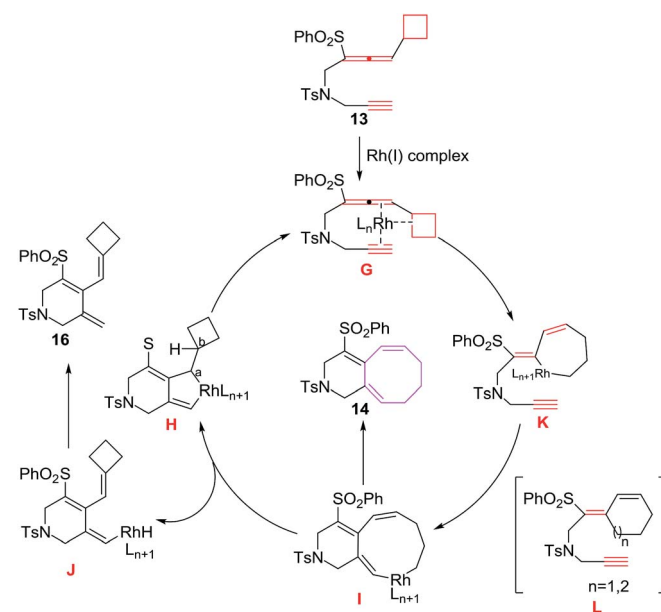

Fig. 4 Proposed mechanism for the formation of **14**.

Mach *et al.* have engaged Ziegler catalyst (TiCl$_4$/Et$_2$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 akynes[34] and **CHT** to substituted allenes.[35]

Wang *et al.* have explored [6 + 2] cycloadditions of cyclo-heptatriene **18** with internal alkynes **19** employing different rhodium(I) catalysts. The [6 + 2] cycloadditions do not occur using PPh$_3$RhCl as catalyst at 60 °C.[36] The [6 + 2] cycloadditions at elevated temperature (120 °C) witness the formation of cyclo-adduct (64%). Further increase in reaction temperature causes decrease in yield of **20** (53%). Introducing additives such as CuI (10 mol%) which acts as phosphine cleavage reagent[37] have increased the yield of **20** (75%). Exchanging the catalyst to [Rh(COD)Cl]$_2$ steers the reaction to better results (71%). Best results for [6 + 2] cycloadditions (88%) are witnessed using [Rh(COD)Cl]$_2$ as catalyst along with PPh$_3$ (10 mol%) and CuI (10 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 [Rh(COD)Cl$_2$] to (Ph$_3$P)Rh(COD)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
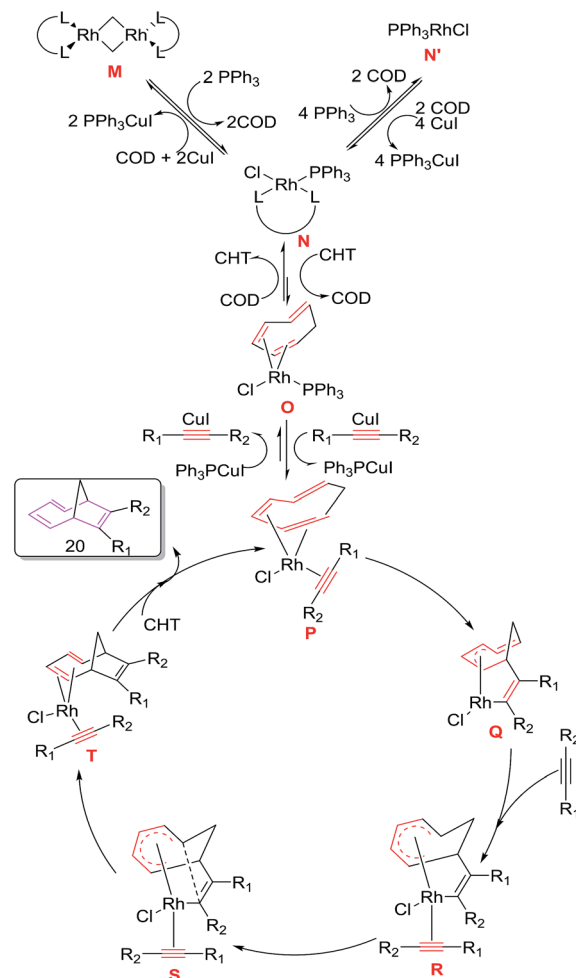

Fig. 5 Proposed Mechanism for rhodium catalysed [6 + 2] cycloaddition reaction of **CHT** with internal alkyne.

intermediate **T**. Ligand exchange of **T** with **CHT** delivers cyclo-adduct **20** and regenerates rhodium complex **P** to renter the catalytic cycle. DFT calculations employing M06 function taking Rh(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

Co(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 Co(I) catalysed intramolecular [6 + 2] cycloadditions are scarcely available in literature.

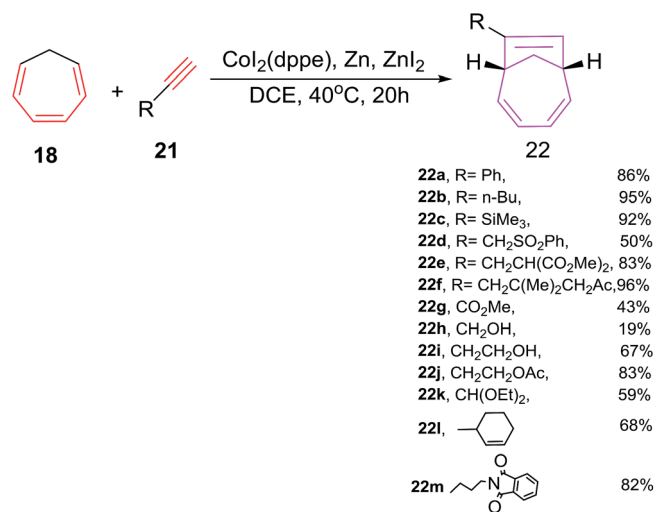## [6 + 2] cycloadditions of cycloheptatriene (CHT) and alkynes

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 systems[39] have been tested for [6 + 2]
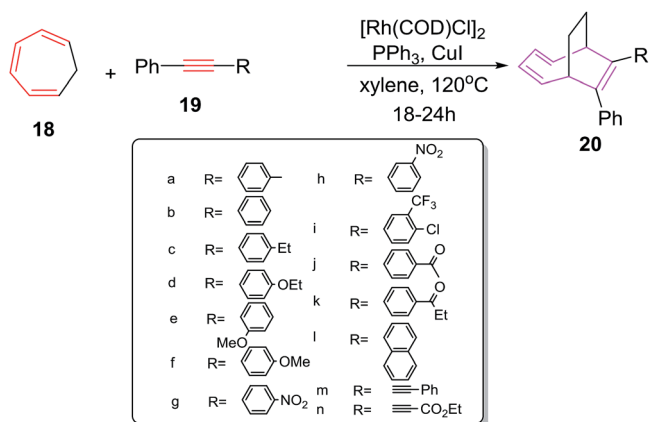
Scheme 9 [6 + 2] cycloaddition of **CHT** with various alkynes.

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

Fig. 6 Proposed Mechanism for cobalt catalysed [6 + 2] cycloadditions 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 CoI_2(dppe)/Zn/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 CoL_2I_2 by zinc metal to cationic $[Co(I)L_2]^+$complex which coordinates with alkyne 21 and CHT 18 followed by oxidative cyclo-metalation to produce cobalta-cyclopentene intermediate U.1,5-migration of the C(sp^3)–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 $[Co(I)L_2]^+$to return to the catalytic cycle[38] (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] cyclo-additions of cycloheptatriene (CHT) 18 with variety of allenes 23 to afford bicyclic 7-bicyclo[4.2.1]nona-2,4-dienes 24 with an

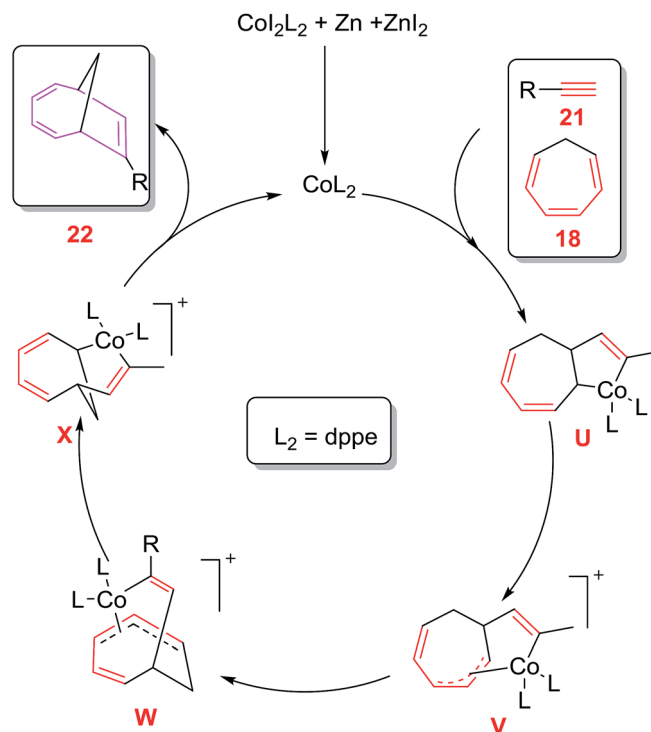improved yield, enhanced regio- and geometrical selectivity (Scheme 11). The treatment of CHT 18 with phenylallene 23a under CoI_2(dppe)/Zn powder/ZnI_2 as catalytic system have resulted in an exclusive formation of E-isomer of 7-benzylidenebicyclo[4.2.1]nona-2,4-diene 24a without the isolation of even 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(diphenyl-phosphino)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 CoI_2(dppe) catalytic system with Zn/ZnI_2 reducing agent in 1,2-dichloroethane as solvent.[40]
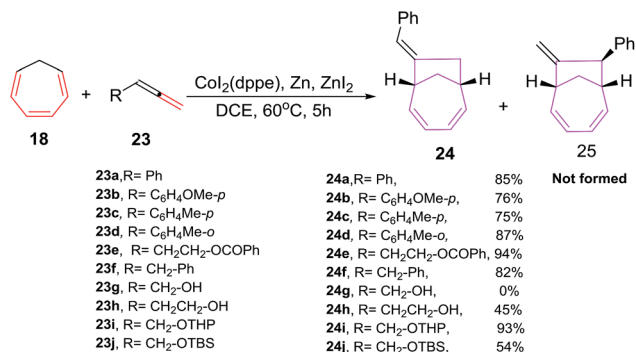
Scheme 11 Cobalt catalysed [6 + 2] reactions of CHT with substituted allenes.

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 selectivity[40] (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 CoI$_2$/dppe/Zn/ZnI$_2$ 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 CoI$_2$ or ZnI$_2$ alone do not conceive the reactions even at elevated temperature (100 °C).
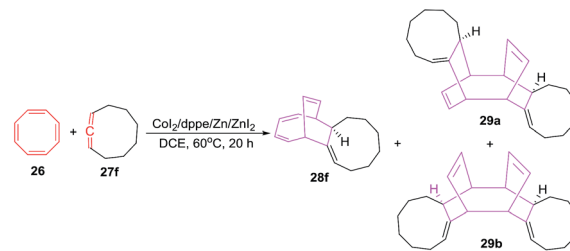
The [6 + 2] cycloadditions of **COTT 26** with 1,2-cyclononadiene **27f** under similar reaction conditions afford tricyclo [9.4.2.0]heptadeca-2,12,14,16-tetraene **28f** in 65% yield. Interestingly, the reactions also proceed further to produce regio- and strereomeric bis-adduct mixture **29a** and **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 CoI$_2$(dppe) as catalyst/ligand and ZnI$_2$/Zn as Lewis acid/reducing agent couple in 1,2-
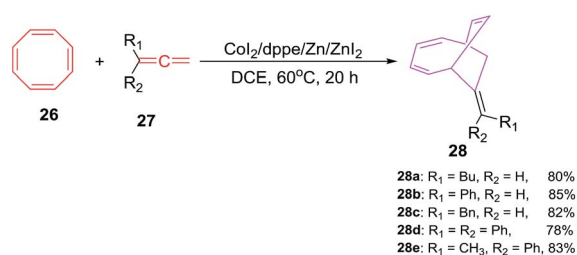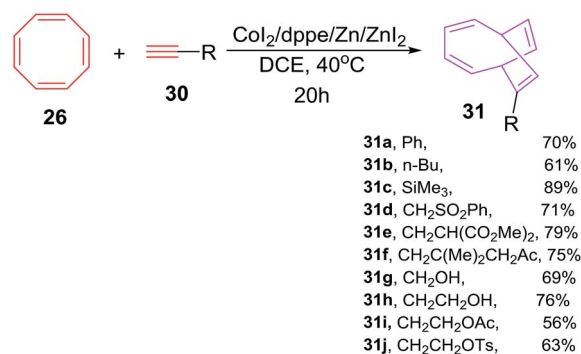

Scheme 13 Cobalt(II) catalysed [6 + 2] cycloaddition reactions of COTT with cyclic allene.

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 CoI$_2$(dppe), Bu$_4$NBH$_4$/ZnI$_2$ 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]
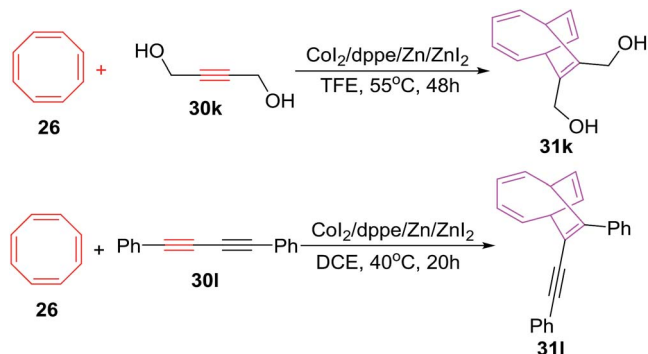
The cobalt-catalyzed cycloadditions of cyclooctatrienes (COT) **32** with various alkynes **30a–e** afford a mixture of desired [6 + 2] cycloadducts **33a–e** and tricyclic adduct **34a–e**. The absence of cycloadducts of type **35** and **36** from the product range rules out the possible [4 + 2] cycloaddition 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 6π 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).

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

28a: R$_1$ = Bu, R$_2$ = H,   80%
28b: R$_1$ = Ph, R$_2$ = H,   85%
28c: R$_1$ = Bn, R$_2$ = H,   82%
28d: R$_1$ = R$_2$ = Ph,   78%
28e: R$_1$ = CH$_3$, R$_2$ = Ph, 83%

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

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%
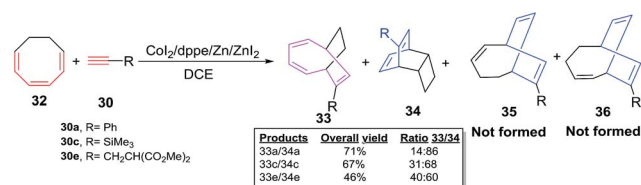**31j**, CH$_2$CH$_2$OTs,   63%

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

Scheme 16 Cobalt-catalyzed [6 + 2] cycloadditions of cyclo-octatriene (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 cobaltabicycle **V**, which on reductive elimination of cobalt affords cycloadduct **31/33** and regenerates active $[CoL_2]^+$ to renter 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 cobaltabicycle adduct **V**. Formation of [4 + 2] cycloadduct proceeds *via* sequential oxidative cyclo-metallation, alkyne insertion and reductive elimination of intermediate **VII** and **VIII** leading to product **34** (Fig. 8).[42]
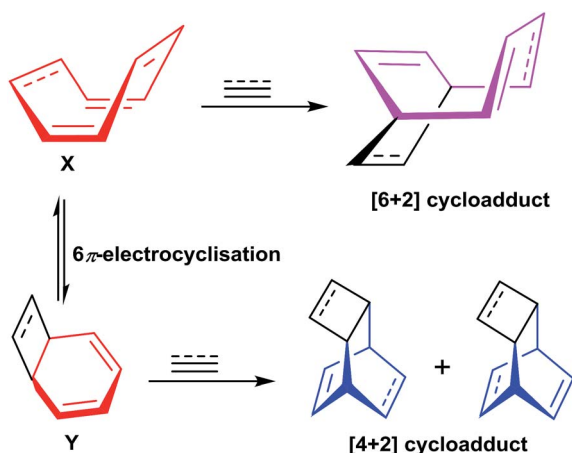
[6 + 2] cycloadditions of dicobalt acetylene complex with enol silyl ethers

Tanino *et al.* have developed methodology for the stereo-selective 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 $EtAlCl_2$.

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,
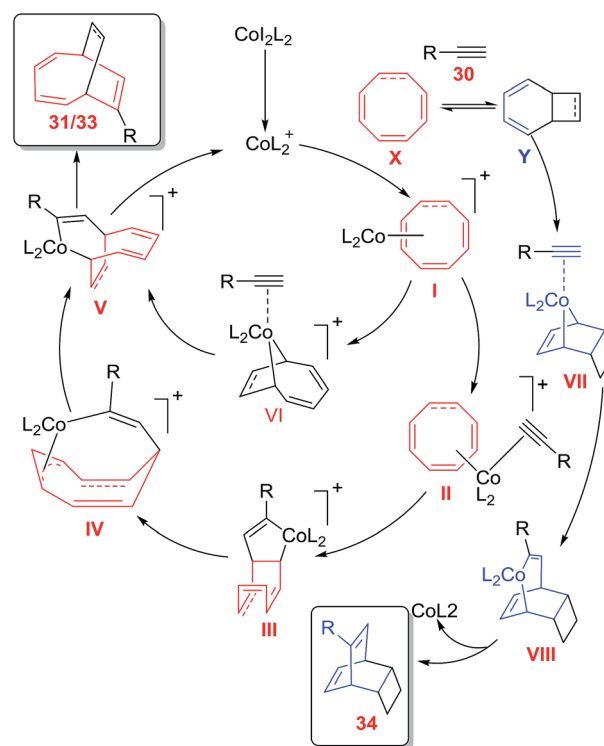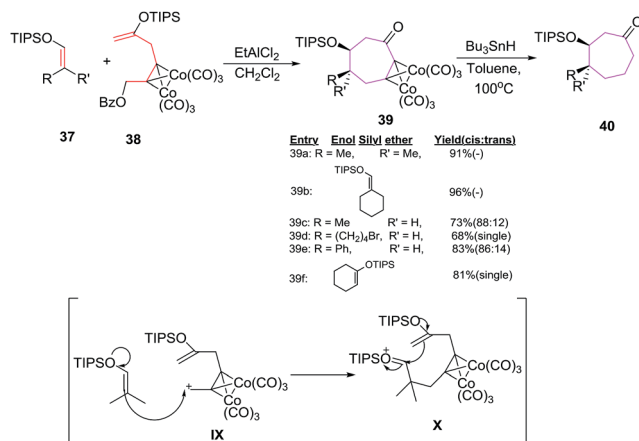

Fig. 7 Valance tautomeric forms of COT/**COTT** and their participation in cycloadditions with alkynes.

Fig. 8 Proposed mechanism for cobalt catalysed 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)lkanes as 6π-components with alkyne, 1,2-dienes, as 2π-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)$_2$Cl$_2$–Et$_2$AlCl 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 **43c–j** *syn*-specificity (Scheme 18).[46]

Symmetrical alkynes such as hex-3-yne, oct-4-yne and dec-5-yne are incompetent 2π components in [6 + 2] cycloadditions and have shown competitive homo-cyclotrimerization. The [6 + 2] reactions afford bicyclic systems **43/44** using (i-PrO)$_2$TiCl$_2$
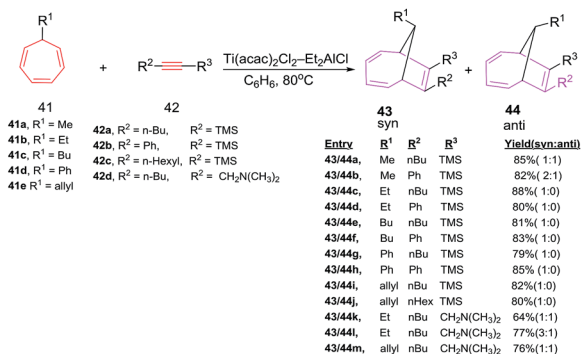
and (*t*-BuO)$_2$TiCl$_2$ or TiCl$_4$ as catalysts.[46] The [6 + 2] reactions of 7-alkyl(allyl,phenyl)-1,3,5-cycloheptatrienes **41** with Si-containing alkynes **45** catalyzed by the Ti(acac)$_2$Cl$_2$/Et$_2$AlCl system, furnish substituted bicyclo[4.2.1]nona-2,4,7-trienes **46** in good yields (79–88%; Scheme 19).
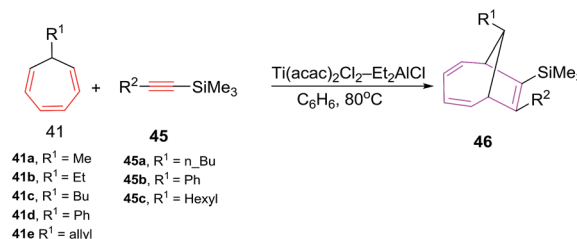
[6 + 2] cycloadditions of cycloheptatrienes with 1,2-dienes

D'yakonov *et al.* have also envisaged [6 + 2] cycloadditions of functionalized cycloheptatrienes **41** with allenes(1,2-dienes) **27** using Ti(acac)$_2$Cl$_2$–Et$_2$AlCl 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 cyclononadiene **27f** to yield a mixture of *syn* and *anti* of isomeric tricycle[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)lkanes 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)$_2$Cl$_2$–Et$_2$AlCl 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-trien-7-yl](trimethyl)silanes **50a–f** and bis(7-trimethylsilyl-8-alkyl(phenyl)bicyclo[4.2.1]nona-2,4,7-trien-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
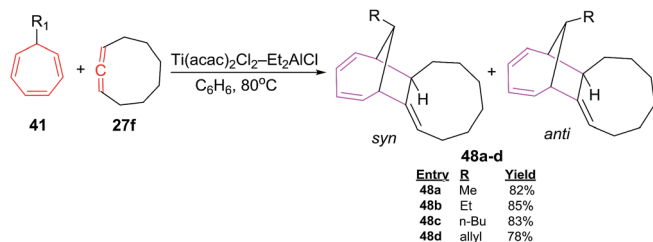

Scheme 19 Ti-catalyzed [6 + 2] cycloadditions of silicon containing alkynes to 7-substituted 1,3,5-cycloheptatrienes (**CHT**).

Scheme 18 Ti-catalyzed [6 + 2] cycloadditions of alkynes to 7-substituted 1,3,5-cycloheptatrienes.
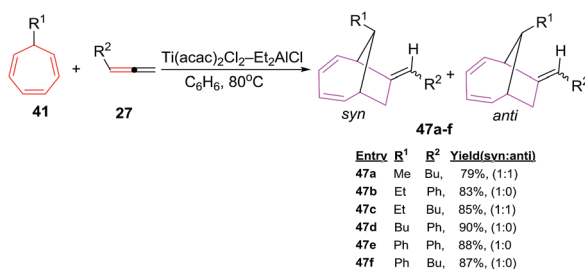
Scheme 20 Ti-catalyzed [6 + 2] cycloadditions of 1,2-dienes to 7-substituted 1,3,5-cycloheptatrienes (**CHT**).

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 has 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 [{RuCl$_2$(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

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 realised[49] (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 trienynes 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] cycloisomerisations of trienynes **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 trigger the cyclisation of **57**, leading to dihydropyran **59**. Endocyclisation of **57** through zwitter ion **X** and platinacarbene 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** respectively[49] (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 Ru(η^4-cod)(η^6-cot) **63** with
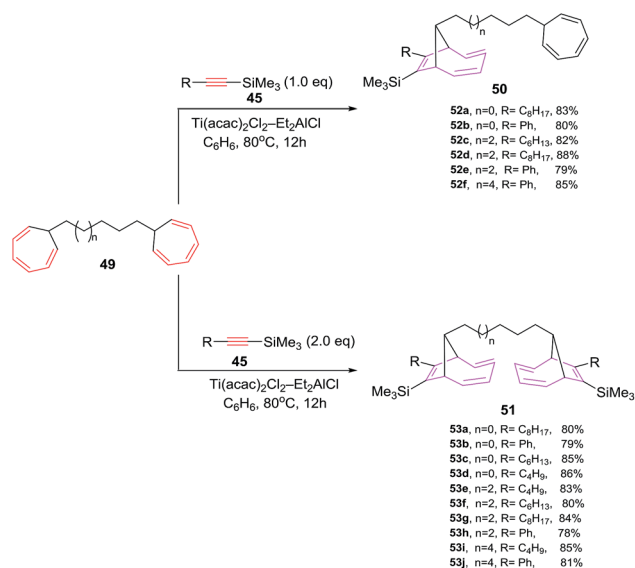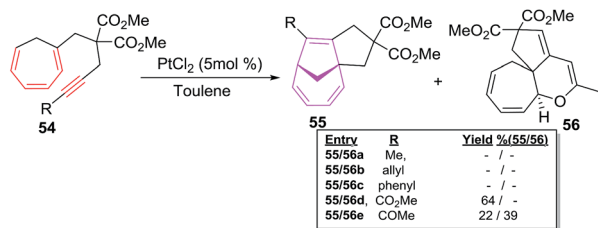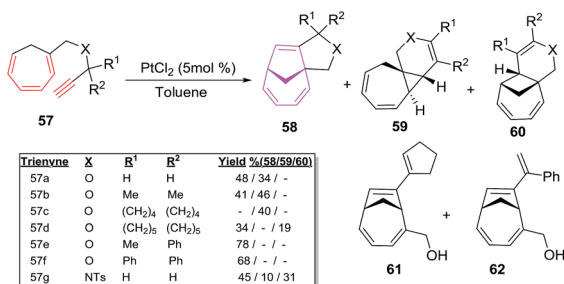

Scheme 22 Ti-catalyzed [6 + 2] cycloadditions of silicon containing alkynes with bis-1,3,5-cycloheptatrienes (**CHT**).
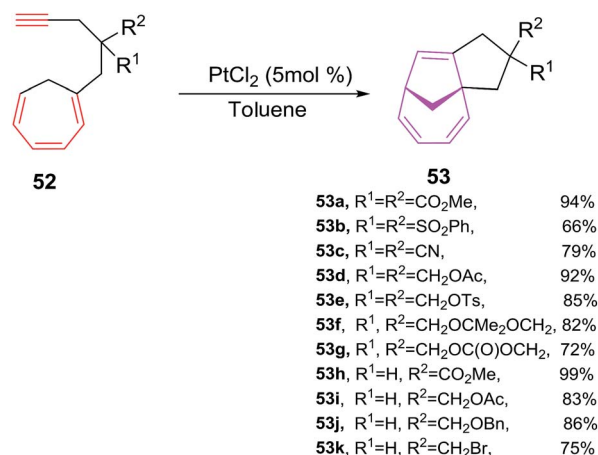
Scheme 23 PtCl$_2$-catalyzed [6 + 2] cycloadditions of alkynes tethered to cycloheptatrienes **54**.

Scheme 24 PtCl$_2$-catalyzed [6 + 2] cycloadditions of trienynes 54a–e.

Scheme 25 PtCl$_2$-catalyzed [6 + 2] cycloadditions of heteroatom tethered trienynes 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 of **63** from 1-6-η^6 to 1-2:5-6-η^4 or 1-4-η^4 followed by **64** occupying
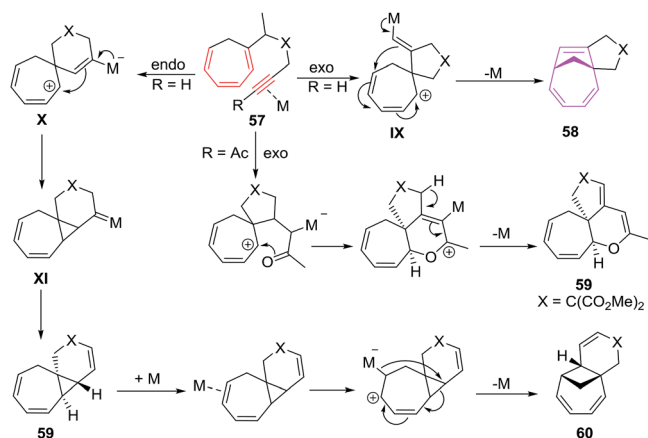
its vacant coordination site to either produce intermediate **XIIa** or **XIIIa**. The oxidative cyclisation of COT and **64** generates ruthenacycles intermediates **XIIb** and **XIIIb**, which re-coordinates of the C=C bond affording desired ruthenacycles **65** (Fig. 10).[50]

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 Et$_2$O, 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 PPh$_3$ 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 ticarbonyl 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 hapicity 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 diastereoselectivity[53] (Scheme 28).

The ester moiety in case of **72** is crucial in controlling diastereoselectivity in these cycloadditions. Other Lewis acid catalysts such as TiCl$_4$, BF$_3$–Et$_2$O, FeCl$_3$, AlCl$_3$, 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

Fig. 9 Proposed mechanism for cycloisomerisations of trienynes.
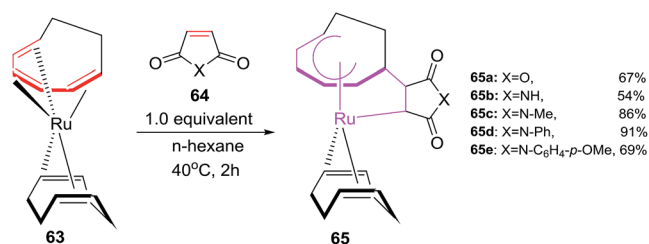
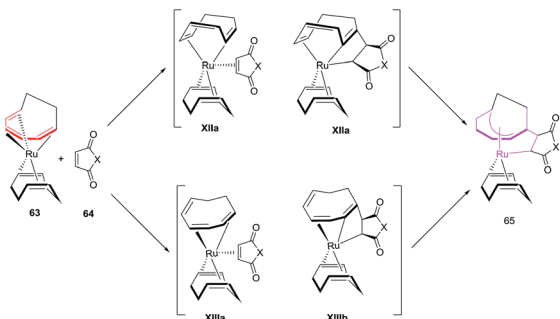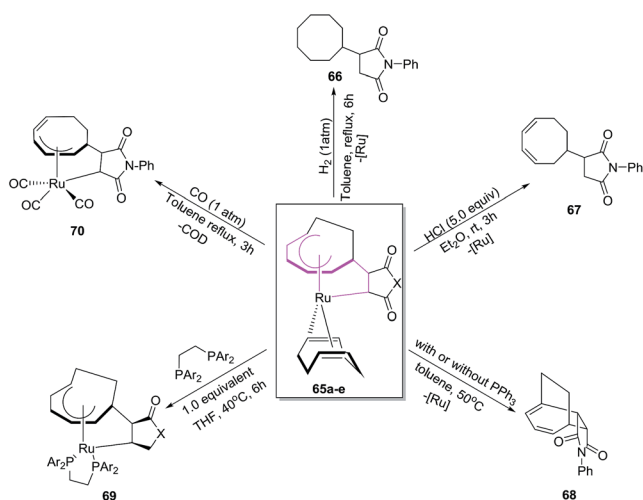Scheme 26 Formation of ruthenacycles 67 *via* oxidative cyclisations.

Fig. 10 Proposed mechanism for formation of ruthenacycles **65**.

Scheme 27 Reactivity of ruthenacycle **65**.

Mimosa hostilis having hallucinogenic and psychoactive effects[54] (Fig. 11).

Chromium catalysed [6 + 2] cycloaddition reactions

Chromium(0) complexes are also been tested in [6 + 2] cyclo-additions and a single report on Cr(0) catalysed [6 + 2] cyclo-additions 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
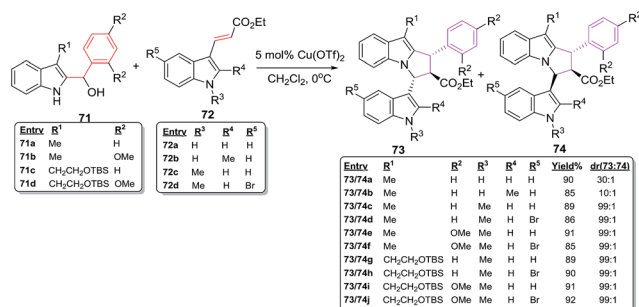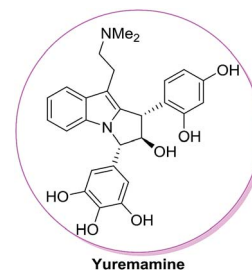

Scheme 28 Cu(OTf)$_2$ catalysed [6 + 2] cycloadditions reactions of **71** and **72**.

Fig. 11 Structure of yuremamine.
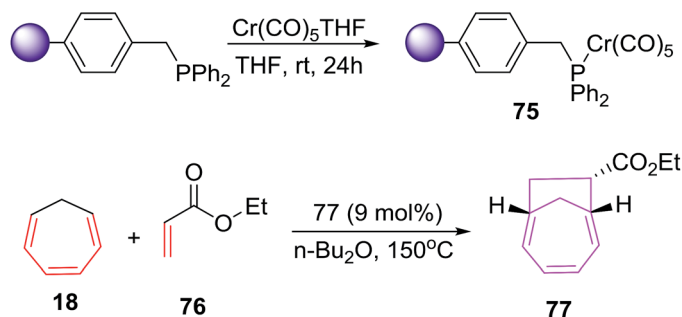
Scheme 29 [6 + 2] cycloadditions of **CHT** with ethyl acrylate catalysed by solid supported chromium(0) complex.
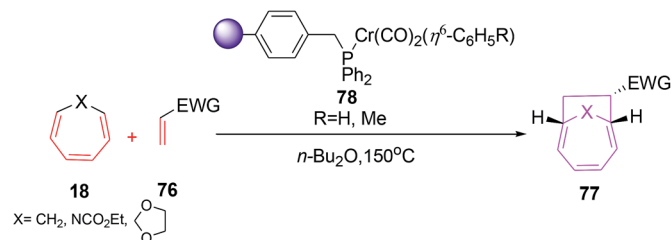
Scheme 30 [6 + 2] cycloadditions of **CHT** with ethyl acrylate catalysed by solid supported chromium(0) complex.

prepared from chloromethylated polystyrene (PS-DVB) (Merrifield 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 η^6-C$_6$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 stereselective 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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