

CATALYTIC ASYMMETRIC INTRAMOLECULAR PAUSON-KHAND AND PAUSON-KHAND-TYPE REACTIONS

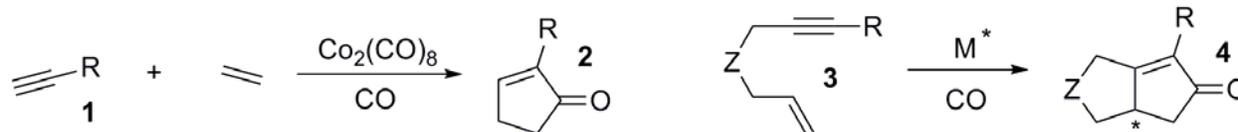
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INTRODUCTION

First reported in 1973 by I. U. Khand and P. L. Pauson, the cobalt-mediated carbonylative [2+2+1] cycloaddition of an alkyne, **1**, an alkene, and carbon monoxide to afford a cyclopentenone, **2**, is referred to as the Pauson-Khand reaction (PKR) (Scheme 1).^{1,2} Since its inception, the PKR has gained interest in the synthetic community and shows increasing use in syntheses of cyclopentenones.³

Scheme 1. Inter- and Intramolecular PKRs.



One of the limitations of the PKR is the poor regioselectivity observed in intermolecular reactions where unsymmetrical alkynes and alkenes can give rise to mixtures of four constitutional isomers. Inherent regiocontrol of the intramolecular PKR of enynes **3** to form bicyclic cyclopentenones **4** (Scheme 1) makes this variant appealing and it has been actively investigated since its inception in 1981.⁴

The original protocol for the PKR required superstoichiometric amounts of a metal complex, which limits its utility. The first catalytic PKR was reported in 1994⁵ and shortly thereafter the first catalytic PKR where a metal other than cobalt, titanium was used.⁶ Further development has produced catalytic, intramolecular PKRs that employ ruthenium⁷ and rhodium(I)⁸ complexes as catalysts.

Although the catalytic, asymmetric, and intramolecular PKRs were developed separately, the demand for a combined, catalytic, asymmetric variant was clear. This demand was met with the report of the first catalytic, asymmetric intramolecular PKR.⁹ Here, a chiral titanocene complex is employed in the enantioselective intramolecular construction of a variety of bicyclo[3.3.0]octenones **4** ($\text{Z} = \text{CR}_2$, O, NR) from 1,6-enynes **3** ($\text{Z} = \text{CR}_2$, O, NR).

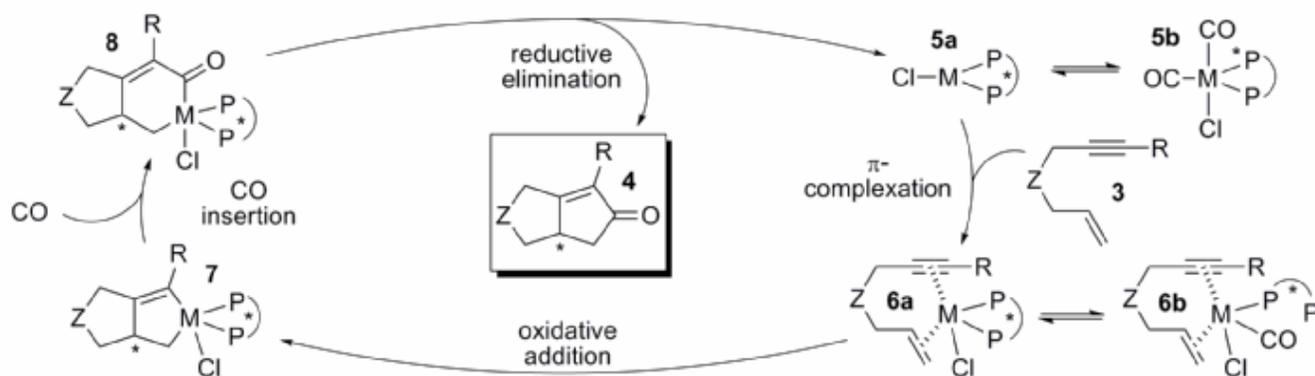
Discussed herein are the critical advances and recent developments toward catalytic asymmetric intramolecular PKRs including the development of new transition-metal, catalytic complexes, adaptation of these systems to a broader substrate base, and applications of the PKR in complex molecule synthesis.

MECHANISM

Although a detailed mechanism for the PKR has yet to be fully elucidated, the pathway originally suggested by Magnus for the dicobalt octacarbonyl-mediated intramolecular PKR is widely accepted.¹⁰ In this mechanism it is suggested that the alkyne and cobalt catalyst form a stable alkyne- $[\text{Co}_2(\text{CO})_6]$ 18-electron complex. Subsequently, the complex suffers loss of a single CO ligand from one Co atom, affording a 16-electron alkyne- $[\text{Co}_2(\text{CO})_5]$ complex. This complex then coordinates the olefin, reforming an 18-electron complex that undergoes alkene insertion to afford the cobaltacycle. Subsequent insertion of CO and reductive elimination affords the cyclopentenone and $[\text{Co}_2(\text{CO})_6]$. Pioneering work in mechanistic elucidation shows that isolation of the decarbonylated alkyne-cobalt complex before alkene association is possible if sulfur-containing ligands are used for stabilization^{11a} and that the argon-matrix-trapped decarbonylated complex is detectable by IR spectroscopy.^{11b}

This basic mechanistic formulation has been adapted to explain the CO pressure-dependent selectivity observed in asymmetric, intramolecular PKRs (Scheme 2). In this cycle, chiral transition metal catalyst **5a**, which can be in equilibrium with **5b** under a carbon monoxide atmosphere, undergoes coordination by enyne **3** to afford enyne/catalyst π -complex **6a** which can be in equilibrium with **6b**. Subsequent oxidative addition/cyclization affords metallacyclopentene **7** stereoselectively. This complex undergoes CO insertion to give metallacycohexenone **8** followed by reductive elimination to afford bicyclic cyclopentenone **4** thereby regenerating **5a**. The suspected equilibria of **5** and **6** suggest that at higher CO pressures both **5b** and **6b** are favored. As **5b** is less reactive than **5a** and oxidative cyclization of **6b** would give diminished stereoselection this proposed cycle rationalizes the coupling acceleration and increased stereoselectivity observed at lower CO pressures.

Scheme 2. Proposed Mechanism for Intramolecular PKR.



More recent studies have shed light on the mechanism of the PKR and support the current hypotheses. Specifically, tandem mass spectrometry studies have detected the decarbonylated cobalt-alkyne complex before association or insertion of the alkene, providing for the first time, solid evidence of the proposed mechanism.^{12a} Furthermore, x-ray crystal analysis of isolated intermediates have provided the first characterized η^2 -alkene-pentacarbonyldicobalt-alkyne complex, again supported the proposed mechanism.^{12b}

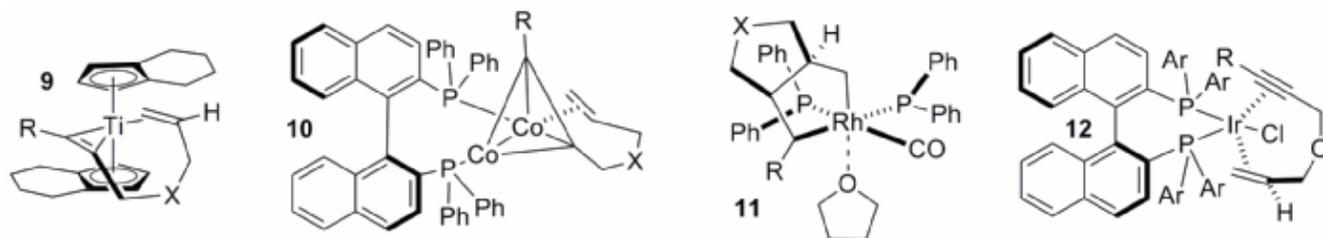
DEVELOPMENT OF CATALYTIC ASYMMETRIC PAUSON-KHAND REACTIONS

The first catalytic, asymmetric, intramolecular PKR employed an enantiomerically pure dicarbonyl titanocene complex with an ethylene bistetrahydroindenyl ligand ((*S,S*)-(EBTHI)Ti(CO)₂), produced *in situ* from (*S,S*)-(EBTHI)Ti Me₂.⁹ With this complex a variety of 1,6-enynes afford bicyclic cyclopentenones in high isolated yields (70-94%) and good enantioselectivities (49:1 to 6:1 er) with as little as 5 mol % catalyst loading. This complex allows for reasonable functional group compatibility as 1,1-disubstituted olefins, ethers, esters, and amines are tolerated. Stereoinduction is believed to arise from the formation of titanocycle **9** (Chart 1). The enyne in **9** adopts a favorable conformation during olefin complexation, reducing the steric strain with the EBTHI ligand that the diastereomeric titanocycle possesses.

The first example of a cobalt-catalyzed, asymmetric PKR employed a dicobalt phosphine complex formed *in situ* from Co₂(CO)₈ and (*S*)-BINAP.¹³ Here, it is rationalized that stereoinduction arises from the formation of dicobaltacycle **10** (Chart 1) where steric strain requires the bidentate phosphine ligand to coordinate both cobalt catalyst atoms separately. The boat-like conformation shown in **10** is favored as the chair-like conformer causes steric strain between the phosphorous phenyl rings

and the opposing naphthyl rings. Furthermore, the alkyne R substituent is favorably positioned to reduced steric interaction with the phenyl rings and the substrate backbone is positioned similarly, giving rise to olefin face selection.

Chart 1. Transition Metal Complexes in PKR.



More stable catalysts with defined structures were sought to address the expansion of late transition-metals and tunable phosphine ligands in PKR catalytic systems. Cationic rhodium (I) phosphine complex $[\text{Rh}(\text{CO})(S)\text{-BINAP}]^+$ generated *in situ* from $[\text{RhCl}(\text{CO})_2]_2$ and an excess of (S)-BINAP in the presence of silver triflate was first employed in 2000.¹⁴ The inclusion of a coordinating solvent (THF) is necessary for high enantioselectivity and at 1 atm of carbon monoxide a variety of 1,6-enynes afford bicyclic cyclopentenones in yields as high as 99% and enantioselectivity as high as 49:1 er. Here, stereinduction arises from the formation of rhodacycle **11** (Chart 1). This diastereomer of **11** is preferred as the R substituent on the alkyne occupies the less sterically encumbered open quadrant created by the (S)-BINAP ligand.

The first iridium catalyst employed for the asymmetric PKR, $[\text{IrCl}(\text{CO})(S)\text{-tolBINAP}]$ is also prepared *in situ* from $[\text{Ir}(\text{COD})\text{Cl}]_2$ and (S)-tolBINAP.¹⁵ With this catalyst, stereinduction is rationalized also by the formation of iridacycle precursor **12** (Chart 1). The alkyne substituent and alkene are positioned favorably in the open quadrants created by the ligand, providing the observed stereoselectivity.

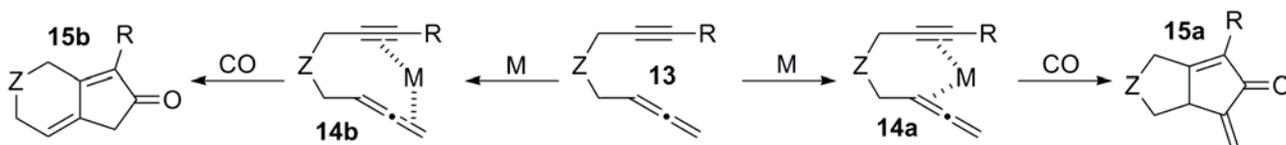
EXPANSION OF SUBSTRATES FOR PAUSON-KHAND REACTIONS

Allenynes

The demand for a greater substrate scope stimulated the development of an allenynyl PKR where an allene moiety replaces the olefin of the common enyne.¹⁶ Allenyne **13** inherently creates two pathways for an impending PKR (Scheme 3). In one path, catalyst complexation occurs at the internal

allenic π -bond (**14a**), affording bicyclic methylenecyclopentenone **15a** after cyclization. The second path affords bicyclic dienone **15b** after catalyst complexation to the external allenic π -bond (**14b**). Although catalytic asymmetric methods for allenynyl PKRs remain largely unexplored and regioselectivity can cause issues, the inclusion of allenynes to PKR substrate base opens a broad avenue toward diversified PKR products.

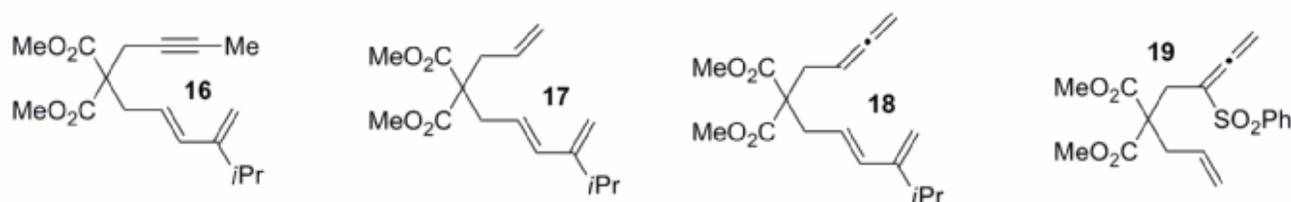
Scheme 3. Two Pathways for Allenynyl PKR.



Dienes and Ene-allenes

Wender and co-workers reported the first use of a dienyne in an intramolecular PKR.¹⁷ Subsequent reports described the use of ene-dienes¹⁸ as well as diene-allenes¹⁹ in then-unprecedented catalytic, asymmetric, intramolecular PKRs. A series of 1,3-dien-8-yne similar to **16** (Chart 2) undergo [2+2+1] cycloaddition in the presence of CO and a rhodium catalyst to afford isoprenylated bicyclo[3.3.0]octenones as single diastereomers in isolated yields as high as 96%. Likewise, a variety of 1,3,8-trienes similar to **17** (Chart 2) undergo [2+2+1] cycloaddition in the presence of CO and a rhodium catalyst to afford bicyclo[3.3.0]octanones as single diastereomers in good yield. A series of diene-allenes such as **18** (Chart 2) afford bicyclic isoprenylated methylenecyclopentanones diastereoselectively in good yield under standard PKR conditions. Finally, ene-allenes have also been conscripted into use in the PKR.²⁰ Here a variety of ene-allenes similar to **19** (Chart 2) combine with CO under rhodium catalysis to afford the corresponding phenylsulfonylbicyclo[4.3.0]nonenones in a diastereoselective fashion and good yield after isomerization of the initial product to the α,β -unsaturated ketone.

Chart 2. Dienyl and Allenic Structures.

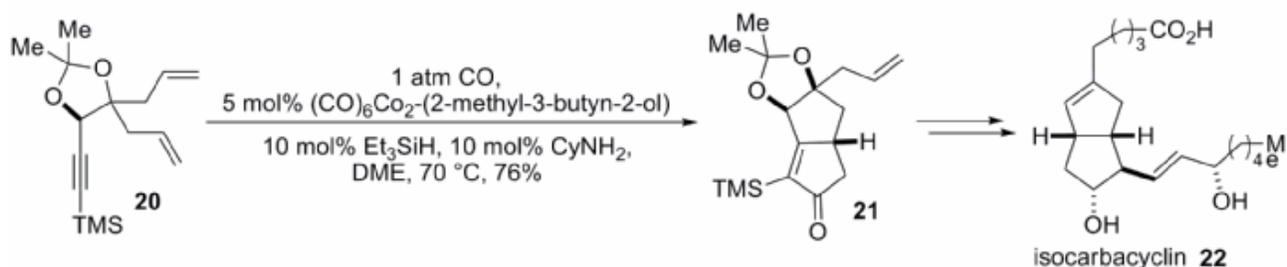


APPLICATIONS IN COMPLEX MOLECULE SYNTHESIS

Total Synthesis of Isocarbacyclin

In an illustration of the power of the PKR, Saito and coworkers reported the diastereoselective, total synthesis of isocarbacyclin (**22**) (Scheme 4), a metabolically stable analogue of the vasodilator prostacyclin.²¹ Bicyclo[3.3.0]octenone intermediate **21** (an obvious PKR product) was targeted as the key precursor for **22**. Dioxolane **20**, available in a few synthetic steps from L-ascorbic acid, is treated with 5 mol % dicobalt hexacarbonyl-(2-methyl-3-butyn-2-ol) complex in the presence of triethylsilane (Et₃SiH) and cyclohexylamine (CyNH₂) in DME under 1 atm of carbon monoxide to afford **21** as a single diastereomer in 76% yield based on a 67% conversion (Scheme 4). Although under these conditions complete conversion of **20** was not achieved, the isolation of **21** as a single isomer suggests that the reaction provides highly efficient discrimination over not only the diastereotopic allyl groups, but also the faces of the double bonds in **20**. Here the authors suggest that the protected diol acts as a prominent stereocontrolling unit in the expected chair-like transition state.

Scheme 4. Synthesis of Isocarbacyclin.

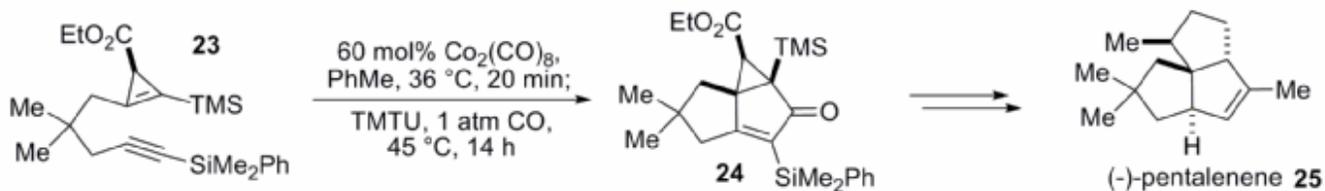


Synthesis of (-)-Pentalenene

Fox and Pallerla reported the first enantioselective synthesis of (-)-pentalenene (**25**) (Scheme 5), the unnatural enantiomer of the angular triquinane natural product pentalenene.²² The ability of the intramolecular PKR to install stereodefined quaternary centers led to the identification of cyclopropane-fused bicyclo[3.3.0]octenone intermediate **24** (Scheme 5) as a key intermediate. Upon treatment of enantiomerically-enriched cyclopropene **23** with dicobalt octacarbonyl (60 mol %) in the presence of tetramethylthiourea (TMTU) in toluene under 1 atm of carbon monoxide, **24** is obtained in 64% yield after separation from its diastereomer (4:1 dr) (Scheme 5). As expected, the key quaternary center is installed stereoselectively. This result, however, comes only after a thorough investigation of other PKR

promoters. The use of N-oxides proves unproductive as only unreacted **23** is isolated and while *n*-butyl methyl sulfide affords **24** as a single diastereomer it does so in a relatively low 45% yield.

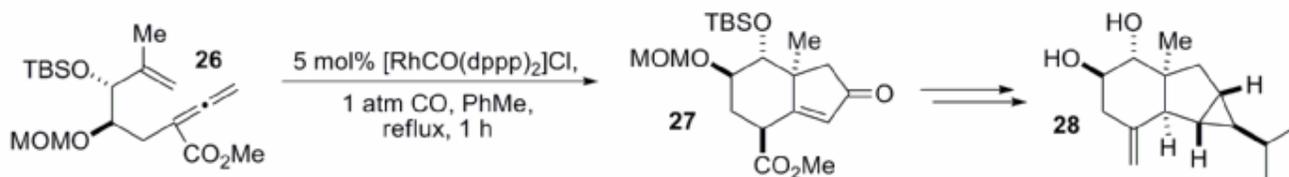
Scheme 5. Synthesis of (-)-Pentalenene.



Total Syntheses of Uncommon Sesquiterpenoids

Drawing on the development of the allenyl PKRs, Mukai and coworkers reported the first total synthesis of cyclopropane-fused *cis*-perhydroindane **28** (Scheme 6), an uncommon tricyclic sesquiterpene isolated from *Jatropha neopauciflora*.²³ Enroute to **28**, bicyclo[4.3.0]nonenone **27** (Scheme 6) represents a promising PKR adduct. Retrosynthetically, allenene **26** (Scheme 6) serves as the required target for the planned intramolecular PKR. Beginning with the readily available dimethyl D-tartrate, **26** is obtained in good fashion and subsequently subjected to PKR conditions. Treatment of **26** with cationic $[\text{RhCO}(\text{dppp})_2]\text{Cl}$ (5 mol %) in toluene at reflux under a carbon monoxide atmosphere affords **27** in 74% yield as a single isomer. Here, stereoinduction can be rationalized by the formation of the expected rhodacycle.

Scheme 6. Synthesis of Sesquiterpenoids.



CONCLUSION AND OUTLOOK

The formal [2+2+1] cycloaddition of an alkyne, an alkene, and carbon monoxide, known as the Pauson-Khand reaction, represents one of the most versatile synthetic routes to cyclopentenones. In addition, the intramolecular variant provides efficient access to fused bicyclic cyclopentenone structures in an atom economical fashion. The recent development of late transition metal catalysis with chiral

complexes has pushed the Pauson-Khand reaction to the mainstream of organic synthetic methods. Newer adaptations of dienyl and allenyl moieties have further expanded the scope of this cycloaddition and its frequent appearance in current literature suggest that it may soon be the method of choice for cyclopentane syntheses.

The utility of the intramolecular Pauson-Khand reaction in complex molecule synthesis is still largely confined to non-catalytic and non-asymmetric methods and relies largely on substrate-directed stereocontrol. Current development and refinement of catalytic asymmetric processes, however, show promise for the rise of the catalytic asymmetric Pauson-Khand reaction in the context of total synthesis.

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