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Recent Advances in the Pauson–Khand Reaction

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Abstract

The Pauson-Khand [2+2+1] cycloaddition of alkynes, alkenes, and carbon monoxide has been a vibrant area of research for more than 40 years. This review highlights recent achievements in the Pauson-Khand reaction, particularly in catalytic and asymmetric variants. Discussion of regioselectivity and advances in substrate scope is also presented.

Keywords

Pauson-Khand reactions; transition metal catalyzed cycloadditions; asymmetric catalysis

Introduction

The Pauson-Khand reaction (PKR), a [2+2+1] cycloaddition between an olefin, alkyne, and carbon monoxide, is among the most common methods to construct cyclopentenones. First discovered as a cobalt-mediated process in the early 1970s,^[1] it has remained the subject of numerous studies to improve the reaction conditions, broaden the scope, and understand the mechanism of reaction. A comprehensive book was published on the subject in 2012,^[2] and this short review highlights achievements since then, particularly in intermolecular reactions and newly developed catalytic systems. Although there have been many spectacular uses of Pauson-Khand chemistry in total synthesis recently,^[3] applications of the PKR in total synthesis are outside of the scope of this review. This manuscript is divided into the following sections: developments in methods for the synthesis of achiral/racemic cyclopentenones, followed by diastereoselective PKR on enantiomerically enriched substrates, and finally asymmetric syntheses of cyclopentenones. Both stoichiometric and catalytic versions will be discussed in each section, and include cobalt, iron and/or rhodium processes. Finally, some recent studies of the regiochemistry of unsymmetrical alkyne incorporation will be discussed.

Achiral/Racemic Processes

To better understand diastereoselection, Baik computationally determined the energetic barriers to the formation of both *cis*- and *trans*-cyclopentenones.^[4] The calculations predicted that changing the alkyne terminus from H to Cl would significantly lower the barrier to formation of the *cis* isomer by 4 kcal/mol, but not significantly reduce the barrier to formation of the *trans* isomer. To verify this, Evans and coworkers treated the

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corresponding enynes with a rhodium catalyst at room temperature (Scheme 1) and observed no reaction when the alkyne was terminal, but were able to isolate the cyclopentenone in 74% yield when substituted with chlorine. When R^1 was chlorine, consistently high yields and diastereoselectivity were observed for a variety of X and R^2 groups (Scheme 1).

The application of allenes as a component in the PKR is a relatively new advance in the field.^[5] In the cobalt-mediated process, linear and unstrained cyclic alkenes are normally poorly reactive partners in the PKR.^[6] Recently, Cazes and coworkers developed an intermolecular Pauson-Khand reaction between cobalt-alkyne complexes and allenic hydrocarbons as mediated by *N*-methyl morpholine (NMO) (Scheme 2).^[7] The reaction temperatures and solvents varied, but the cyclopentenones could often be isolated in reasonably good yields. The authors were unable to effect efficient cycloannulation from alkyne, allene and dicobalt octacarbonyl due to the propensity of $Co_2(CO)_8$ to polymerize allenes,^[8] necessitating the preformation of the alkyne-cobalt-hexacarbonyl complex. Allene itself was unreactive under all conditions examined. When unsymmetrical allenes were utilized as substrates, regioisomeric allene insertion was normally observed, except in the case of silyl-substituted allenes. The authors proposed a mechanism for the reaction, analogous to the generally accepted Magnus mechanism.^[9]

Williams and Baik have studied a similar iron carbonyl mediated Pauson-Khand reaction between allenes and alkynes, both experimentally and computationally (Scheme 3).^[10] Observation of an allene- $Fe(CO)_4$ adduct that persisted throughout all experiments prompted the researchers to perform a stoichiometric reaction between the allenes and $Fe_2(CO)_9$ (Scheme 4, top), revealing a metallocycle that was crystallographically and computationally characterized. This species proved to be competent in a reaction with an alkyne to provide the corresponding cyclopentenone. The authors proposed a mechanism for the reaction (Scheme 4, below) and kinetic experiments suggest that the rate-limiting step is sometime after complexation of the allene to the iron carbonyl.

An interesting advance in expanding the scope of the alkene component of the PKR came from Lledó and Riera and coworkers.^[11] The team developed a cobalt-mediated PKR between alkynes and *trans*-cycloalkenes. The reaction was optimized and the scope was established for the reaction between symmetric and terminal alkynes and medium sized *trans*-cycloalkenes (Scheme 5). Notably, a competition experiment between a cobalt-trimethylsilylacetylene complex and a 1:1 mixture of *trans*-cyclooctene and norbornene yielded a 1:1 mixture of the corresponding cyclopentenones, suggesting that *trans*-cyclooctene is similar in reactivity to norbornene, the prototypical PK alkene.^[12] Analogous reactions with *cis*-cyclooctene resulted in very low (0–18%) isolated yields of the cyclopentenone. Reactions with (*E*)-1-methylcyclooctene were very regioselective, though more modest in yield (22–62% yields, not shown), though this was partially attributed to a smaller excess of alkene used in the experiments. *Trans*-Cyclononenes and –cyclodecenes were also examined as potential substrates in the PKR. They appeared to be less reactive than the cyclooctenes as expected, but practical yields of the cyclopentenones could be achieved in some cases.

As discussed above, internal and unactivated olefins are not often able to be employed in the PKR. To circumvent the low reactivity and regioselectivity of linear internal olefins, Verdaguer and Riera devised an alternate route to 4,5-disubstituted cyclopentenones.^[13] Their approach began with the PKR between a propargylamine-cobalt complex and norbornadiene. After a sequence of conjugate addition-elimination-conjugate addition-retro Diels-Alder, a 4,5-disubstituted cyclopentenone is produced (Scheme 6). This compound represents the challenging, formal PKR between acetylene and an internal linear olefin. The authors also demonstrated that the PKR could be performed asymmetrically using a chiral P-S ligand precomplexed to the alkyne-dicobalt complex.

Diastereoselective PK and PK-Like Reactions

Yu and Pu studied the diastereoselective intramolecular PKR of enantioenriched enynes prepared by asymmetric acetylide additions.^[14] The authors generally found that the NMO required to promote the PKR following complexation of cobalt to the acetylene could be achieved without isolation of the intermediate, but in some cases solvent removal prior to the cycloaddition was necessary for high yields (Scheme 7). For example, in the synthesis of 6,5-fused rings, non-terminal alkynes specifically required removal of DCM as in those cases, *n*-butyl methyl sulfide in 1,4-dioxane was far superior in promoting those more challenging cycloadditions. Though the (*R*)-enantiomer is specifically shown in Scheme 7, the process was demonstrated to be equally successful from the antipode as indicated in some of the examples. The propargylic alcohol required protection, as no reaction occurred otherwise.

Ruano, Martin-Castro and coworkers developed a four-step synthesis of enantioenriched bicycle[3.3.0]-octenones.^[15] Their approach used a stereogenic sulfonyl or sulfinyl group to effect asymmetric α -allylations and α -propargylations of α -aryl acetonitrile derivatives. Those could then be sequentially treated with $\text{Co}_2(\text{CO})_8$ and NMO to yield the chiral bicyclic cyclopentenones (Scheme 8).

When all of the R groups on the enyne are protons, decent diastereoselectivity is only observed if the sulfinyl group is still on the arene; if it is reductively removed prior to the Pauson-Khand reaction, approximately 1:1 diastereoselectivity is observed in the cycloaddition. The method is moderately tolerable to steric bulk, but the authors found that trisubstituted olefins were completely unreactive to dicobalt octacarbonyl.

Fustero, Barrio and coworkers utilized the intramolecular PKR to produce tricyclic amines with a benzofused indenyl backbone.^[16] This transformation was used within a reaction sequence to diastereoselectively obtain amino steroid analogues. Following asymmetric allylation and Sonogashira coupling, the intramolecular PKR pictured in Scheme 9 gave good to excellent yields and diastereoselectivities regardless of the substituents on the aryl tether and cross-coupled alkyne including original usage of a CF_3 substituted alkyne in the intramolecular PKR.

Hong et. al. recently described an organocatalytic Michael addition-lactonization sequence that generated enantioenriched enynes.^[17] The enynes were produced in high

enantioselectivities, between 96 and 99% ee. The diastereoselectivities observed in the Pauson-Khand products were generally consistent with the diastereoselectivities of the starting enynes, though there was some variability. Most observed diastereomeric ratios were equal to or above 80:20, though products from alkyl-substituted alkynes were generated with lower levels of selectivity (Scheme 10). Li, Yang and coworkers were also able to subject similarly densely substituted cyclohexanes appended with olefins and alkynes to Pauson-Khand chemistry to yield 6,6,5-tricyclic rings with a quaternary center at C4 of the cyclopentene.^[18] Walsh and Pericas later showed that benzofused enynes were amenable to Pauson-Khand cyclization to yield 6,6,5-fused rings containing an aromatic rings.^[19]

Brummond and coworkers have developed a diastereoselective rhodium catalyzed intramolecular allene-alkyne Pauson-Khand reaction to yield 5,7,5-tricyclic systems (Scheme 11).^[20] Yields of the cycloadducts were generally good, and no erosion in the diastereomeric purity was observed between the enyne and the cyclopentenone. Moreover, no depropargylation was observed throughout the process.

Yu, Pu and coworkers designed a synthesis of a tetracyclic ring system.^[21] A single stereogenic center was established by asymmetric enyne addition to an aldehyde. Allylation of the resulting alcohol yielded a multifunctional system, that upon treatment with a rhodium catalyst and an atmosphere of carbon monoxide triggered sequential intramolecular Pauson-Khand-intramolecular Diels-Alder (IMDA) cycloadditions (Scheme 12). Diastereocontrol was complete in most cases, and the tetracyclic compounds were isolated with high enantioselectivity. The authors proposed that the Pauson-Khand reaction occurred first, and between the alkyne and the least substituted olefin; the resulting diene then reacted with the other olefin, forming the remaining two rings in cascade fashion.

Asymmetric Pauson-Khand Reactions

Jeong and coworkers developed a rhodium-catalyzed intramolecular asymmetric Pauson-Khand reaction (APKR).^[22] The authors varied the tether, and studied the behavior of coordinating and uncoordinating tethers under Pauson-Khand cyclization conditions. Two possible binding modes are shown in Figure 1. These catalysts are most reactive in a polar coordinating solvent and show excellent activity at ambient temperature and low CO pressure. The oxygen-containing enynes were found to be more reactive and yielded the cyclopentenones with greater selectivity.

The authors prepared substrates that contains two enynes poised for intramolecular PKR; one enyne was linked by an oxygen atom, and the other enynes were linked by sulfur, nitrogen or carbon-based groups. These were used as competition substrates to directly study the difference in reactivity and selectivity between those two groups (Scheme 13). The authors noted that the non-oxygen tethered enyne only underwent cyclization after the oxygen tethered enyne reacted completely, very clearly demonstrating the superior reactivity of those substrates. The authors attribute these differences in reactivity to the greater ability of oxygen to coordinate to rhodium.

All experiments on a sulfur-containing substrate were unsuccessful; strong sulfur ligation has previously shown to greatly slow a cobalt-catalyzed PKR.^[23] Another interesting result came from the desymmetrization of the dienyne shown in Scheme 14. The authors proposed that a rigid transition state with oxygen chelation leads to the high enantioselectivity observed, while with the *N*-tosyl tethered substrate, steric hindrance between the tosyl group and vinyl groups causes a reversal in diastereoselectivity and decrease in enantioselectivity.

Riera, Verdaguer and coworkers recently described a cobalt-catalyzed PKR.^[24] The authors employed ThaxPHOS, a bidentate ligand that coordinates to $\text{Co}_2(\text{CO})_8$ in a bridging fashion; this rendered the intermolecular PKR with various substituted alkynes catalytic and generated cyclopentenones with excellent enantioselectivity (Scheme 15). The authors posit that the ThaxPHOS ligands stay coordinated to the dicobalt scaffold throughout the catalytic cycle and does not function as a hemilabile ligand. The large *t*-butyl group attached to the phosphorus is believed to be the source of the selectivity in TMS-acetylene insertion into the cobalt complex.

Furthering their work in developing asymmetric PKR, Riera and Verdaguer developed electron rich, small bite angle diphosphine Rh(I) complexes to catalyze an asymmetric intramolecular Pauson-Khand reaction.^[25] The P-stereogenic MaxPHOS-Rh complex (Scheme 16, top) had previously been successfully employed in asymmetric hydrogenation chemistry.^[26] As shown in Scheme 16 (bottom), the reaction was higher yielding and more selective with the *N*-tosyl tethered enyne. Low CO pressure and low temperature tended to favor the side [2+2+2] reaction, which was only observed as a 1:1 mixture of regioisomers. Representative results of the substrate scope are given below. Further mechanistic studies led them to the conclusion that the COD ligand plays a pivotal role in the high stereoselectivity of the reaction.

Nordlander and co-workers applied a tris- μ carbyne cobalt pre-catalysts to the intermolecular PKR. While they were able to use the catalyst in 2 mol%, yields were modest and enantioselectivity was poor (Scheme 17).^[27] Additionally, they used dicobalt octacarbonyl and tetracarbonyl dodecacarbonyl within the PKR and exogenous chiral phosphine ligands and obtained excellent yields, though again no enantiomeric excess. They also suggest, similarly to Krafft^[28] and Lee,^[29] that the $\text{Co}_4(\text{CO})_{12}$ may simply be decomposing to the dicobalt complex, with the caveat that the tetra-nuclear complex may be a superior option due to less propensity to be air-oxidized.

Regioselectivity with unsymmetrical alkynes

Fairlamb and coworkers^[30] used various (2-phenylethynyl)-aromatic heterocycles to investigate how the regioselectivity in the intermolecular PKR changes based on the relative electron richness of the heterocycles (Scheme 18). An exact correlation with the electronic nature of the heterocycle was not observed within the substrates used, however several general trends were observed. With 2-pyrrole, and 2-indole heterocycles the α -isomer predominated. With 6-membered N-heterocycles, the β -isomer predominates if the nitrogen atom is close to the cobalt center, the β -isomer also predominates with the 2 pyrone, 2-/3-thiophene, and 2-furan substrates.

Fager-Jokela and coworkers provided further insight into electronic vs. steric effects at work within the cobalt mediated PKR using sterically equivalent, but electronically dissimilar *meta*- and *para*-substituted diaryl acetylenes.^[31] This study was meant to further probe the “push-pull” effect, electronic cooperativity between electron donating and electron withdrawing groups substituted on opposite sides of diaryl alkynes. Mono *para*-substituted alkynes generally follow expected regioselectivity with diaryl alkynes functionalized with electron donating group resulted in slightly favoring production of the α -isomer and reactions with electron poor diaryl alkynes yielded the β -isomer (Scheme 19), though not in strict correlation with Hammett values. The alkynes substituted with both electron donating and electron withdrawing groups showed no apparent “push-pull” cooperativity. This result was puzzling and led to extensive computational work in an attempt to rationalize these results. Computational studies reinforced the “push-pull” theory, despite lack of observation in the particular system studied experimentally.

Their next aim was to test inductively polarized aliphatic alkynes in the intermolecular PKR and determine what impact this electronic inductive effect would have on the regioselectivity of the reaction (Scheme 20).^[32] The authors also explored this reaction computationally. Alkynes with propargylic oxygens, and to a lesser extent nitrogen, selectively form mainly the β -exo isomer. This regiochemical outcome correlates best with their calculated NBO charges at the more electron deficient carbon α to the alkyne, with C-C bond formation taking place at alkynyl carbon with more electropositive α -carbon. Of the alkynes with less electron-withdrawing and bulkier TMS and *t*-butyl groups, sterics played a more decisive factor in determining the regioselectivity, which in the examples given produces the α -exo isomer. Overall, electronic induction plays a decisive role in determining the regiochemical outcomes of the system studied when steric effects are minimized.

Riera, Verdaguer and co-workers recently discovered an intermolecular PKR using variously substituted trifluoromethylacetylenes.^[33] These substrates result in the trifluoromethyl group alpha to the carbonyl in the final cyclopentenone. This is the reverse regiochemical outcome of what is normally expected based on electronic considerations. The authors propose electronic effects are outweighed by steric effects in this system. Scheme 21 shows representative PK reactions and products. Removal of the trifluoromethyl group was achieved in moderate to good yields using 1–8-diazabicyclo[5.4.0]undec-7-ene (DBU) and water in nitromethane at reflux, yielding the otherwise challenging to access β -substituted cyclopentenones.

León and Fernández very recently explored the intermolecular PKR with substituted alkynylboronic esters.^[34] Representative products of the broad substrate scope can be seen in Scheme 22. They reported exclusive formation of *exo*-isomer with boronic acid beta to carbonyl after cyclization in moderate to good yields. After subsequent Suzuki-Miyaura coupling, this strategy gives access to diarylacetylene PKR products with control of regiochemistry. The authors note a strong solvent and temperature dependence. Additionally, highly hindered alkynes like *tert*-butylalkynylboronic pinacol ester failed to yield PKR product.

Conclusions

Since the discovery of the Pauson-Khand reaction, numerous research groups have continued to develop creative ways to expand the scope of the PKR and improve its efficiency. The usage of allenes with both cobalt and iron, and other diastereoselective and catalytic intermolecular variants of the PKR were highlighted, as well as the asymmetric synthesis of tri- and tetracyclic ring systems. Other groups have explored the electronic and steric peculiarities of both the intra- and intermolecular PKR with both cobalt and rhodium. However, Verdaguer and Riera, with their syntheses of 4,5-disubstituted cyclopentenones, underscore one of the major limitations of the intermolecular PKR. The limited scope of alkenes currently able to undergo the PKR in high yield limits an even larger application of this reaction to date. Despite the important advances highlighted in this review, there remains room for improvement in both the scope and catalytic congener of this useful reaction.

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Figure 1.
Two possible binding modes of 1,6-enynes with and without coordinating tethers.

Scheme 1.

Improved reactivity in the intramolecular PKR containing chloroacetylenes.

Scheme 2.

The PKR between cobalt-alkyne complexes and allenes and some selected examples.

Scheme 3.

Examples of iron-mediated PKR with 1,1'-disubstituted allenes.

Scheme 4.

Synthesis of an iron-allene complex and the proposed mechanism of reaction with an alkyne.

Scheme 5.
Application of *(E)*-cyclooctene in the PKR.

Scheme 6.

Sequential conjugate additions and retro-Diels-Alder to traditional Pauson-Khand products to yield structures analogous to internal alkene incorporation.

Scheme 7.
syn-Diastereoselective cyclization of enantioenriched enynes.

Scheme 8.

Diastereoselective cyclization of sulfinyl and sulfenyl-containing enynes.

Scheme 9.
Intramolecular PKR of chiral enynes.

Scheme 10.

Synthesis of enantioenriched (5,5,6)-tricycles via PKR of enynes.

Scheme 11.

Synthesis of enantioenriched (5,7,5)-tricycles via PKR of allene-ynes.

Scheme 12.

Sequential PKR-IMDA cycloadditions to yield enantioenriched (5,5,5,6)-tetracycles.

Scheme 13.

Preferential cyclization of the oxygen-containing enyne over nitrogen- and carbon-containing enynes in an intramolecular competition.

Scheme 14.

Enantioselective desymmetrization of a dieneyne to yield a vinyl bicyclic cyclopentenone.

Scheme 15.

Enantioselective PKR between norbornadiene and TMS-acetylene as catalyzed by various bisphosphine-cobalt catalysts.

Scheme 16.

Enantioselective cyclization of 1,6-enynes catalyzed by cationic rhodium-MaxPHOS

Scheme 17.

Trinuclear cobalt-WalPHOS catalyzed coupling of phenylacetylene and norbornene.

Scheme 18.

Regioselectivity in the cobalt-mediated PKR between norbornene and aryl-heteroaryl unsymmetrical alkynes.

Scheme 19.

Evaluation of “push-pull” effects in electronically unsymmetrical alkynes in the cobalt-mediated PKR.

Scheme 20.

Steric vs inductive effects in unsymmetrical alkyl alkynes

Note: Yields are over the whole sequence shown above.

Scheme 21.

Trifluoromethyl-containing enynes in the intermolecular PKR.

Scheme 22.

Acetylenic boronic esters in the intermolecular PKR.