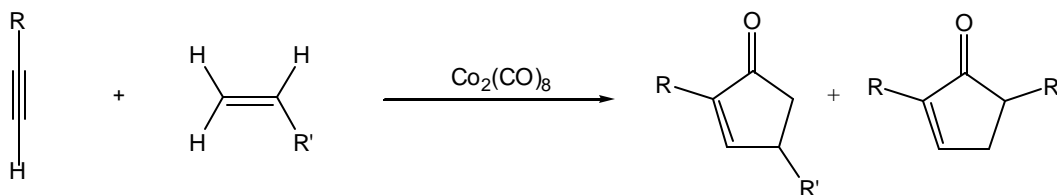


## The Pauson-Khand Reaction

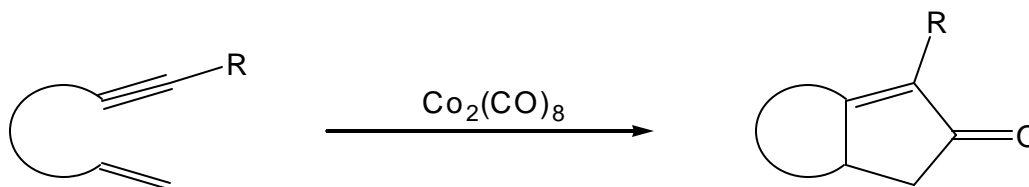
The Pauson-Khand reaction is a widely utilized method for making cyclopentenones.<sup>1</sup> The cyclopentenone is formed by cyclization of an alkyne, olefin, and carbon monoxide in the presence of  $\text{Co}_2(\text{CO})_8$  in a formal [2+2+1] cycloaddition (Scheme 1). Pauson and Khand first reported the reaction in detail in 1973.<sup>2</sup> General reaction conditions involved heating the premade alkyne- $\text{Co}_2(\text{CO})_6$  with the alkene to receive moderate yields of cyclopentenones. The Pauson-Khand reaction is tolerant of a wide variety of functionality such as esters, ethers, thioethers, tertiary amines, amides, sulfonamides, nitriles, and alcohols, which makes it an attractive reaction for organic synthesis.



**Scheme 1. General Pauson-Khand reaction.**

While the Pauson-Khand reaction was shown to tolerate many functional groups, it also had many limitations. Though the idea of catalysis was mentioned in the original publication, the traditional Pauson-Khand reaction involved a stoichiometric amount of  $\text{Co}_2(\text{CO})_8$ .<sup>2</sup> Also, harsh conditions were employed to effect the transformation, and such high temperatures often led to decomposition of substrates and/or products. Regioselectivity was also a problem. While the reaction is usually selective with respect to substituents on the alkyne, the alkene substituents are not selectively incorporated. Strained olefins were necessary for efficient conversion to product, with the exception of ethylene itself. Internal alkynes were less effective than terminal alkynes, and trisubstituted alkenes were often unreactive. The limitations mentioned sometimes resulted in competition with the formation of aromatic compounds from alkyne trimerization.

In 1981, Schore introduced the first examples of the intramolecular Pauson-Khand reaction (Scheme 2).<sup>3</sup> A carbon tether was added that linked the

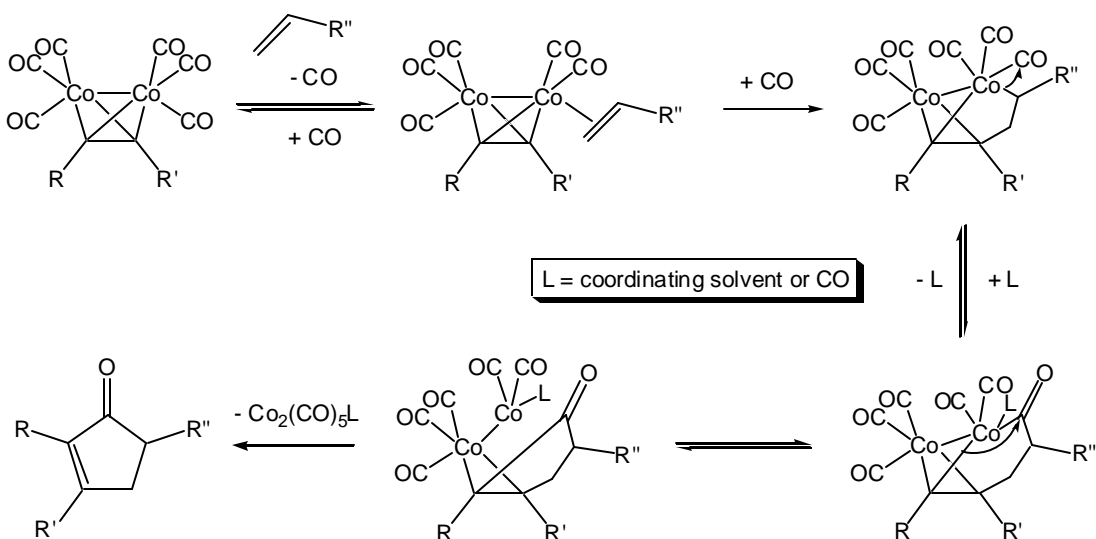


**Scheme 2. Intramolecular Pauson-Khand reaction.**

alkene and alkyne moieties, resulting in a bicyclic product from an acyclic substrate. Strained alkenes are not necessary for the intramolecular cycloaddition, and regioselectivity is not an issue.

### *Proposed Mechanism*

While there is no solid mechanistic data for the Pauson-Khand reaction, a mechanism has been proposed based on regio- and stereochemical observations from many examples (Scheme 3).<sup>4</sup> The only intermediate that has been isolated is the initial, stable alkyne- $\text{Co}_2(\text{CO})_6$  complex. It is assumed that the next step involves dissociation of a CO ligand and coordination of the alkene. The alkene then irreversibly inserts into one of the cobalt-carbon bonds. This step is thought to be rate-determining as well as product-determining. Migratory insertion of a CO ligand bound to cobalt to form the carbonyl moiety and reductive elimination of the  $\text{Co}(\text{CO})_3$  fragment follows. Loss of the  $\text{Co}_2(\text{CO})_5\text{L}$  fragment liberates the cyclopentenone product.



**Scheme 3. Proposed mechanism of the Pauson-Khand reaction.**

The alkene insertion step is proposed to determine the regioselectivity of the product. In the case of an unsymmetrical alkyne, alkene insertion will take place exclusively at the carbon bearing the smaller substituent. Therefore, regioselectivity with respect to the alkyne is usually readily predicted. Regiochemistry of the alkene is less predictable.

### *Promotion*

In order to circumvent the high temperatures and long reaction times necessary to effect the Pauson-Khand cycloaddition, methods were soon developed for the promotion of the reaction. A real advance in the utility of the Pauson-Khand reaction was reported by Schreiber<sup>5</sup> and Jeong,<sup>6</sup> who independently found that tertiary amine *N*-oxides were useful promoters of the reaction. It is assumed that loss of CO ligand is one of the first steps of the mechanism leading to coordination of the alkene. Harsh reaction conditions were necessary for CO loss in the thermally promoted Pauson-Khand reaction. Schreiber found that *N*-methyldmorpholine *N*-oxide (NMO) was effective in promoting the Pauson-Khand reaction at room temperature, and Jeong investigated both NMO and trimethylamine *N*-oxide (TMANO). It is most likely that the *N*-oxides function by removing a CO ligand from the metal oxidatively as carbon dioxide. The use of *N*-oxides in promoting the Pauson-Khand cycloaddition has been prevalent ever since these discoveries, and provides much milder conditions for effecting the transformation. Other promoters such as silica,<sup>7</sup> amines,<sup>8</sup> sulfides,<sup>9</sup> and molecular sieves<sup>10</sup> have been reported, but tertiary amine *N*-oxides are widely employed.

### *Synthetic Example*

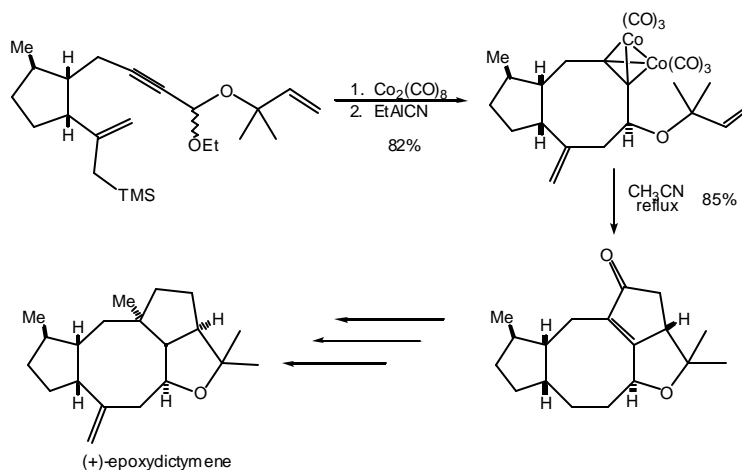
Once the scope of the reaction had been widened, the use of the Pauson-Khand reaction in organic synthesis exploded. The synthesis of (+)-epoxydictymene by the Schreiber group made elegant use of tandem cobalt-mediated reactions, an intermolecular Nicholas reaction followed by a Pauson-Khand reaction to construct the ring system (Scheme 4).<sup>11</sup>

### Asymmetric Pauson-Khand

Many advances have been made in the development of asymmetric Pauson-Khand reactions.

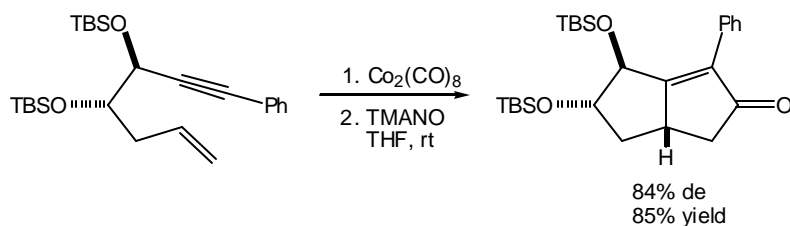
There are four major approaches that have been employed: 1) chiral precursors (chiral pool approach), 2) chiral auxiliaries, 3) chiral metal

complexes, and 4) chiral promoters.



**Scheme 4. Synthesis of (+)-epoxydictymene.**

Many people have taken advantage of the chiral pool to transfer chirality in



**Scheme 5. Optically active products derived from diethyl L-tartrate.**

the Pauson-Khand cycloaddition. One such example utilizes diethyl L-tartrate as the precursor for the cycloaddition substrate.

Good diastereoselectivity and good yields were observed, depending on reaction conditions (Scheme 5).<sup>12</sup>

Chiral auxiliaries have also been used for stereoselective control in the Pauson-Khand reaction. Chiral auxiliaries are attractive because the diastereomers that result are usually separable by chromatography, and the auxiliary can usually be recycled. A wide variety of auxiliaries have been employed in this cycloaddition, including *tert*-butylsulfinyl group,<sup>13</sup> chiral oxazolidinones,<sup>14</sup> and Oppolzer's sultam (as a steric controller).<sup>15</sup> A set of chiral auxiliaries derived from 10-methylthioisoborneol have also been developed.<sup>16</sup> Spectroscopic data show that the sulfur moiety coordinates to the cobalt, and the authors propose that this chelation could be acting to improve diastereoselectivity.

Chiral cobalt complexes are another promising avenue for effecting enantioselectivity in Pauson-Khand cycloaddition products. Most of the work done in this area has involved the use of chiral phosphine ligands such as (*R*)-(+)-glyphos or

(S)-BINAP to give a diastereomerically pure metal complex.<sup>17</sup> These complexes give rise to good to excellent enantiomeric excesses. Another approach has been to use a heterobimetallic complex, in which the reaction should take place at one metal center preferentially.<sup>18</sup> These complexes also give enantiomerically pure products.

An interesting approach to the asymmetric Pauson-Khand reaction involves the use of chiral amine *N*-oxides. The idea behind this approach is that the chiral promoter should be able to differentiate between two enantiotopic CO ligands in the cobalt-alkyne complex. Brucine *N*-oxide<sup>19</sup> as well as various (-)-sparteine *N*-oxides<sup>20</sup> have been investigated, but with limited success (highest ee: 44%).

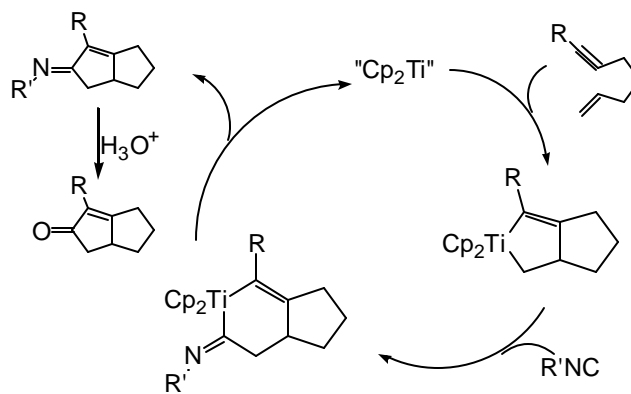
### *Catalytic Pauson-Khand*

The reactions discussed to this point have been stoichiometric in cobalt. Studies are underway to find generally useful catalysts, and some advances have been made in recent years.

Rautenstrauch reported an early catalytic version of the Pauson-Khand reaction (0.22 mol% catalyst), but the conditions were only optimized for ethylene.<sup>21</sup> Jeong reported the use of triphenylphosphite as a co-ligand with  $\text{Co}_2(\text{CO})_8$  (3 mol%) in moderate to good yields.<sup>22</sup> Jeong also developed an (indenyl)cobalt(I)(cod) complex that gave good yields with 2 mol% catalyst.<sup>23</sup> Photochemical<sup>24</sup> and thermal<sup>25</sup> versions of a catalytic system were reported by Livinghouse, and later improved on by Krafft.<sup>26</sup> Livinghouse<sup>27</sup> and Krafft<sup>28</sup> have also developed methods for generating high purity  $\text{Co}_2(\text{CO})_8$  catalyst *in situ* from hexacarbonyldicobalt-alkyne complexes, which is very effective. While much has been accomplished recently in the area of Pauson-Khand reaction catalysis by cobalt complexes, the search for a general catalytic system has branched out into other transition metals.

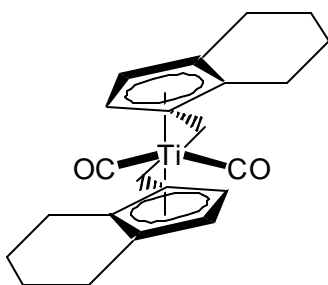
### Other Transition Metals

Other transition metals have been used to effect the Pauson-Khand reaction to varying degrees of success. One system that deserves mention is the titanocene catalyst developed by Buchwald. Early work involved the development of a "Cp<sub>2</sub>Ti" titanocene catalyst (Cp<sub>2</sub>Ti(PMe<sub>3</sub>)<sub>2</sub>, 10 mol%) that was capable of forming metallocyclopentenenes in a Pauson-Khand type reaction (Scheme 6).<sup>29</sup> The metallocyclopentene was then trapped by an isocyanide and converted to the cyclopentenone by hydrolysis of the resulting



**Scheme 6. Titanocene catalysis.**

imine. Modest yields resulted from inefficient hydrolysis. A new system was developed using Cp<sub>2</sub>Ti(CO)<sub>2</sub> (5-20 mol%) that formed the cyclopentenone directly, and led to improved yields.<sup>30</sup>



**Figure 1. (S,S)-(EBTHI)Ti(CO)<sub>2</sub>**

An asymmetric version of the reaction was developed using (S,S)-(EBTHI)Ti(CO)<sub>2</sub> generated *in situ* from (S,S)-(EBTHI)TiMe<sub>2</sub> (Figure 1).<sup>31</sup> The catalyst showed good enantioselectivities (72-96% ee) and good to excellent yields. The transformation is also effective for nitrogen-tethered enynes.<sup>32</sup> It should be noted that all of the reactions mentioned are only

effective for the intramolecular reaction.

### Conclusion

Many improvements have been made on the Pauson-Khand reaction since its discovery in 1973. A variety of catalytic and asymmetric versions have been discovered. While all of these systems have their own limitations, they are often complementary to one another. The Pauson-Khand reaction will continue to be a powerful synthetic tool for forming cyclopentenones.

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