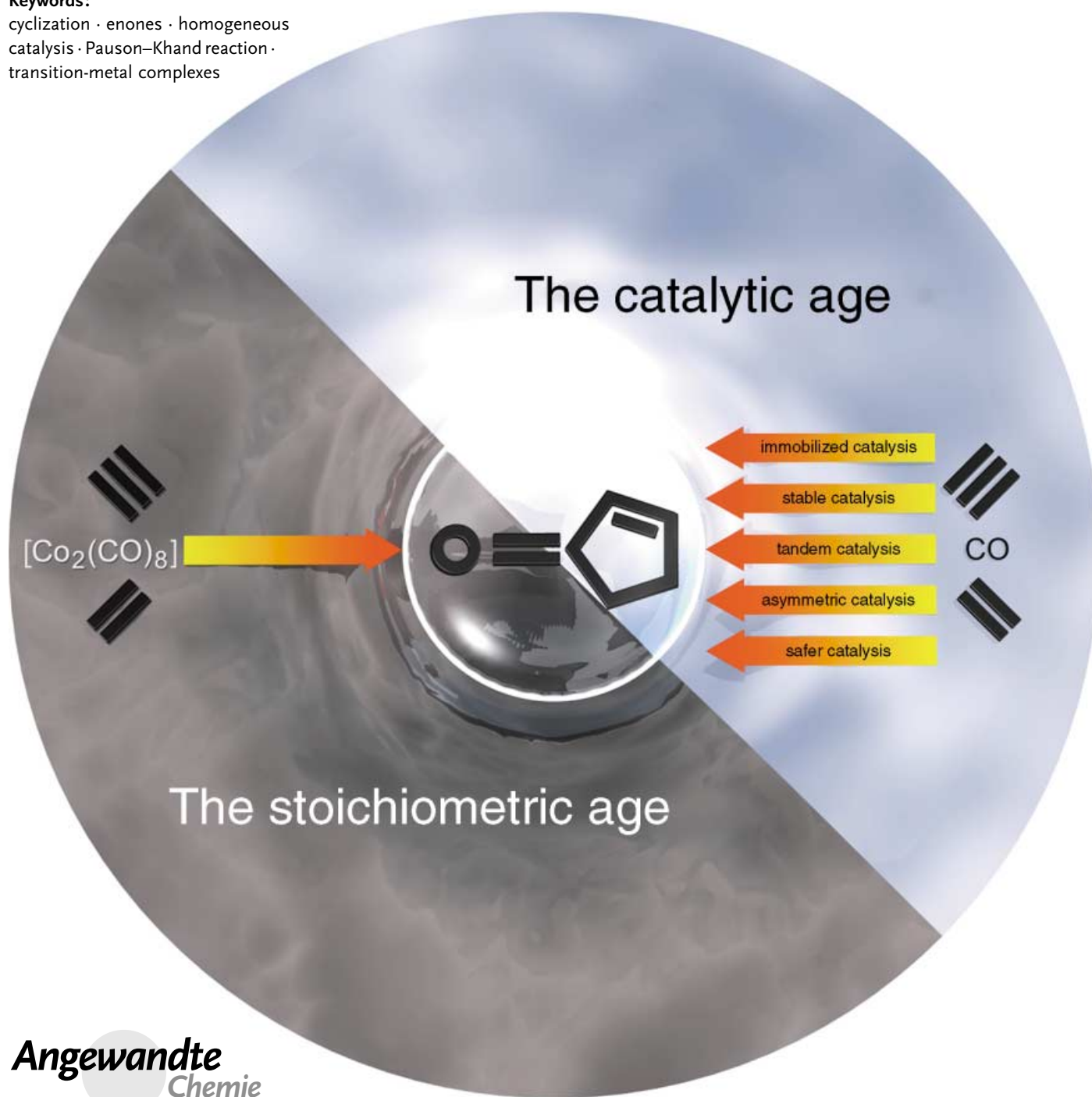


## Catalytic Pauson-Khand Reaction

**The Pauson–Khand Reaction: the Catalytic Age Is Here!***Susan E. Gibson (née Thomas)\* and Andrea Stevenazzi\****Keywords:**

cyclization · enones · homogeneous catalysis · Pauson–Khand reaction · transition-metal complexes

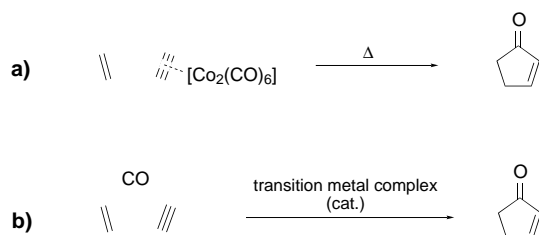


As a consequence of growing environmental awareness, it is now inappropriate to design a synthetic metal-mediated transformation that involves a noncatalytic use of toxic and expensive transition-metal species. One of the earliest examples of such a metal-mediated transformation is the Pauson–Khand reaction, a [2+2+1] cyclo-carbonylation that generates a cyclopentenone. Despite the early descriptions by Pauson and co-workers of catalytic versions of the reaction with octacarbonyldicobalt(0), applications of the Pauson–Khand reaction have to date almost exclusively used approaches that involve stoichiometric quantities of cobalt–carbonyl complexes. In the last decade, and, most markedly, in the last two to three years, however, there have been many exciting and novel developments in the catalytic Pauson–Khand reaction. Furthermore, asymmetric catalysis of the Pauson–Khand reaction has been shown to be a viable process. In view of the impressive developments in Pauson–Khand catalysis in the last two to three years, we present a comprehensive and critical coverage of the catalytic Pauson–Khand reaction that is designed to facilitate its application and to point to exciting future developments.

## 1. Introduction

The chemical industry is under increasing pressure to develop novel methodologies that reduce both the consumption of raw materials and the generation of toxic waste, as environmental issues acquire increasing relevance within the scientific community and amongst the general public. To fulfill the issue of atom economy raised by Trost, “an ideal chemical reaction must be not only selective, but also a simple addition in which the other reactants are required only in catalytic amounts”.<sup>[1]</sup> Metal-mediated transformations and catalysis play an important role in addressing the atom-economy issue. One of the earliest examples of a metal-mediated transformation is the Pauson–Khand reaction (PKR), first reported in 1971.<sup>[2]</sup> This is a [2+2+1] cycloaddition that results in the formation of a cyclopentenone from hexacarbonyldicobalt(0) complexes of alkynes, heated in the presence of an alkene (Scheme 1 a).

In view of the considerations expressed above it is unthinkable, in terms of cost and waste, to conceive a process that involves a stoichiometric use of a toxic and expensive transition-metal species. A superior approach would be to use



**Scheme 1.** The PKR: a) the stoichiometric approach; b) the catalytic version.

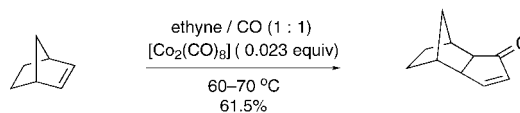
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catalytic amounts of transition-metal complexes to combine an alkyne, an alkene, and carbon monoxide (Scheme 1 b). Indeed, in 1973, Pauson and co-workers reported the first examples of the catalytic cycloaddition with octacarbonyldicobalt(0).<sup>[3]</sup> These early examples involved only constrained reactive alkenes such as norbornene and were carried out with a continuous supply of ethyne (Scheme 2). All the reactions were conducted within a narrow thermal window (60–70 °C), and a range of pressures of carbon monoxide were employed.

Despite early documentation of the catalytic PKR (CPKR) by Pauson and co-workers, applications of the PKR have to date almost exclusively exploited the stoichiometric approach (Scheme 1 a).<sup>[4]</sup> In the last decade, and most markedly in the last two to three years, however, there have been many exciting and novel developments in the CPKR. More practical alternatives to the original catalyst,  $[\text{Co}_2(\text{CO})_8]$ , have been designed, and investigations of other transition-metal complexes based on titanium, rhodium, ruthenium, and iridium have been rewarded with the discovery of impressive catalytic activity. Asymmetric variants of the catalytic cycloaddition are now available,<sup>[5]</sup> while safer and more environmentally friendly procedures that avoid the use of toxic carbon monoxide are starting to appear.

We believe that the developments of the last two to three years mean that we are now entering the catalytic age of the PKR, rendering the stoichiometric use of toxic metal



**Scheme 2.** One of the first examples of the CPKR employing a continuous supply of ethyne (Pauson and co-workers).

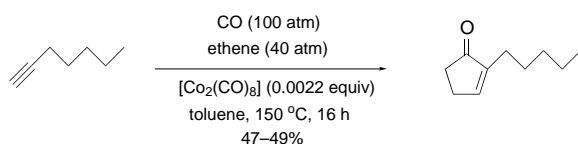
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complexes more and more difficult to justify. We have thus provided in this Review a comprehensive and critical coverage of the catalytic PKR that is designed to a) facilitate the matching of synthetic problems with catalyst systems, b) highlight areas in need of further development, and c) point to the potential of the CPKR in one-pot multicomponent catalysis.

## 2. Towards More Practical Catalysis

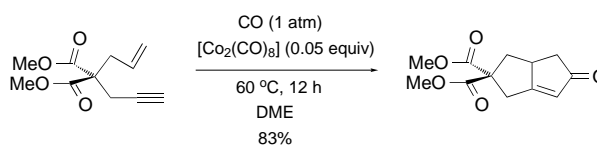
### 2.1. Tuning the Reaction Conditions

Following the work of Pauson and co-workers described in Section 1,<sup>[3]</sup> it was not until 1990 that the next truly CPKR was reported.<sup>[6]</sup> Rautenstrauch et al. used nonconstrained alkenes, and in one of their best experiments a TON (turnover number)<sup>[7]</sup> of 110 was obtained employing 0.0022 equivalents of the catalyst  $[\text{Co}_2(\text{CO})_8]$ , under very high partial pressures of carbon monoxide and ethene (Scheme 3). However, as reported by the author, the results were not always reproducible.



**Scheme 3.** CPKR under high pressures of carbon monoxide and ethene (Rautenstrauch et al.).<sup>[6]</sup>

More than 20 years after the initial results of Pauson and co-workers, Livinghouse and Pagenkopf drew our attention again to a catalytic approach of the PKR with a partial pressure of carbon monoxide of just 1 atm. In 1996 he reported a procedure in which photoactivation of  $[\text{Co}_2(\text{CO})_8]$  was required,<sup>[8]</sup> but a subsequent report from the same group related that careful control of the temperature to within the same narrow window employed earlier by Pauson and co-workers<sup>[3]</sup> dispenses with the need for photolytic promotion (Scheme 4).<sup>[9]</sup> For both the thermal and photochemical variations of the CPKR, Livinghouse and Pagenkopf stressed the importance of using high purity  $[\text{Co}_2(\text{CO})_8]$  to ensure reproducible results. One approach to overcoming this



**Scheme 4.** Thermal CPKR employing just one atmosphere pressure of carbon monoxide (Livinghouse and Pagenkopf).<sup>[9]</sup>

problem, as shown in Section 2.2, is the introduction of additives with the aim of stabilizing intermediates in the CPKR.

### 2.2. Use of Additives

Since the discovery of the PKR in the early 1970s, new procedures have been developed to improve the performances of the stoichiometric variants of the reaction. A wide range of compounds have been employed as promoters or additives, and the scope and limitations of the use of tertiary amine *N*-oxides, phosphanes, phosphane oxides, dimethyl sulfoxide (DMSO), hard Lewis bases, and sulfides have been well documented.<sup>[4]</sup> However, the employment of promoters such as tertiary amine *N*-oxides or DMSO in the CPKR produced only trace amounts of the desired products.<sup>[10]</sup> Presumably, the regeneration of  $\text{Co}^0$  species within the catalytic process is not permitted under these oxidizing conditions.

It has been suggested that the formation of cobalt clusters is an impediment to catalysis in the thermal PKR. At 50 °C,  $[\text{Co}_2(\text{CO})_8]$  is converted into  $[\text{Co}_4(\text{CO})_{12}]$ , which was believed to be inert towards alkyne substrates.<sup>[11]</sup> In an attempt to overcome the formation of inactive clusters, Pauson, Billington, and co-workers studied the influence of phosphanes and phosphites as coligands for the stoichiometric variants of the PKR.<sup>[12]</sup> Subsequently, a catalytic conversion of enynes into cyclopentenones employing phosphites as coligands was reported by Jeong, Chung, and co-workers (Table 1, entry 3).<sup>[10]</sup> Remarkably, under 1 atm of CO the use of phosphites as coligands did not show any positive effect on the PKR conversions (they were either ineffective or detrimental); the advantages of this procedure were only apparent at pressures of 3 atm.

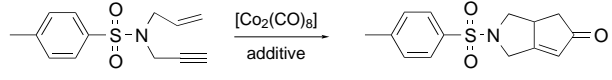


Sue E. Gibson obtained her BSc in Cambridge and her D. Phil. in Oxford under the supervision of Prof. S. Davies. She was then awarded a Royal Society European Fellowship to study at the ETH, Zürich, with Prof. A. Eschenmoser. In 1985 she returned to the UK as a lecturer in organic chemistry at the University of Warwick. In 1990 she was appointed as a lecturer at Imperial College, London, and in 1999 she took up the Daniell Chair of Chemistry at King's College London. Her research interests revolve around the application of transition metals in organic synthesis.



Andrea Stevenazzi completed a degree in chemistry at the Università degli Studi, Milan, in 1999. Under the supervision of Prof. S. Gibson at King's College London and Dr. C. Johnstone of AstraZeneca, his PhD has focused on the development of novel cobalt(0)–carbonyl complexes as catalysts of the Pauson–Khand reaction. In particular, he has been investigating the catalytic properties of phosphane-substituted cobalt–carbonyl complexes, both in homogeneous protocols and immobilized on a solid support.

**Table 1:** The influence of different additives on the cobalt-catalyzed Pauson–Khand reaction.



Entry	[Co <sub>2</sub> (CO) <sub>8</sub> ] [mol %]	Additive (mol %)	T [°C]	p(CO) [atm]	Yield [%]
1 <sup>[a]</sup>	7.5	none	60	1	86
2 <sup>[b]</sup>	10	none	70	1	63
3 <sup>[c]</sup>	5	P(OPh) <sub>3</sub> (20)	120	3	94
4 <sup>[d]</sup>	3	DME (12)	120	7	84
5 <sup>[e]</sup>	10	CyNH <sub>2</sub> (20)	70	1	89
6 <sup>[f]</sup>	5	Bu <sub>3</sub> PS (30)	70	1	87

Solvents and reaction times: [a] DME (12 h).<sup>[9a]</sup> [b] DME (10.5 h).<sup>[16]</sup> [c] DME (24 h).<sup>[10]</sup> [d] Toluene (10 h).<sup>[14]</sup> [e] DME (14 h).<sup>[16]</sup> [f] Benzene (4 h).<sup>[17]</sup>

Based on their own previous work on the stoichiometric version of the reaction,<sup>[13]</sup> Sugihara and Yamaguchi used hard Lewis bases to effect both the inter- and the intramolecular CPKR, employing 0.01–0.03 equivalents of octacarbonyldicobalt(0).<sup>[14]</sup> Hard Lewis bases are known to make the ligands of low-valent organotransition metal complexes more labile. 1,2-Dimethoxyethane (DME) was found to be the best promoter, giving cycloaddition products in very good yields (Table 1, entry 4). Water was found to be less efficient under the same conditions, but comparable yields were obtained at higher concentrations. It should be noted that under the conditions developed by Sugihara and co-workers the use of DME as solvent was detrimental to catalysis.<sup>[15]</sup> Interestingly, although cyclohexylamine was the best promoter in the stoichiometric version of the reaction,<sup>[13]</sup> it had no effect on the progress of the CPKR under 7 atm of CO.<sup>[14]</sup> On the other hand, Krafft et al. used cyclohexylamine as an additive for the thermal CPKR (Table 1, entry 5)<sup>[16]</sup> when they developed a set of conditions that removed the need for the “rigorous purification” of [Co<sub>2</sub>(CO)<sub>8</sub>] reported by Livinghouse and purification.<sup>[8,9a]</sup>

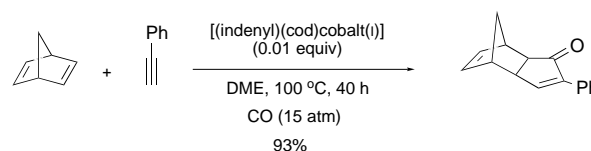
Hashimoto and co-workers has proved that the addition of phosphane sulfides to the CPKR results in higher yields and faster conversions under 1 atm of CO (Table 1, entry 6).<sup>[17]</sup> The TONs were high and they was even able to catalyze an intermolecular PKR under these mild conditions.

Although some success has been achieved by the use of additives, it has clearly emerged that in most cases the advantages observed are restricted to the particular conditions employed. The examples of CyNH<sub>2</sub> and phosphites reported earlier in this section show how the same additive can be either effective or ineffective depending on the reaction conditions utilized, which suggests that the use of additives cannot be considered as a universal approach to the CPKR.

### 2.3. Generation of Cobalt(0) In Situ

Problems associated with the very labile [Co<sub>2</sub>(CO)<sub>8</sub>] have led to the development of catalytic variants of the reaction

that generate the active catalyst in situ from Co<sup>I</sup> or Co<sup>II</sup> precursors. One of the first systems studied employed [(indenyl)(cod)cobalt(I)] (cod = cycloocta-1,5-diene) as the precatalyst, presumably reduced in situ to cobalt(0) by carbon monoxide.<sup>[18]</sup> Under high pressures of CO, very good conversions were obtained for both intramolecular cyclizations and intermolecular reactions between constrained alkenes and terminal alkynes (Scheme 5); TONs up to 97 in 40 h. Experiments with nonconstrained alkenes, however, were unsuccessful.



**Scheme 5.** The use of [(indenyl)(cod)cobalt(I)] as a precatalyst for the PKR (Chung and co-workers).<sup>[18]</sup>

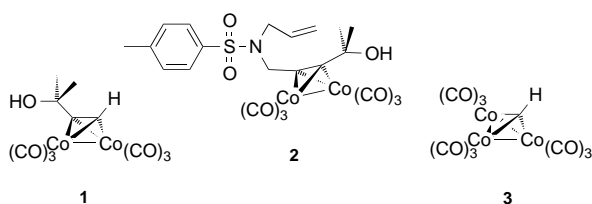
Inspired by work of Lautens and co-workers,<sup>[19]</sup> Lee and Chung reported that a catalytic combination of [Co(acac)<sub>2</sub>] and NaBH<sub>4</sub> can effectively promote both inter- and intramolecular versions of the PKR under high pressures of CO.<sup>[20]</sup> Despite the fact that the use of a strong reducing agent may limit the range of compatible functional groups, this system gave high TONs. It was presumed by the author that NaBH<sub>4</sub> prevented the formation of inactive cobalt species.

Rajesh and Periasamy developed a system in which the cobalt catalyst was obtained in situ by reducing CoBr<sub>2</sub> with Zn under 1 atm of CO.<sup>[21]</sup> Under these mild conditions a demanding substrate such as cyclopentene was cyclized. This system gave very low TONs, however, and can hardly be termed catalytic.

### 2.4. More Stable Sources of Cobalt(0)–Carbonyl Complexes

As reported by several research groups, the cobalt species [Co<sub>2</sub>(CO)<sub>8</sub>] is not very easy to handle: it is highly toxic and it ignites spontaneously upon contact with air. The development of more practical catalyst precursors that can either retain or improve the performance of [Co<sub>2</sub>(CO)<sub>8</sub>], without requiring reducing steps in situ, would bring substantial advantages to the catalytic versions of the PKR.

It has been known since the earliest investigations of the PKR that complexation of [Co<sub>2</sub>(CO)<sub>8</sub>] with the alkyne to form a more stable alkyne–[Co<sub>2</sub>(CO)<sub>6</sub>] species, is the first step of the cyclization.<sup>[3,22]</sup> Early attempts by Billington to use preformed ethyne–[Co<sub>2</sub>(CO)<sub>6</sub>] in a catalytic protocol, employing demanding alkenes such as 2,5-dihydrofuran under an ethyne/CO atmosphere, however, resulted in very low TONs.<sup>[23]</sup> Subsequently, Livinghouse and Belanger tried a similar protocol employing complex **1** for the cyclization of simpler intramolecular substrates (Scheme 6). Unfortunately, this species did not prove to be very active towards the enynes and Et<sub>3</sub>SiH was required to get good conversions.<sup>[24]</sup> This



**Scheme 6.** Examples of more stable sources of cobalt(0)-carbonyl complexes.

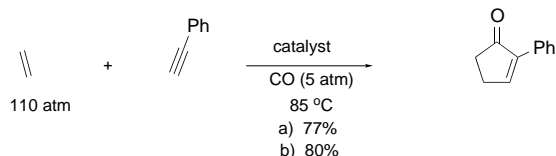
additive can be avoided, as Krafft reported, by using hexacarbonyldicobalt(0) complexes of enynes (**2**, Scheme 6).<sup>[25]</sup>

The use of cobalt(0)-carbonyl clusters as a more stable source of catalytically active species has been investigated by independent research groups.<sup>[26–29]</sup> Sugihara and Yamaguchi reported that air-stable alkylidyne nonacarbonyltricobalt clusters mediated the PKR under catalytic conditions.<sup>[26]</sup> Methylidyne nonacarbonyltricobalt (**3**, Scheme 6), easily prepared from octacarbonyldicobalt(0) and trihalomethanes,<sup>[30]</sup> catalyzed both inter- and intramolecular cycloadditions under 7 atm of CO, with TONs of up to 17.

The cobalt cluster compound  $[\text{Co}_4(\text{CO})_{12}]$  has always been believed to be catalytically inactive towards the PKR. Exploiting the equilibrium established under high pressures of CO between  $[\text{Co}_4(\text{CO})_{12}]$  and  $[\text{Co}_2(\text{CO})_8]$ , Chung and Kim utilized  $[\text{Co}_4(\text{CO})_{12}]$  (which is commercially available and more air-stable than  $[\text{Co}_2(\text{CO})_8]$ ) as a source of cobalt for both inter- and intramolecular cyclocarbonylations.<sup>[27]</sup> Under 10 atm of CO,  $[\text{Co}_4(\text{CO})_{12}]$  proved to be a more active catalyst than  $[\text{Co}_2(\text{CO})_8]$ .

Jeong et al. have demonstrated that supercritical fluids promote the CPKR.<sup>[28,31]</sup> Advantages of this technique, as reported by the author, include high solubility of gaseous reactants, rapid diffusion of solutes, and weakening of the solvation around the reacting species. In a recent communication, they described the intermolecular versions of the CPKR in supercritical ethene, employing  $[\text{Co}_2(\text{CO})_8]$  and the two cobalt clusters  $[\text{Co}_4(\text{CO})_{12}]$  and  $[\text{Co}_4(\text{CO})_{11}\{\text{P}(\text{O}^i\text{Pr})_3\}]$  as catalysts under 5 atm of carbon monoxide (Scheme 7).<sup>[28]</sup> Although the TONs were generally not impressive, it noteworthy that the phosphite-substituted cobalt species was remarkably easier to handle than the unsubstituted complexes.

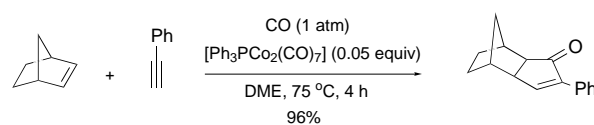
Evidence that  $[\text{Co}_4(\text{CO})_{12}]$  cannot be considered inactive towards the CPKR, even under atmospheric pressures of carbon monoxide, has recently been provided by Krafft and Boñaga.<sup>[29]</sup> In early experiments from this group, the observed



**Scheme 7.** CPKR in supercritical ethene according to Jeong et al.:<sup>[28]</sup> a)  $[\text{Co}_4(\text{CO})_{12}]$  (0.03 equiv), 24 h; b) more practical  $[\text{Co}_4(\text{CO})_{11}\{\text{P}(\text{O}^i\text{Pr})_3\}]$  (0.03 equiv) was used, 46 h.

activity of  $[\text{Co}_4(\text{CO})_{12}]$  was associated with the use of  $\text{CyNH}_2$  as an additive, but it was shown in the same study that the cobalt cluster  $[\text{Co}_4(\text{CO})_{12}]$  was active even in the absence of the amine. Indeed, a test conducted employing different solvents revealed that under certain conditions  $[\text{Co}_4(\text{CO})_{12}]$  can give higher TONs than the less-stable cobalt species  $[\text{Co}_2(\text{CO})_8]$ .<sup>[29]</sup>

Despite the significant use of phosphane- and phosphite-substituted alkyne complexes in the stoichiometric PKR, in which coordination leads to a decrease in the rate and overall efficiency of the reaction,<sup>[12,22]</sup> and despite the fact that triphenylphosphite additive in the  $[\text{Co}_2(\text{CO})_8]$ -mediated catalytic PKR leads to an improved reaction efficiency,<sup>[10]</sup> only recently was it shown that preformed complexes of phosphanes and phosphites can catalyze the PKR under atmospheric pressures of carbon monoxide.<sup>[32,33]</sup> The TONs observed in work by our own group with these stable complexes were comparable with those of other similar mild systems (Scheme 8). The triphenylphosphane derivative,  $[\text{Ph}_3\text{PCo}_2(\text{CO})_7]$ , in particular,<sup>[33]</sup> proved to be amongst the most robust species examined so far for the CPKR. Like other phosphite-substituted cobalt complexes examined earlier,<sup>[28]</sup>  $[\text{Ph}_3\text{PCo}_2(\text{CO})_7]$  does not ignite spontaneously upon contact with air. Moreover, this species retains its catalytic activity even after being stored at 4 °C for many months exposed to air.

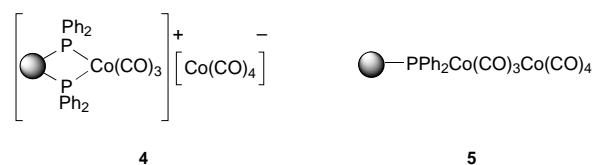


**Scheme 8.** PKR catalyzed by the robust complex  $[\text{Ph}_3\text{PCo}_2(\text{CO})_7]$  carried out by our group.

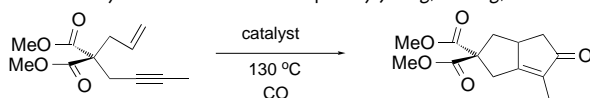
## 2.5. Heterogeneous Catalysts

The increasing awareness of the environmental and handling advantages conferred by solid-phase methodologies has recently spurred different research groups to develop new heterogeneous catalysts for the PKR.

The first example of a polymer-supported catalyst for the PKR, the resin-bound mixture of phosphane-substituted cobalt-carbonyl complexes **4** and **5**, was reported by our group in 2000 and proved to be an effective and practical catalyst of the PKR under mild conditions (Scheme 9).<sup>[34]</sup> Despite relatively low TONs, this system so far remains the only example of an effective heterogeneous catalyst for the PKR under only 1 atm of carbon monoxide.



**Scheme 9.** The polymer-supported cobalt(0)-carbonyl complexes employed by our group.

**Table 2:** Heterogeneous catalysts for the PKR developed by Jeong, Chung, and co-workers.<sup>[35–38]</sup>


Entry	Catalyst	Co loading [mol %]	Solvent	$p(\text{CO})$ [atm]	Yield [mol %]	Reuse <sup>[a]</sup>
1 <sup>[b]</sup>	Co/silica	13	DCM	20	92	3
2 <sup>[c]</sup>	Co/charcoal	16	THF	20	98	9
3 <sup>[d]</sup>	colloidal Co	45	THF	5	97	4
4 <sup>[e]</sup>	colloidal Co	67	H <sub>2</sub> O	20	96	4

[a] Number of times that the catalyst was reused without any loss in activity. Reaction times: [b] 18 h.<sup>[35]</sup> [c] 18 h.<sup>[36]</sup> [d] 12 h.<sup>[37]</sup> [e] 12 h.<sup>[38]</sup>

Chung and co-workers recently showed clearly how the dream of “more practical heterogeneous catalysts” for the PKR may be realized. They developed catalytic systems that require harsh conditions (high CO pressures and high catalyst loading), but are reusable and clean (Table 2).<sup>[35–38]</sup> The first system documented employs a 13 mol % loading of metallic cobalt supported on mesoporous silica as the catalyst precursor of the PKR.<sup>[35]</sup> This material proved to be active towards different intramolecular substrates under 20 atm of CO and could be recovered and reused three times without any loss of catalytic activity (Table 2, entry 1). Intermolecular substrates failed to cyclize in good yields under these conditions.

The next heterogeneous catalyst precursor reported by Chung and co-workers was cobalt on charcoal.<sup>[36]</sup> In this system a 16 mol % loading of cobalt was required for the cyclizations, but this time the catalyst could be recovered and reused nine times without losing any catalytic activity (Table 2, entry 2). Moreover, several intermolecular substrates could be cyclized in very good yields.

Colloidal cobalt nanoparticles were also observed to act as a reusable catalyst for the PKR.<sup>[37]</sup> Milder pressures of CO were used (5 atm), but a 45 mol % loading of cobalt was necessary for the cycloadditions. Colloidal cobalt gave good results for both inter- and intramolecular variants of the reaction and could be recovered and reused four times without showing any loss of activity (Table 2, entry 3). More recently, they were able to apply this technique in an aqueous environment.<sup>[38]</sup> Although this reaction can hardly be considered catalytic (loading = 67 mol %), this colloidal cobalt system proved to be active under highly oxidizing conditions for cobalt(0), and it could be recovered and reused four times without any loss of activity (Table 2, entry 4).

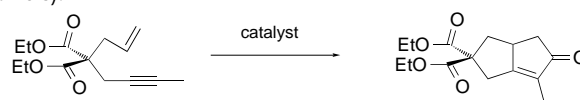
### 3. Towards Different Metals

#### 3.1. Optimization of Titanium Catalysts

Following the work of Negishi et al. on the zirconocene-mediated cyclization of enynes,<sup>[39]</sup> Buchwald and co-workers showed that the cyclocarbonylation of enynes could be mediated<sup>[40]</sup> and even catalyzed by titanocene complexes (Table 3).<sup>[41–43]</sup> The first protocol involved the use of the complex  $[\text{Cp}_2\text{Ti}(\text{PMe}_3)_2]$ , which proved to be extremely air-

sensitive and failed to cyclize common enynes under 1 atm of carbon monoxide.<sup>[41]</sup> To overcome this problem, trialkylsilyl cyanides were used to generate isocyanides in situ. The resulting bicyclic iminocyclopentenes were hydrolyzed to the classical cycloadducts of the PKR (Table 3, entry 1). A slightly more practical procedure was subsequently developed by the same group: The extremely unstable complex  $[\text{Cp}_2\text{Ti}(\text{PMe}_3)_2]$  was replaced by the commercially

available and stable catalyst precursor  $[\text{Cp}_2\text{TiCl}_2]$ .<sup>[42]</sup> In the presence of *n*BuLi and triethylsilyl cyanides, this system showed the same activity as the previous one. The overall yields were still generally poor, however, because of the hydrolysis step.

**Table 3:** PKR catalyzed by titanocene complexes (Buchwald and co-workers).<sup>[41–43]</sup>


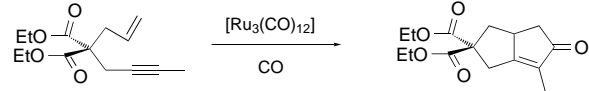
Entry	Catalyst (mol %)	R <sub>3</sub> SiCN (equiv)	$p(\text{CO})$ [atm]	Yield [%]
1 <sup>[a]</sup>	$[\text{Cp}_2\text{Ti}(\text{PMe}_3)_2]$ (10)	Et <sub>3</sub> SiCN (1.3)	–	71
2 <sup>[b]</sup>	$[\text{Cp}_2\text{Ti}(\text{CO})_2]$ (5)	–	1.22	91

[a] Ar, benzene, 45 °C, 16–24 h, then CuSO<sub>4</sub> (sat. aq.), room temperature, 3–5 h.<sup>[41]</sup> [b] Toluene, 90 °C, 12–48 h.<sup>[43]</sup>

Remarkable improvements were achieved by Buchwald and co-workers when the commercially available species  $[\text{Cp}_2\text{Ti}(\text{CO})_2]$  was employed as a catalyst for the cyclocarbonylation.<sup>[43]</sup> This complex cyclized a range of enynes under low pressures of carbon monoxide (1.22 atm), thus avoiding the use of isocyanides and the unwanted hydrolysis step (Table 3, entry 2). Moreover, the TONs were substantially higher and the system displayed an increased level of functional-group compatibility. Notably, in the cases of some 1,2-disubstituted alkene substrates, lower pressures of CO (0.34 atm) were required for complete consumption of the starting materials. Another protocol developed by the same group uses a nickel(0) complex as a catalyst for a Pauson–Khand-type reaction.<sup>[44]</sup> Despite its higher tolerance of different functional groups, this system showed only slight advantages over previous ones, and the TONs were very low.

#### 3.2. Ruthenium-Catalyzed Variants

In 1997 two research groups independently showed that  $[\text{Ru}_3(\text{CO})_{12}]$  can catalyze the PKR (Table 4).<sup>[45,46]</sup> Murai and co-workers reported that catalytic quantities of  $[\text{Ru}_3(\text{CO})_{12}]$  (0.02 equiv) cyclized a range of enynes with a disubstituted alkyne group under 10 atm of carbon monoxide (Table 4,

**Table 4:** The  $[\text{Ru}_3(\text{CO})_{12}]$ -catalyzed PKR (Murai and co-workers<sup>[45]</sup> and Mitsudo and co-workers<sup>[46]</sup>).


Entry	$[\text{Ru}_3(\text{CO})_{12}]$ [mol %]	$T$ [°C]	$t$ [h]	$p(\text{CO})$ [atm]	Yield [mol %]
1 <sup>[a]</sup>	2	160	20	10	86
2 <sup>[b]</sup>	2	140	8	15	78

[a] In dioxane.<sup>[45]</sup> [b] In *N,N*-dimethylacetamide (DMAc).<sup>[46]</sup>

entry 1).<sup>[45]</sup> On the other hand, enynes with a terminal alkyne group proved to be poor substrates for the cycloaddition. One month later, Mitsudo and co-workers reported that  $[\text{Ru}_3(\text{CO})_{12}]$  in DMAc (*N,N*-dimethylacetamide), under 15 atm of CO, catalyzed the cyclocarbonylation of several enynes with disubstituted alkyne groups (Table 4, entry 2); examples of enynes with terminal alkyne groups were not included.<sup>[46]</sup>

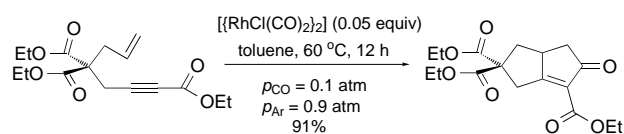
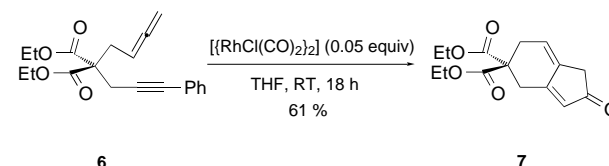
### 3.3. The Rhodium Approach

Rhodium catalyzed PKRs have recently attracted much attention.<sup>[47]</sup> Early studies by Narasaka and co-workers revealed that 0.02 equivalents of  $[\{\text{RhCl}(\text{CO})_2\}_2]$  catalyzed the reaction under 1 atm of CO.<sup>[47a]</sup> Later, the performance of the catalyst was optimized with respect to the solvent (xylene was replaced by toluene) and the catalyst loading (decreased to 0.05 equivalents).<sup>[47b]</sup> This system is excellent for substrates containing electron-deficient alkenes and alkynes (Scheme 10). Notably, the catalytic cycle for these particularly demanding substrates was accelerated by decreasing the partial pressure of CO down to 0.1 atm. Moreover, this rhodium-based catalyst has proven to be good even in the cyclizations of the allenyne **6** (Scheme 11). Under these catalytic conditions, the reaction is regioselective and involves exclusively the external double bond of the allene, yielding cyclopentenone **7**. This result in the rhodium-catalyzed PKR of allenes was subsequently confirmed by Mukai et al.<sup>[47d]</sup> and Brummond et al.<sup>[47e]</sup>

### 3.4. A Safety Note

As described above, the catalytic PKR has improved remarkably in terms of reaction conditions, TONs, and practicability over the last decade. The use of highly toxic carbon monoxide, however, still represents a major drawback to this procedure. A cyclocarbonylation reaction that did not use carbon monoxide would be a safer reaction and would be an important breakthrough in this area.

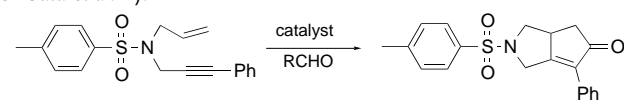
Based on one example reported earlier by Schore,<sup>[48]</sup> Krafft and Boñaga reported that cyclocarbonylation of a range of enynes can be achieved under an atmosphere of  $\text{N}_2$  employing 35–50% of  $[\text{Co}_2(\text{CO})_8]$ .<sup>[49]</sup> This procedure removes

**Scheme 10.** Rhodium-catalyzed PKR (Narasaka and co-workers).<sup>[47b]</sup> Note that this example employs an electron-deficient alkyne.**Scheme 11.**  $[\{\text{RhCl}(\text{CO})_2\}_2]$ -catalyzed cyclization of the allenyne **6**.

the need to use highly toxic carbon monoxide by increasing the amount of a toxic cobalt species and, therefore, cannot be considered the ideal approach to solve the toxicity problem.

More recently two astonishing communications from two independent research groups have reported the use of aldehydes as a CO source for the PKR (Table 5).<sup>[50,51]</sup> In the search for CO-transfer catalysts, Morimoto et al. tested different aromatic aldehydes with Rh, Ir, and Ru species. The most active system was a combination of the complex  $[\{\text{RhCl}(\text{cod})\}_2]$  (0.05 equiv) with  $\text{C}_6\text{F}_5\text{CHO}$  (2 equiv), and several enynes could be cyclized under a nitrogen atmosphere (Table 5, entry 1).<sup>[50]</sup>

Shibata et al. tested different aldehydes in a solvent-free system, employing the rhodium species  $[\text{Rh}(\text{dppp})_2\text{Cl}]$  (dppp = 1,3-bis(diphenylphosphanyl)propane) as the catalyst.<sup>[51]</sup> In this case, cinnamaldehyde was the most efficient aldehyde of those tested. The reactions were carried out employing 0.05 equivalents of the catalyst under 1 atm of argon (Table 5, entry 2). In a preliminary experiment, Shibata et al. tested this protocol under asymmetric conditions using tolbinap (0.1 equiv) as a chiral ligand and  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$  as the catalyst (0.05 equiv). Only one commonly used enyne was employed under these conditions, but a very encouraging result was obtained (89% yield, 83% ee).<sup>[51]</sup>

**Table 5:** The CPKR using aldehydes as CO source (Morimoto et al.<sup>[50]</sup> and Shibata et al.<sup>[51]</sup>).


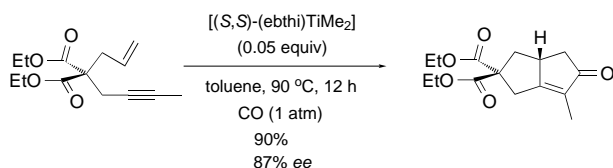
Entry	Catalyst (mol %)	Additive (mol %)	RCHO	Solvent	Yield [mol %]
1 <sup>[a]</sup>	$[\{\text{RhCl}(\text{cod})\}_2]$ (5)	dppp (11)	$\text{C}_6\text{F}_5\text{CHO}$	xylene	95
2 <sup>[b]</sup>	$[\text{Rh}(\text{dppp})_2\text{Cl}]$ (5)	–	cinnamaldehyde	–	98

[a]  $\text{N}_2$ , 130 °C, 4 h.<sup>[50]</sup> [b] Ar, 120 °C, 2 h, cinnamaldehyde (20 equiv).<sup>[51]</sup>

#### 4. Towards Asymmetric Catalysis

Until a few years ago, asymmetric protocols for the PKR were restricted to stoichiometric approaches to the reaction.<sup>[4,5]</sup> At that time, catalytic systems that could induce asymmetry were only speculative, presumably because in most of the cases they required very harsh conditions (high temperatures and very high pressures of carbon monoxide).<sup>[6,10,18,20]</sup>

In 1996, however, Buchwald and Hicks reported the first example of an asymmetric PKR involving a catalytic amount of a chiral titanocene complex (Scheme 12).<sup>[52]</sup> Following their own work on the use of the highly active species  $[\text{Cp}_2\text{Ti}(\text{CO})_2]$

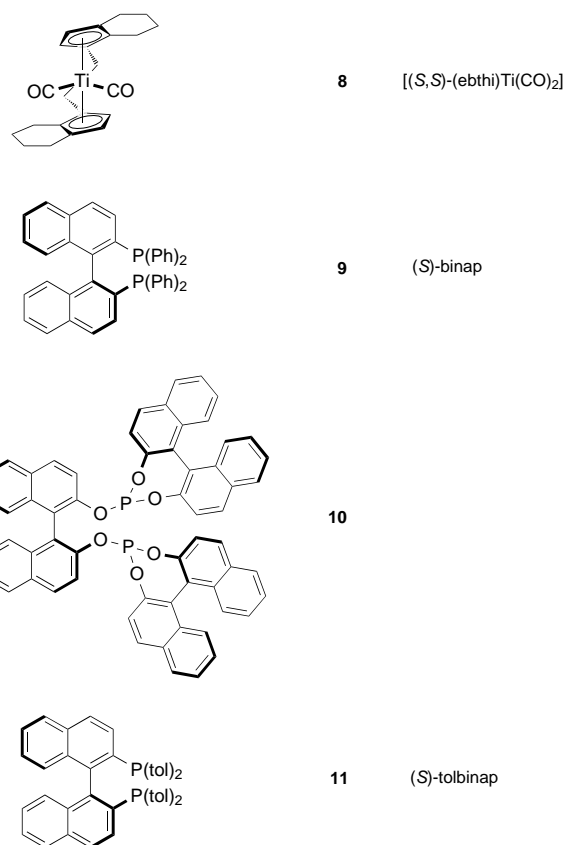


**Scheme 12.** Asymmetric CPKR employing the chiral titanocene complex **8** (Buchwald and Hicks).

as a catalyst for the cyclization of enynes under mild conditions, they succeeded in inducing asymmetry by employing the enantiomerically pure analogue  $(S,S)\text{-}[(\text{ebthi})\text{Ti}(\text{CO})_2]$  (**8**)—generated in situ from  $(S,S)\text{-}[(\text{ebthi})\text{Ti}(\text{Me})_2]$  (Scheme 13,  $\text{ebthi} = \text{ethylene-1,2-bis}(\eta^5\text{-4,5,6,7-tetrahydro-1-indenyl})$ ). This methodology showed some limitations in terms of substrate scope as a result of the sterically hindered nature of the  $\text{ebthi}$  ligand; otherwise good yields and  $ee$  values were obtained employing 0.05–0.2 equivalents of the catalyst. Subsequently the same group undertook a systematic study to develop an asymmetric protocol for nitrogen-containing enynes.<sup>[53]</sup> In the presence of  $(S,S)\text{-}[(\text{ebthi})\text{Ti}(\text{Me})_2]$  precatalyst, high levels of enantioselectivity could be achieved for the cyclization of substrates bearing an electron-rich, sterically undemanding nitrogen substituent.

The first example of an asymmetric cobalt-catalyzed PKR was reported by Hiroi et al.,<sup>[54]</sup> who employed chiral phosphanes as ligands. The chelating diphosphane  $(S)$ -binap (**9**; Scheme 13) induced the highest enantioselectivity. Unfortunately, high catalyst loadings were required for this system and consequently the TONs were quite low. More recently, Buchwald and Sturla studied the influence of a chiral phosphite on the cobalt-catalyzed PKR.<sup>[55]</sup> The reaction conditions were optimized with respect to solvent, temperature, partial pressure of carbon monoxide, and ligand/metal ratio. Good  $ee$  values (64–75%) were obtained for just two substrates in the presence of  $[\text{Co}_2(\text{CO})_8]$  (0.06 equiv) and the chiral biaryl phosphite **10** (0.1 equiv; Scheme 13).

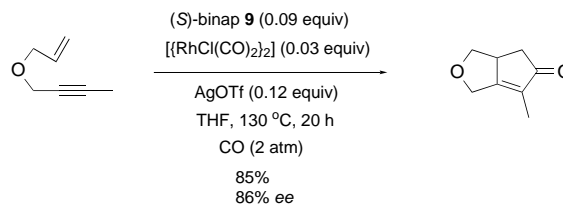
Following on the good results in their own work on a rhodium(I)-containing catalyst for the PKR,<sup>[47c]</sup> Jeong and co-workers recently reported an asymmetric rhodium-based system.<sup>[56]</sup> The conditions were optimized with respect to partial pressure of carbon monoxide, reaction temperature, and time. Good to very good  $ee$  values were found for a small



**Scheme 13.** Asymmetric ligands and catalysts employed in the CPKR.

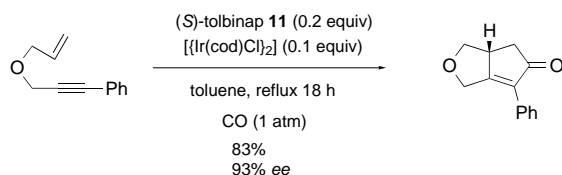
range of intramolecular substrates treated with  $[\{\text{RhCl}(\text{CO})_2\}_2]$  (0.03 equiv),  $(S)$ -binap (**9**) (0.09 equiv, Scheme 13), and  $\text{AgOTf}$  (0.12 equiv), as shown in Scheme 14.

In view of the interest in cobalt(0) and rhodium(I) catalysts, it was natural that attention would turn to iridium complexes at some point.<sup>[57]</sup> In preliminary studies by Shibata and Tagaki with a catalytic amount of  $[\{\text{Ir}(\text{cod})\text{Cl}\}_2]$  for the cyclization of a commonly used enyne, only relatively low conversions were achieved. After observing that the addition of phosphanes as coligands improved the yields of the reaction, Shibata and Tagaki decided to move directly to chiral phosphanes and examine the enantioselectivity of this protocol. Impressively, the use of  $(S)$ -tolbinap (**11**, Scheme 13) as an additive resulted in both excellent yields and enantiomeric excesses (Scheme 15). A small range of enynes were cyclized and the first catalytic example of an asymmetric intermolecular cyclization was reported.



**Scheme 14.** Rhodium-catalyzed asymmetric PKR under optimized conditions (Jeong et al.).<sup>[56]</sup>





**Scheme 15.** Iridium-catalyzed asymmetric PKR employing the chiral diphosphane **11** (Shibata and Tagaki).<sup>[57]</sup>

## 5. Summary and Outlook

To rationalize all the results obtained thus far in the CPKR, we have analyzed all the catalytic systems reported and made a number of observations with respect to catalyst–substrate compatibility and to catalyst activity and practicability.

### 5.1. Substrate Compatibility

Before discussing our general observations on catalyst–substrate compatibility, it should be noted that different metals have been studied and documented to different degrees. Cobalt complexes are the most thoroughly investigated system,<sup>[58]</sup> followed by titanium<sup>[59]</sup> and rhodium<sup>[60]</sup> systems; only two reports on ruthenium complexes<sup>[45,46]</sup> and one on an iridium species<sup>[57]</sup> are available. As the nature of the catalytic species is unknown in most cases and to provide a simple comparison of catalyst activity, TONs have been calculated with respect to the number of moles of Co<sub>1</sub>, Ti<sub>1</sub>, Rh<sub>1</sub>, Ru<sub>1</sub>, and Ir<sub>1</sub> in the catalysts. Based on an analysis of all the results reported to date, the following observations can be tentatively made:

- The PKR of enynes with terminal alkyne groups is more favorable under Co or Rh catalysis than under Ti catalysis (Table 6, entry 1).
- Enynes with disubstituted alkyne groups are annelated better by Ti and Rh systems than by Co, Ru, and Ir systems (Table 6, entry 2).

- Enynes with a disubstituted alkyne group and a substituted alkene function react well with Ti-based catalysts, but give poorer results with Co, Rh, and Ru catalysts (Table 6, entry 3).
- Oxygen-containing enynes cyclize well in the presence of Ti-, Rh-, and Ru-based systems, but not with Co catalysts (Table 6 entry 4).<sup>[61]</sup>
- Nitrogen-containing enynes react well under Rh and Ru catalysis, but not under Ti and Ir catalysis (Table 6, entry 5).
- As a general trend, polar functionalities are tolerated better by late-transition-metal complexes (cobalt and rhodium) than by titanium complexes.
- Enynes containing electron-withdrawing groups, either on the alkyne or on the alkene moiety, have been successfully cyclized only by Rh complexes under a particular set of conditions.<sup>[47b]</sup>
- Intermolecular substrates have only really been examined with Co systems; in these cases, they show greater limitations than intramolecular substrates.

### 5.2. Catalyst Activity and Practicability

To identify the most attractive approaches to the CPKR, we have analyzed all the systems reported to date with respect to cost, sensitivity, and activity, as defined by TON.<sup>[7]</sup> The 16 systems that gave the best results are listed in Table 7. Given that TONs can be highly sensitive to the pressure of carbon monoxide employed, and that CO pressure may be a key concern for a potential user of the PKR, the systems have been divided into four groups: 1) systems that do not employ CO (Table 7, entries 1 and 2), 2) systems that employ 1 atm of CO (Table 7, entries 3–8), 3) systems that employ 5–7 atm CO (Table 7, entries 9–12), and 4) systems that employ 10–40 atm CO (Table 7, entries 13–16). Within these groups the systems are ranked with respect to TONs. The details in Table 7 should not be overinterpreted as the different catalysts reported have been employed under different reaction conditions (different temperatures, reaction times, and solvents).

**Table 6:** Average TONs observed with different metal-based complexes.

Entry	Substrates	TON Co <sup>[a]</sup>	TON Ti <sup>[b]</sup>	TON Rh <sup>[c]</sup>	TON Ru <sup>[d]</sup>	TON Ir <sup>[e]</sup>
1		12 ± 4	4	14 ± 10	8	–
2		10 ± 5	18	20 ± 10	13 ± 2	4
3		10 ± 5	19	7	12	–
4		2 ± 2	18	14 ± 7	12	4
5		10 ± 4	6	16 ± 6	15	4

[a] Average value according to references [8, 9a, 10, 16, 17, 26, 33]. [b] Average value according to references [43, 53]. [c] Average value according to references [47b,c, 50, 51]. [d] Average value according to references [45, 46]. [e] The generally low values observed herein may be a function of the high catalyst loading employed to obtain good enantioselectivity.<sup>[57]</sup>

**Table 7:** Catalyst activity and practicability.

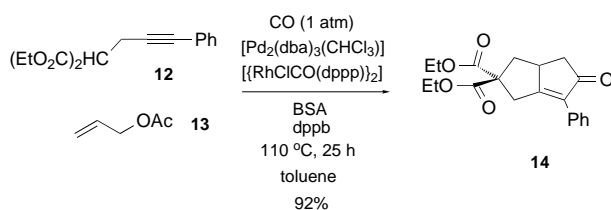
Entry	Catalyst system	$p(\text{CO})$ [atm]	TON <sup>[a]</sup>	Cost	Sensitivity grade <sup>[b]</sup>
1 <sup>[51]</sup>	[Rh(dppp) <sub>2</sub> Cl]	0	20–11	–	–
2 <sup>[50]</sup>	[[RhCl(cod)] <sub>2</sub> ]	0	10–7	high	1
3 <sup>[47b]</sup>	[[RhCl(CO) <sub>2</sub> ] <sub>2</sub> ]	1	82–7	high	3
4 <sup>[43]</sup>	[Cp <sub>2</sub> Ti(CO) <sub>2</sub> ]	1.22	19–9	high	4
5 <sup>[17]</sup>	[Co <sub>2</sub> (CO) <sub>8</sub> ] + R <sub>3</sub> PS	1	16–4	low	3
6 <sup>[33]</sup>	[Ph <sub>3</sub> PCo <sub>2</sub> (CO) <sub>7</sub> ]	1.05	11–5	–	1
7 <sup>[8]</sup>	[Co <sub>2</sub> (CO) <sub>8</sub> ] + <i>hν</i>	1	10–7	low	3
8 <sup>[16]</sup>	[Co <sub>2</sub> (CO) <sub>8</sub> ] + CyNH <sub>2</sub>	1	10–4	low	3
9 <sup>[14]</sup>	[Co <sub>2</sub> (CO) <sub>8</sub> ] + DME	7	50–36	low	3
10 <sup>[26]</sup>	[Co <sub>3</sub> (CO) <sub>9</sub> (μ <sup>3</sup> -CH)]	7	17–4	–	2
11 <sup>[28]</sup>	[Co <sub>4</sub> (CO) <sub>12</sub> ] <sup>[c]</sup>	5	7–2	medium	2
12 <sup>[28]</sup>	[Co <sub>4</sub> (CO) <sub>11</sub> P(OPh) <sub>3</sub> ] <sup>[c]</sup>	5	7–2	–	1
13 <sup>[20]</sup>	[Co(acac) <sub>2</sub> ] + NaBH <sub>4</sub>	30–40	100–7	low	0
14 <sup>[18]</sup>	indenyl cobalt(I)	15	97–10	–	0
15 <sup>[27]</sup>	[Co <sub>4</sub> (CO) <sub>12</sub> ]	10	50–38	medium	2
16 <sup>[45, 46]</sup>	[Ru <sub>3</sub> (CO) <sub>12</sub> ]	10–15	16–7	medium	1

[a] TONs calculated with respect to the number of moles of Co<sub>1</sub>, Ti<sub>1</sub>, Rh<sub>1</sub>, and Ru<sub>1</sub> in the catalysts. [b] 0 = stable, 4 = highly sensitive. [c] Reaction run in supercritical ethene.

### 5.3. Tandem Reactions—The Shape of Things to Come

Before ending this report on the CPKR we would like to highlight one of its most promising areas of application. It is common knowledge that in living organisms most of the required metabolites are synthesized by a programmed sequence of enzymes that show high specificity towards the different intermediates involved. Consequently, as an extension of the principle of atom economy,<sup>[1]</sup> a whole sequence of organic reactions should ideally be carried out in one pot, employing a range of catalysts that likewise show high specificity towards the different substrates. Tandem reactions, in which one or more catalysts are employed in one pot, can be considered as an approach to this ideal situation. Demonstrations of this strategy employing some of the most recently developed catalysts for the PKR are starting to appear in the literature.<sup>[62]</sup>

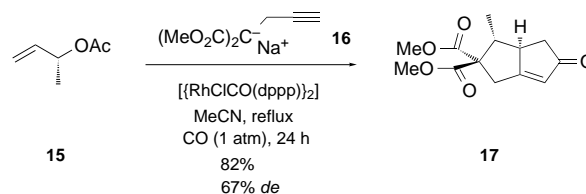
In one of the first examples, Jeong et al. reported that the catalytic combination of [Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>)] with [[RhCl(CO)(dppp)]<sub>2</sub>] converts the malonate derivative **12** and allyl acetate **13** into the bicyclic cyclopentenone **14** in high



**Scheme 16.** Tandem palladium and rhodium catalysis (Jeong et al.):<sup>[62a, b]</sup> **12** (1 equiv), **13** (2 equiv), [Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>)] (0.015 equiv), [[RhClCO(dppp)]<sub>2</sub>] (0.07 equiv), dppb (0.03 equiv), and BSA (1.2 equiv). BSA = bis(trimethylsilyl)acetamide.

yield (Scheme 16) through a palladium-catalyzed allylic substitution and a rhodium-catalyzed PKR.<sup>[62a, b]</sup>

A different approach was subsequently reported by Evans and Robinson. Cyclopentenone **17** was synthesized from allylic acetate **15** and the nucleophile **16** (prepared in situ by deprotonation of the malonate with a strong base) in the presence of catalytic rhodium-based complex [[RhClCO(dppp)]<sub>2</sub>] according to Scheme 17.<sup>[62c]</sup>



**Scheme 17.** The rhodium-catalyzed tandem reactions (Evans and Robinson):<sup>[62c]</sup> **16** (1.2 equiv) and [[RhClCO(dppp)]<sub>2</sub>] (0.06 equiv).

### 5.4. Final Comments

The catalytic protocols available in the literature represent excellent alternatives to the stoichiometric reaction types studied to date. And so, in view of the need for even more economic and environmentally friendly processes, high priority should now be given to the application and development of the catalytic PKR rather than to the stoichiometric version. In particular, the substrate scope needs to be broadened, especially to include more-demanding intermolecular systems, while convincing catalytic applications of the PKR in the synthesis of more-sophisticated molecules would strengthen this approach even further.

Asymmetric catalysis of the PKR is now a viable process and we are confident that developments in coming years will produce an efficient approach to chiral cyclopentenones, effectively replacing the currently favored noncatalytic chiral-auxiliary approach. From a personal perspective, the authors believe that recent developments in the areas of CO-free catalysis<sup>[50, 51]</sup> and one-pot multicomponent catalysis<sup>[62]</sup> are very exciting and we look forward to seeing these areas develop in the near future.

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