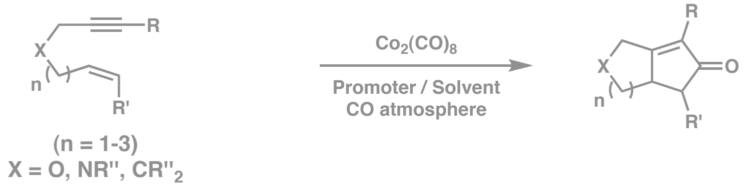
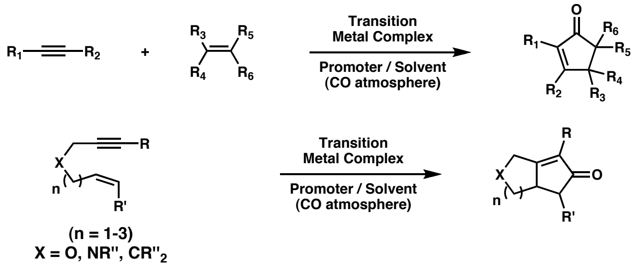
$Co_2(CO)_8$ Mediated Pauson–Khand Reaction (PKR)

Nathan Bennett

May 11, 2009



Pauson-Khand Reaction (PKR) General Information



Transition Metals = Co, Rh, Ti, Ru, Mo, W, Fe, Ni, Zr, Ir, Pd

Promoters = $NaBH_4$, Amines, Nitriles (CH_3CN), Amine N-Oxides (NMO, TMAO), Thioureas, Phophines, Phosphites, Sulfoxides (DMSO), Sulfides, Thioacetals, Silica Gel

Solvent = Benzene, Toluene, DCM, Acetonitrile, DMSO, Methanol, Hexanes, Ethyl Acetate, etc.

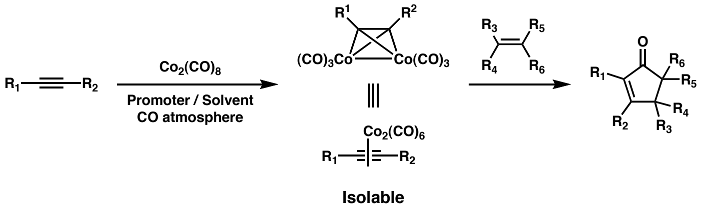
Completely compatible with ethers, alcohols, 3° amines, thioethers, ketones, ketals, esters, 3° amides, aromatic rings (benzene furan, thiophene)

Partial tolerance to alkyl/aryl halides, vinyl ethers and esters, ordinary alkene and alkynes in presence of more reactive unsaturation

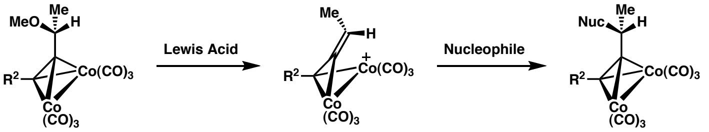
Kürti and Czakó. Pauson Khand Reaction, In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Amsterdam and Boston : 2005, pp 334–335.
Schore, *Chem. Rev.* **1988**, *88*, 1081–1119. (PKR 1085–1091)

PKR General Information

Geometry Changes



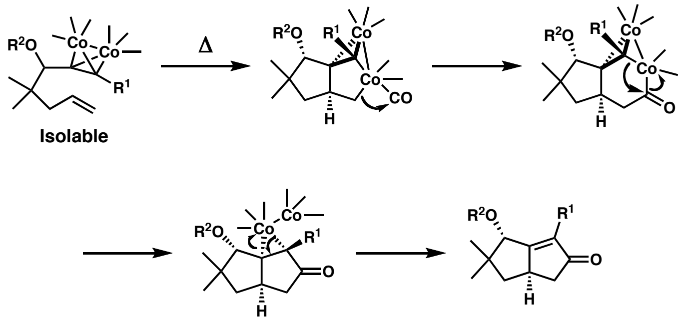
Electronic Changes – Nicholas Reaction



Kürti and Czakó. Pauson Khand Reaction, In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Amsterdam and Boston : 2005, pp 334–335.
Schreiber, *J. Am. Chem. Soc.* **1986**, *108*, 3128–3130.

PKR Mechanism

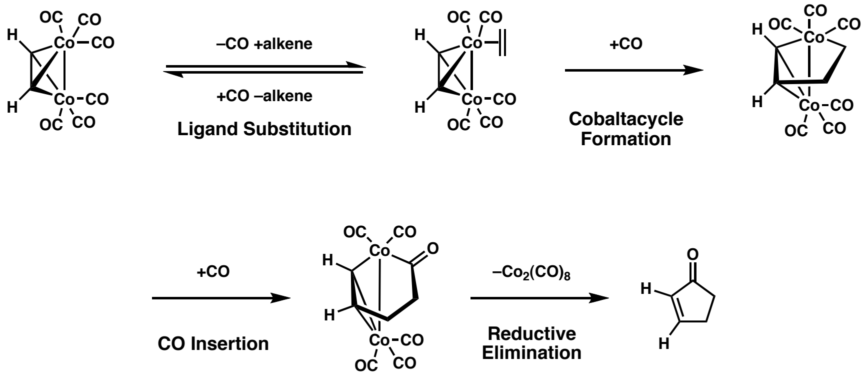
Magnus Mechanism



Magnus, *Tetrahedron Lett.* **1985**, *26*, 4851–4854.
Magnus, *Tetrahedron* **1985**, 41, 5861–5869.

PKR Mechanism

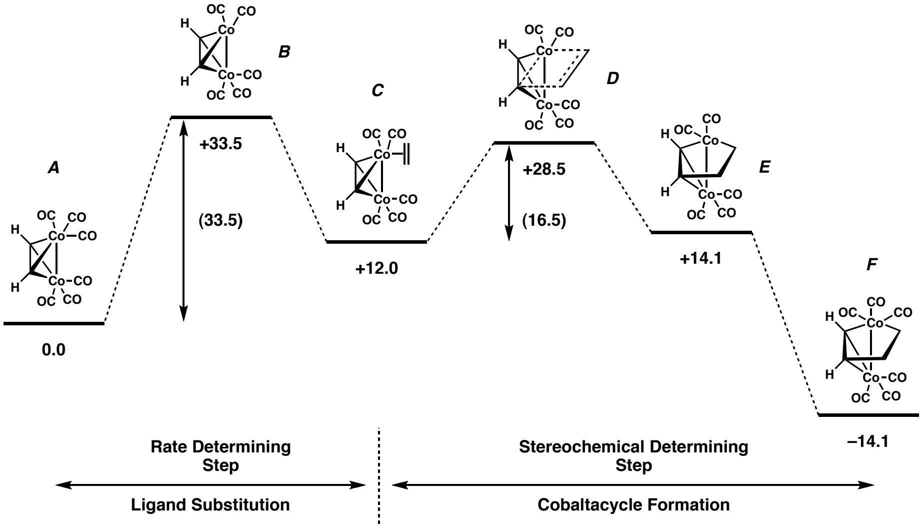
General Mechanism



Pericàs, Pure Appl. Chem. **2002**, *74*, 167–174.

PKR Mechanism

DFT Calculations



Pericàs, Pure Appl. Chem. **2002**, *74*, 167–174.

PKR Early Work

Origin

First Example in Literature

J. Chem. Soc., Perkin Trans. 1 **1973**, *9*, 975–977 and 977–981

- **Originally reported by Peter L. Pauson in 1973**
- **First Author: Ihsan U. Khand**
- **Two Other Authors: Graham R. Knox and William E. Watts**
- **Department of Pure and Applied Chemistry**
  University of Strathclyde in Glasgow, Scotland
- **Pauson refers to as "Khand Reaction"**

Peter L. Pauson

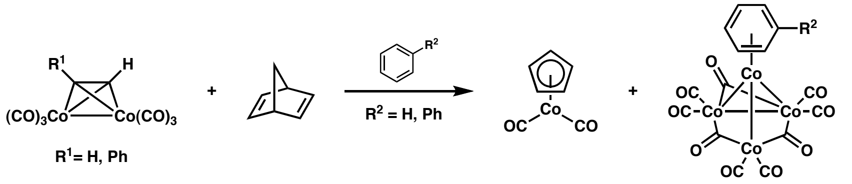
Four Main Papers

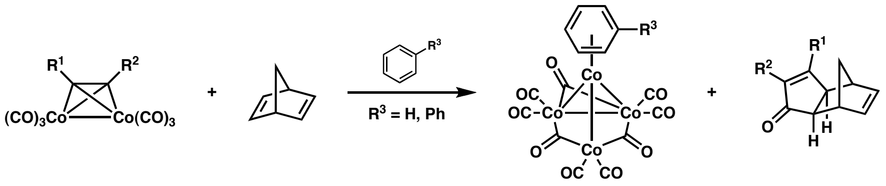
Khand and Pauson, *J. Chem. Soc. Chem. Comm.* **1971**, 1, 36.
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 975–977.
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1976**, *1*, 30–32.

Adam Hoye, (Jun 2007) http://ccc.chem.pitt.edu/wipf/Frontiers/Adam.pdf, (Accessed May 2, 2009).
Connection with Ferrocene: Hoffmann, *Angew. Chem., Int. Ed.* **2000**, *39*, 123–124.

PKR Early Work

First Publications

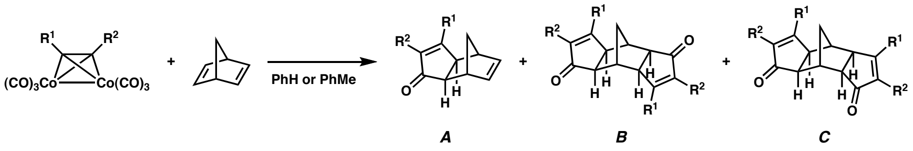




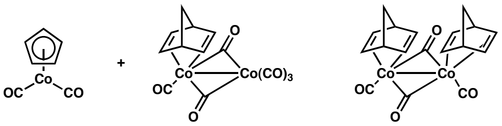
Khand and Pauson, *J. Chem. Soc. Chem. Comm.* **1971**, 1, 36.
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1*, **1973**, *9*, 975–977.

PKR Early Work

Publication Main Results



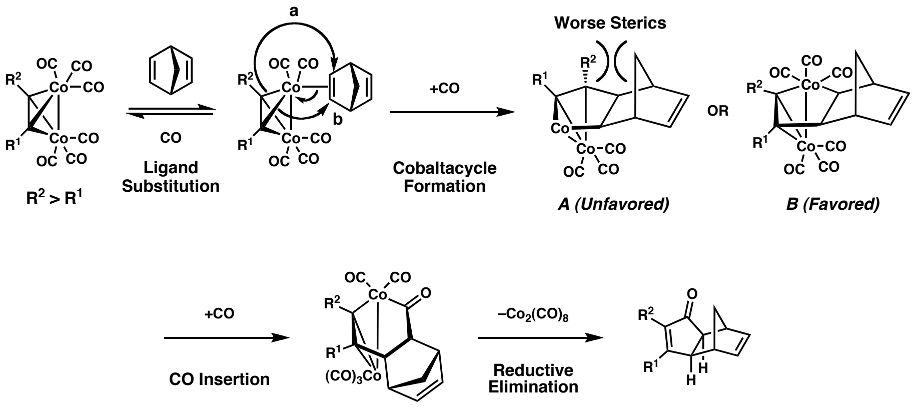
			% Yield		
entry	R¹	R²	A	B	C
1	H	H	43	29	4
2	H	Me	33	17	4.4
3	H	Ph	45	13	n/a
4	Ph	Ph	28	n/a	n/a
5	Et	Et	23	n/a	n/a



Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.

PKR Mechanism

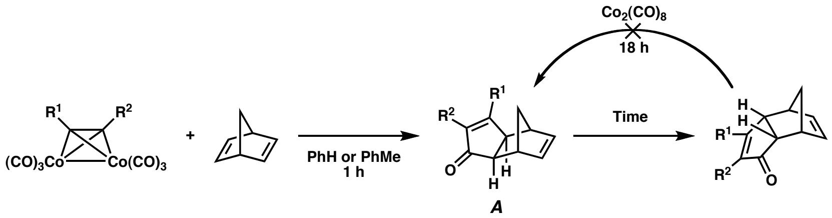
Determining Stereochemistry



Magnus, *Tetrahedron Lett.* **1985**, *40*, 4851–4854.
Magnus, *Tetrahedron* **1985**, 2*4*, 5861–5869.
Pericàs, *Pure Appl. Chem.* **2002**, *74*, 167–174.

PKR Early Work

Exo–Endo Isomerization



"Moreover when the samples of the mixture from the condensation reaction were withdrawn at intervals and examined by g.l.c. it was found that the endo-isomer was barely detectable after 1 h but increased steadily with reaction time. Thus, endo-isomer arises by catalysed isomerisation of the exo-isomer formed in the initial reaction.

This isomerisation is irreversible: a sample of pure endo-ketone was heated in the presence of octacarbonyldicobalt for 18 h showed no trace of the exo-isomer . . .

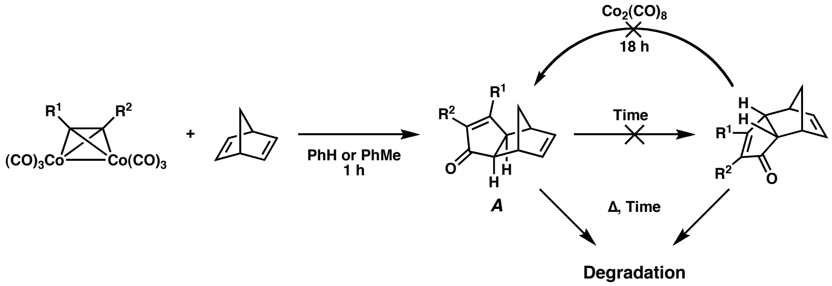
The isomerisation, unlike the condensation reaction must require the second double bond since no endo-isomer of ketone (A) was found.

Moreover it is strongly hindered by substitution: we do not detect peaks attributable to endo-isomers in the ketones from substituted acetylenes . . . "

Pauson and Khand, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.
Billington and Pauson, *J. Organomet. Chem.* **1988**, *354*, 233–242.

PKR Early Work

Exo–Endo Isomerization



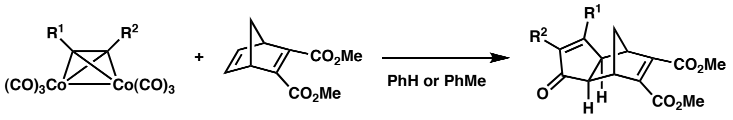
On working with rate enhancing procedures:

"This conflicted with the earlier conclusion that the *endo*–compound results from isomerisation of the *exo* form. Indeed, when a sample of pure *exo*–ketone was kept at 70 °C in the presence of octacarbonyldicobalt for 24 h no such isomerisation occurred but less than 50% of the ketone was recovered. We concluded that the previously noted change in isomer ratio of a mixed sample must have resulted from differential rate of loss of the two stereoisomers and not from isomerisation."

Pauson and Khand, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.
Billington and Pauson, *J. Organomet. Chem.* **1988**, *354*, 233–242.

PKR Early Work

Other Substrates

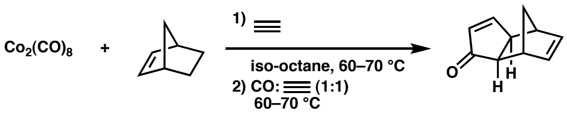


entry	R^1	R^2	% Yield
1	H	H	23
2	H	Me	38
3	H	Ph	31
4	Ph	Ph	28

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.

PKR Early Work

First Catalytic Example

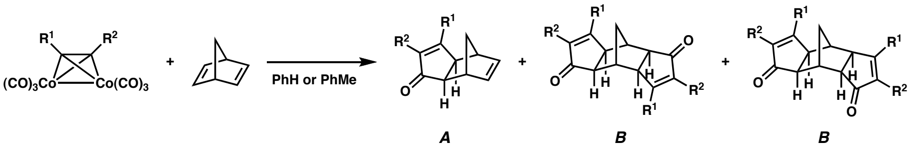


$Co_2(CO)_8$			Norbornene		Product	
g	mmol	mol %	g	mmol	g	% Yield
1.0	3	9.4	3	32	3.54	74
.52	1.5	2.3	6.05	64.25	5.8	61.5

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.

PKR Early Work

Publication Summary



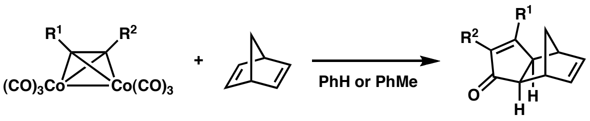
entry	R^1	R^2	% Yield A	% Yield B	% Yield C
1	H	H	43	29	4
2	H	Me	33	17	4.4
3	H	Ph	45	13	n/a
4	Ph	Ph	28	n/a	n/a
5	Et	Et	23	n/a	n/a

— **Bulkier alkyne substituent located at C–2 position**
— ***Exo*-isomer major product**
— **Bis–functionalized product possible**
— **Dicobalt mono– and bis–norbornadiene carbonyl complexes not part of mechanism**
— ***Endo* and *Exo*-isomers degrade (no isomerization)**
— **Impact of substitution and electronics of alkene**
— **First catalytic example**

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.

PKR Early Work

Expanding Reaction Scope



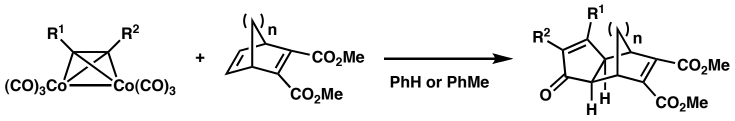
entry	R^1	R^2	% Yield	entry	R^1	R^2	% Yield
1	H	H	43	6	Me	Ph	65
2	H	Me	33	7	Me	$SiMe_3$	38
3	H	Ph	45	8	Me	$CH_2C{\equiv}CMe$	a
4	Ph	Ph	28	9	Me	$CH_2CH{=}CHMe$	a
5	Et	Et	23				

[a] **Unpublished results.**

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1976**, *1*, 30–32.

PKR Early Work

Expanding Reaction Scope



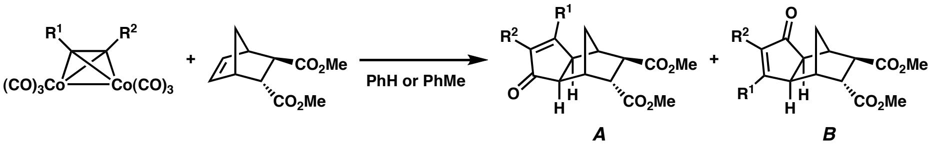
entry[a]	n	R^1	R^2	% Yield
1	1	H	H	23
2	1	H	Me	38
3	1	H	Ph	31
4	1	Ph	Ph	28
5	2	H	H	80
6	2	H	Me	36
7	2	H	Ph	85

[a] Entries 1-4, see Ref 1. Entries 5-7, see Ref 2.

1. Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1973**, *9*, 977–981.
2. Khand and Pauson, J. Chem. Res., Synop. **1978**, 346–347.

PKR Early Work

Impact of Distant Sterics

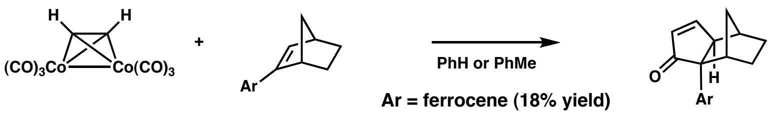


entry	R^1	R^2	% Yield A	% Yield B
1	H	H	25	8
2	H	Me	53	9
3	H	Ph	44	14
4	Me	Ph	28	14

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1976**, *1*, 30–32.

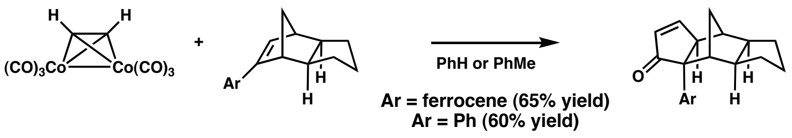
PKR Early Work

First Substituted Alkene Examples



PhH or PhMe

Ar = ferrocene (18% yield)

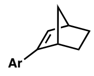
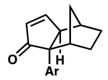
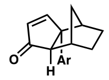
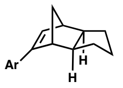
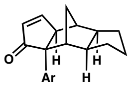
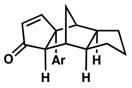
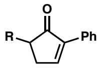
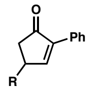
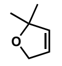
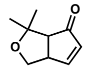
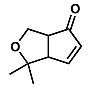
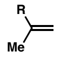
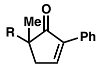
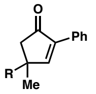
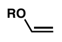
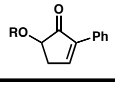
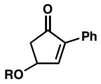


PhH or PhMe

Ar = ferrocene (65% yield)
Ar = Ph (60% yield)

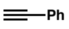
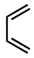
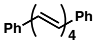
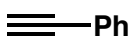
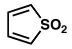
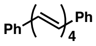
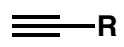
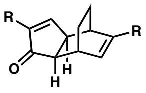
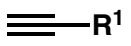
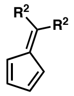
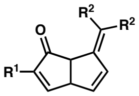
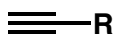
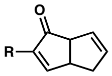
Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1976**, *1*, 30–32.

Alkene Selectivity Using $Co_2(CO)_8$

entry	Alkyne	Alkene	2,5–Product	2,4–Product		2,5 : 2,4
1	$\equiv$				Ar = Ferrocene	100:0
2	$\equiv$				Ar = Ferrocene	100:0
3					Ar = Ph	100:0
4	$\equiv$–Ph				R = Cp	100:0
5					R = Me	1:1
6					R = C_6H_{13}	5:6
7	$\equiv$					100:0
8	$\equiv$–Ph				R = $(CH_2)_2NMe_2$	24:1
9					R = CH_2OTHP	Mix
10	$\equiv$–Ph				R = OMe	1:1
11					R = t-Bu	1:1

Khand and Pauson, *J. Chem. Soc., Perkin Trans. 1* **1976**, 30.
Khand and Pauson, *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2–14.
Schore, *J. Org. Chem.* **1981**, *46*, 5357–5363.
Pauson, *Organometallics* **1982**, *1*, 1560–1561.
Pauson, Tetrahedron **1985**, *41*, 5855–5860.
Krafft, *J. Am. Chem. Soc.* **1988**, *110*, 968–970.

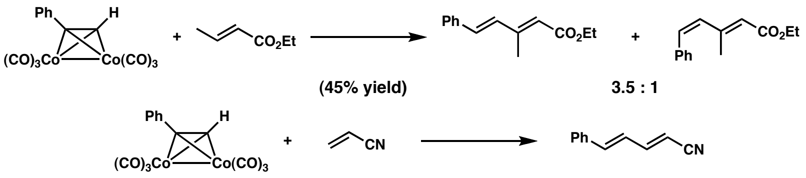
Diene Reactivity

entry	Alkyne	Alkyne	Product		% Yield
1					Not Reported
2					Not Reported
3				R = H	20
4				R = Me	38
5				R = Ph	65
6				R^1 = H, R^2 = Ph	15
7				R^1 = Me, R^2 = Ph	15
8				R^1 = Ph, R^2 = Me	23
9				R = Me	55
10				R = Ph	60

Khand and Pauson, *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2–14.
Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 346–347.
Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 348–349.
Pauson, *Tetrahedron* **1985**, *41*, 5855–5860.

Electronic Effects

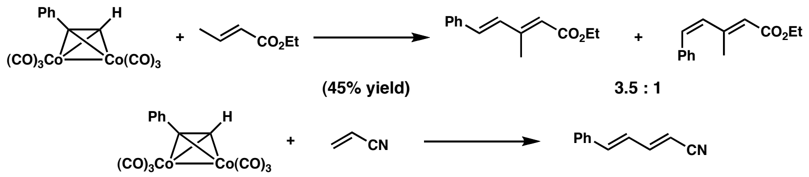
1,3–Diene Products

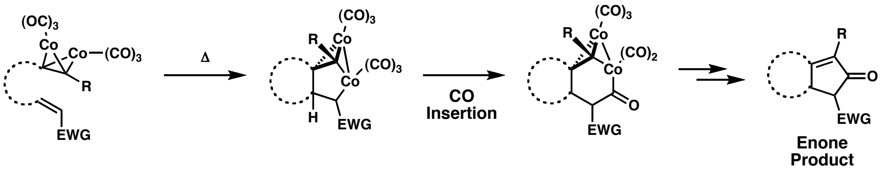


Khand and Pauson, *Chem. Commun.* **1974**, 379.
Pauson, *Tetrahedron* **1985**, *41*, 5855–5860.

Electronic Effects

1,3–Diene Mechanism

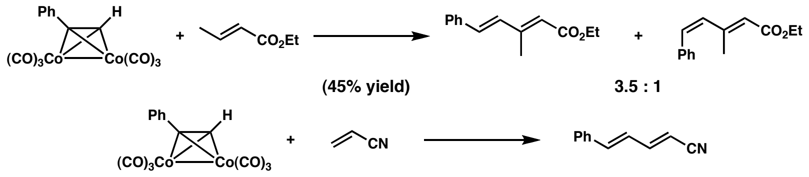


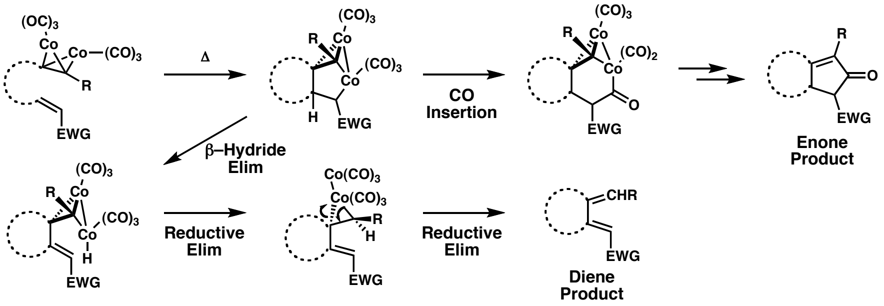


Khand and Pauson, *Chem. Commun.* **1974**, 379.
Pauson, *Tetrahedron* **1985**, *41*, 5855–5860.

Electronic Effects

1,3–Diene Mechanism

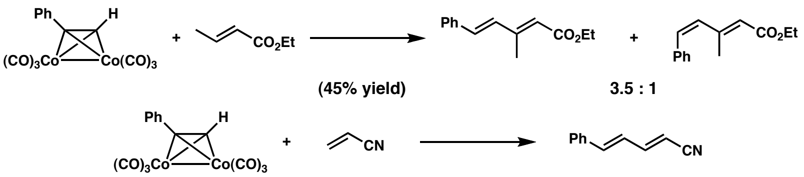


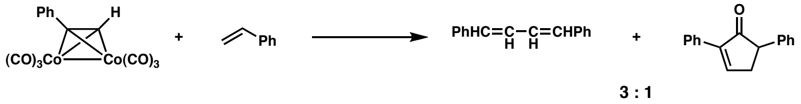


Khand and Pauson, *Chem. Commun.* **1974**, 379.
Pauson, *Tetrahedron* **1985**, *41*, 5855–5860.

Electronic Effects

1,3–Diene Products

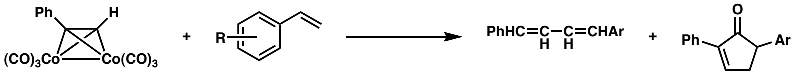




Khand and Pauson, *Chem. Commun.* **1974**, 379.
Pauson, *Tetrahedron* **1985**, 41, 5855–5860.
Khand and Pauson, *J. Chem. Res., Synop.* **1977**, 9.

Electronic Effects

Substituted Styrene

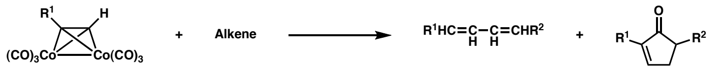


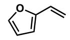
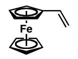
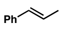
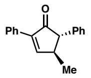
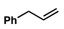
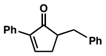
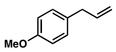
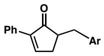
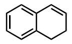
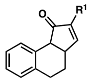
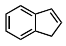
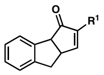
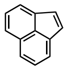
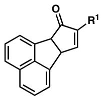
		% Yield	
entry	R	Diene	Enone
1	4–Me	26	13
2	4–F	0	35
3	4–Cl	8	8
4	2–Cl	16	4
5	4–MeO	42	27

Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 350–351.

Electronic Effects

Aromatic Alkenes

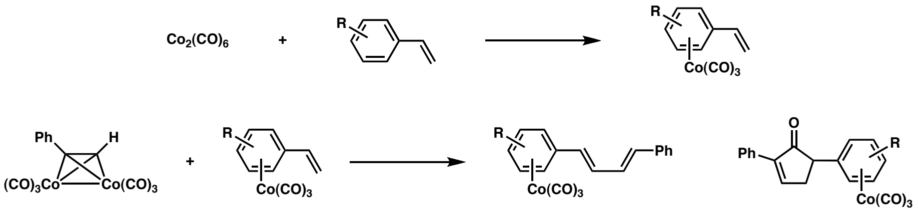


entry	R¹	Alkene	% Yield Diene	 Enone
1	Ph		*trans, trans*: 15	0
2	Ph		*trans, trans*: 49	trace
3	Ph		0	 15
4	Ph		0	 25
5	Ph		*trans, trans*: 3 *cis, trans*: 2	 25
6 7	Ph Me		Ph: 4 Me: 0	 Ph: 38 Me: 35
8 9	H Me		H: 0 Me: 0	 H: 31 Me: 41
10 11 12	H Me Ph		H: 0 Me: 0 Ph: 0	 H: 24 Me: 26 Ph: 38

Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 348–349.
Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 350–351.

Electronic Effects

Coordinated Substituted Styrene



entry	R	% Yield Diene	 Enone
1	H	32	37
2	4–Me	29	39
3	4–Cl	29	0
4	4–F	44	29
5	4–MeO	35	38

Khand and Pauson, *J. Chem. Res., Synop.* **1978**, 352–353.

Selectivity Summary

1,3–Diene Summary

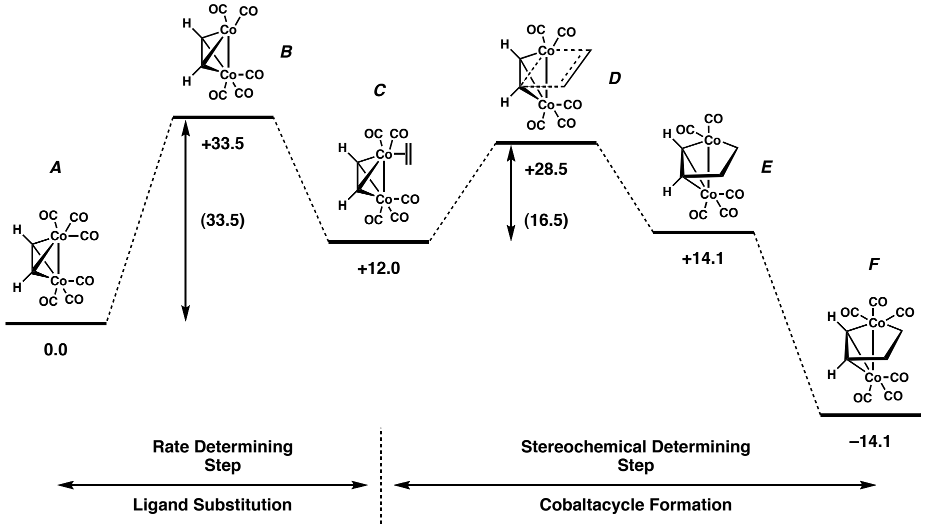
— **Alkynes**
  - **Bulkier substituent located at C2 position of cylcopentenone**
  - **Swich functionality to C3 through use of silyl protecting groups**

— **Alkenes**
  - **Aryl alkenes favor 2,5–products**
  - **Alkyl alkenes are generally mixtures of 2,5– and 2,4–products**
  - **Bidentate ligands can improve selectivity**

— **1,3–Diene Products**
  - **EWG favor 1,3–diene**
  - **Styrenes have intermediate reactivity producing both 1,3–dienes and enones**
  - **Other aromatics have mixed reactivity greatly dependent on substrate**
  - **$Co_2(CO)_8$ does not offer the best path to diene products**

PKR Mechanism

DFT Calculations



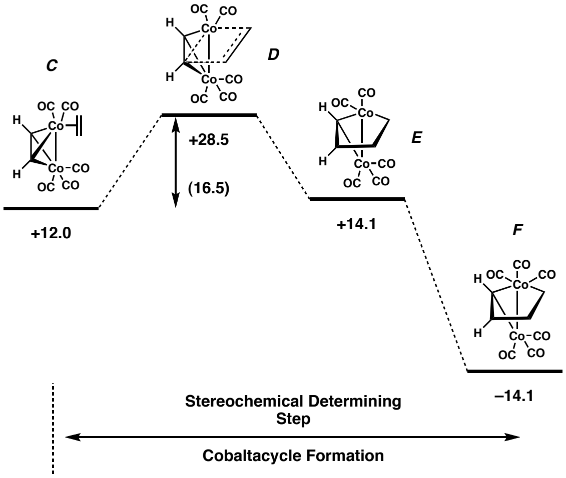
Pericàs, Pure Appl. Chem. **2002**, *74*, 167–174.

PKR Mechanism

Influence of Alkene Strain on Reaction

Strain Impact on E_a

- — **Alkene strain impacts energy of 2nd step**
- — **Intermediate D releaves alkene strain ⇒ ↓ E_a**
- — **Co back donation ≈ Cobaltcycle barrier**
  - **Looking for lower LUMO of Alkene**
  - **$\angle_{alkene}$ ≈ $LUMO_{alkene}$**
- — **Less strained alkenes proceed at higher T**



Pericàs, *Pure Appl. Chem.* **2002**, *74*, 167–174.
Milet and Gimber, *J. Org. Chem.* **2004**, *69*, 1075–1080.
Gibson, *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037.

PKR Mechanism

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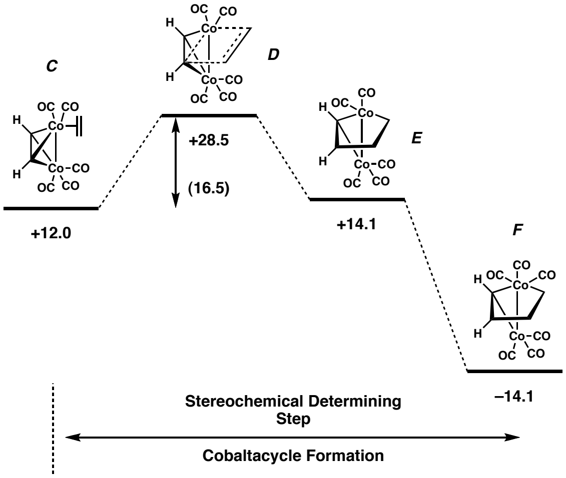
  - **$\angle_{alkene}$ ≈ $LUMO_{alkene}$**
- — **Less strained alkenes proceed at higher T**

Alkene	ΔH°_f (kcal/mol)	Alkene	ΔH°_f (kcal/mol)
	–47.3		–27.8
	–32.0		
	–31.3		–21.7
	–32.5		–21.6



Pericàs, *Pure Appl. Chem.* **2002**, *74*, 167–174.
Milet and Gimber, *J. Org. Chem.* **2004**, *69*, 1075–1080.
Gibson, *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037.

PKR Mechanism

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- — Intermediate D releaves alkene strain ⇒ ↓ E_a
- — Co back donation ≈ Cobaltcycle barrier
  - Looking for lower LUMO of Alkene
  - $\angle_{alkene} \approx \text{LUMO}_{alkene}$
- — Less strained alkenes proceed at higher T

Alkene	ΔH°$_f$ (kcal/mol)	Alkene	ΔH°$_f$ (kcal/mol)
	–47.3		–27.8
	–32.0		
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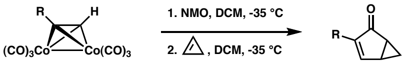
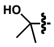
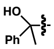
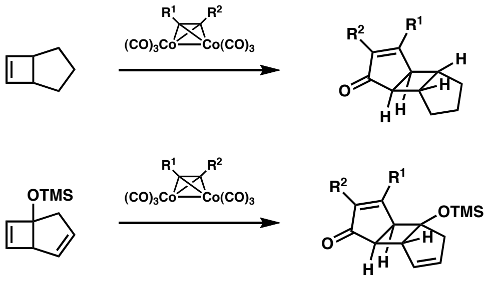


entry	R	% Yield
1	tBu	93
2	Ph	50
3		51
4	Ph_3Si	82
5		45
6	C_6H_{13}	62

Pericàs, *Pure Appl. Chem.* **2002**, *74*, 167–174.
Milet and Gimber, *J. Org. Chem.* **2004**, *69*, 1075–1080.
Gibson, *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037.

Alkene Reactivity

Alkene Strain Impact



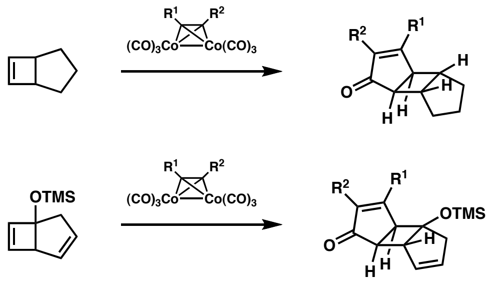
- **a. $R^1 = R^2 = H$**
- **b. $R^1 = H, R^2 = Me$**
- **c. $R^1 = H, R^2 = Ph$**
- **d. $R^1 = Me, R^2 = Ph$**
- **e. $R^1 = R^2 = Et$**
- **f. $R^1 = R^2 = Ph$**

> **"Only strained alkenes (e.g. norbornene) are reactive under mild conditions (60–80 °C), while simple alkenes participate only at much higher temperatures (e.g. 140–150 °C) and usually produce very low yields of cyclopentenones."**
>
> — Schore, *J. Org. Chem.* **1981**, *46*, 5436–5438.

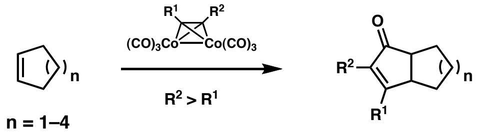
Khand and Pauson, *J. Chem. Res., Synop.* **1977**, 8.

Alkene Reactivity

Alkene Strain Impact



a. $R^1 = R^2 = H$
b. $R^1 = H, R^2 = Me$
c. $R^1 = H, R^2 = Ph$
d. $R^1 = Me, R^2 = Ph$
e. $R^1 = R^2 = Et$
f. $R^1 = R^2 = Ph$

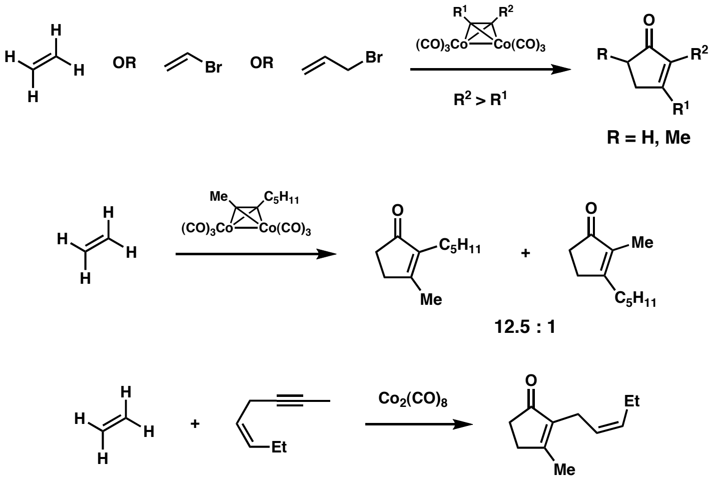


— Cycloalkenes possible at higher temp (60 – 120 °C)
— 5 and 7 rings work best
— 6 ring is "sluggish"

Khand and Pauson, *J. Chem. Res., Synop.* **1977**, 8.
Khand and Pauson, *J. Chem. Res., Synop.* **1977**, 9.

Alkene Reactivity

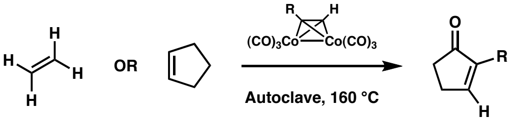
Ethylene and Equivalents

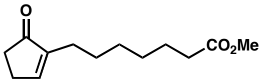
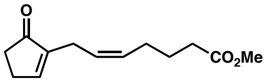
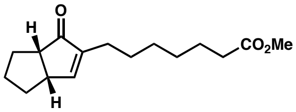


Khand and Pauson, *J. Chem. Res., Synop.* **1977**, 9.
Pauson, *Tetrahedron Lett.* **1985**, *41*, 5885–5860.

Alkene Reactivity

Examples En Route to Prostoglandins



entry	R	Product	% Yield
1	$C_6H_{12}CO_2Me$		46
2	$CH_2CH{=}C_3H_6CO_2Me$		57
3	$C_6H_{12}CO_2Me$		33

Pauson, *J. Chem. Res., Synop.* **1980**, 277.

Intramolecular PKR

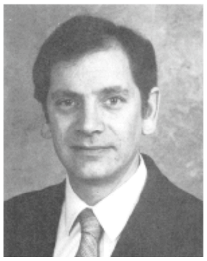
First Publications

First Intramolecular PKR

J. Org. Chem. **1981**, *46*, 5357–5363 and 5436–5438

- **— Originally reported by Neil E. Schore in 1981**
- **— University of California, Davis**
- **— 1st Paper Focus: Synthesis of Vinyl Ether and Ester Enynes**
- **— 2nd Paper Focus: Intramolecular PKR**

"Unfortunately, unstrained alkenes are considerably less reactive in this cyclization process, thus severely limiting its generality: simple olefins react only under forcing conditions, and the yields of cyclopentenones obtained vary greatly. We suspected, however, that the intramolecular disposition of the functional groups in a,w–enynes might enhance the desired mode of reactivity."



Neil E. Schore

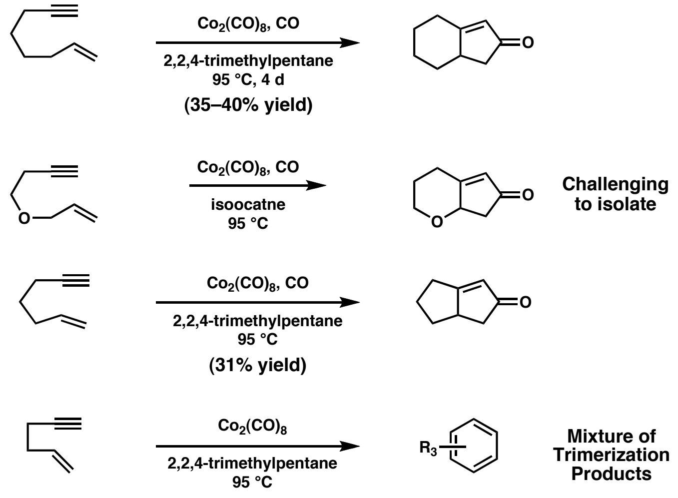
Articles

J. Org. Chem. **1981**, *46*, 5357–5363.
J. Org. Chem. **1981**, *46*, 5436–5438.
Chem. Rev. **1988**, *88*, 1081–1119.

Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.

Intramolecular PKR

First Publications



(35–40% yield)

Challenging to isolate

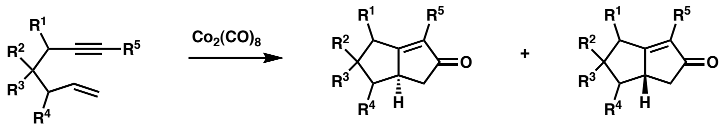
(31% yield)

Mixture of Trimerization Products

Schore*, J. Org. Chem.* **1981**, *46*, 5357–5363 and 5436–5438.

Intramolecular PKR

Thorpe–Ingold Precursors



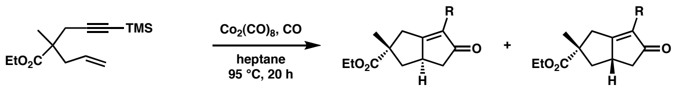
“While yield of the cyclopentenones, whether formed inter– or intramolecularly, are relatively modest, we felt that this could be easily improved by choice of appropriate substituents connecting alkyne and alkene.

Undoubtedly, the $Co_2(CO)_8$ mediated conversion . . . should greatly benefit from the *gem*–methyl group (**Thorpe–Ingold effect**) . . .” [bold added]

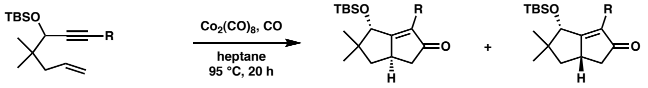
Magnus*, Tetrahedron* **1985**, *41*, 5861–5869.
Magnus, *J. Am. Chem. Soc.* **1987**, *28*, 5465–5468.

Intramolecular PKR

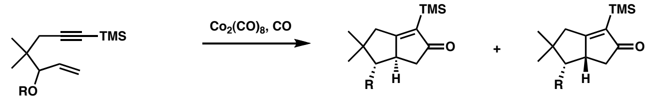
Influence of Substituents



(31% yield) **(55:45)**



R = TMS	**79 %**	**3 %**	**(26:1)**
R = Me	**50 %**	**15 %**	**(3:1)**

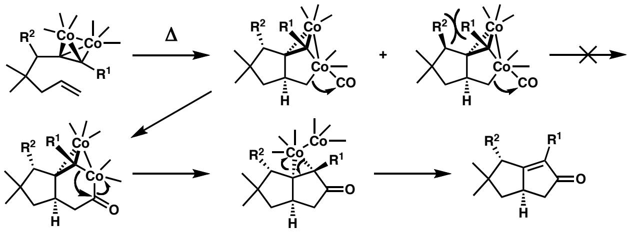


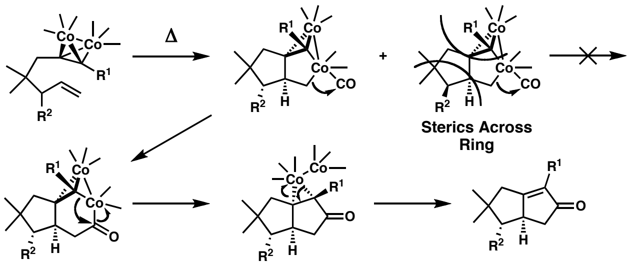
R = TBS OR H (80 °C, 48 h)	**(25% yield)**	**(55:45)**
R = MOM (125 °C, 36 h)	**(20 % yield)**	**(2.6:1)**
R = $(CH_2)_2$OMOM (115 °C, 36 h)	**(78 % yield)**	**(100:0)**

Magnus, *Tetrahedron* **1985**, *41*, 5861–5869.
Magnus, *J. Am. Chem. Soc.* **1987**, *28*, 5465–5468.
Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.

Intramolecular PKR

Influence of α–Substituent

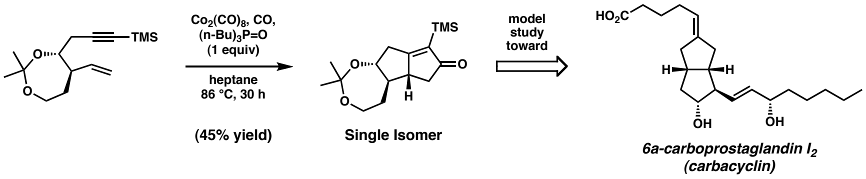




Magnus, *Tetrahedron Lett.* **1985**, *26*, 4851–4854.

Intramolecular PKR

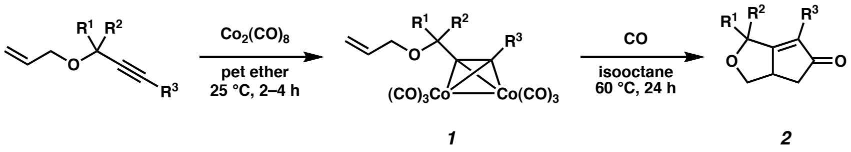
Influence of α–Substituents



Magnus, *J. Org. Chem.* **1987**, *52*, 1483–1486.
Magnus, *J. Am. Chem. Soc.* **1987**, *28*, 5465–5468.

PKR Intramolecular

Other Substrates

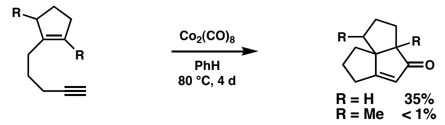


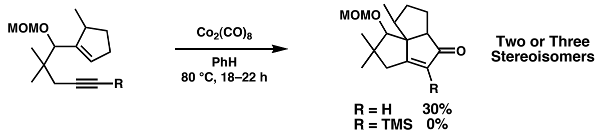
entry	R^1	R^2	R^3	% Yield 1	% Yield 2
1	H	H	H	90	14
2	Me	H	H	86	29
3	Me	Me	H	69	29
4	H	H	Me	87	41
5	H	H	$(CH_2)_2OTHP$	92	41

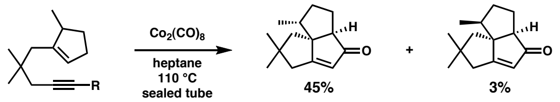
Billington, *Tetrahedron Lett.* **1984**, *25*, 4041–4044.

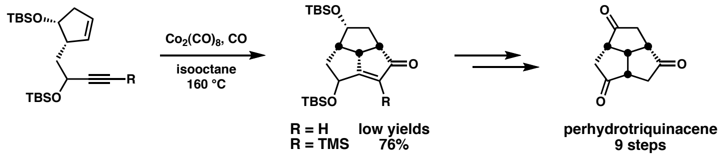
PKR Intramolecular

Other Substrates





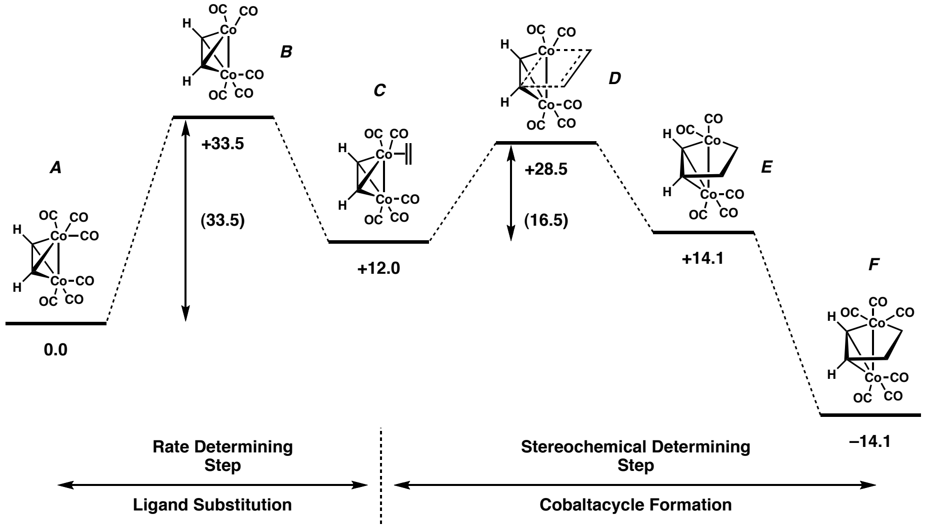




Schore, *J. Org. Chem.* **1984**, *49*, 5025–5026.
Schore, *J. Org. Chem.* **1987**, *52*, 569–580.
Schore, *J. Am. Chem. Soc.* **1988**, *110*, 5224–5225.
Sarratosa, *Tetrahedron Lett.* **1985**, *26*, 2475–2476.

PKR Mechanism

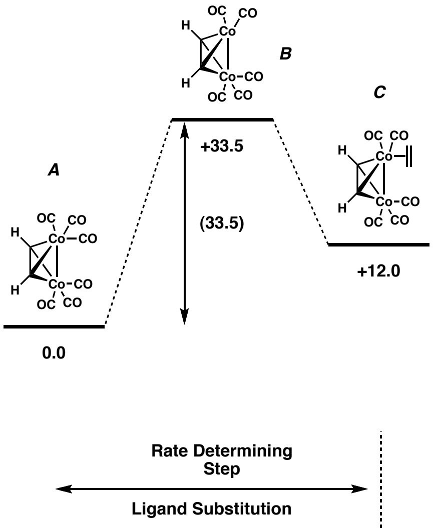
DFT Calculations



Pericàs, Pure Appl. Chem. **2002**, *74*, 167–174.

PKR Mechanism

Lowering E_a



Increasing Reaction Rate

- — Substrate assisted dissociation
- — Increase rate of CO removal
  - Oxidize CO → CO_2
  - Ligand Substitution
  - Induce CO Dissociation
- — Stabilize intermediates

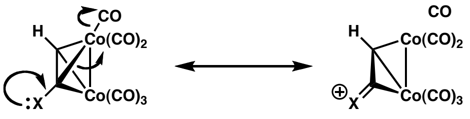
Additives

- — Increase rate of CO removal
  - Irradition, microwave
  - Tertiary Amine N-Oxides (TMO, NMO)
  - Phosphine Oxides, Phosphines, Sulfoxides, Sulfides, Thioacetals, Nitriles, Amines, Thioureas
- — Stabilize intermediates
  - SiO_2, Al_2O_3
  - Molecular Sieves

Pericàs, Pure Appl. Chem. **2002**, *74*, 167–174.

Electronic Effects

Substrate Assisted Dissociation



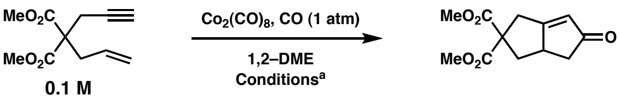
X = NR_2, OR, SR,

- — **Extremely reactive**
- — **Stored in freezer under CO**

Pericàs, *Pure Appl. Chem.* **2002**, *74*, 167–174.
Pericàs, *J. Org. Chem.* **2000**, *65*, 7291–7302.

Additives

Photoinduced CO Dissociation



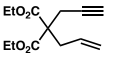
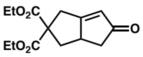
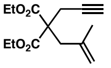
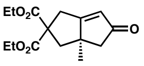
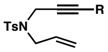
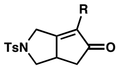
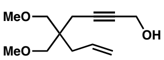
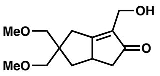
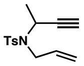
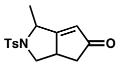
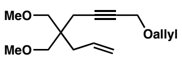
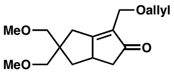
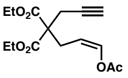
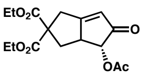
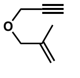
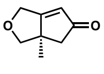
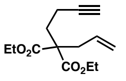
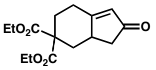
entry	$Co_2(CO)_8$[b] mol %	hν Source	Time (h)	Temp (°C)	%Yield
1[c]	5.0	Q Beam[d]	4	50–55	95
2	0.5	Q Beam[d]	12	50–55	30
3	5.0	Q Beam[d]	12	0 or 17	no rxn
4	12.5	Vitalite	12	50	64

[a] 30 min equilibration then 4 h Irradition. [b] Purity important.
[c] EtOAc – 80% yield. [d] Q Beam Max Million by Brinkmann, Inc.

Livinghouse, *J. Am. Chem. Soc.* **1996**, *118*, 2285–2286.

Additives

Photoinduced CO Dissociation

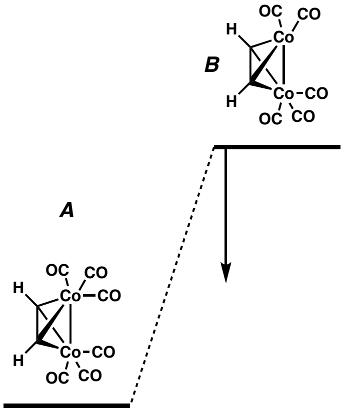
entry	Enyne[a]	Product	%Yield	entry	Enyne[a]	Product	%Yield
1[b]			95	7			91
2 3			R = H 81 R = Ph 75	8			80
4			90	9[d]			67
5[c]			67	10			no rxn
6			74				

[a] Standard conditions: 5 mol% $Co_2(CO)_8$, 0.1 M in 1,2–DME, 12 h irradiation, 50–55 °C except where stated.
[b] 4 h irradtion. [c] 10 mol% $Co_2(CO)_8$. [d] 12.5 mol% $Co_2(CO)_8$.

Livinghouse, *J. Am. Chem. Soc.* **1996**, *118*, 2285–2286.

Additives

Tertiary Amine N–Oxides



Details

— **Indications of Decarboxylation with N–Oxides**

$\mathbf{(CO)_nFeL \longrightarrow L + NR_3 + CO_2}$ **+ "Iron Compounds**

Shvo, *Chem. Commun.* **1974**, 336–337.
Shi and Baslow, *Organometallics* **1987**, *6*, 1528–1531.
Shi and Baslow, *Organometallics* **1989**, *8*, 2144–2147.

— **First suggested by Pauson in 1988 ("erratic results")**

J. Organomet. Chem. **1988**, *354*, 233–242

— **Further development by Nakcheol Jeong**

". . . encountered some limitations because of its intrinsic problems in reaction conditions such as requiring high temperature (usually 60–120 °C) and long reaction time (6h – 4 days).

. . . we envisioned that these reagents [tertiary amine N–oxides] could serve as promoters to generate vacancy for incoming olefins and accelerate the overall reaction."

Jeong, *Synlett* **1991**, 204–206

— **$\mathbf{NR_3}$ removable by evaporation**

Additives

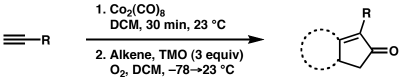
Tertiary Amine N–Oxides

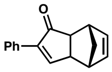
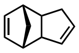
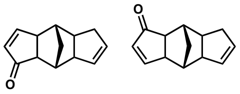
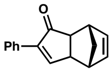
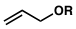
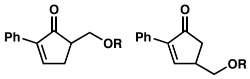
entry	Conditions	% Yield Product	 SM
1	TMANO (3 equiv), O_2, DCM, 3 h	90	0
2	CAN (3 equiv), DCM, 16 h	32	45
3	CAN (3 equiv), acetone, 3h	0	80
4	NMO (3 equiv), DCM, 8 h	87	0

Jeong, *Synlett* **1991**, 204–206.

Tertiary Amine N–Oxides

Intermolecular

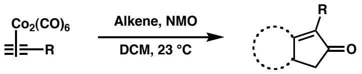


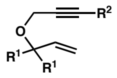
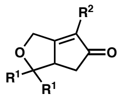
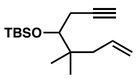
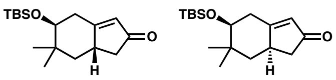
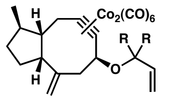
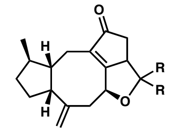
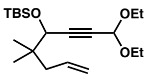
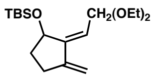
entry	Alkyne	Alkene	Product	% Yield Catalyzed	 Uncatalyzed
1	≡—Ph			80 (83:17 = exo:endo)	45 (exo only)
2	≡			80 Inseparable	74
3	≡—(CH$_2$)$_3$OH			93 (88:12 = exo:endo)	69 (exo only)
4 5	≡—Ph			R = H 64 (2:1) R = THP 30 (3:1)	Not Provided

Jeong, *Synlett* **1991**, 204–206.

Tertiary Amine N–Oxides

Intramolecular



entry	Alkyne	Product	% Yield
1 2		 R^1 = R^2 = H R^1 = Me, R^2 = H	85 (14[a]) 92 (29[a])
3			70 (5:1)
4 5		 R = H R = Me	86 (5:1) 68 (11:1)
6			83

[a] Uncatalyzed yields.

Schreiber, *Tetrahedron Lett.* **1990**, *21*, 5289–5292.
Jeong, *Synlett* **1991**, 204–206.

Additives

Tertiary Amine N–Oxides

Review Articles

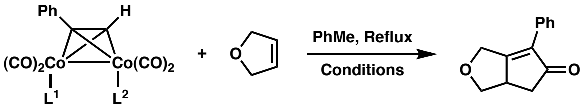
Chung, *Coordination Chemistry Reviews* **1999**, *188*, 297–341.

Articles

Jeong, *Synlett* **1991**, 204–206.
Jeong, *Tetrahedron Lett.* **1991**, *32*, 2137–2140.
Krafft, *J. Org. Chem.* **1992**, *57*, 204–206.
Takno, *Chem. Commun.* **1992**, 169–170.
Kerr, *Synlett* **1995**, 457–458.
Kerr, *Synlett* **1995**, 1083–1084.
Kerr, *Synlett* **1995**, 1085–1086.
Chung, *Organometallics* **1995**, *14*, 3104–3107.
Greene, *J. Org. Chem.* **1995**, *60*, 6670–6671.
Kerr, *Organometallics* **1995**, *14*, 4986–4988.
Kerr, *Tetrahedron* **1996**, *52*, 7391–7420.
Krafft, *J. Am. Chem.* Soc. **1996**, *118*, 6080–6081.
Kerr, *Synlett* **2000**, 1573–1576.

Additives

Phosphorous Compounds



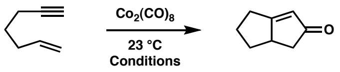
entry	L^1	L^2	Time (h)	% Yield
1	CO	CO	24	36
2^a	PPh_3	CO	5	8
3^b	PBu_3	CO	36	45
4^b	$P(OPh)_3$	CO	8	14
5^b	$P(OMe)_3$	CO	16	6
6^b	Ph_2P	PPh_2	40	5
7^c	Bu_3PO	CO	36	69 (36^d)

[a] Reflux in PhH. [b] Based on > 10% recovery.
[c] Reflux in hexane. [d] Uncatalyzed yield.

Billington and Pauson, *J. Organomet. Chem.* **1988**, 233–242.

Additives

Amines



entry	Solvent	Temp (°C)	Time	% Yield
1	*n*-hexane	35	3 d	0
2	PhMe	35	3 d	0
3	1,2–dichloroethane	35	3 d	0
4	1,4–dioxane	35	3 d	0
5	EtOH	35	3 d	0
6	Et_3N	35	3 d	0
7	Et_2NH	35	3 d	46
8	*n*-$PrNH_2$	35	5 min	52
9	*i*-$PrNH_2$	35	5 min	68
10	$CyNH_2$	35	5 min	72
11	*t*-$BuNH_2$	35	3 d	54

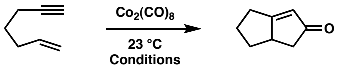
Amine Impact

- Amines act as hard ligands to:
  - Displace CO
  - Activate Alkynes
- Primary amines work best
- Also investigated NH_4OH
  - 1,4–dioxane/NH_4OH sol (1:3 v/v) works best
  - High yields and fast rxn time

Sugihara and Yamaguchi, *Angew. Chem., Int. Ed.* **1997**, *36*, 2801–2804.

Additives

Amines



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3	1,2–dichloroethane	35	3 d	0
4	1,4–dioxane	35	3 d	0
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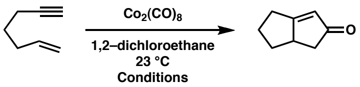


entry	$CyNH_2$ (equiv)	Temp (°C)	Time	% Yield
1	10	25	10 d	46
2	6	83	5 min	99
3	3.5	83	5 min	99
4	3	83	15 min	99
5	1	83	90 min	94
6	0	83	10 h	62

Sugihara and Yamaguchi, *Angew. Chem., Int. Ed.* **1997**, *36*, 2801–2804.

Additives

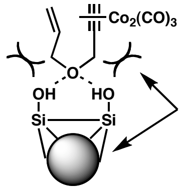
SiO_2 and Al_2O_3 (DSAC)

First Silica Gel Example

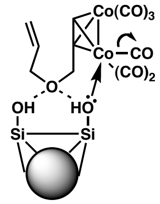
Tetrahedron Lett. **1986**, *27*, 1241–1244

- — First reported by W. A. Smit in 1986
- — Dry State Adsorption Conditions (DSAC)
- — SiO_2 (mostly used) and Al_2O_3 (pH independent)
- — 10–20% H_2O Optimal; 5–30% H_2O Inactive
- — Substrate must have polar groups
- — Procedure
  - • Add silica gel
  - • Evaporate solvent
  - • Heat under appropriate gas
  - • Reaction finished when silica turns gray
- — Increase reaction rate
  - • Interaction of polar groups with silica surface limits molecular movement (↓ ΔS), bringing the alkyne and alkene closer together
  - • Surface displace carbonyl ligands

Increasing Rate



Non-polar repulsion with silica surface brings alkene and alkyne closer together ⇒ ↓ ΔS

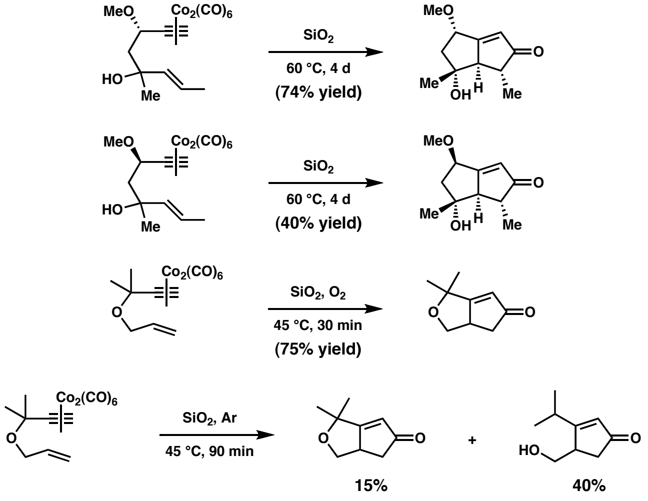


Lower E_a reaction barrier

Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.
Marco–Contelles, *Organic Preparations and Procedures Int.* **1998**, *30*, 121–143.

Additives

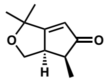
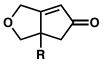
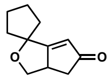
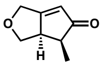
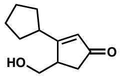
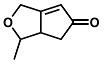
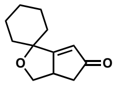
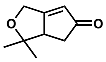
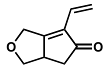
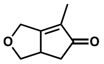
Silica Gel (DSAC)



Smit, *Tetrahedron Lett.* **1986**, *27*, 1241–1244.
Smit, *Tetrahedron Lett.* **1986**, *27*, 1245–1248.

Additives

Silica Gel (DSAC)

entry	Product	Temp (°C)	Temp (min)	%Yield	entry	Product	Temp (°C)	%Yield	Temp (min)
1		45	120	92	6 7	 R = H R = Me	50 60	58 46	210 90
2		60	45	64	8		60	46	90
3		60	45	50	9		60	48	60
4		50	45	80	10		50	60	120
5		50	20	58	11		45	60	150

Smit, *Tetrahedron Lett.* **1986**, *27*, 1245–1248.

Additives

DSAC References

Review Articles

Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.
Marco–Contelles, *Organic Preparations and Procedures Int.* **1998**, *30*, 121–143.

Articles

Smit, *Tetrahedron Lett.* **1986**, *27*, 1241–1244.
Smit, *Tetrahedron Lett.* **1986**, *27*, 1245–1248.
Smit, *Synthesis* **1989**, 472–476.
Smit, *Tetrahedron Lett.* **1989**, *30*, 4021–4024.
Smit, *Tetrahedron Lett.* **1991**, *32*, 2105–2108.
Smit, *Tetrahedron Lett.* **1991**, *32*, 2109–2112.
Smit, *J. Am. Chem. Soc.* **1992**, *114*, 5555–5556.
Becker, *Tetrahedron Lett.* **1993**, *34*, 2087–2090.
Becker, *Tetrahedron Lett.* **1993**, *49*, 5047–5050.

PKR Review References

Review Articles

Pauson and Khand. Uses of Cobalt–Carbonyl Acetylene Complexes in Organic Synthesis. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2–14.

Schore. Transition metal-mediated cycloaddition reactions of alkynes in organic synthesis. *Chem. Rev.* **1988**, *88*, 1081–1119.

Geis and Schmalz. New developments in the Pauson-Khand reaction. *Angew. Chem., Int. Ed.* **1998**, *37*, 911–914.

Marco-Contelles et al. The asymmetric Pauson-Khand reaction. A review. *Organic Preparations Procedures Int.* **1998**, *30,* 121–143.

Chung. Transition metal alkyne complexes: the Pauson-Khand reaction. *Coordination Chemistry Review* **1999**, *188*, 297,Äì341.

Adrio and Carretero. The tert-Butylsulfinyl Group as a Highly Efficient Chiral Auxiliary in Asymmetric Pauson,àíKhand Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 7411–7412.

Brummond and Kent. Recent advances in the Pauson-Khand reaction and related [2+2+1] cycloadditions. *Tetrahedron* **2000**, *56*, 3263–3283.

Fletcher and Christie. Cobalt mediated cyclisations. *J. Chem. Soc., Perkin Trans. 1* **2000**, *11*, 1657–1668.

Sugihara et al. Advances in the Pauson-Khand reaction: development of reactive cobalt complexes. *Chem.–Eur. J.* **2001**, *7*, 1589–1595.

Rivero et al. Pauson–Khand reactions of electron-deficient alkenes. *Eur. J. Org. Chem.* **2002**, *17*, 2881–2889.

Rivero and Carretero. Intramolecular Pauson-Khand reactions of alpha,beta-unsaturated esters and related electron-deficient olefins. *J. Org. Chem.* **2003**, *68*, 2975–2978.

Gibson (Née Thomas) and Stevenazzi. The Pauson–Khand Reaction: the Catalytic Age Is Here! *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810.

Bonaga and Krafft. When the Pauson-Khand and Pauson-Khand type reactions go awry: a plethora of unexpected results. *Tetrahedron* **2004**, *60*, 9795–9833.

Blanco-Urgoiti et al. The Pauson-Khand reaction, a powerful synthetic tool for the synthesis of complex molecules. *Chemical Society Reviews* **2004**, *33*, 32,Äì42.

Alcaide and Almendros. The Allenic Pauson,àíKhand Reaction in Synthesis. *Eur. J. Org. Chem.* **2004**, *18*, 3377–3383.

Laschat et al. Regioselectivity, Stereoselectivity and Catalysis in Intermolecular Pauson-Khand Reactions: Teaching an Old Dog New Tricks. *Synlett* **2005**, 2547–2570.

Gibson (Née Thomas) and Mainolfi. The Intermolecular Pauson-Khand Reaction. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037.

Pérez-Castells and Müller. Cascade Reactions Involving Pauson–Khand and Related Processes. *Topics in Organometallic Chemistry* **2006**, *19*, 207–257.

Shibata. Recent Advances in the Catalytic Pauson–Khand-Type Reaction. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336.