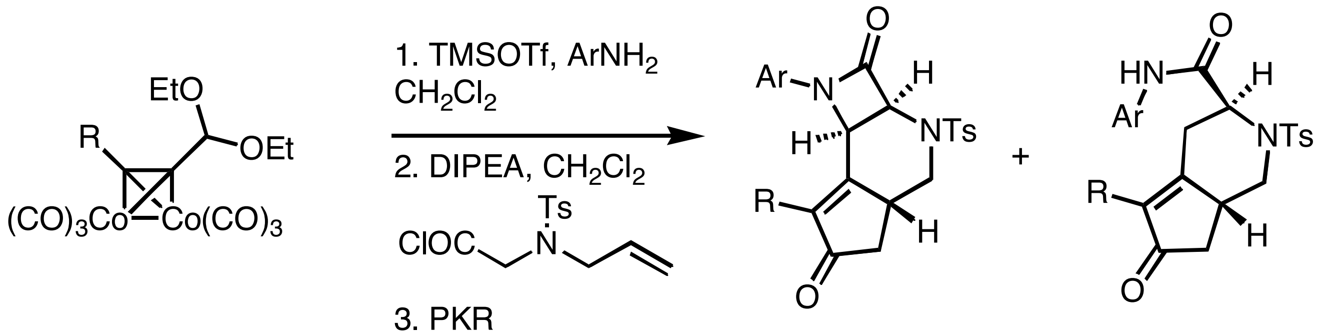
Dicobalt Hexacarbonyl Complexes of Alkynyl Imines in a Sequential Staudinger/Pauson-Khand Process. A Route to New Fused Tricyclic β-Lactams

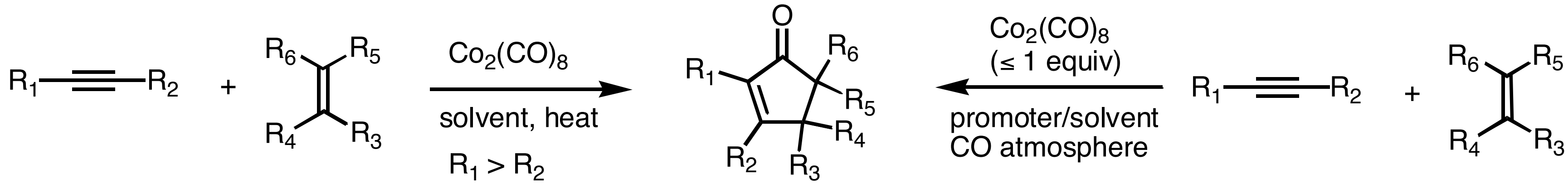
Clarisse Olier, Nadia Azzi, Gérard Gil, Stéphane Gastaldi, and Michèle P. Bertrand

J. Org. Chem. **2008,** *73,* 8469–8473.



Presented by Melissa Sprachman, December 20, 2008

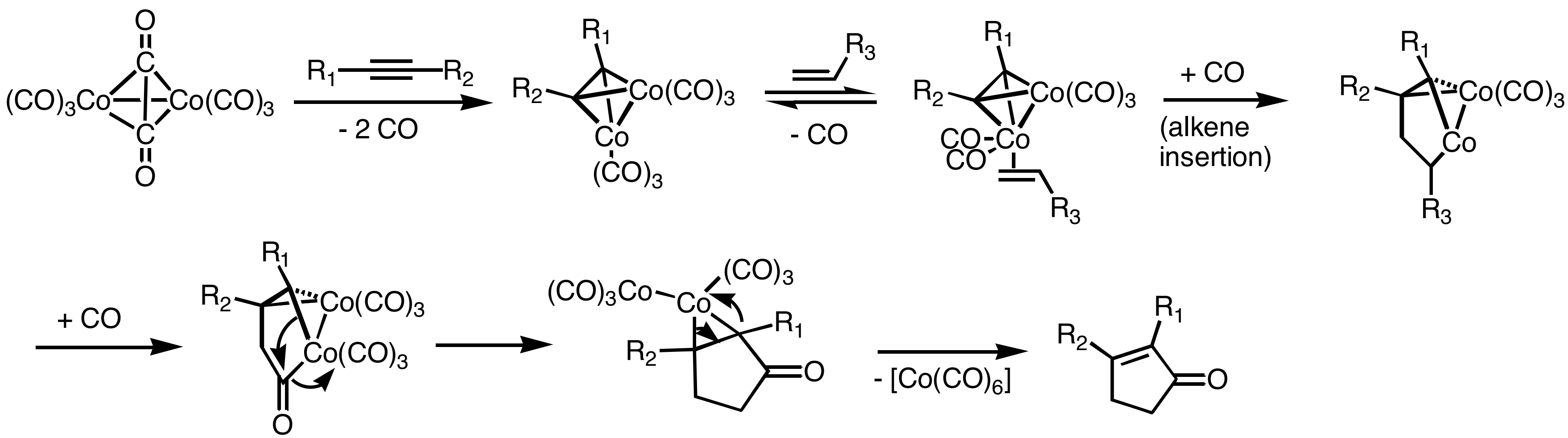
The Pauson-Khand Reaction



Other metal complexes used: $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2, $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$

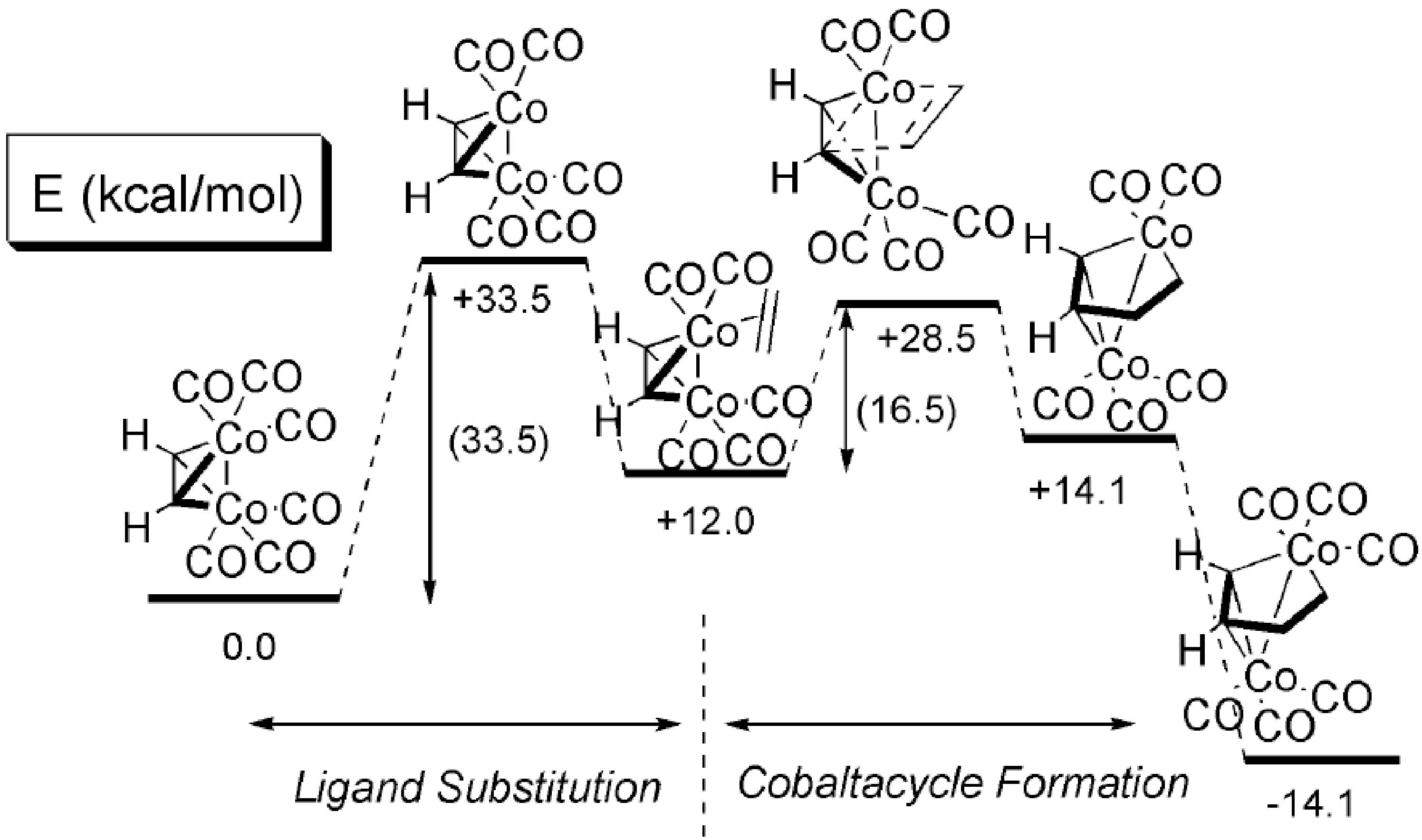
Common promoters: NMO, high-intensity light/photolysis, “hard” Lewis bases

Mechanism:



Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2005.

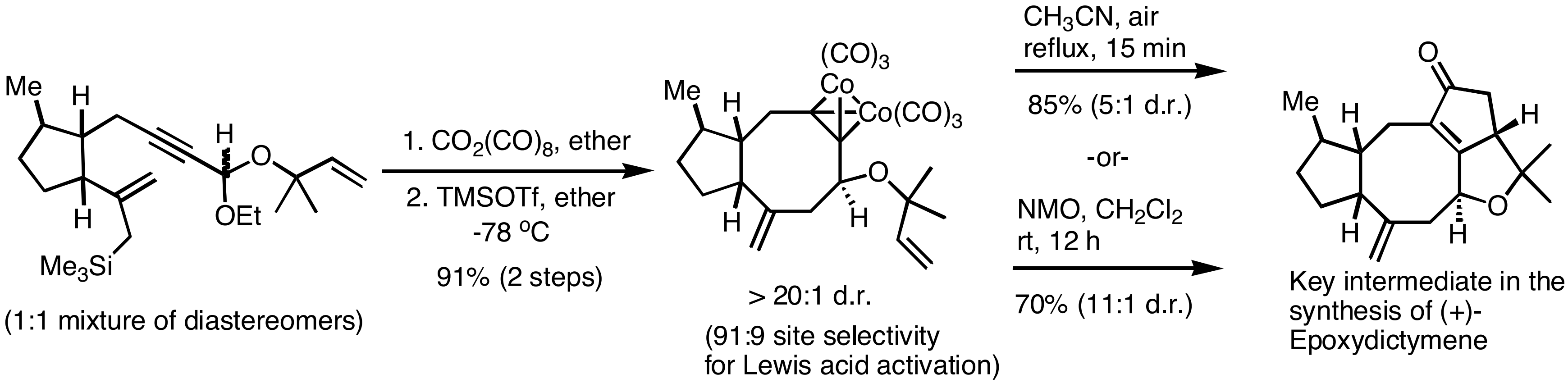
The Pauson Khand Reaction: CO Labilization is Rate-Determining



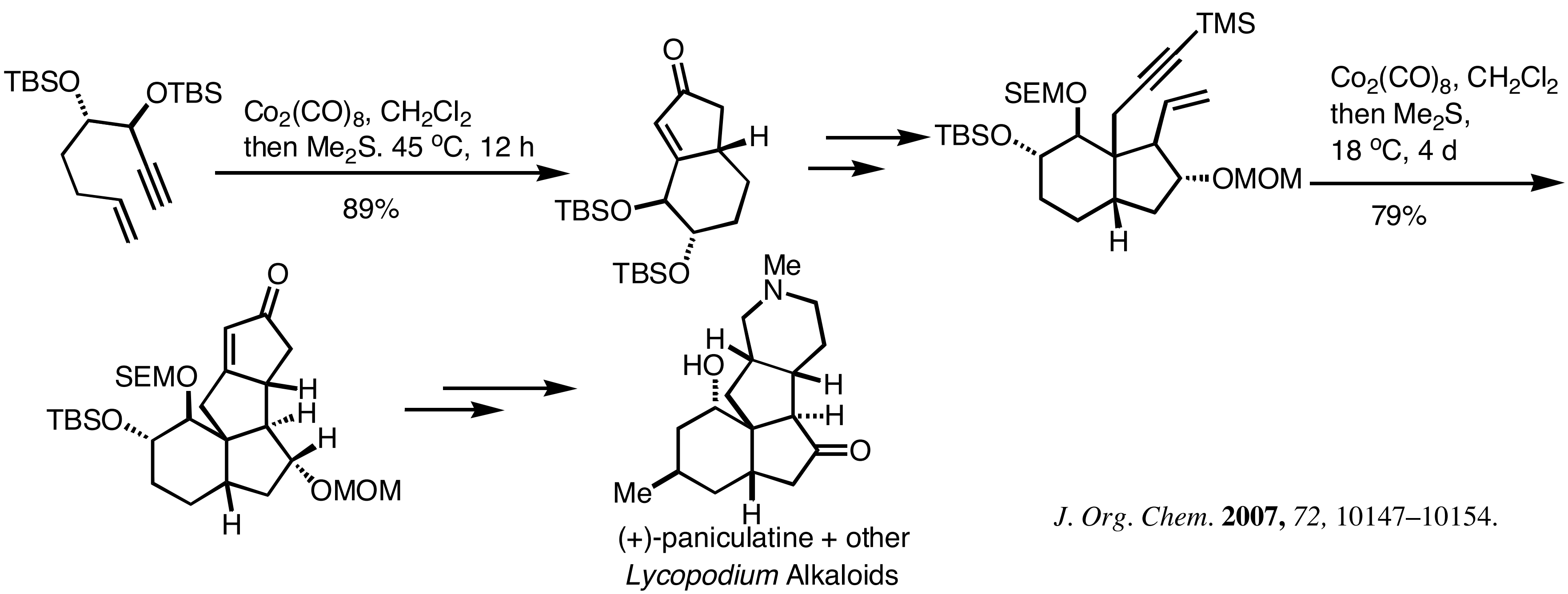
DFT (VWN/PW91xc)

Pure Appl. Chem. **2002,** *74,* 167-174.

Schreiber's synthesis of (+)-epoxydictymene:



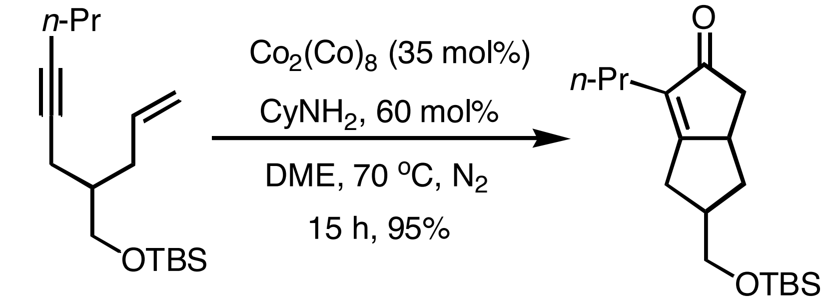
J. Am. Chem. Soc. **1997,** *119,* 4353–4363.



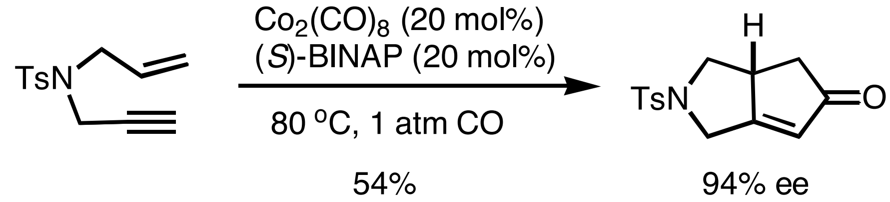
J. Org. Chem. **2007,** *72,* 10147–10154.

Advances in Pauson-Khand Reaction Methodology

Catalytic Pauson-Khand Reactions:

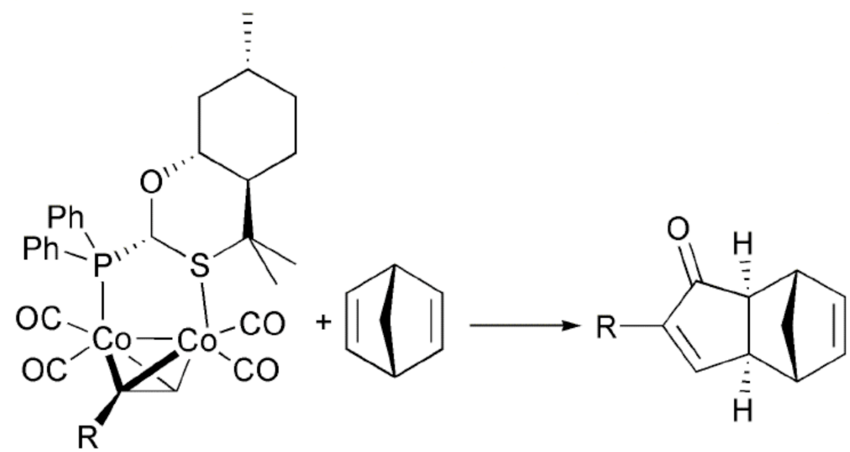


J. Org. Chem. **2001,** *66,* 3004-3020.



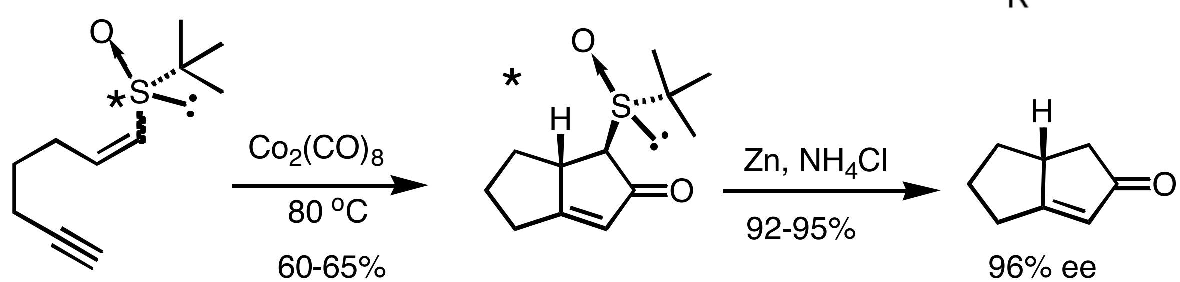
Tetrahedron: Asymmetry, **2000,** *11,* 797-808

Asymmetry by use of chiral auxiliaries or chiral metal complexes:



Yields: 92-99%
ee%: 97-99%

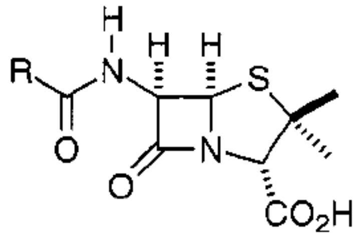
J. Am. Chem. Soc. **2000,** *122,* 10242-10243.



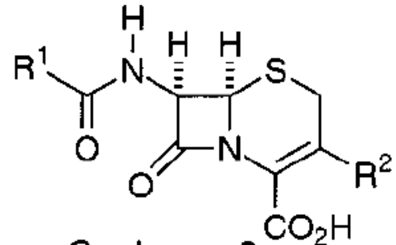
Eur. J. Org. Chem. **2002,** 2881-2889.

Chem. Soc. Rev. **2004,** *33,* 32-42.

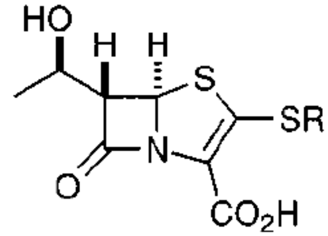
β-Lactam Antibiotics



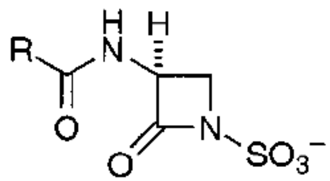
Penam, **1**



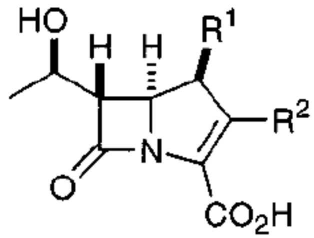
Cephem, **2**



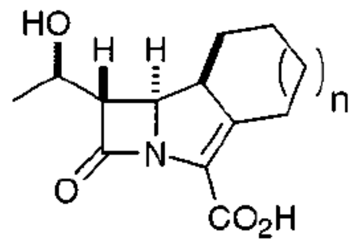
Penem, **3**



Monobactam, **4**



Carbapenem, **5**



Trinem, **6**

Eur. J. Org. Chem. **1999,** *3223-3235*

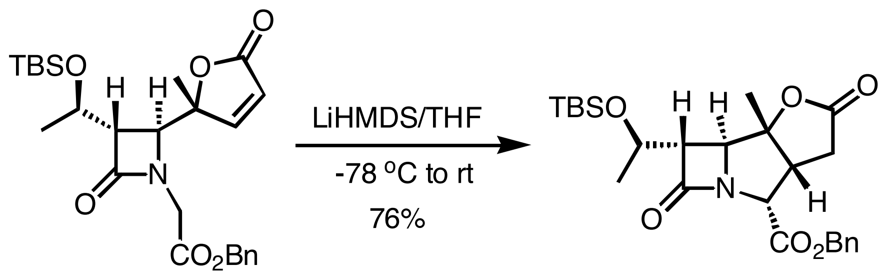
"The biologically active principle of all β-lactam antibiotics is the β-lactam ring, the reactivity and selectivity of which towards biological substrates can be decisively influenced by substituents or fused rings."

Angew. Chem. Int. Ed. Engl. **1985,** *24,* 180-202.

-->Motivation to diversify β-lactam scaffolds?

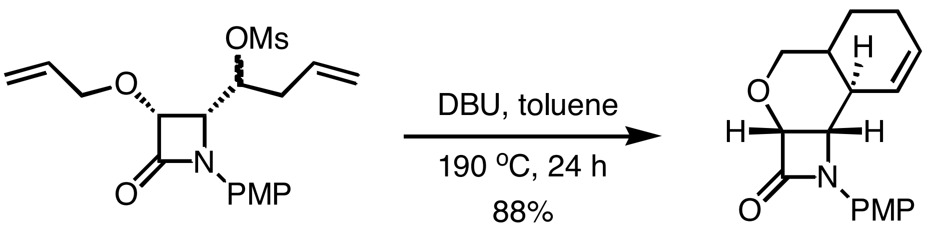
Construction of Polycyclic β-Lactams

Reaction of substituents on the azetidinone:



Tetrahedron Lett. **1997,** 38, 5913-5916.

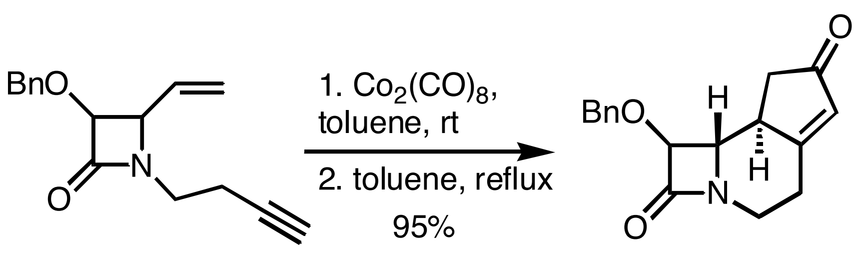
Cycloadditions:

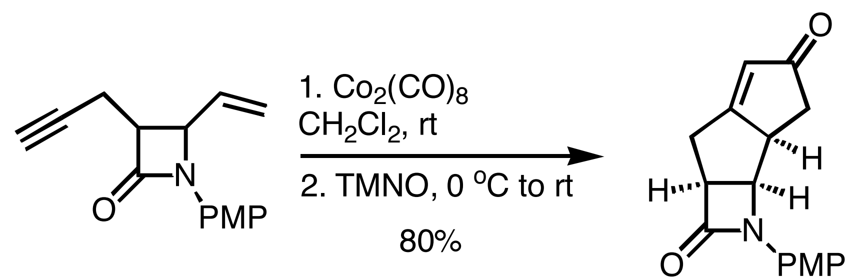


Tetrahedron Lett. **1999,** *40,* 1015-1018.

80 :10 :10 (mixture of diastereomers)

Precedence: Pauson-Khand Reactions:

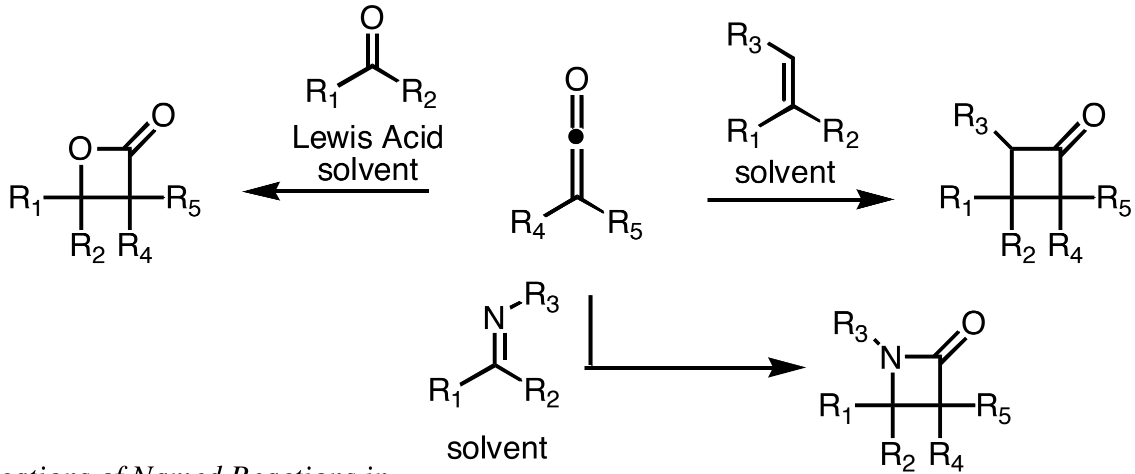




J. Org. Chem. **1998,** *63,* 6786-6796.

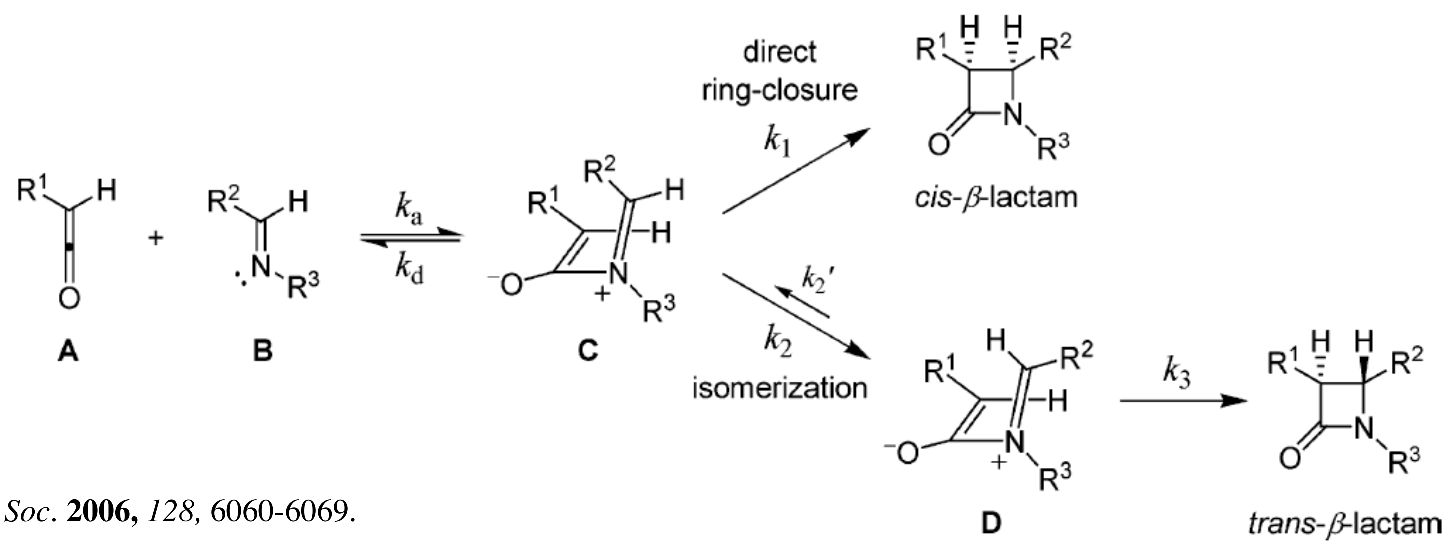
The Staudinger Reaction

The Staudinger Reaction:



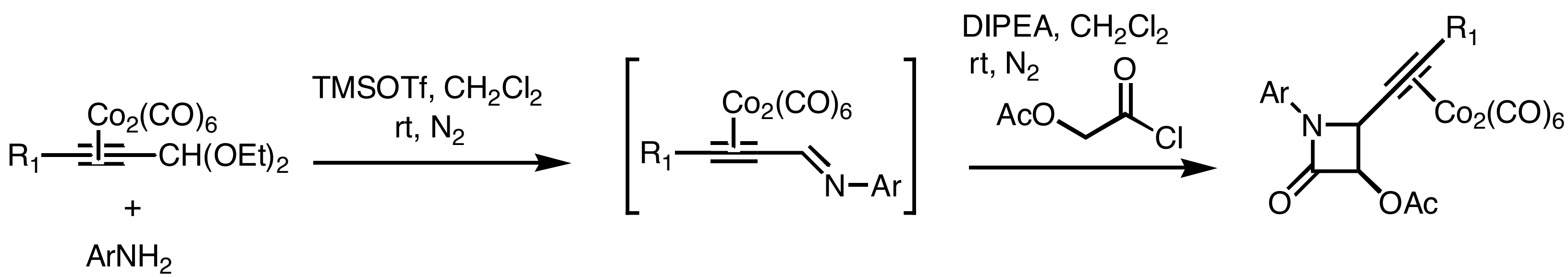
Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2005.

Suggested mechanism and explanation of stereochemistry in the case of imines:



J. Am. Chem. Soc. **2006,** *128,* 6060-6069.

Tandem Imine Formation-Staudinger Reaction

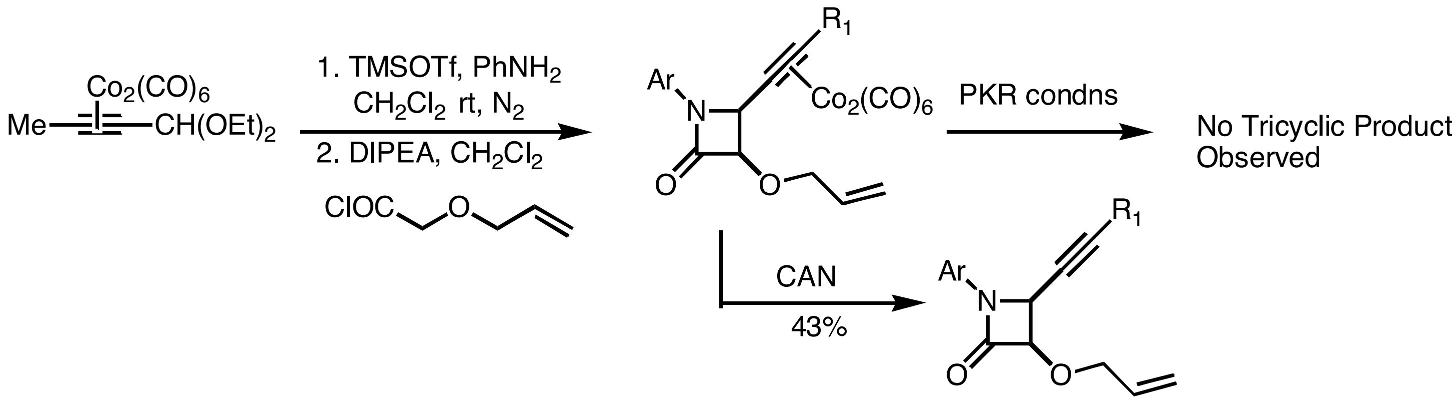


Entry	R^1	Ar	Yield (%)	Ratio *cis*:*trans*
1	H	Ph	19	100:0
2	Me	Ph	81	100:0
3	Me	*p*-$MeOC_6H_4$	47	100:0
4	Me	*p*-$NO_2C_6H_4$	36	79:21
5	$SiMe_3$	Ph	42	100:0

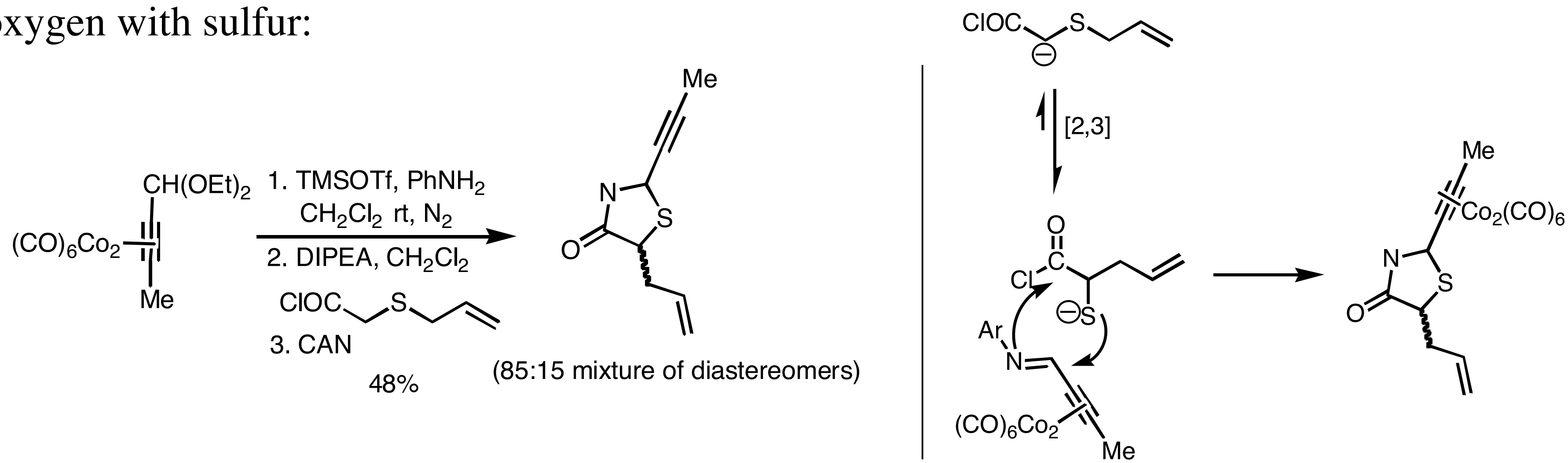
The observed stereoselectivities are consistent with the electronic effects of the zwitterionic model.

Tandem Staudinger-Pauson Khand Reactions

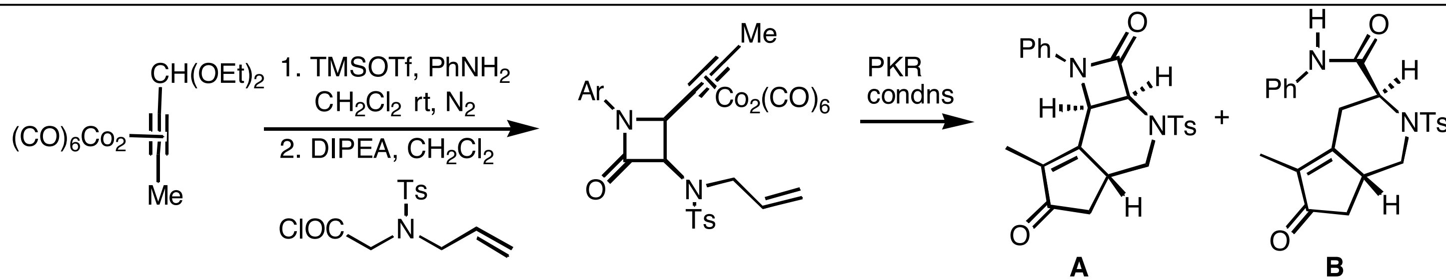
Allyl ethers were not reactive toward the Pauson Khand Conditions



Only thiazolidin-3-ones formed when trying to replace oxygen with sulfur:

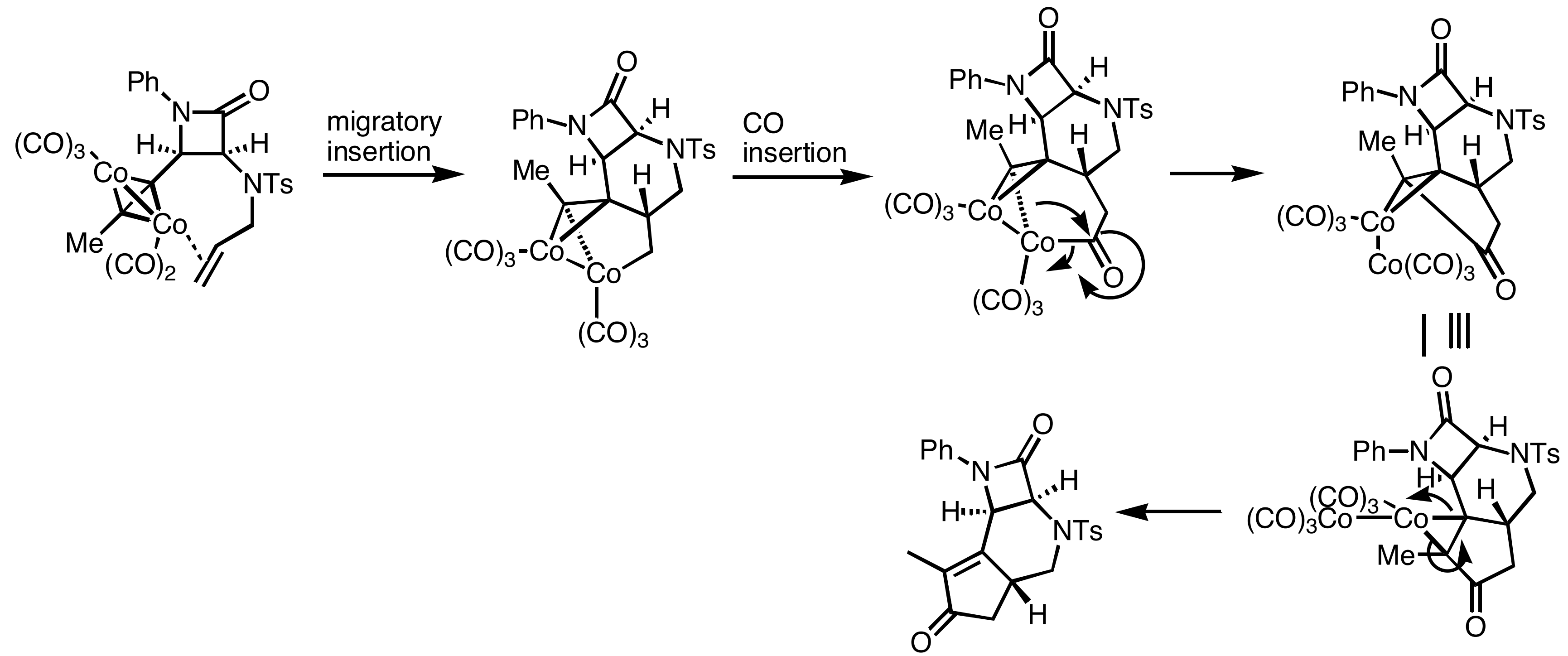


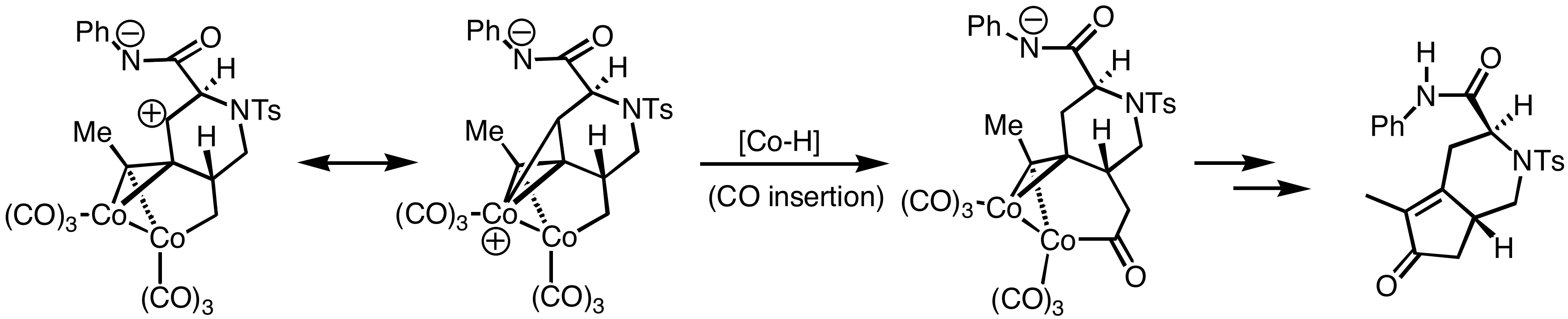
Pauson Khand Reactions with the Nitrogen Analog



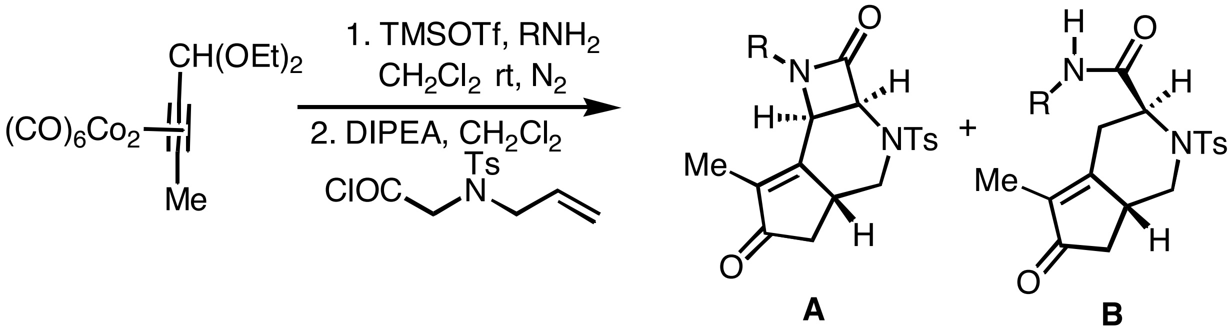
Entry	Conditions	*T* (ºC)	Yield (%) (3 steps)	Ratio **A** : **B**
1	SiO_2, Ar, 18 h	40	53	65:35
2	SiO_2, Ar 18 h	60	54	35:65
3	SiO_2, Ar, 18 h	80	48	38:62
4	Basic Al_2O_3, Ar, 18 h	40	15	47:53
5	SiO_2, H_2O (10 equiv), Ar, 18 h	40	44	54:46
6	SiO_2, O_2, Ar, 18 h	40	44	58:42
7	DMSO (6 equiv), CH_2Cl_2, 18 h,	rt	61	44:56
8	NMO•H_2O (1.8 equiv), CH_2Cl_2, 18 h	-20	53	52:48
9	NMO•H_2O (1.8 equiv), DIPEA (2.7 equiv) CH_2Cl_2, 18 h	rt	49	35:65
10	NMO•H_2O (1.8 equiv), DIPEA (2.7 equiv) CH_2Cl_2, 18 h	rt	32	30:70
11	Toluene, 18 h	110	33	71:29

Mechanism for Formation of the Tricycle and Open Amide



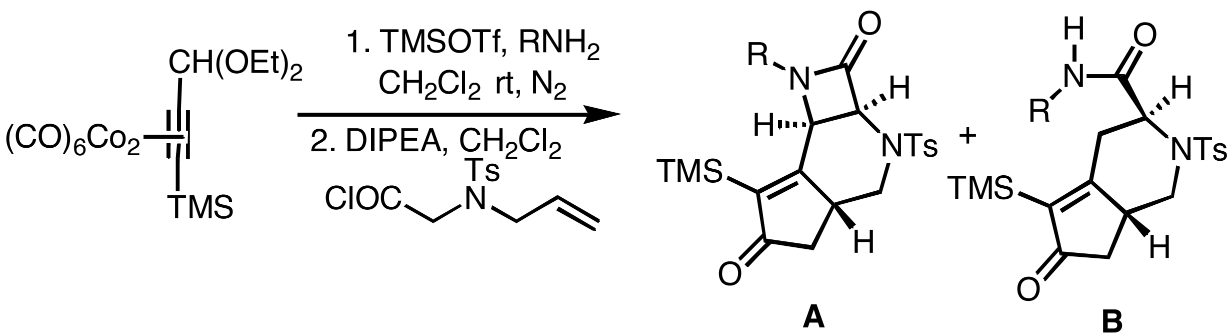


Tandem Staudinger-Pauson Khand Scope



3. A: SiO_2, Ar, 40 °C   R = Ph, 53%, ratio **A:B** = 65:35; R = PMP, 15%, ratio **A:B** = 52:48

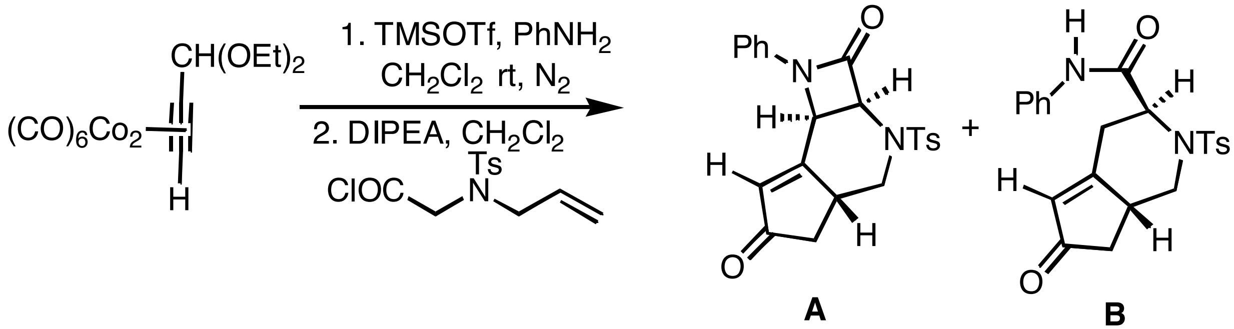
B: NMO•H_2O, rt, 18 h   R = Ph, 49%, ratio **A:B** = 35:65; R = PMP, 49%, ratio **A:B** = 48:52



3. A: SiO_2, Ar, 40 °C   R = Ph, 39%, ratio **A:B** = 77:23; R = PMP, 55%, ratio **A:B** = 60:40

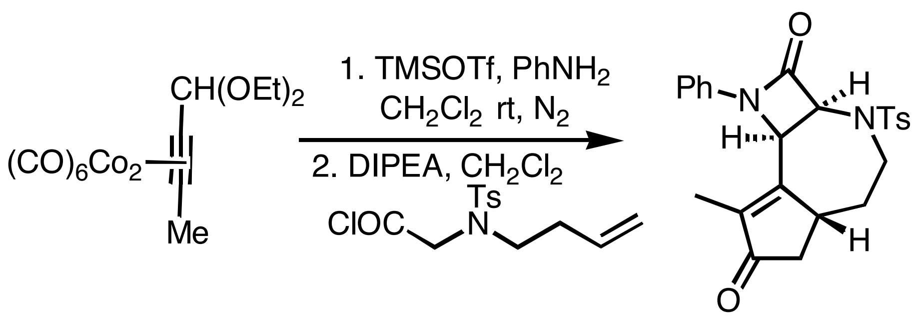
B: NMO•H_2O, rt, 18 h   R = Ph, 33%, only **A** isolated;   R = PMP, 49%, ratio **A:B** = 55:45

Tandem Staudinger-Pauson Khand Scope



3. A: SiO_2, Ar, 40 ^oC — 23%, ratio **A:B** = 29:71

B: NMO•H_2O, rt, 18 h — 14%, ratio **A:B** = 29:71



3. A: SiO_2, Ar, 40 ^oC — 30%

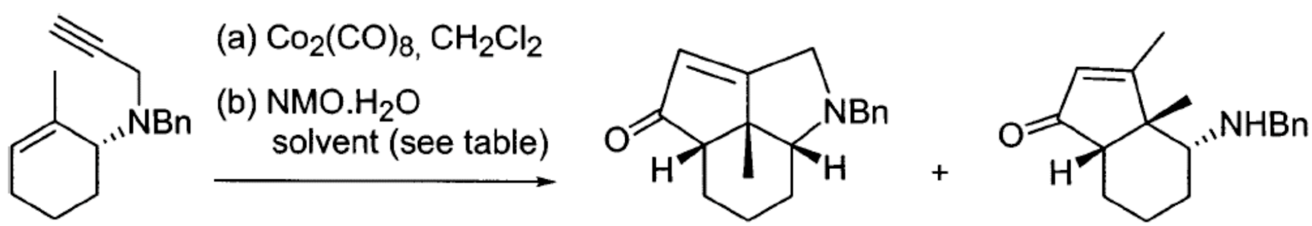
B: NMO•H_2O, rt, 18 h — 30%

Summary

Novel tricyclic scaffolds were synthesized via a tandem Staudinger/Pauson-Khand process

Although overall yields are low, the methodology provides a route for rapid formation of complex substrates with possible utility in medicinal applications

The approach is limited to stoichiometric use of $Co(CO)_8$, and cleavage of the β-lactam is an unsolved problem in this methodology. Suppression of N-C cleavage has been achieved, but the precedence is for amines:



C **D**

solvent	C	D
CH_2Cl_2	34%	14%
CH_2Cl_2 / THF	52%	10%
CH_3CN	63%	—

J. Organomet. Chem. **2001,** *624,* 316-326.