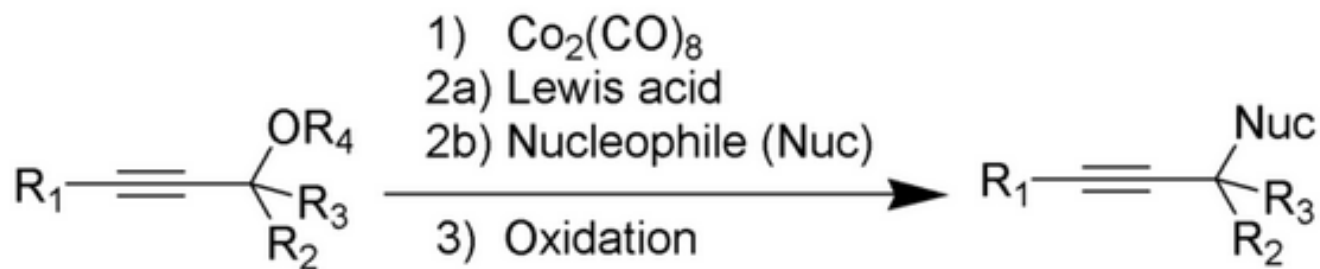
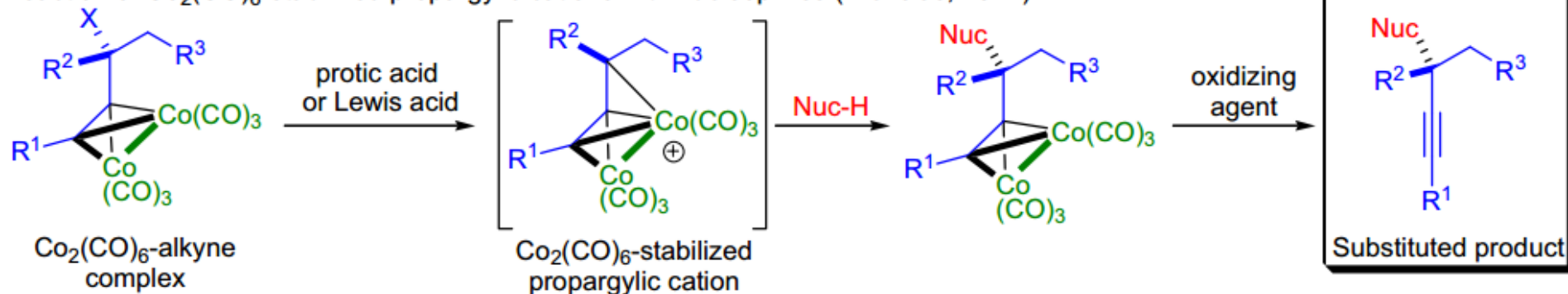


NICHOLAS REACTION



NICHOLAS REACTION

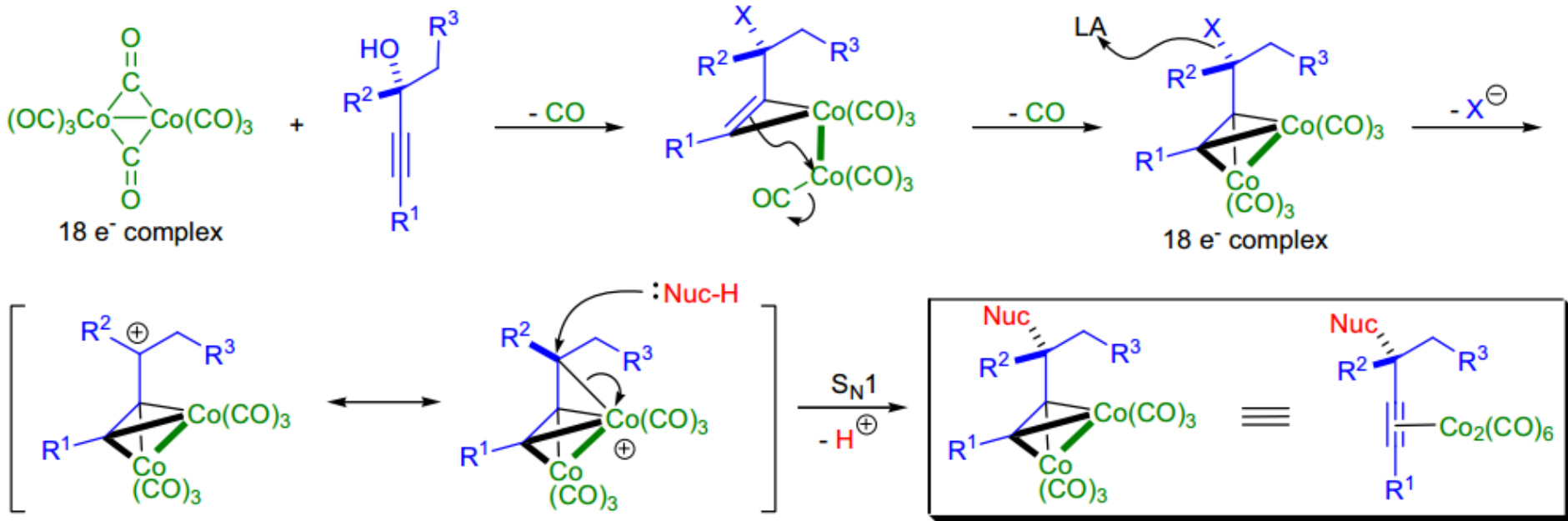
Reaction of $\text{Co}_2(\text{CO})_6$ -stabilized propargylic cations with nucleophiles (Nicholas, 1977):



R^{1-3} = H, alkyl, aryl; X = OH, O-alkyl, O-benzyl, O-silyl, acetal, OAc, OCOAr, OCOt-Bu, OMs, OTf, Cl; **Nuc-H** = e-rich aromatics, simple alkenes, allylsilanes, allylstannanes, enol ethers, silylketene acetals, ROH, N_3^- , RNH_2 , $\text{RR}'\text{NH}$, RSH, $\text{HS}(\text{R})\text{SH}$, F^- ;
oxidizing agent: CAN, $\text{Fe}(\text{NO}_3)_3$, NMO, TMANO, TBAF, $\text{C}_5\text{H}_5\text{N}/\text{air}/\text{ether}$, DMSO/ H_2

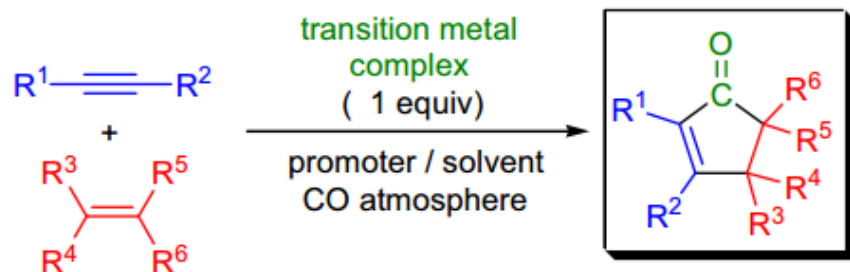
- 1) A wide range of nucleophiles reacts with the resulting propargylic cations including C-, O-, N-, and S-nucleophiles;
- 2) When the cobalt complex is not removed, it can be used in a subsequent Pauson-Khand reaction;
- 3) The reaction can be both inter- and intramolecular, and even **macrocyclization** can be achieved

Mechanism

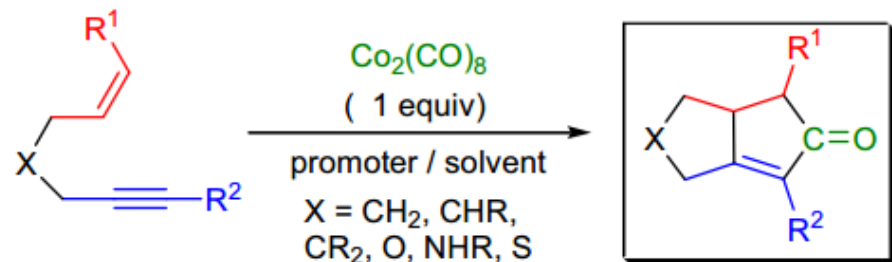


Pauson-Khand reaction

Modified P-K reaction:



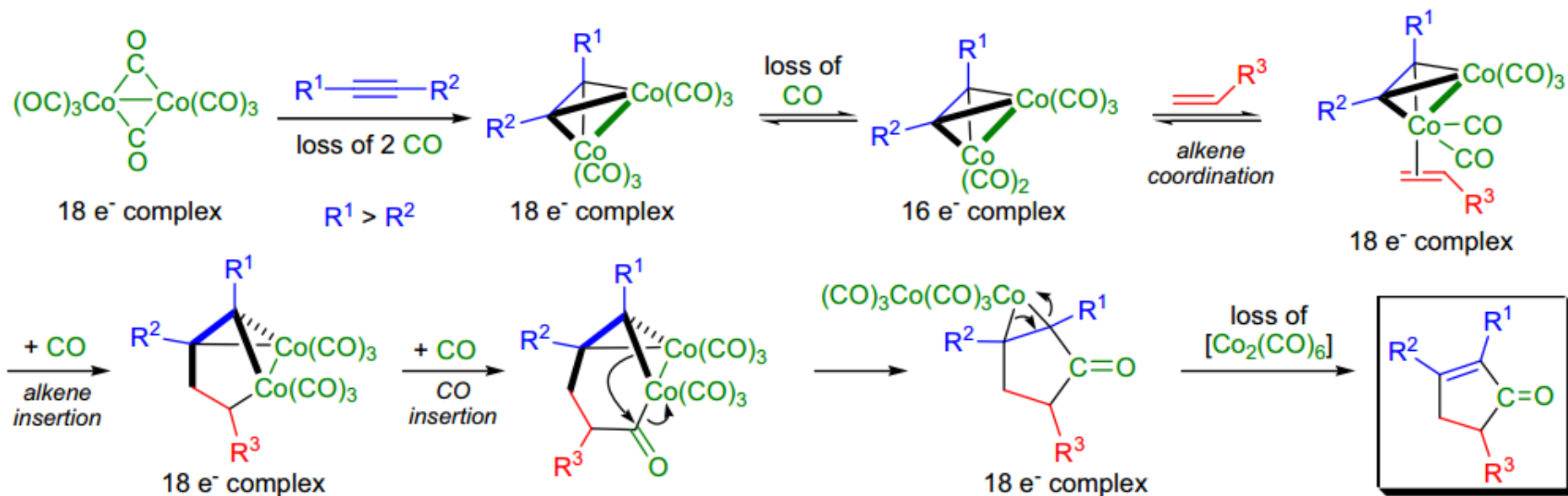
Intramolecular variant:



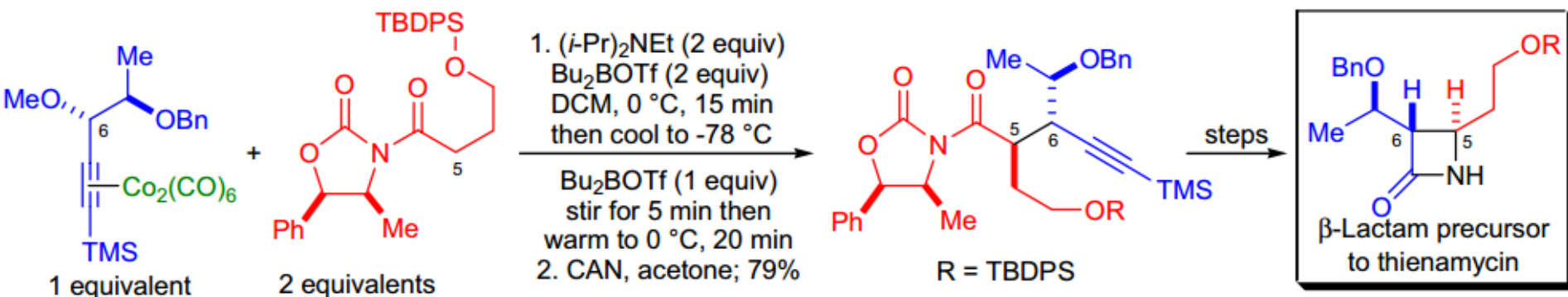
$R^{1-6} = \text{H, alkyl, aryl, substituted alkyl and aryl}$; transition metal complex: $\text{Co}_2(\text{CO})_8, \text{Fe}(\text{CO})_5, \text{Ru}_2(\text{CO})_{12}, \text{Cp}_2\text{TiR}_2, \text{Ni}(\text{COD})_2, \text{W}(\text{CO})_6, \text{Mo}(\text{CO})_6, [\text{RhCl}(\text{CO})_2]_2$; promoter: NMO, TMAO, RSCH_3 , high-intensity light/photolysis, "hard" Lewis base

Mechanism: ⁴⁸⁻⁶²

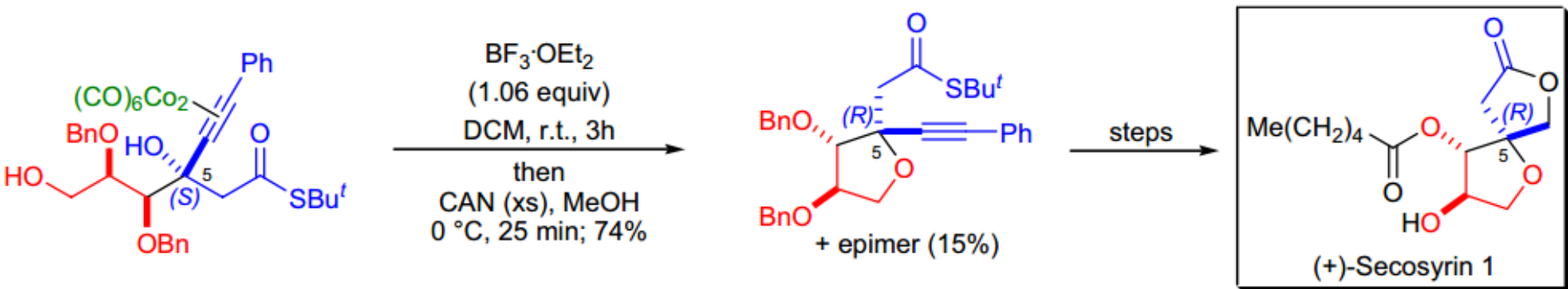
The mechanism of the *Pauson-Khand reaction* has not been fully elucidated. However, based on the regio- and stereochemical outcome in a large number of examples, a reasonable hypothesis has been inferred.

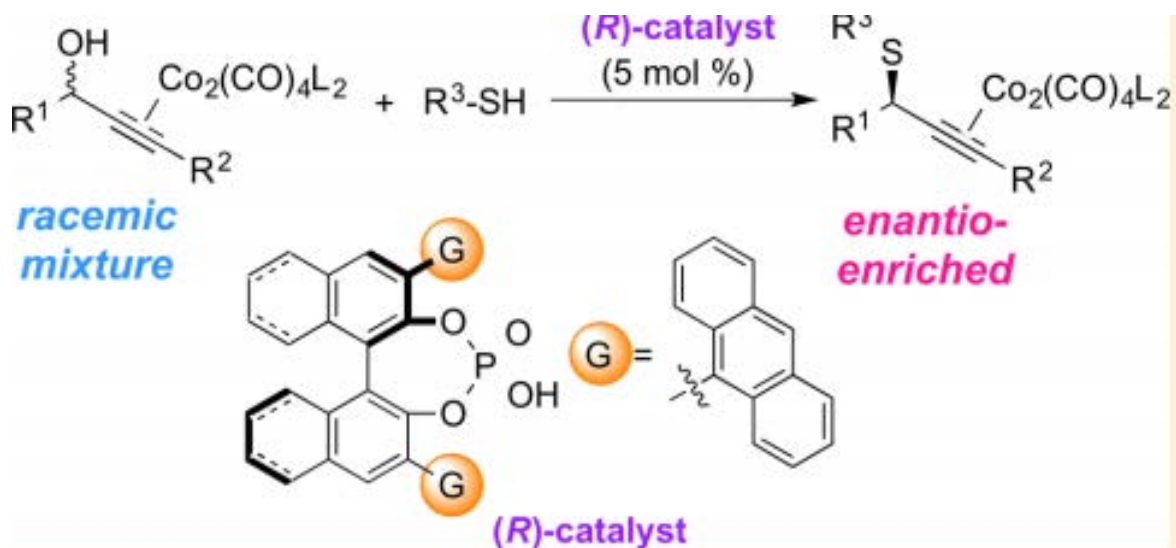


The *Nicholas reaction* was used to synthesize the β -lactam precursor of thienamycin in the laboratory of P.A. Jacobi and thereby accomplish its formal total synthesis.²⁴ The necessary β -amino acid was prepared by the condensation of a boron enolate (derived from an acylated oxazolidinone) with the cobalt complex of an enantiopure propargylic ether. The resulting adduct was oxidized with ceric ammonium nitrate (CAN) to remove the cobalt protecting group from the triple bond, and the product was obtained with a 17:1 *anti:syn* selectivity and in good yield.



The total syntheses of (+)-secosyrins 1 and 2 was achieved and their relative and absolute stereochemistry was unambiguously established by C. Mukai and co-workers.²⁵ To construct the spiro skeleton of these natural products, the *intramolecular Nicholas reaction* was utilized. The alkyne substrate was first converted to the dicobalt hexacarbonyl complex by treatment with $\text{Co}_2(\text{CO})_8$ in ether. Exposure of the resulting complex to boron trifluoride etherate at room temperature brought about the ring closure with inversion of configuration at C5 to afford the expected tetrahydrofuran derivative. The minor product was the C5 epimer which was formed only in 15% yield.





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