



Trip Report for
“The 40th Middle Atlantic Regional Meeting”
Bayside, New York
May 17-21, 2008

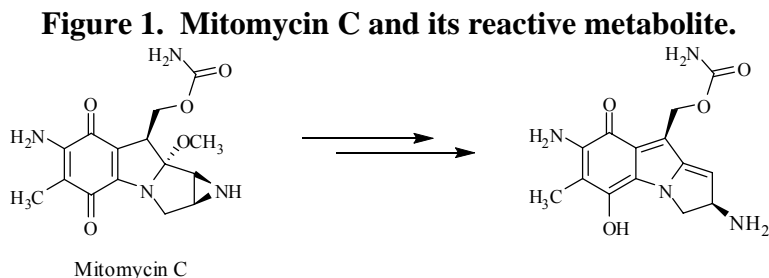
James R. Coats and Geoffrey Giarmo
Medicinal Chemistry Department

Abstract: *The 40th Middle Atlantic Regional Meeting was held in Bayside, New York from May 17-21, 2008. The overall theme for this year’s Regional Meeting was “Chemistry and Health” and was attended by scientists from local academia and industry. This report highlights select material from seminars and posters presented at the conference.*

“Synthesis of an Oligodeoxyribonucleotide Adduct of Mitomycin C by the Postoligomerization Method via a Triamino Mitosene”

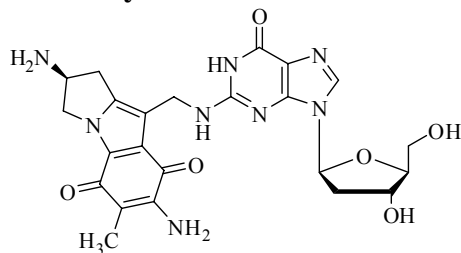
Elise Champeil (John Jay College, New York, New York), Manuel M. Paz (Universidade de Santiago de Compostela, Lugo, Spain) and Maria Tomasz (Hunter College, New York, New York)

Mitomycin C (Figure 1) is a natural product from the mitomycin family of aziridine-containing natural products that has shown very potent antitumor and antibiotic activity. It works via a DNA-crosslinking mechanism, and as little as one crosslink has been shown to be fatal to the cell. Mitomycin C itself does not react with DNA, but first undergoes several reactions *in vivo* to form the reactive species as shown in Figure 1. This is a highly sequence-selective agent, requiring a CpG sequence. Less than 5% of guanine in mammalian DNA is in this sequence, whereas up to 70% of guanine can be in the DNA sequence for bacteria. Mitomycin C has been used as a clinical antitumor agent since 1974, with broad spectrum activity against solid tumors.



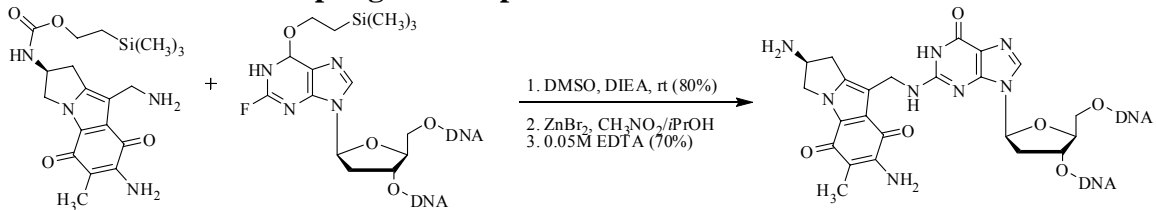
Cells treated with mitomycin C show that six adducts are formed. One of these adducts (Figure 2) was shown to be non-cytotoxic in mouse tumor cells. Attempts to synthesize this adduct through biomimetic routes gave very low yields of the desired compound. The solution to this problem was to use a post-oligomerization synthesis, which reversed the nucleophile and electrophile relationship to provide the target compound.

Figure 2. Non-cytotoxic adduct of Mitomycin C.



Initial efforts did provide the adduct, albeit not incorporated into a DNA strand. The problem was in the protecting group for the amine, which was not removable while the compound was reacted with DNA for incorporation, as intended. As the protecting group had to be removable under both non-acidic and non-basic conditions, the group ultimately chose to use the Teoc protecting group. De-protection using this group was then accomplished using $ZnBr_2$ in a nitromethane/isopropanol cosolvent mixture (Scheme 1).

Scheme 1. Coupling and De-protection to Give Desired DNA Adduct.



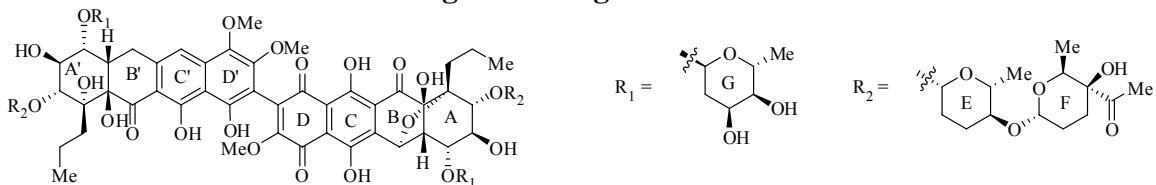
Using this method, material was obtained for NMR analysis of the incorporated product, as well as to conclusively identify the adduct. The site of incorporation was verified by digesting the artificial DNA strand and using MS/MS and HPLC analyses to identify the corresponding nucleobase with the compound incorporated. Future work by the group is planned to examine the local DNA structure with the compound incorporated. Also, the synthesis of two other adducts, including the bis-adduct, to ascertain the properties of those compounds in DNA is planned as well as to prepare adducts of alternative stereochemistry.

“Studies toward Total Synthesis of Angelmicin B”

Jialiang Li, Louis J. Todaro and David R. Mootoo (*Hunter College New York, New York*)

Angelmicin B (Figure 3) has attracted interest as a potential agent in differentiation therapy because it inhibits proliferation and also induces differentiation in HL-60 human myeloid leukemia tumor cells, with an IC₅₀ value of 0.10 ± 0.02 µg/mL.

Figure 3. Angelmicin B.

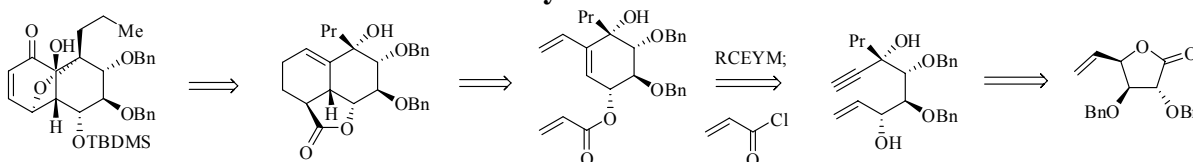


Angelmicin B was first isolated from *Microbispora rosea* by Uehara and co-workers in 1993, and later independently found with other congeners in a different subspecies, and named hibarimicin B. It has been suggested that the biological effects might be linked to the specific inhibition of *src* tyrosine kinase. Angelmicin B is a pseudo-dimer comprised of similar anthraquinoid-derived cyclitol segments ABCD and A'B'C'D' segments, which are connected through a D-D' biaryl bond. The A and A' cyclitol residues are glycosylated and the BCD and B'C'D' segments vary in the oxidation states of the individual rings. Other research groups have reported the use of a Diels-Alder approach to a relatively simple model for the AB and A'B' rings, as well as the use of an intramolecular aldol reaction.

The retrosynthetic strategy of the AB subunit was envisioned through the use of a known carbohydrate starting material, with the key steps in the synthetic pathway utilizing a

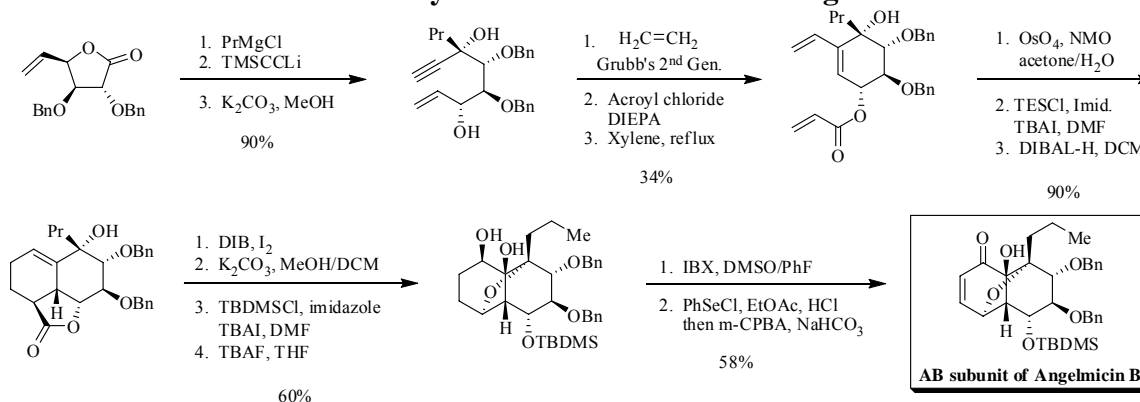
ring-closing enyne metathesis (RCEYM) and an intramolecular Diels-Alder (IMDA) reaction (Scheme 2).

Scheme 2. Retrosynthesis of AB subunit.



The synthesis began with a known lactone (Scheme 3) which was elaborated using the key IMDA reaction and RCEYM steps to provide the AB subunit of Angelmicin B in 15 steps and 9% isolated yield. Relative and absolute stereochemistry was confirmed by NOESY NMR and single-crystal X-ray crystallography.

Scheme 3. Synthesis of AB subunit of Angelmicin B.



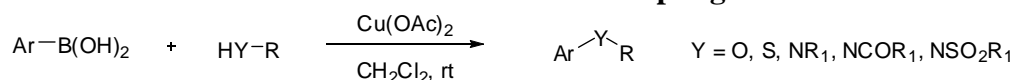
“Copper-Promoted C-Heteroatom Bond Cross-Coupling Via Boronic Acids: Chan-Lam Coupling Reaction”

Patrick Y. S. Lam, Bristol-Myers Squibb, Princeton, New Jersey

Two common synthetic methods have been popularized for forming carbon-heteroatom bonds via cross-coupling mechanisms: the Buchwald-Hartwig amination coupling and the related Chan-Lam coupling (Scheme 4). Each of these protocols have both strengths and drawbacks. The Buchwald-Hartwig reaction involves the use of an aryl-halide or pseudo-halide, a primary or secondary amine or alcohol and a catalytic amount of palladium with ligand. The drawback to this reaction is the use of expensive catalysts and ligands, the requirement to tailor a catalyst to the particular system, and that the reaction must be heated under inert atmosphere. The Chan-Lam coupling reaction involves the coupling any amino- or hydroxyl-containing compound with an arylboronic acid, arylstannane or arylsiloxane. This is done with stoichiometric amounts of copper(II) acetate at room temperature in the presence of air (or oxygen). The disadvantage is the use of more expensive arylboronic acids or related stannanes and siloxanes. Advantages include the requirement to be done in open air (oxygen speeds up

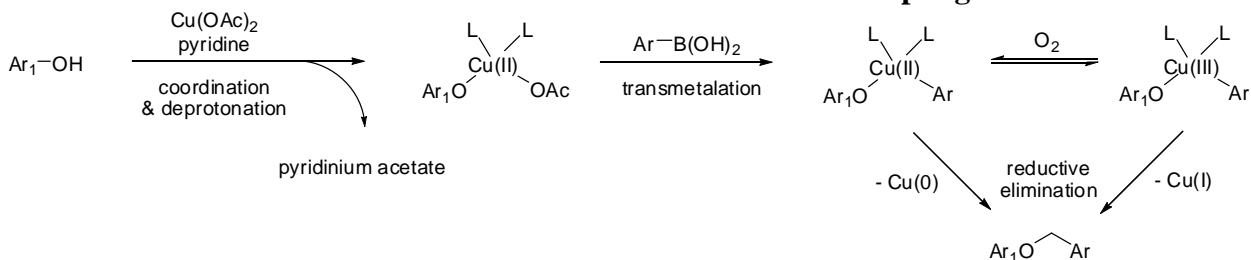
the reaction) and the retention of stereochemistry on the carbon α to the amine or alcohol moiety.

Scheme 4. Chan-Lam Coupling.



The Chan-Lam coupling requires a base in order to proceed, where pyridine, Hünig's base or triethylamine are commonly used. Solvent choices include methylene chloride, dichloroethane, dioxane or methanol. With an alcohol reaction substrate, the use of a drying agent (*e.g.*, molecular sieves) can minimize consumption of the arylboronic acid to unwanted byproducts. The reaction is postulated to go through a copper(III) species as shown in Scheme 5. Conducting the reaction in a pure oxygen atmosphere decreases the overall reaction time by regenerating the copper catalyst more rapidly.

Scheme 5. Postulated Mechanism of Chan-Lam Coupling.



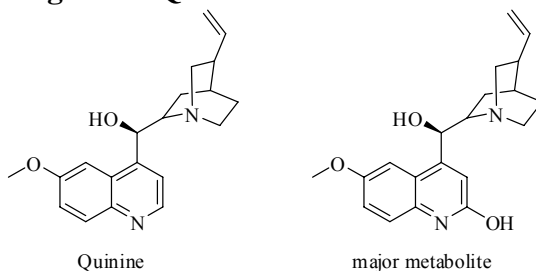
Many examples of the utility of this reaction were presented, from N-vinylation to application in the synthesis of complex biologically active molecules.

“Phototoxicity of 2-Substituted Quinoline Analogs”

J. Cobar, E Milner, D Goodine, T Heady, W McCalmont and G Dow, Walter Reed Army Institute of Research, Silver Spring, Maryland

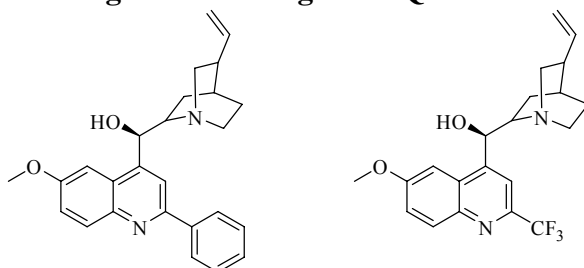
The antimalarial properties of quinine have been known for almost 400 years, having been used by the Romans in the 1600s, by Peruvian natives, and was exported to Europe allowing the successful colonization of Africa. However, among other drawbacks, there is extensive metabolism of the drug substance, leading the author to seek changes. The major metabolite is 2-hydroxylated quinine excreted through the urine (Figure 4).

Figure 4. Quinine and its Metabolite.



The addition of a phenyl substituent in the C-2 position removes many of the metabolic issues and also increases antimalarial activity. However, this analogue was removed from clinical trials due to a strong, long-lasting phototoxic reaction. This phototoxicity is believed to be the result of the extended π -electron system involving the phenyl substituted quinoline. Other substituents have been tried to remove this latter effect. Introduction of a trifluoromethyl group instead of a phenyl group not only removed all phototoxicity, but also removed antimalarial activity and introduced chemotoxicity issues (Figure 5).

Figure 5. Analogues of Quinine.



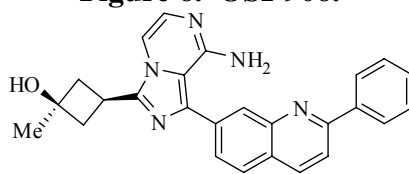
A new series of compounds has been synthesized with a methylene spacer between the phenyl group and the quinoline ring system in an attempt to break up the π -electron system. The new rotational freedom at this position prevents the compound from adopting a planar conformation. The new compounds are currently in testing for antimalarial activity and phototoxicity.

“Identification of Clinical Candidate OSI-906 as a Potent, Selective and Orally Bioavailable IGF-1R Inhibitor”

Brian Volk, Mark J. Mulvihill, Elizabeth Buck, Andrew Cooke, Andrew Crew, Hanqing Dong, Alexandra Eyzaguirre, Maryland Franklin, Lixin Feng, Kenneth W. Foreman, Qun-Sheng Ji, Darla Landfair, Yunyu Mao, Matthew O'Connor, Caroline Pirritt, Stacia Silva, Kam Siu, Arno Steinig, Kathryn Stolz, Paula Tavares and Doug Werner, OSI Pharmaceuticals, Melville, New York and Farmingdale, New York

Insulin-like growth factor receptor (IGF-1R) is a membrane bound tyrosine kinase activated by insulin-like growth factor. This receptor activates cell growth and is critical during childhood. During adulthood, it continues to have anabolic effects in the cell. It has recently been pursued as an oncology target, and there are no therapeutics on the market that target IGF-1R, although OSI Pharmaceuticals has been developing a candidate compound, **OSI-906** (Figure 6). This compound is potent, selective and orally bioavailable.

Figure 6. OSI-906.



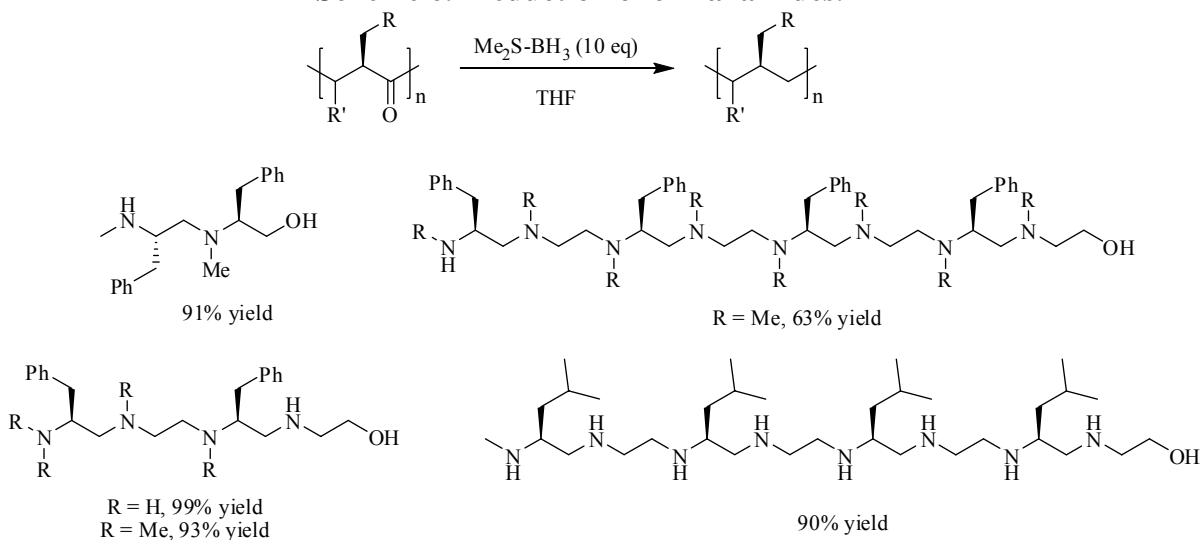
Initial efforts during the SAR focused on the C-1 position of the imidazo-pyrazine core. The initial benzyloxyphenyl substituent was replaced with the constrained 2-phenylquinolinyl moiety. This change was identified through co-crystals of the lead compound with IGF-1R. This change resulted in a 10-fold boost in potency. Additional changes at the C-3 position of the imidazopyrazine gave favorable DMPK properties. Further efforts around an imidazo-triazine core instead of the imidazo-pyrazine were also reported.

“Synthesis and Catalytic Properties of Novel Chiral Polyamines”

Mindy Levine, Craig S. Kenesky, Shengping Zheng and Ronald Breslow, Columbia University, New York, New York

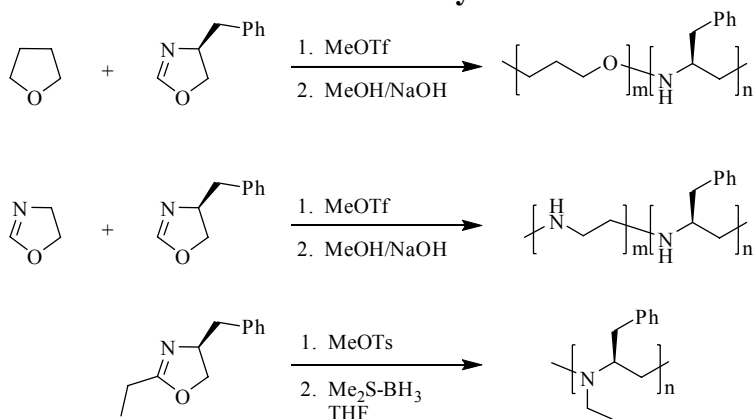
Chiral polyamines can be utilized for a variety of potential applications, ranging from asymmetric catalysis to nonviral gene delivery systems for DNA and RNA. One method for synthesizing these amines to reduce chiral peptides with dimethylsulfide borane as shown in Scheme 6.

Scheme 6. Reduction of chiral amides.



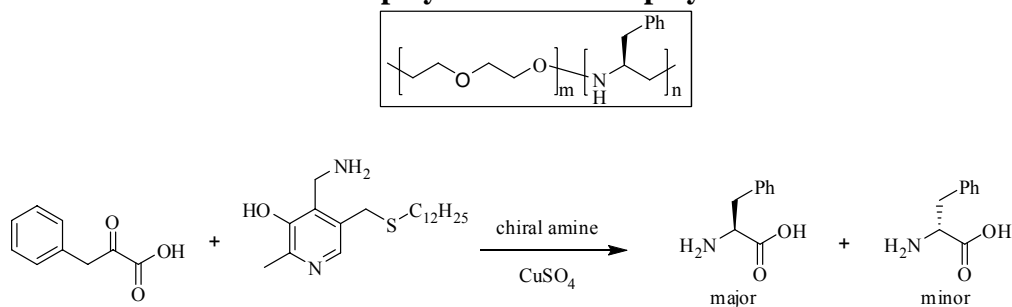
Cationic polymerization will also afford chiral polyamines with oxazolidine starting materials (Scheme 7). Treatment of oxazolidines with either methoxy triflate followed by sodium hydroxide, or with methoxy tosylate followed by dimethylsulfide borane yields the polyamine products.

Scheme 7. Cationic Polymerization.



Polyamines can be used in asymmetric catalysis, such as the transamination reaction, to increase enantiomeric excess (Scheme 8).

Scheme 8. Synthesis of L-phenylalanine (52.5% ee) by transamination with chiral PEG-polyamine block copolymer.

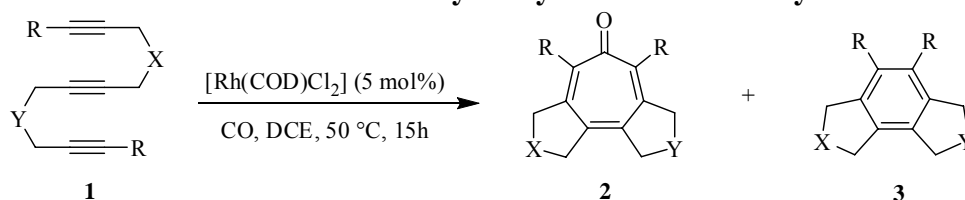


“Formation of Novel Fused-Ring Systems by Rhodium-Catalyzed Cycloaddition Reactions”

Yu-Han Gary Teng, Joseph J. Kaloko and Iwao Ojima, State University of New York, Stony Brook, New York

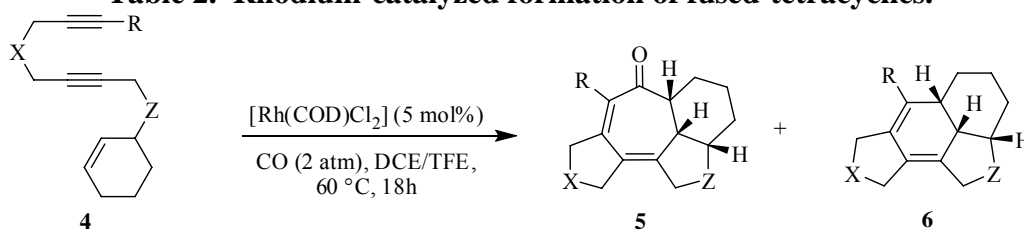
Cycloaddition reactions where multiple carbon-carbon or carbon-heteroatom bonds are formed are strategically helpful in organic synthesis. The following compounds were synthesized via rhodium-catalyzed cycloadditions with various conditions.

Formation of tropones via rhodium-catalyzed [2+2+2+1] cycloadditions were demonstrated, as shown in Tables 1 and 2. Tricyclization of triynes has yielded the following tropones and polysubstituted benzenes which are useful in organic synthesis.

Table 1. Rhodium-catalyzed cycloadditions of triynes.

X, Y	R	Concentration (M)	CO pressure	Conversion by ¹ H NMR (2, 3)
X = Y = C(CO ₂ Et) ₂	Me	0.1	Ambient	100 (20,80)
X = Y = C(CO ₂ Et) ₂	Et	0.1	Ambient	100 (25, 75)
X = Y = C(CO ₂ Et) ₂	H	0.1	Ambient	100 (0,100)
X = Y = C(CO ₂ Et) ₂	Me	0.01	Ambient	62 (14,86)
X = NTs, Y = C(CO ₂ Et) ₂	Me	0.1	Ambient	100 (18, 82)
X = Y = NTs	Me	0.1	Ambient	100 (27, 73)
X = Y = O	Me	0.1	Ambient	100 (30, 70)
X = O, Y = C(CO ₂ Et) ₂	Me	0.1	Ambient	100 (19, 81)
X = O, Y = C(CO ₂ Et) ₂	Me	0.1	400 psi	30 (0, 100)

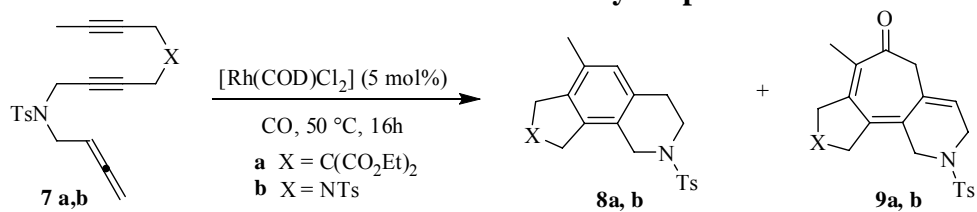
This is the first reported fused-tetracyclic formation by rhodium-catalyzed cycloaddition. It was noted that no β-hydride elimination occurred with these conditions.

Table 2. Rhodium-catalyzed formation of fused-tetracyclics.

X	Z	R	% isolated yield of 5 (Ratio of 5:6)
C(CO ₂ Et) ₂	NTs	Me	81% (16:1)
C(CO ₂ Et) ₂	C(CO ₂ Et) ₂	Me	85% (1:0)
NTs	NTs	Me	85% (13:1)
C(CO ₂ Et) ₂	NTs	Ph	44% (1:1)
C(CO ₂ Et) ₂	NTs	TMS	92% (16.2:1)
NTs	NTs	TMS	100 (9.5:1)

Selectivity for the synthesis of the 5-7-6 fused ring product was accomplished by increasing the CO pressure in the reaction conditions (Table 3).

Table 3. Formation of 5-7-6 tricyclic products.



X	Pressure (atm)	Concentration (M)	Products Ratio (8:9)
C(CO ₂ Et) ₂	1	0.1	4.5:1
C(CO ₂ Et) ₂	2	0.1	1:4
C(CO ₂ Et) ₂	5	0.1	1:4
C(CO ₂ Et) ₂	10	0.1	1:5.2
C(CO ₂ Et) ₂	2	0.05	1:3.4
C(CO ₂ Et) ₂	2	0.025	1:2.8
NTs	2	0.1	1:11