

Enhanced synthetic efficiency towards natural products via transition metal catalyzed reactions

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Abstract: The invention of new reactions provides insight into new synthetic strategies of biologically important natural products. Enhancing selectivity and atom economy in our synthetic tools provide opportunities for enhanced synthetic efficiency. An overview of some recent efforts directed towards several natural products is presented.

INTRODUCTION

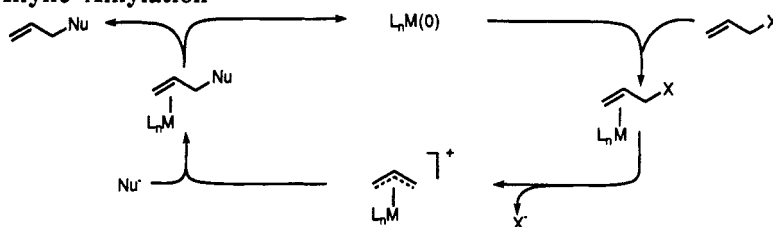
As our needs to construct ever more complicated molecular arrays for innumerable applications grows, refining our synthetic tools in order to evolve practical synthetic strategies becomes imperative. The ever increasing role that natural products or close analogues play in therapy provides a powerful stimulus to have synthetic access to these highly diverse and frequently structurally complicated molecules. Enhancement of synthetic efficiency involves two aspects. Firstly, we must exercise selectivity- chemo-, regio-, diastereo-, and enantio-. Secondly, we must minimize our use of raw materials and generation of waste -- i.e., be atom economical (1). Transition metal complexes as catalysts offer an unprecedented opportunity to achieve these twin goals wherein we can tune reactivity in a coarse fashion by choice of metal with fine tuning occurring by choice of ligand environment.

SELECTIVITY

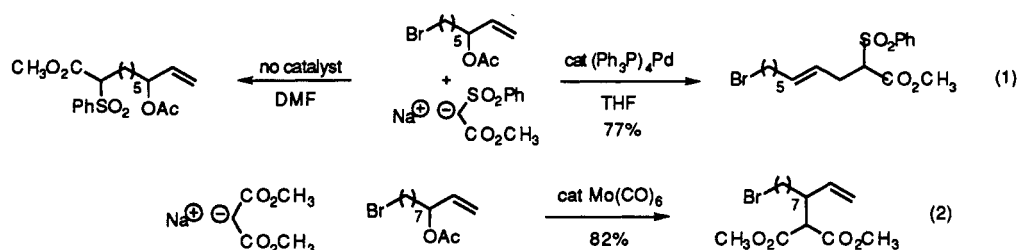
Chemoselectivity

Changing the way molecules normally react addresses the issue of chemoselectivity. Imparting reactivity that previously did not exist is an approach to achieve this goal. One way to accomplish this feat involves pre-coordination of the substrate such that the subsequent process becomes intramolecular. Scheme 1 illustrates this concept with respect to allylic alkylation wherein, by prior olefin coordination,

Scheme 1. Allylic Alkylation

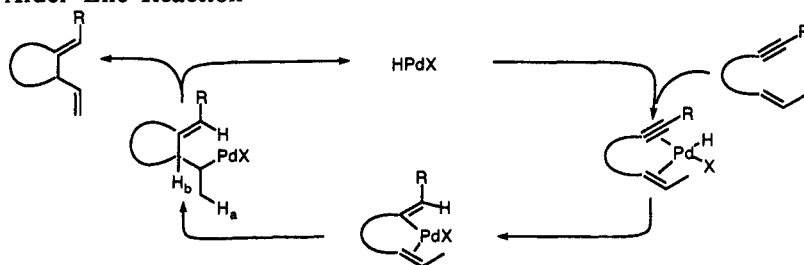


X groups that normally do not function as leaving groups in displacement reactions may now do so (2). Eqs 1 and 2 illustrate the realization of this concept using a palladium (3) and molybdenum catalyst (4).

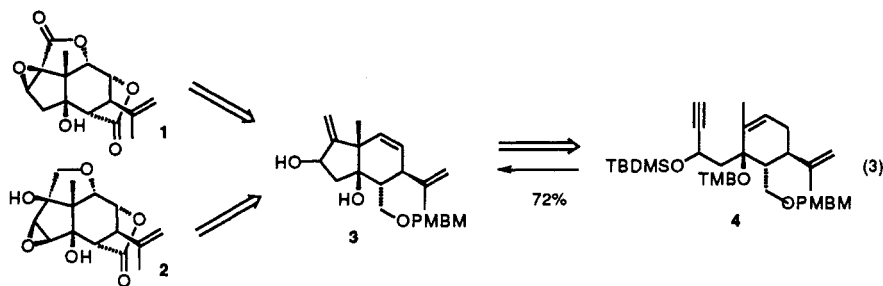


The Alder ene reaction has immense potential since it is a simple addition, but normally lacks selectivity because of the high temperatures. Scheme 2 outlines a catalytic cycle for an intramolecular version (5). Precoordination of the substrate to the palladium facilitates the hydrometallation that initiates the subsequent carbapalladation to form the ring. β -Hydrogen elimination involving H_a generates the Alder ene product and regenerates the catalyst.

Scheme 2. Alder Ene Reaction



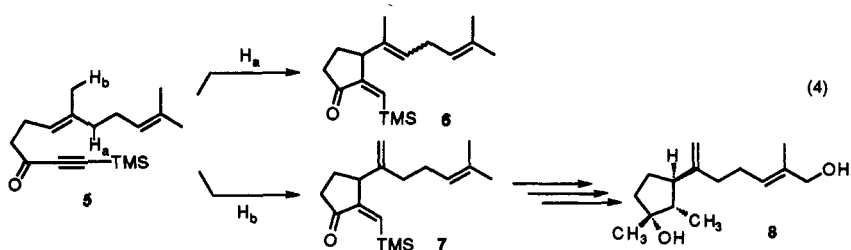
For the synthesis of the picrotoxane family of terpenes illustrated by picrotoxinin **1** (6,7) and corianin **2** (7,8), we can envision the bicycle **3** to be a key intermediate (eq. 3). In principle, an intramolecular Alder ene reaction of enyne **4**, easily available from carvone, would provide the requisite bicycle. The inability to perform this thermal reaction led to a synthesis of a close analogue (available



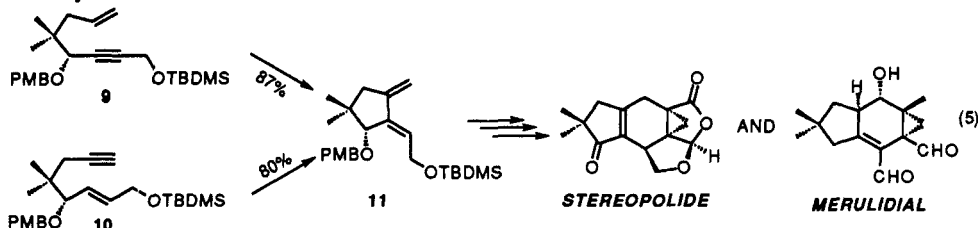
from **3** by chemoselective oxidation of the allylic alcohol and interchange of the protecting group of the primary alcohol) in over 25 steps from carvone (**9**). The invention of a palladium catalyzed reaction allows smooth cyclization of **4** to the desired bicycle **3** in fewer than half the previous number of steps from carvone. Syntheses of both picrotoxinin and corianin then follow from this common pivotal intermediate.

Regioselectivity

An advantage of this metal catalyzed version of the Alder ene process is the ability to redirect the reaction along pathways not feasible by thermal methods. For example, in a synthesis of chokol (**8**), a member of a novel class of terpenoid antifungal agents, the question of regioselectivity of the insertion into $\text{C}-\text{H}_a$ or $\text{C}-\text{H}_b$ of **5** arises (eq. 4). In related substrates, thermal cycloisomerizations involve H_a exclusively. On the other hand, the palladium catalyzed reaction completely redirects the reaction to effect migration of H_b to give **7** which was transformed to chokol in a total of 7 steps and 19% overall yield from geranyl bromide (**10**).

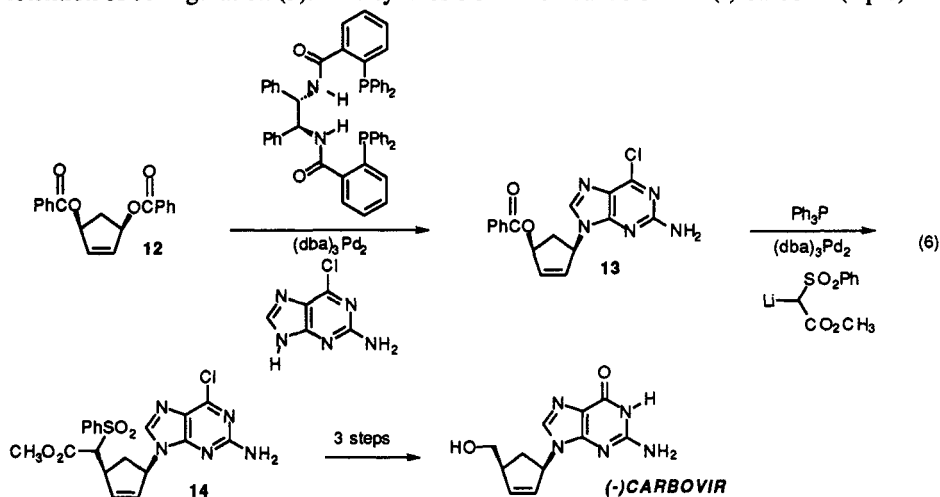


A most exciting prospect arises by considering the penultimate intermediate in Scheme 2 whereby the palladium may elect H_b rather than H_a to give a 1,3-diene. With a substrate that lacks H_a as in **9** or one that possesses an electronegative substituent at the allylic position as in **10**, the palladium catalyzed reaction proceeds in excellent fashion to produce the 1,3-diene **11** which proved to be a very effective intermediate for the asymmetric synthesis of both stereopolide (**11**) and merulidial (**12**). The effectiveness of the strategy that emerged is illustrated by the fact that (-)-stereopolide was synthesized in only 11 steps in 34% overall yield.



Diastereoselectivity

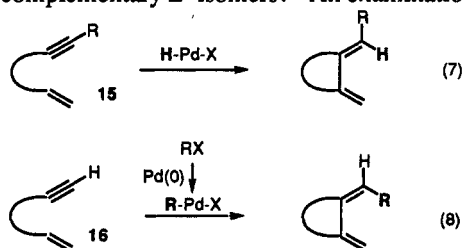
Controlling relative stereochemistry represents a continuing challenge -- to intrinsically change the normal stereochemical course of events is a most exciting one. Palladium catalyzed allylic alkylations achieve just that since, as Scheme 1 suggests, the process involves two S_N2 substitutions which gives rise to a net retention of configuration (**3**). The synthesis of the carbanucleoside (-)-carbovir (eq. **6**) illustrates



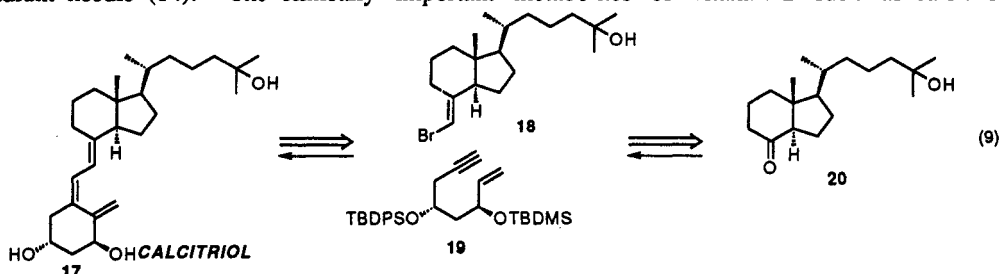
the advantage of this methodology since the readily available *cis*-dibenzoate **12** allows sequential substitution of both benzoates with retention of configuration using both heteroatom (e.g., 2-amino-6-chloropurine) and carbon (e.g., methyl phenylsulfonylacetate) nucleophiles to give **13** and **14** respectively (**13**). Three additional steps completes the synthesis of (-)-carbovir. Since the two palladium (0) catalyzed reactions may be telescoped into a single operation, (-)-carbovir may be synthesized in only 4 steps!

Controlling olefin geometry is also an issue of relative stereochemistry. Our synthesis of 1,3-dienes by cycloisomerization of enynes provides *E*-1,3-dienes as illustrated in eq. **7**. How might we

address the synthesis of the complementary *Z* isomers? An examination of eq. 7 suggests a solution



since the diene geometry arises from the *cis*-hydropalladation of the disubstituted acetylene. If we simply interchange **R** and **H**, i.e., replace the **R** in **15** by **H** as in **16** and the **H** in HPdX by **R**, the *cis*-carbapalladation should give the *Z*-diene. Since the required RPdX derives from an oxidative addition of Pd(0) with **RX**, a simple catalytic cycle emerges whereby **RX** and an enyne may be stitched together by a palladium needle (**14**). The clinically important metabolites of vitamin D such as calcitriol **17**



highlight the importance of such a reaction (15). The vinyl bromide **18** is available in a geometrically selective olefination reaction of the well-known ketone **20**. Simply heating a mixture of the vinyl bromide **18** and enyne **19** with Pd(0) in the presence of triphenylphosphine and triethylamine gives crystalline calcitriol in approximately 60-65% yields after desilylation. This simple alkylative enyne cyclization provides a most practical synthesis of this difficultly accessible but important family of compounds.

Enantioselectivity

Prospects for imposing control of absolute stereochemistry is one of the major advantages of transition metal catalyzed reactions, but not necessarily simple. Asymmetric allylic alkylation is differentiated from all transition metal catalyzed reactions in that bond breaking and making occur outside the sphere of the metal and its ligands. To approach the problem of asymmetric induction, a chiral pocket or cleft much like that of an enzyme represents a reasonable strategy. Using a model as depicted in Figure 1 wherein chiral space results from the conformational bias of a diphenylphosphino induced by a chiral scaffold, a chiral pocket into which the substrate must slip will result if the P-Pd-P "bite" angle is made as large as possible. Ligand **21** (eq. 6) achieves this result by separating the two phosphines by a long tether

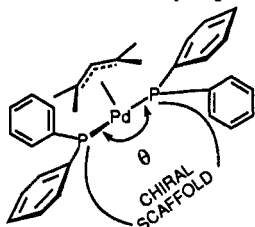


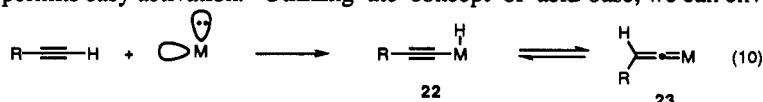
Figure 1. A Model for Enantioselectivity in Allylic Alkylations

so that chelation requires formation of a large ring (**16**). Indeed, enantioselective ionization of dibenzoate **12** proceeds with >90% chiral recognition and thereby converts the carbanucleoside synthesis into an asymmetric one.

ATOM ECONOMY

To the extent that we can construct complex molecules by simple addition reactions, we maximize atom economy. Unfortunately, our repertoire of addition reactions is very limited. Our ability to implement more efficient synthetic strategies depends upon the invention of a broader array of reactions that are simple additions with anything else just needed catalytically. To the extent that we employ reactions of the form $A+B \rightarrow C+D$ in which C is the desired product, we want to make D as small and innocuous as possible.

Acetylenes are marvelous building blocks from this perspective since their ready coordination to transition metal permits easy activation. Utilizing the concept of acid-base, we can envision a transition

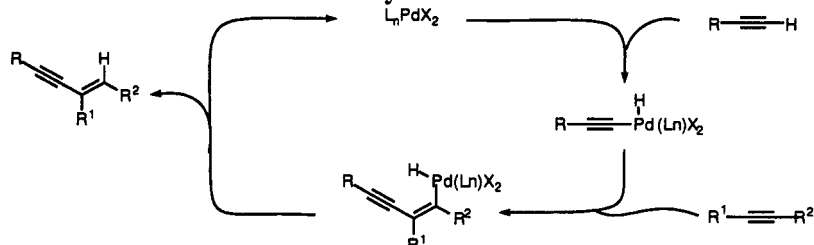


metal serving as a "base" and the acetylene serving as an "acid" to generate **22**. Furthermore, tautomerization of **22** generates another interesting reactive intermediate **23**. Both of these species offer opportunity for new invention.

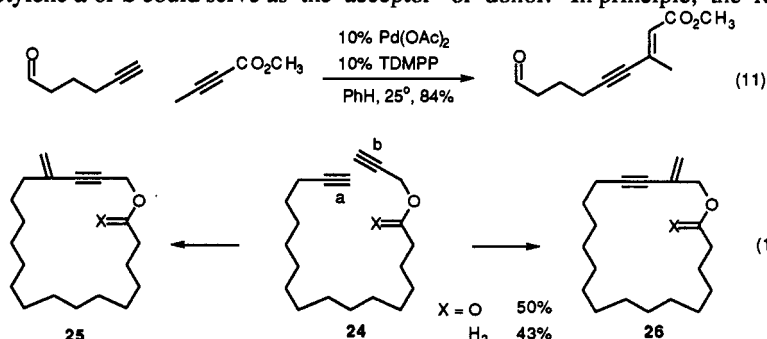
Metal Acetylide Intermediate

The presence of a carbon-transition metal bond in **22** raises the question of its ability to participate in carbametallations as envisioned in Scheme 3. Indeed, an excellent yield of the cross coupling

Scheme 3. An Addition of Terminal Acetylenes



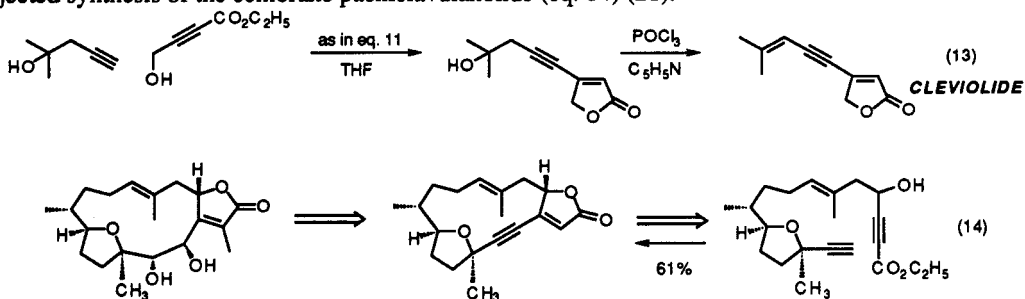
product predicted arises via both inter- (eq. 11) (17) and intramolecular (eq. 12) (18) processes. The former illustrates the marvelous chemoselectivity of this new addition whereby an unprotected aldehyde shows no propensity to undergo addition. The latter raises an intriguing question of chemoselectivity since either acetylene **a** or **b** could serve as the acceptor or donor. In principle, the reaction might be



anticipated to give an equimolar mixture of **25** and **26**. In fact, only **26** is isolated in both cases. This remarkable chemoselectivity with such a simple catalyst highlights the potential power of transition metal catalyzed reactions.

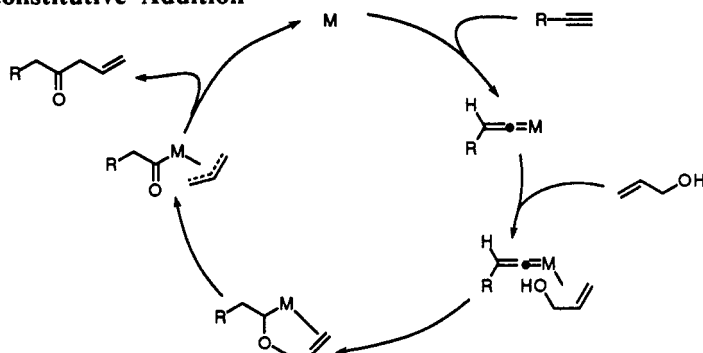
Using γ -hydroxybutynoates as the acceptors provides γ -butyrolactones as the direct product so that cyclization with expulsion of alcohol accompanies addition. This simple synthesis of γ -butyrolactones allows a two step synthesis of cleviolide (**19**), a monoterpene from Compositae *Senecio Clevelandii* (eq.

13) which compares to a five step synthesis from methyl 4-hydroxybutynoate previously published (20). Since cleviolide has been semihydrogenated to *E*- and *Z*- scobinolide, this route constitutes a formal synthesis of these terpenoids as well. An intramolecular version of this reaction forms a key step in a projected synthesis of the cembrane pachiclavulanolide (eq. 14) (21).

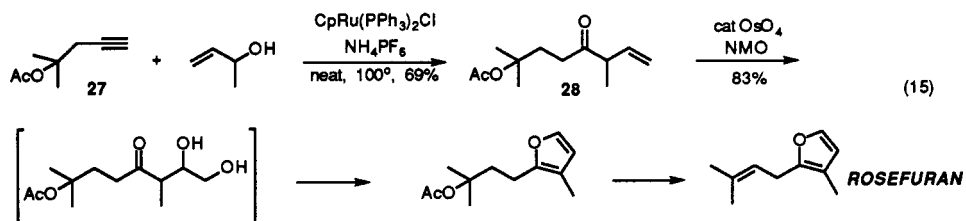


Vinylidene Intermediate

The prospect of generating vinylidene metal complexes simply from terminal acetylenes led to the conceptualization of the catalytic cycle depicted in Scheme 4. Thus, β,γ -unsaturated ketones derive from Scheme 4. **Reconstitutive Addition**



simple allyl alcohols and terminal acetylenes (22). Using $\text{CpRu}(\text{Ph}_3\text{P})_2\text{Cl}$ as catalyst, 3-hydroxy-1-butene and acetate **27** gave the β,γ -unsaturated ketone **28**. *cis*-Hydroxylation gave a very unstable diol which undergoes loss of two molecules of water in the presence of even weak acids to generate furans (23). Thus, in only two steps, 2,3-disubstituted furans are readily available.



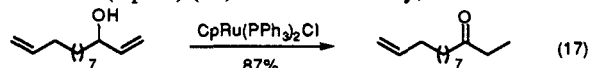
Elimination of the elements of acetic acid completes the synthesis of rosefuran, the prized fragrance of oil of rose. The ease of isomerization of β,γ -unsaturated ketones to α,β -unsaturated ones allows use of

conjugate addition to elaborate the adducts. The creation of the functionalized steroid side chain of the

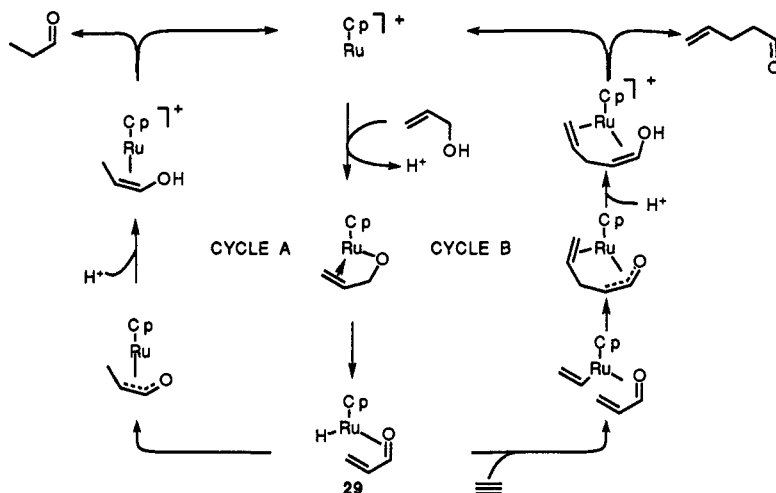
ganoderic acids, novel ACE inhibitors, highlights this application (eq. 16) (24). In this case, extending the reaction time of the ruthenium catalyzed addition allows direct isolation of the α,β -unsaturated ketone.

Alder Ene Reactions

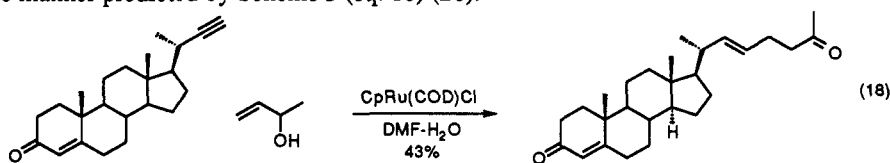
As a control reaction, we discovered that the allyl alcohols undergo a highly chemoselective isomerization to saturated ketones (eq. 17) (25). Mechanistically, we can envision this reaction proceeds



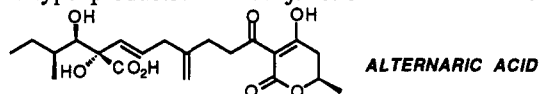
as outlined in Scheme 5, Cycle A. Can the purported intermediate **29** be intercepted by an acceptor such



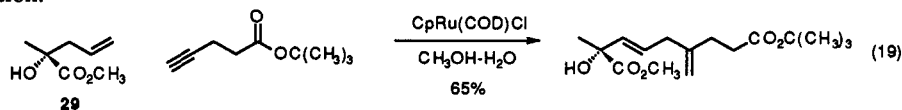
as an acetylene to create Cycle B? In this event, the terminal acetylene and allyl alcohol combine to generate γ,δ -unsaturated ketones. This process requires more open coordination sites on ruthenium which led to our exploration of CpRu(COD)Cl as the catalyst. Indeed, our acetylenic steroid of eq. 16 reacts in a completely different fashion with this new ruthenium complex compared to the previous complex and in exactly the manner predicted by Scheme 5 (eq. 18) (26).



Is the presence of the allyl alcohol required for this process? Can any acetylene react with an olefin to give the equivalent of ene-type products? In conjunction with an interest in the synthesis of the



antifungal agent alternaric acid, we explored the reaction of the allylated lactic ester **29** and t-butyl 4-pentynoate (eq. 19) (27). The core chain unit of alternaric acid is created in a single simple step via this new reaction.



CONCLUSION

While interest in natural products saw the birth of the science of organic chemistry, this interest has

not dwindled in the intervening hundreds of years. If anything, as we learn more about natural products, we become even more enchanted with the diversity of nature. This diversity of nature creates a constant challenge to the synthetic chemist to be as diverse but more efficient. It is a challenge that stimulates new concepts of reactivity since, only by doing so can whole new insights that enhance synthetic efficiency become possible. The above reflects some of the possibilities that designing new processes based upon transition metal complexes may provide.

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