

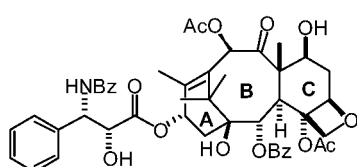
Toward the ideal synthesis. New transition metal-catalyzed reactions inspired by novel medicinal leads*

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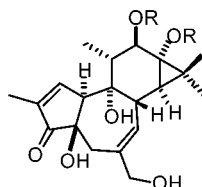
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Abstract: Studies in our laboratory are directed at the advancement of synthesis, biology, and medicine. This lecture will focus on new transition metal-catalyzed reactions that have been inspired by biologically potent targets such as phorbol and Taxol[®] and by the more general interest in producing syntheses that are concise, efficient, cost- and resource-effective, environmentally benign, quick, and simple to conduct—in essence, ideal. A special emphasis in our program is placed on new transition metal-catalyzed reactions that, in the absence of catalyst, would be forbidden or difficult to achieve. We have thus far reported the first examples of intramolecular metal-catalyzed [4+2], [5+2], and [4+4] cycloadditions, reactions that produce 6-, 7-, and 8-membered rings, respectively. Recent advances in our [5+2] cycloaddition studies will be presented, including new catalysts for relative and absolute stereochemical control. We will also describe recyclable catalysts that can be used in water, thereby minimizing cost and environmental concerns about solvent waste streams. New multicomponent reactions will also be presented. Finally, we will report a new [6+2] cycloaddition that produces an 8-membered ring.

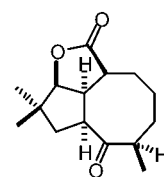
One of the major programs in our laboratory centers on the design and development of fundamentally new reactions and strategies for the synthesis of complex molecules. A special emphasis is placed on synthetic targets with novel structural features, profound biological activity, a unique mode of action, and significant clinical potential. Representative targets are Taxol[®] [1], phorbol esters [2], and bryostatin analogs [3], molecules that are currently either in clinical use or clinical trials and at the outset of our studies presented unmet and formidable synthetic challenges.



Taxol[®]



Phorbol Esters



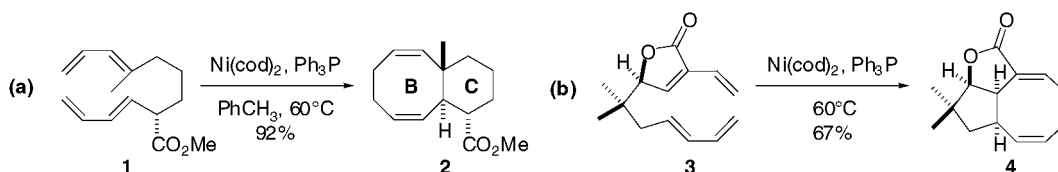
Asteriscanolide

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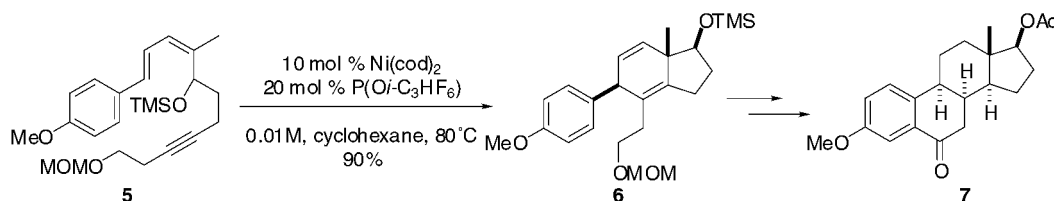
Taxol serves as an exemplary starting point and background for this overview. It possesses a novel mode of action and has more recently been shown to have remarkable effectiveness in the treatment of breast and ovarian cancers. From a synthetic perspective, it presents a number of challenges, among which 8-membered ring synthesis is central. As previously analyzed by connectivity analysis, which has now been converted to a computer program (CONAN) for synthesis design [4], there exist 153 one- and two-bond retrosynthetic disconnections of the Taxol diterpene core. Significantly, only 6 disconnections produce fragments of equal complexity, as required for optimal strategic convergency, and all 6 involve the 8-membered B ring. In short, this connectivity analysis underscores the strategic importance of reactions for the synthesis of 8-membered rings for taxol synthesis design and more generally for other targets incorporating fused or bridged 8-membered rings.

Given this need, it is noteworthy that relatively few cycloadditions existed for the synthesis of substitutionally complex 8-membered rings at the beginning of our studies [5]. However, a promising approach to this goal was suggested by the impressive work of Reppe, Reed, Wilke, and others who had shown that various transition metals can catalyze *intermolecular* [4+4] cycloadditions of dienes [6]. Unfortunately, alkyl substitution of the diene either inhibits these cycloadditions or often leads to complex mixtures of regio- and stereoisomers. To circumvent these limitations, we explored the first transition metal-catalyzed *intramolecular* [4+4] reactions and found that these processes tolerate alkyl substitution and proceed with remarkably high regio-, stereo-, and facial selectivities (Scheme 1, **a**) [7]. Superbly suited for the synthesis of Taxol analogs, this process creates the BC ring system **2** with requisite *trans* ring fusion selectivity and positions two double bonds at sites that in the target possess vicinal oxidation. Its pivotal role in the total synthesis of (+)-asteriscanolide (Scheme 1, **b**) further illustrates the breadth and utility of this [4+4] cycloaddition reaction yielding precursor **4** in 67% yield [8].



Scheme 1

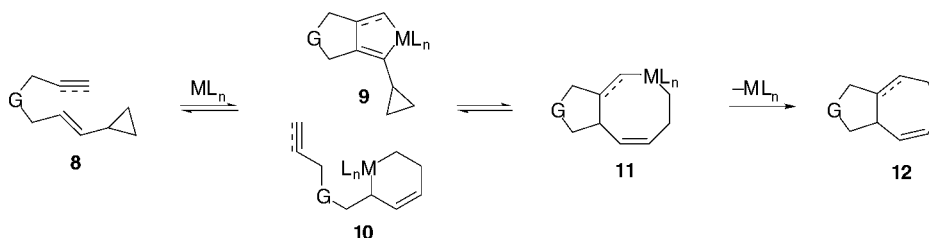
Generalization of the concept of metal-catalyzed [4+4] cycloadditions to [m+n] cycloadditions led to the first metal-catalyzed intramolecular [4+2] reactions of unactivated alkynes and dienes [9]. As demonstrated in the synthesis of vitamin D analogs **7** (Scheme 2), these metal-catalyzed reactions proceed efficiently at 80 °C. In dramatic contrast, in the absence of catalyst, reaction of **5** does not occur until 175 °C, at which point only decomposition products are produced.



Scheme 2

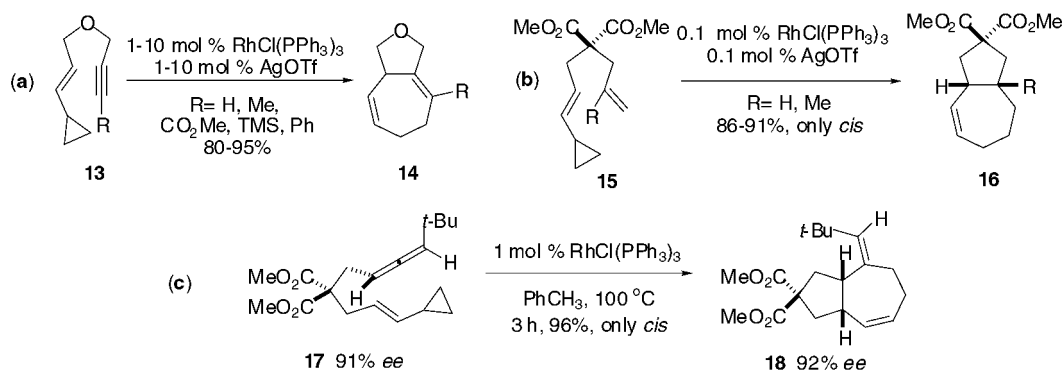
Following introduction of the metal-catalyzed intramolecular [4+4] and [4+2] cycloadditions for 8- and 6-membered rings, we sought to develop an approach to 7-membered rings [10] that would have the robust generality of the Diels–Alder cycloaddition in 6-membered ring synthesis. Impressive cycloaddition reactions for 7-membered ring synthesis have been devised such as [4+3] cycloadditions [11] and [5+2] cycloadditions [12]. However, these approaches have been limited by the often difficult formation of highly reactive ionic or zwitterionic species.

Our conceptual approach to the design of a [5+2] cycloaddition started with the idea that it could be viewed as a homolog of the Diels–Alder [4+2] cycloaddition and therefore could be realized with a homolog of the 4-carbon diene, namely a 5-carbon vinylcyclopropane (VCP). The literature reveals attempts to achieve such a process thermally, but without apparent success [13]. Our plan was to employ a transition metal to choreograph the required bond-cleaving and -forming events (Scheme 3). According to this plan, initial and well-precedented oxidative addition would be expected to give metallacycle **9**. Alignment of the C–ML_n bond with the C–C bond of the cyclopropane followed by cleavage would then lead to **11**, which, upon reductive elimination, would provide cycloadduct **12** and regenerate the catalyst. An alternative pathway involving initial VCP cleavage (**8** → **10**) followed by insertion is also possible.



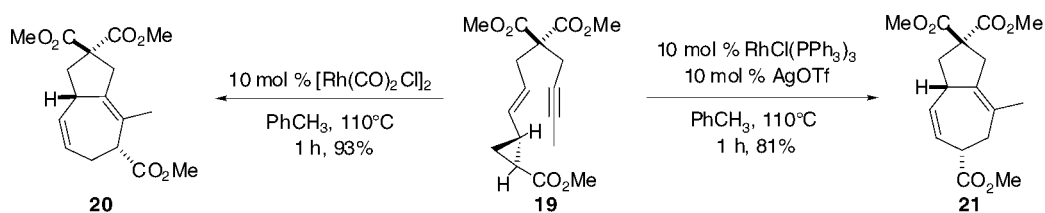
Scheme 3

In 1995, we reported the viability of this process in the form of the first metal-catalyzed [5+2] cycloaddition between unactivated VCPs and tethered alkynes (Scheme 4, a) [14]. It is noteworthy that the reaction proceeds well for a range of alkyne substituents (R in **13** → **14**) from H to electron donating and withdrawing. Alkenes (**15**) are also superb 2C components in this process [15], giving cycloadducts **16** with exquisite *cis* diastereoselectivity in 86–91% yield with only 0.1 mol % Wilkinson's catalyst and silver triflate (Scheme 4, b). The use of internal olefins was problematic; however, allenes that would access a similar product after cycloadduct hydrogenation proved to be excellent partners [16]. For example, chiral allene **17** in the presence of 1 mol % catalyst gives cycloadduct **18** in 96% yield. Finally, a study centered on the nature of tether revealed that modifications to the three-atom tether did not have a deleterious effect on the [5+2] reaction. Diester, monoester, dimethyl, ether, siloxane, and sulfonamide linkers are tolerated.



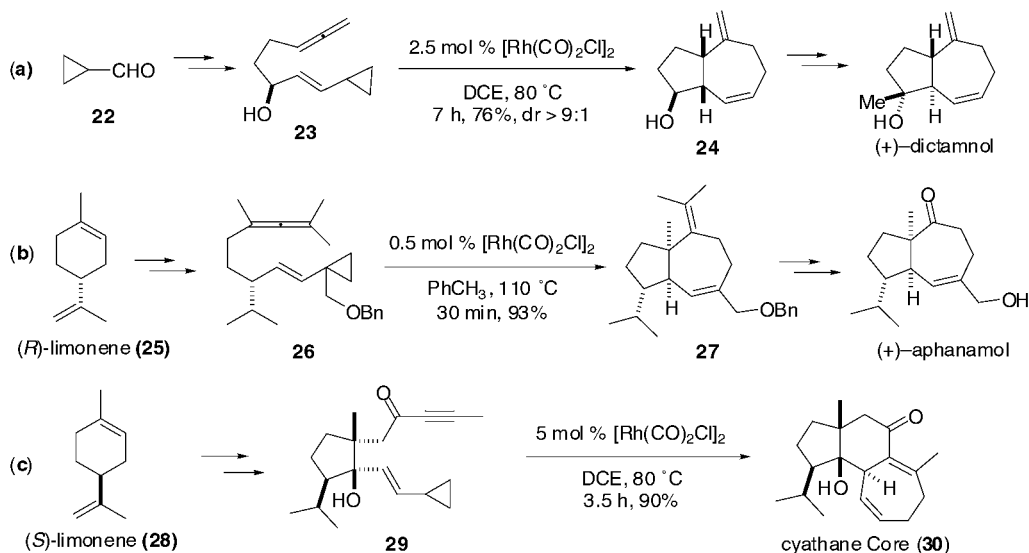
Scheme 4

Studies on 1,2-disubstituted VCPs revealed that not unlike the Diels–Alder reaction, the stereochemistry of the starting VCP is conserved in cycloadduct formation (Scheme 5) [17]. Moreover, by changing the catalyst, one can also change the regioselectivity of cleavage. Thus, while **19** reacts with [Rh(CO)₂Cl]₂ to give cleavage of the more-substituted bond cycloadduct producing **20**, cleavage of the less-substituted bond occurs with Wilkinson's catalyst to give **21**.



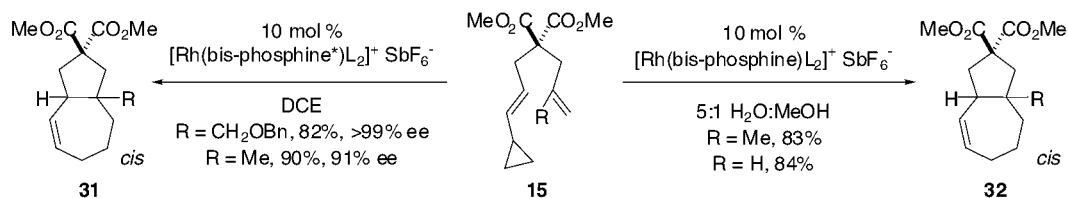
Scheme 5

Testing this new cycloaddition in the context of total synthesis showed that it is indeed a robust process. For example, a total synthesis of (+)-dictamnol was readily achieved in only 6 steps and 9% overall yield through a rhodium(I)-catalyzed cycloaddition of an allenyl-VCP **23** that gave cycloadduct **24** in 76% yield (Scheme 6, a) [18]. Similarly, a total synthesis of (+)-aphanamol was realized in only 10 steps and 13.6% overall yield from (*R*)-limonene (**25**) through a rhodium(I)-catalyzed intramolecular [5+2] cycloaddition of an allenyl-VCP **26** which gave cycloadduct **27** in 93% yield (Scheme 6, b) [19]. More recently, a concise asymmetric synthesis of the tricyclic core of nerve growth factor-inducing cyathane diterpenes has been achieved through a rhodium(I)-catalyzed cycloaddition of ynone-VCP **29** that provided **30** in 90% yield (Scheme 6, c) [20].



Scheme 6

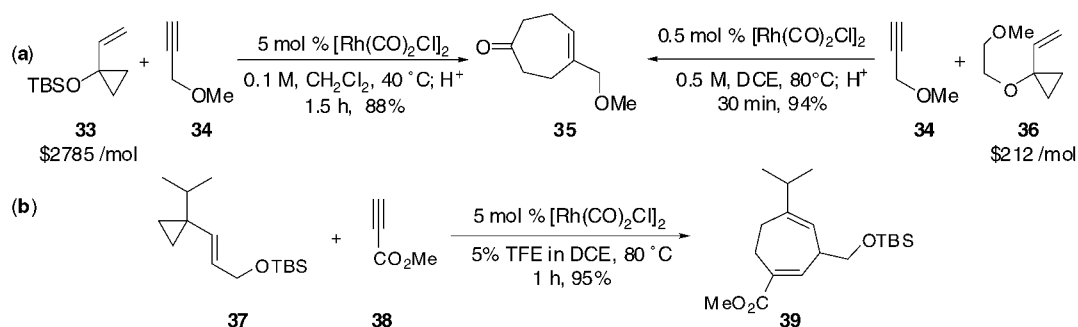
The above examples illustrate how pre-existing chirality can be used in conjunction with the [5+2] cycloaddition to achieve asymmetric syntheses. We have also found that the process itself can be rendered asymmetric through the use of chiral catalysts. Asymmetric bidentate phosphine ligands have been found to induce good to excellent enantioselectivity (91–99% ee) in the [5+2] cycloaddition reac-



Scheme 7

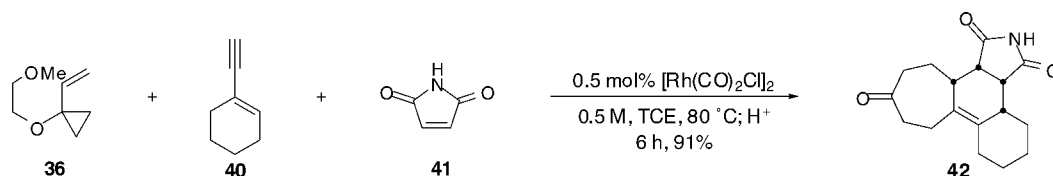
tion of **15**, affording **31** in 82–90% yield. We have also prepared a water-soluble catalyst and have found that it will catalyze the cycloaddition of **15** in water without the need for an organic solvent, generating **32** in 83–84% yield. This procedure minimizes organic solvent waste streams, perhaps the biggest source of atom inefficiency and, importantly, allows the water-based catalyst to be recycled without removal from the water layer (Scheme 7) [21].

Given the ready availability of alkynes, we were delighted to find that these [5+2] cycloadditions can be conducted *intermolecularly* [22]. For example, siloxy-VCP **33** in the presence of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ affords, upon hydrolysis of the initial enol ether, a cycloheptanone **35** in 88% yield (Scheme 8, **a**). Many of these reactions occur in high yield at room temperature or slightly above in minutes to under 3 hours. For applications in which the cost of a TBS group would be a concern, the readily available (2 steps) and significantly lower cost VCP **36** can be used. This new reagent **36** works superbly, providing with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ cycloadduct **35** in 94% yield [23]. Significantly, recent studies have shown that excellent cycloadduct yields can be achieved with a simple alkyl-substituted VCP **37** and alkyne **38** (Scheme 8, **b**) [24].



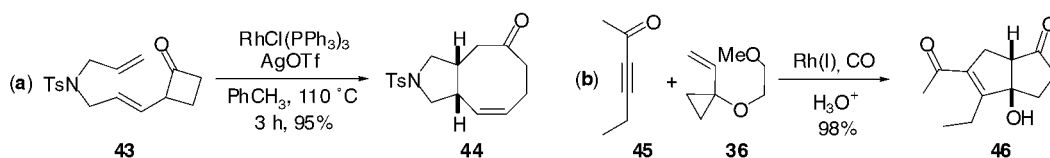
Scheme 8

The chemoselectivity of the intermolecular [5+2] cycloaddition for alkynes and its functional group tolerance enables its use in a new multicomponent processes, involving serial [5+2]/[4+2] cycloadditions [25]. These reactions form two new rings, four carbon–carbon bonds, and up to four stereocenters in one step, producing **42** in 91% from three readily available materials (Scheme 9).



Scheme 9

While our studies on metal-catalyzed [5+2] cycloadditions continue, we have also found that replacement of a cyclopropane with a cyclobutanone moiety as in **43** provides a new reaction for 8-membered ring synthesis (Scheme 10, **a**) [26]. These [6+2] cycloadditions proceed efficiently and give preferentially, if not exclusively the *cis* fused product **44**. Of mechanistic significance, a minor decarbonylation reaction leading to a [5+2] product was observed in two cases.



Scheme 10

Prompted by the decarbonylation observed in the [6+2] cycloaddition, we proposed that a [5+2+1] cycloaddition could be achieved if the [5+2] cycloaddition were conducted under a CO atmosphere. This indeed proved to be the case with the [5+2+1] cycloadduct undergoing a “bonus” intramolecular aldol reaction to give the bicyclic product **46** in 98% yield (Scheme 10, **b**) [27].

Overall, this program has thus far led to the introduction of metal-catalyzed [4+2], [5+2], [4+4], [6+2], and [5+2+1] cycloadditions providing the basis for fundamentally new strategies for 6-, 7-, and 8-membered ring synthesis. The selectivities of these processes have been substantially delineated, and new catalysts for control of absolute stereochemistry and for water-based reactions have been introduced. Our continuing efforts are directed at enhancing the scope and selectivity of these processes, at exploring new catalyst ligands and metals, at testing the synthetic potential of these new processes, and at discovering and inventing additional new reactions.

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