A. Introduction and Background

The discovery and development of new chemical reactions is a major focus of research activities in organic chemistry. The chemical synthesis of molecules provided by Nature has traditionally been the arena in which the utility of new reactions is critically evaluated. A vast array of new methods and creative strategies has arisen from this activity.[1–6] The development of new strategies and reactions is also stimulated by efforts to rationally design syntheses of non-natural compounds with interesting molecular architectures. Concepts of bonding, binding, reactivity, as well as inter- and intramolecular interactions can then be examined. The reactions and classes of reactions which have found the broadest applicability in organic chemistry are those, that address the issues of stereo- and enantiocontrol and are compatible with a variety of functional groups. Reactions which form multiple bonds, rings, and/or stereocenters are particularly important tools for the efficient assembly of complex molecular structures.[7] Among those families of reactions discovered over the past 75 years, cycloaddition reactions hold a prominent place in the arsenal of synthetic methods currently available to organic chemists. Moreover, research activity in this field shows no signs of abatement.[8, 9]

Cycloadditions have been promoted by heat, light, LEWIS acids, high pressure or sonication. Many of these reaction conditions require the presence of polarized functional groups in the substrate to facilitate transformation. In general, reactions of unactivated alkenes, dienes, allenes and acetylenes are notoriously poor and extreme conditions or special methods are necessary to achieve good yields of the cycloadducts. Particular difficulty is encountered in the cycloaddition of two unactivated species since homodimerization can be a competitive and dominant reaction pathway.

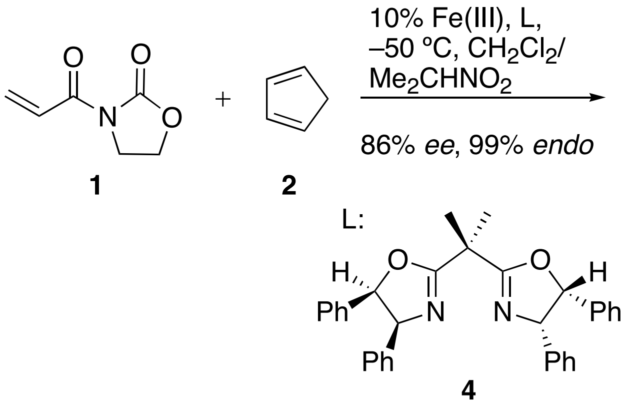
Metal catalysts provide new opportunities for highly selective cycloaddition reactions since complexation of the metal to an alkene, diene, or acetylene significantly modifies the reactivity of this moiety, opening the way for improved reactivity and novel chemistry.[10] One of the most important consequences of complexation is the temporary polarization and activation of otherwise unreactive species. In addition to the rate enhancements observed in the presence of the metal catalyst, the opportunity to achieve enantioselective transformations by adding chiral ligands is one of the most attractive features of this strategy.

The remarkable versatility of the Diels-Alder reaction for the stereospecific construction of six-membered rings has made this reaction one of the most widely studied methods in organic chemistry.[11–15] The severity of the reaction conditions required for a purely thermal $[4+2]$ cycloaddition depends on the substituents on the diene and on the dienophile. Various modifications have been developed to enhance the rate of the cycloaddition and to improve selectivities including the following: the use of high pressure,[16–19] ultrasound,[20–23] Broensted acids,[24–29] traditional Lewis acids,[11–13, 30] special solvent effects,[31–36] molecular sieves,[37–40] adsorption on chromatography sorbents,[41–44] *in situ* radical cation formation,[45–47] and the use of transition metals.[48–50]

The past 15 years experienced a tremendous increase in the development of useful transition metal catalysts promoting cocyclization reactions. This interest stems from mild reaction conditions and the ability to modify the chemo- and regioselectivities as the metal and ligands are varied. Two main classes of metal-catalyzed Diels-Alder reactions can be identified. The metal either serves as a Lewis acid and complexes to a carbonyl or other polarized group[48, 49] or the metal complexes to the π-bonds of the alkene or alkyne and the diene.[50–54]

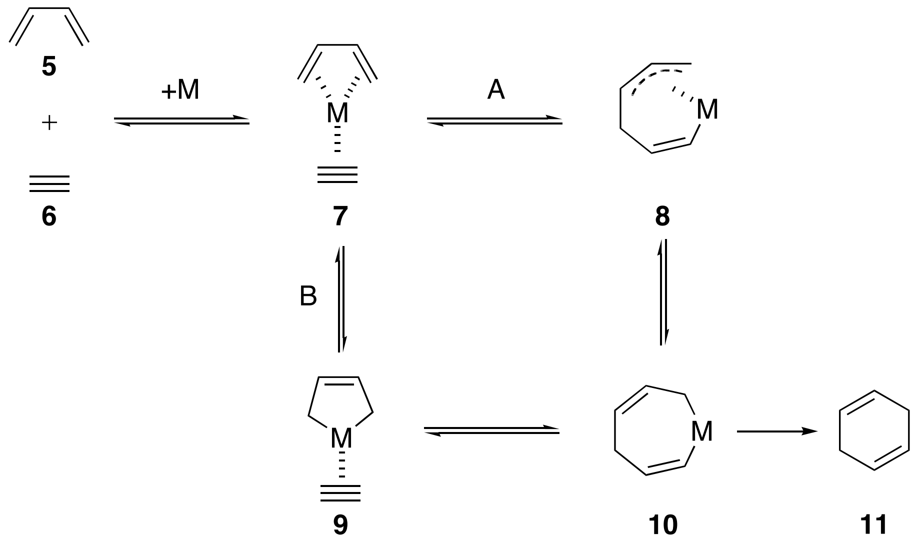
The vast majority of synthetically useful $[4+2]$ cycloaddition reactions reported contain electronically dissimilar dienes and dienophiles. Lewis acid catalysts were the first to be investigated and are now the most widely used ones. When the metal acts as a Lewis acid, complexation with a functional group in the substrate generates a highly polarized η^1-complex. The enhancement in reactivity and regio- and stereoselectivity has been attributed to a change in the coefficients in the LUMO of the dienophile upon complexation.[11–13] Recently, impressive advancements in the development of new chiral ligands which induce high levels of enantioselectivity have been reported. Excellent enantionmeric exesses (*ee*'s) have been achieved although the range of dienes is still somewhat limited (Scheme 1).[11–13, 30, 48]

In contrast, dienes and dienophiles which are electronically similar undergo cycloadditions under more extreme reaction conditions which has severely limited their use in organic synthesis until the relatively recent discovery of metal catalysts which accelerate these reactions. Activation occurs by a combination of proximity- and



Scheme 1. LEWIS acid-catalyzed asymmetric DIELS-ALDER reactions.

complexation-induced polarization effects. Interaction of the π-bonds of the diene and the dienophile leads to the formation of the π-complex **7** (Scheme 2).

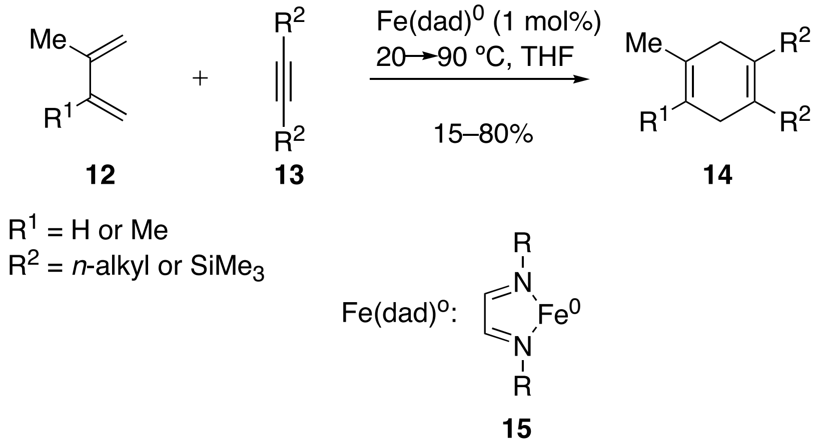


Scheme 2. Different pathways in the transition metal-catalyzed DIELS-ALDER reaction.

Oxidative coupling could occur via pathway A to generate an η^1,η^3-complex **8**.[51,52] A reasonable alternative would involve the formation of the metallacyclopentene **9** via pathway B. Both **8** and **9** could lead to the formation of the metallacycle **10** which could undergo reductive elimination of the metal to give the carbocycle and regenerate the active catalyst. To date, Rh, Ni, Ti, Fe and Pd have been reported to catalyze $[4+2]$ cycloadditions.[50–54]

Early findings by Ficini et al.,[50] tom Dieck et al.,[50] and Matsuda et al.[51] on the use of low-valent iron and low-valent rhodium complexes to catalyze intermolecular [4 + 2] cycloadditions between 1,3-butadienes and unactivated alkynes were important breakthroughs in this area.

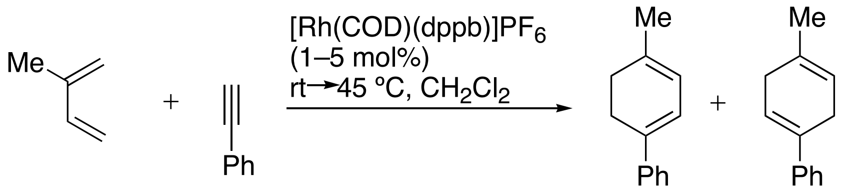
In the presence of “Fe(dad)^{0}“ [generated *in situ* by reduction of Fe^{2+} or Fe^{3+} salts with Et_3Al or EtMgBr in the presence of diazadiene (dad)], internal alkynes react with 1,3-butadienes to afford [4 + 2] cycloadducts in moderate yields (Scheme 3).[50] Terminal alkynes do not undergo [4 + 2] cycloadditions under these conditions; trimerization of the alkyne was observed instead.



Scheme 3. Fe-catalyzed intermolecular [4 + 2] cycloadditions.

The cationic rhodium(I) complex, $[Rh(COD)(dppb)]^+$, in contrast to iron-based catalysts, catalyzed the [4 + 2] cycloadditions of terminal but not internal alkynes with dienes (Scheme 4).[52] Use of a rhodium catalyst with 2-substituted 1,3-butadienes and unactivated terminal acetylenes generated the *para* regioisomer. When R^1 = Me, conjugated 1,3-cyclohexadienes **18** were formed preferentially indicating that isomerization to the thermodynamically favored isomer occurred under these reaction conditions.

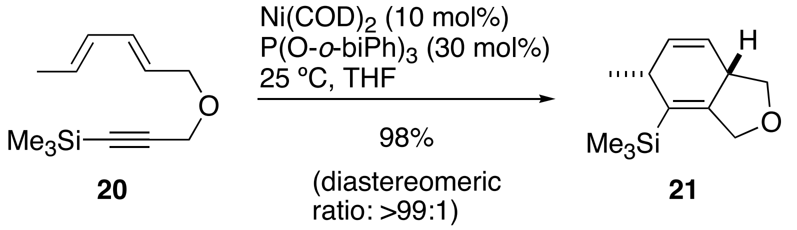
Wender et al. studied the intramolecular variant of the dienyne Diels-Alder reaction and reported that nickel catalysts gave high yields of cycloadducts under mild conditions (Scheme 5). In contrast, thermal cycloadditions required prolonged heating at 80–200 °C. The diastereoselectivities reported range from modest to excellent (1.2:1 to >99:1).[51]



16 **17** **18** **19**

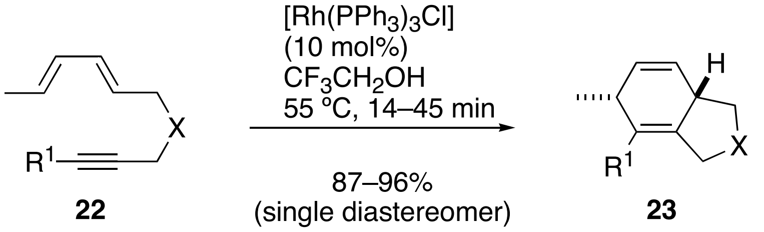
93% 3%

Scheme 4. A Rh-catalyzed intermolecular [4 + 2] cycloaddition.



Scheme 5. A Ni-catalyzed intramolecular [4 + 2] cycloaddition by Wender et al.

Livinghouse et al. recently observed the advantages of rhodium catalysts in intramolecular Diels-Alder reactions.[52] These cycloadditions are not confined to substrates bearing nonterminal alkynes as [4 + 2] addends. Terminal alkynes and, even more important, unactivated alkenes readily participate in the cycloadditions to provide the corresponding bicyclic products in good to excellent yields (Scheme 6).



X = O, $C(COOMe)_2$
R^1 = H, CH_2OTBS

Scheme 6. Rh-catalyzed intramolecular [4 + 2] cycloadditions by Livinghouse et al.

In addition, Rh(I)-catalyzed cycloadditions are highly diastereoselective giving a