

[3+2] Cycloadditions

Enantioselective Palladium-Catalyzed Trimethylenemethane [3+2] Cycloadditions**

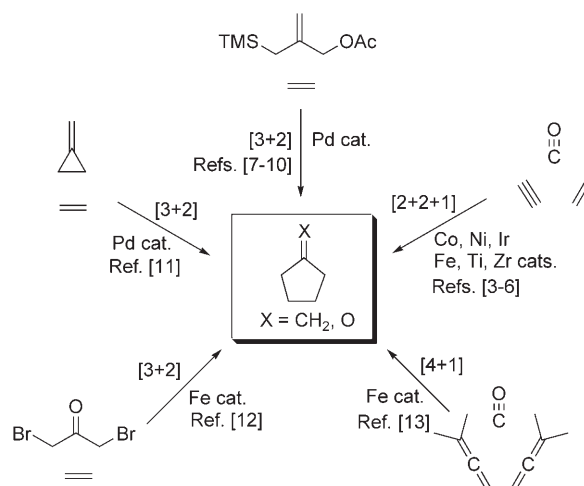
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asymmetric synthesis · chiral ligands · cycloadditions · palladium · trimethylenemethane

Cycloaddition reactions are among the most powerful and efficient methods for the construction of rings. Unfortunately, unactivated substrates usually require extreme reaction conditions, such as high temperatures and pressures, in order to achieve good yield of the cycloadduct. Transition-metal catalysts provide new opportunities for highly selective cycloaddition reactions. These novel reactions are possible as the complexation of the metal to the substrates temporarily polarizes and activates the otherwise unreactive species.^[1] In addition to the rate enhancements observed in the presence of the metal catalyst, the opportunity to achieve asymmetric transformations by the use of chiral ligands is another attractive feature of this strategy.

Since natural products containing five-membered rings are widespread, much attention has been directed to developing methods for their construction.^[2] A number of metal-catalyzed cycloadditions have been developed for the formation of five-membered rings (Scheme 1).^[3–13]

Trost and co-workers reported the first examples of Pd-catalyzed trimethylenemethane (TMM) [3+2] cycloadditions in 1979.^[7a] Since then, various aspects of the cycloadditions have been studied, including chemo-, regio- and stereoselectivities,^[7b–e] intramolecular^[7f,g] and heterocyclic^[7h,i] variants, and applications in the total synthesis of natural products.^[7j–l] The investigation of the asymmetric version for control over absolute stereochemistry was limited to the use of chiral auxiliaries.^[7m] In 1989, Hayashi's group reported the first examples of the asymmetric Pd-catalyzed cycloadditions of this type; however, the level of asymmetric induction was only low to moderate (4–78% *ee*).^[14] The major difficulty in designing a catalyst for this reaction is that the initial nucleophilic attack of the zwitterionic intermediate to the alkene (which is believed to be the selectivity-determining step) occurs distal to the coordinated chiral ligand on the palladium. When Trost and co-workers recently used bulky



Scheme 1. Formation of five-membered rings by various metal-catalyzed cycloadditions. TMS = trimethylsilyl.

chiral phosphoramidite ligands (Figure 1) to overcome this problem, high levels of asymmetric induction were observed for the Pd-catalyzed TMM [3+2] cycloadditions.^[8–10] For example, in the presence of 5 mol % of $[\text{Pd}(\text{dba})_2]$ (dba = dibenzylideneacetone) and 10 mol % of chiral phosphorami-

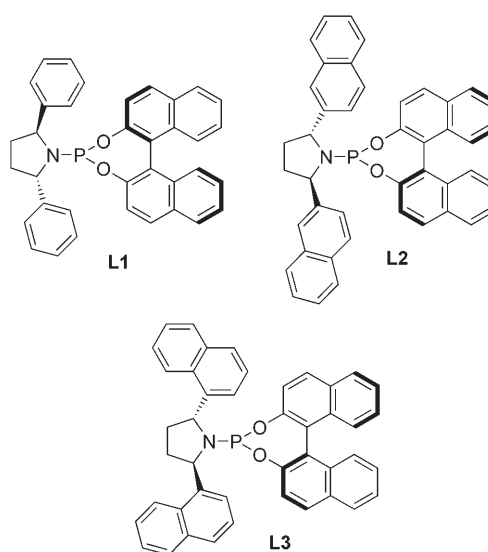
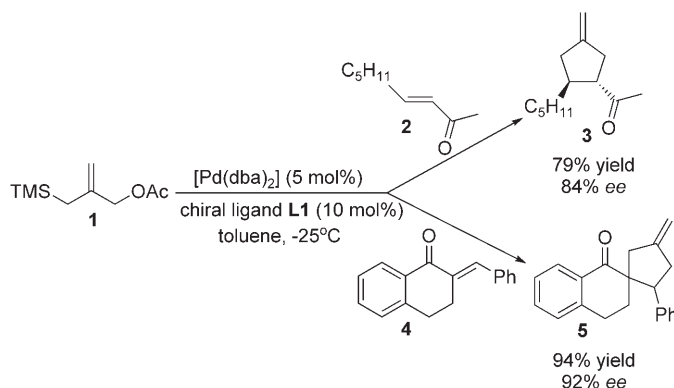


Figure 1. Chiral phosphoramidite ligands.

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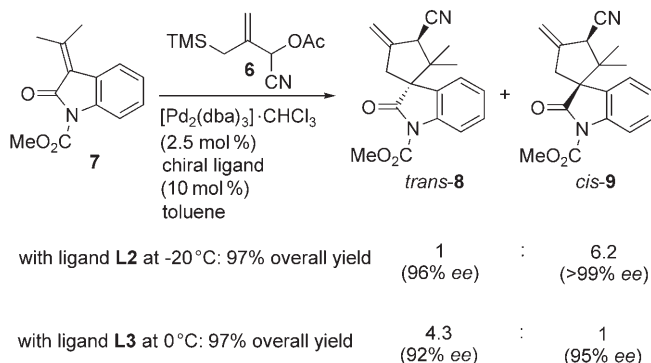
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dite ligand **L1**, 3-acetoxy-2-trimethylsilylmethyl-1-propene (**1**) reacted with the electron-deficient alkene **2** to provide the corresponding *exo*-methylenecyclopentane **3** in 79% yield with a stereoselectivity of 84% *ee* (Scheme 2).^[8] Under the same reaction conditions, the analogous reaction of benzylidene tetralone **4** gave the corresponding spirocyclic cycloadduct **5** in 94% yield and 92% *ee* (Scheme 2).



Scheme 2. Asymmetric palladium-catalyzed [3+2] cycloadditions of TMM and alkenes **2** and **4**.

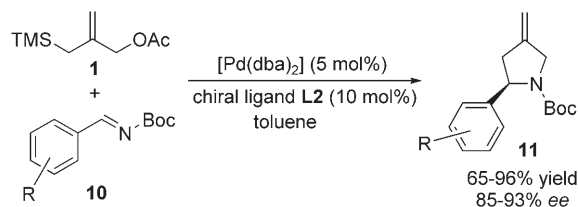
More recently, Trost and co-workers have expanded the scope of this approach to include the enantioselective construction of spirocyclic oxindolic cyclopentanes and pyrrolidines.^[9,10] In the presence of 2.5 mol% of [Pd₂(dba)₃·CHCl₃] and 10 mol% of chiral ligand **L2** or **L3**, asymmetric Pd-catalyzed [3+2] cycloadditions of 3-alkylidenoxindolin-2-one **7** and the cyano-substituted TMM precursor **6** gave the corresponding cycloadducts, spirocyclic oxindolic cyclopentanes *trans*-**8** and *cis*-**9**, in excellent yields and selectivities (Scheme 3).^[9] The ratio of the *trans* and *cis* [3+2] cycloadducts ranged from 1.3:1 to >20:1 depending on the choice of ligand as well as the structure of the 3-alkylidenoxindolin-2-ones. Enantiomeric excesses greater than 90% were generally observed in these cycloadditions when chiral ligands **L2** or **L3** were employed. Interestingly, ligand **L3** usually provided *trans*-**8** as the major cycloadduct, while ligand **L2** (which differs from ligand **L3** only by the



Scheme 3. Enantioselective construction of spirocyclic oxindolic cyclopentanes by asymmetric palladium-catalyzed [3+2] cycloadditions of TMM.

position of the naphthyl substituents) often gave *cis*-**9** as the major product.

The first examples of the asymmetric palladium-catalyzed [3+2] cycloadditions of TMM and imines were recently reported by Trost and co-workers (Scheme 4).^[10] In the presence of 5 mol% of [Pd(dba)₂] and 10 mol% of the chiral ligand **L2**, imines **10** and 3-acetoxy-2-trimethylsilylmethyl-1-propene (**1**) were converted into the corresponding [3+2] cycloadducts, pyrrolidines **11**, in good yields and high enantioselectivity (Scheme 4).^[10]



Scheme 4. Asymmetric palladium-catalyzed [3+2] cycloadditions of TMM and imines. Boc = *tert*-butoxycarbonyl.

These studies on the asymmetric palladium-catalyzed [3+2] cycloadditions of TMM are very significant. They represent an important breakthrough in this area of research not only because it is the first time such a high level of asymmetric induction has been achieved for this type of reaction, but also because they provide a very efficient method for the asymmetric synthesis of carbocyclic and heterocyclic five-membered ring systems. Thus, the methodologies described will be extremely useful in the asymmetric synthesis of many biologically important natural products containing these ring systems. Finally, the concept of using bulky phosphoramidite ligands will also have a major impact on future research involving transition-metal-catalyzed cycloaddition reactions.

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