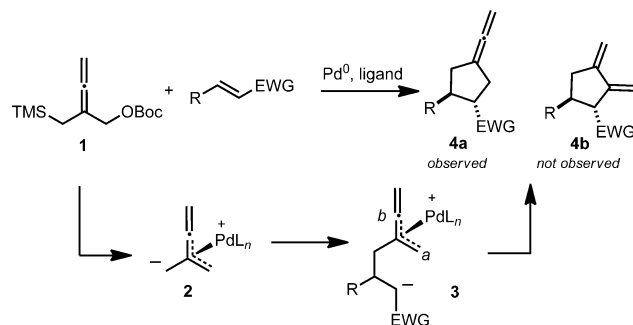


# Enantioselective Construction of Highly Substituted Vinylidenecyclopentanes by Palladium-Catalyzed Asymmetric [3+2] Cycloaddition Reaction\*\*

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The transition-metal catalyzed [3+2] trimethylenemethane (TMM) cycloaddition reaction is a versatile method for the construction of highly substituted five-membered rings with high chemo-, regio-, and diastereoselectivity.<sup>[1]</sup> Since 2006, the first asymmetric TMM reactions utilizing a series of chiral phosphoramidite ligands to form substituted carbocycles<sup>[2]</sup> and heterocycles<sup>[3]</sup> with high enantioselectivity have been reported.

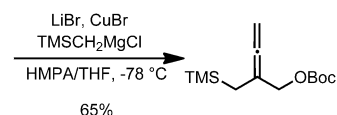
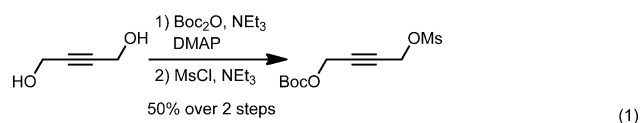
The search for novel TMM donors bearing diverse functionalities represents an important dimension to enhance the power of this methodology. Recently, asymmetric methodologies for cyano-<sup>[4]</sup> and vinyl-substituted<sup>[5]</sup> donors to generate tetrasubstituted cyclopentanes with three contiguous stereocenters were reported. Methylene-substituted donor **1** constitutes a structurally and electronically distinct donor of a nature quite different than any examined. Previous work by our group established that allene acetates could participate in asymmetric allylic alkylation reactions.<sup>[6]</sup> We envisioned this methylene-TMM donor could give rise to two interesting and useful products through the generation of the unsymmetrical Pd-TMM complex **2**, which features electronically distinct sp<sup>2</sup>- and sp-hybridized electrophilic carbons (Scheme 1).



**Scheme 1.** Palladium-catalyzed TMM cycloaddition reaction with methylene-TMM donor. EWG = electron-withdrawing group, Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl.

Attack at position *a* of the zwitterionic intermediate **3** would lead to the vinylidenecyclopentane **4a**, while attack at position *b* would yield diene **4b**. Initial efforts to effect this cycloaddition with achiral phosphite or phosphorus triamine ligands typically used for TMM cycloadditions failed to generate any desired cycloadducts. Herein, we describe our efforts to develop this methodology, which led to excellent yields of the cycloaddition products with concomitant enantioselectivity. We also demonstrate a unique synthetic application of the cycloadducts evolving from their selective behavior in further catalytic transformations.

The methylene-TMM donor is synthesized readily in three steps by S<sub>N</sub>2' addition of an organocopper reagent to a 1,4-butanediol derivative [Eq. (1); DMAP = 4-dimethylamino-pyridine, Ms = mesyl, HMPA = hexamethylphosphoric triamide]. The *tert*-butyl carbonate was required for ionization of the donor.



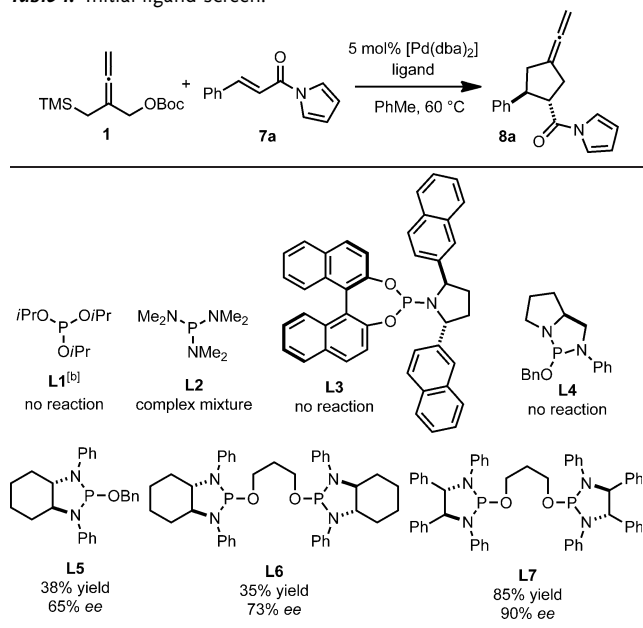
The reactivity and synthetic utility of  $\alpha,\beta$ -unsaturated *N*-acyl pyrroles<sup>[7]</sup> prompted us to examine acceptor **7a**, derived from cinnamic acid. In the initial ligand screen (Table 1), we were surprised to observe limited reactivity under typical TMM reaction conditions. While no reactivity was observed with triisopropylphosphite (**L1**) as a ligand, the reaction using hexamethylphosphorus triamide (**L2**) as ligand was very messy with complete consumption of the starting donor but only trace amounts of vinylidene cycloadduct. Furthermore, no reaction was observed with chiral bis(2-naphthyl) ligand **L3**, which was developed as a preferred ligand for the asymmetric TMM reaction with other donors.<sup>[8]</sup>

These data indicated that reactivity of methylene-TMM intermediate was sensitive to the electronic environment of the ligand—while more electron-deficient phosphite and phosphoramidite ligands were not reactive enough, phosphorus triamide ligands were too reactive. This led to the investigation of diamidophosphite systems, which contain two nitrogen atoms and an oxygen atom around the phosphorus center. Inspired by monodentate diamidophos-

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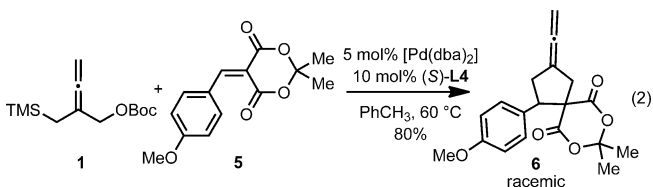
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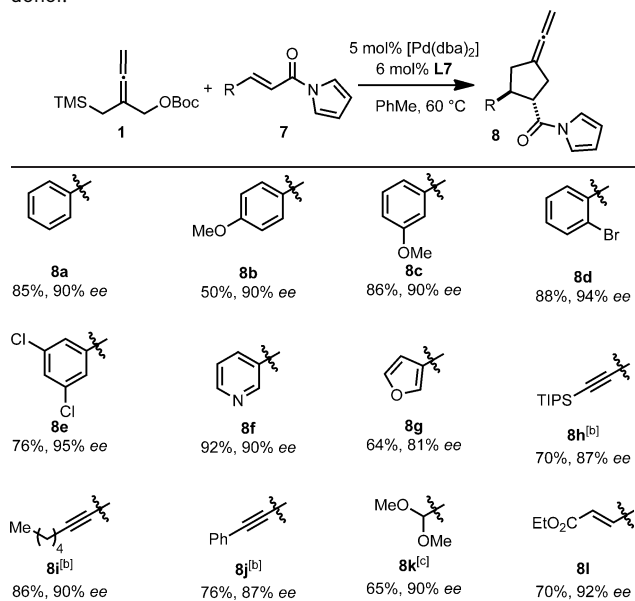
**Table 1:** Initial ligand screen.<sup>[a]</sup>


[a] Reactions were conducted for 12 h at 60 °C in 0.2 M toluene with 1.5 equiv of **1**, 5% [Pd(dba)<sub>2</sub>], and 10% (for **L1**–**L5**) or 6% (for **L6** and **L7**) ligand. Yields are isolated values; ee values were determined by chiral HPLC with a chiral stationary phase column. [b] Reaction conducted with 5% Pd(OAc)<sub>2</sub>.

phosphites like Quiphos and its derivatives<sup>[9]</sup> we began our studies with **L4** as a ligand. While we did observe reactivity using this ligand [Eq. (2); dba = dibenzylideneacetone], addi-



tion of the donor was limited to highly activated acceptors such as benzylidene Meldrum's acid **5** and there was no enantioinduction. No reaction was observed with *N*-acyl pyrrole **7a**. However, encouraged by the this limited reactivity, we investigated ligands derived from *trans*-1,2-cyclohexanediamine.<sup>[5]</sup> In the presence of monodentate ligand **L5**, the cycloadduct **8a** was obtained in 38% yield and 65% ee. While the yield remained modest, employing ligand **L6** led to an increase in enantioselectivity from 65% to 73% ee. Further structural and electronic modifications to this class of ligand did not improve yield or enantioselectivity. Changing the chiral scaffold to the sterically more demanding *trans*-1,2-stilbenediamine backbone of **L7** dramatically improved reactivity and enantioselectivity. Under all reaction conditions, only the allene cycloadduct was formed, which is consistent with the initially formed trimethylenemethane intermediate reacting with the acceptor to give **4a** faster than it can equilibrate to its regioisomer, which would have given **4b**.

**Table 2:** Palladium-catalyzed [3+2] reactions with methylene-TMM donor.<sup>[a]</sup>


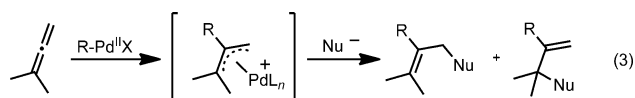
[a] Reactions were conducted for 12 h at 60 °C in 0.2 M toluene with 5% [Pd(dba)<sub>2</sub>], 6% **L7**, and 1.5 equiv **1**. Yields are combined isolated values; ee values were determined by HPLC with a chiral stationary phase column and represent absolute values. [b] Reaction conducted at 40 °C, 2.0 equiv **1**. [c] 80% yield based on recovered starting material.

Using our optimized conditions, we examined the scope of the cycloaddition reaction with respect to *N*-acyl pyrrole acceptor (Table 2). Excellent yields and enantioselectivities were obtained with a broad range of substrates. The regioselectivity of the cycloaddition that led to adduct **8l** is particularly noteworthy, showing the strong activation of the acyl pyrrole subunit.

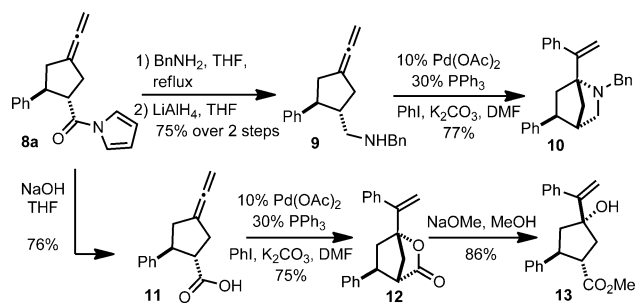
Aromatic substituents were well tolerated and ee was insensitive to substitution pattern of the aromatic ring or electronic nature of the substituent, including aryl chlorides and aryl bromides (**7b**–**7e**). Heterocycles were also well tolerated (**7f** and **7g**). Acceptors bearing aliphatic substituents at the β-position did not undergo addition to the donor; however, a range of acceptors bearing non-aromatic substituents performed well, including alkynes (**7h**–**7j**) and dimethyl acetal (**7k**). Only 1,4-addition was observed with **7l**. Lowering the temperature of the reaction to 40 °C when non-aromatic acceptors were used improved the ee of the cycloadducts while increasing the equivalents of TMM donor maintained the yield.<sup>[10]</sup>

Allenes are stable functional groups that possess versatile reactivity and selectivity in organic reactions.<sup>[11]</sup> The exocyclic allene of **8** serves as a useful handle for further transformations to a diverse range of highly substituted cyclopentane products. One particularly useful reaction is the carbopalladation of allenes,<sup>[12]</sup> which leads to a π-allyl intermediate that is subject to nucleophilic attack [Eq. (3)]. Both terminal carbons of the allene are electrophilic, which may lead to a mix of products.

Tethering of the nucleophile to the allene to control selectivity is well documented<sup>[13]</sup> and we envisioned that



elaboration of the acyl pyrrole moiety would allow directed nucleophilic addition to the allene to generate a third stereocenter (Scheme 2). Heating the cycloadduct with benzylamine at reflux furnished the corresponding amide, which



**Scheme 2.** Functionalization of allene in TMM cycloadduct **8a**. Bn = benzyl, THF = tetrahydrofuran, DMF = dimethylformamide.

was then reduced to protected amine **9**. This amine was well positioned to participate in palladium-catalyzed carboamination of the allene to form the bridged piperidine bearing a tertiary amine stereocenter and vinyl phenyl substituent producing the novel azabicyclo[2.2.1]heptane **10**. Similarly, tertiary alcohols such as **13** could be formed through the carbolactonization of **11** and subsequent methanolysis of the lactone **12** with sodium methoxide.

In summary, we have demonstrated a palladium-catalyzed asymmetric addition of a unique donor to  $\alpha,\beta$ -unsaturated *N*-acyl pyrroles in the [3+2] TMM cycloaddition, providing substituted vinylidenecyclopentanes in excellent yield and enantioexcess. This transformation forms a new and unusual class of TMM cycloadducts and uses a new type of diamido-phosphite ligand being developed by our group for substituted asymmetric TMM reactions. The uniqueness of the efficacy of **L7** is remarkable and a topic for future efforts. Both the allene and acyl pyrrole moieties can be functionalized to yield complex products. Investigations into the full scope of this reaction, including the use of other acceptors and new applications of this methodology are underway.

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