

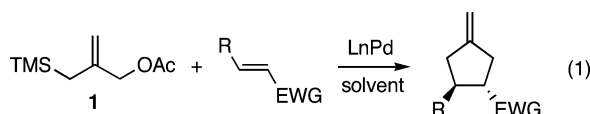
Palladium-Catalyzed Asymmetric [3 + 2] Trimethylenemethane Cycloaddition Reactions

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Natural products containing five-membered rings are found throughout the chemical literature. Transition metal-catalyzed [3 + 2] trimethylenemethane (TMM) cycloadditions provide direct routes to substituted cyclopentanes.¹ In 1979, we first reported that Pd–TMM complexes generated from 3-acetoxy-2-trimethylsilyl-methyl-1-propene (**1**) and catalytic palladium react with electron-deficient olefins to produce *exo*-methylene-cyclopentanes (eq 1).² We have shown that this palladium-catalyzed [3 + 2] TMM cycloaddition reaction is a highly chemo-, regio-, and diastereoselective process.^{3,4} This methodology has also been extended to [4 + 3] and [6 + 3] cycloadditions^{5,6} and has been employed in a number of total syntheses.^{3,7–9} Unfortunately, the formation of stereogenic centers in the cycloadducts produced in this chemistry has mainly been limited to the use of chiral auxiliaries.¹⁰ The sole example of a palladium-catalyzed asymmetric [3 + 2] sulfone-substituted TMM cycloaddition was reported from the Hayashi lab with enantiomeric excesses ranging from 4 to 78% ee.¹¹

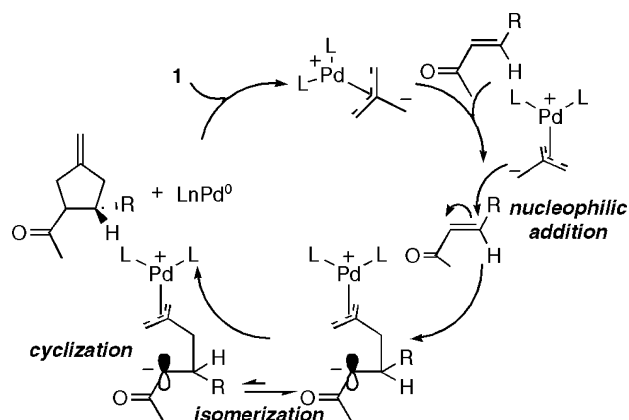


The difficulty in designing a catalyst for the asymmetric Pd–TMM cycloaddition reaction is illustrated in our proposed stepwise mechanism (Scheme 1).^{12,13} The formation of the zwitterionic intermediate is generated by insertion of LnPd into the C–O bond followed by attack of the displaced acetate anion onto the trimethylsilyl group, which deposits its electrons onto the TMM fragment.¹⁴ The enantiodetermining step is most likely the initial nucleophilic attack. This step occurs distal to the set of coordinated chiral ligands. Our early work on the beneficial effect of phosphite and phosphoramidite ligands on the efficiency of the cycloaddition induced us to examine palladium complexes of chiral phosphoramidites^{15a} as asymmetric catalysts.

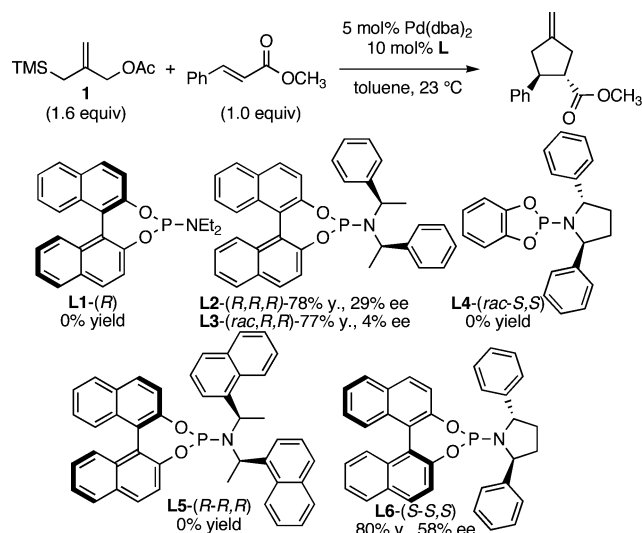
Initially, we examined the reaction of **1** with methyl cinnamate in the presence of 5 mol % of Pd(dba)₂ and 10 mol % ligand (**L1**–**L6**) in toluene at 23 °C (Scheme 2). Interestingly, catalysts formed from **L1**, **L4**, or **L5** gave 0% yield; however, catalysts formed from **L2** gave 78% yield and 29% ee. We thought an increase in the rigidity of **L2** may lead to an increase in % ee. Indeed, the synthesis of **L6**^{15b} and its application in the asymmetric TMM [3 + 2] cycloaddition gave 80% yield and 58% ee of the desired cyclopentane product.

Although toluene has typically been used in previous TMM [3 + 2] reactions, we decided to screen a number of solvents to examine the effect on the yield and selectivity of this process (Table 1). Reactions conducted in THF, ether, and DME gave good yields (68–80%) with modest (48–55% ee, entries 2–4) selectivities, while reactions conducted in DCM, CH₃CN, DMF, or dioxane gave low yields of the desired product (entries 5–8). Thus, toluene appears optimal.

Scheme 1



Scheme 2



Using the optimized catalytic conditions, we examined the initial scope of the TMM accepting olefin (Table 2). All cyclopentane products were formed in >19:1 *trans:cis* selectivity. The reaction of methyl cinnamate with **1** at 0 °C increased the enantioselectivity from 58 (at 23 °C) to 62%. Cooling the reaction to –25 °C failed to produce >5% product as determined by GC analysis. Employing the more reactive (*E*)-benzalacetone allowed the reaction to be performed at –25 °C, which increased selectivity to 82% ee (entry 2). Lowering the reaction temperature to –50 °C failed to produce any noticeable product by GC analysis. The selectivity of this reaction does not rely on the presence of the phenyl group as *trans*-nonenone reacts with yields and enantiomeric excesses that are comparable to those of benzalacetone (entry 3). Switching the methyl group to an ethyl (entry 4) or phenyl (entry 5) gives yields and enantiomeric excesses that are comparable to those of benza-

Table 1. Solvent Effect on Asymmetric TMM [3 + 2] Cycloadditions

entry	solvent	% yield ^a	% ee
1	toluene	80	58
2	THF	68	48
3	DME	80	53
4	ether	69	55
5	DCM	10	32
6	CH ₃ CN	0	0
7	DMF	0	0
8	dioxane	35	39

^a Determined by GC analysis with an internal standard.**Table 2.** Initial Scope of Palladium-Catalyzed [3 + 2] TMM Cycloaddition Reactions

entry	substrate	product	T (°C)	Yield (%) ^a	ee (%)
1	Ph-CH=CH-CO ₂ CH ₃	Ph-CH-Cyclopentane-CO ₂ CH ₃	23 0	80 81	58 62
2	Ph-CH=CH-CO ₂ Me	Ph-CH-Cyclopentane-CO ₂ Me	23 -25	76 63	72 82
3	Ph-CH=CH-CO ₂ Et	Ph-CH-Cyclopentane-CO ₂ Et	23 -25	72 79	73 84
4	Ph-CH=CH-CO ₂ Pr	Ph-CH-Cyclopentane-CO ₂ Pr	23 -25	84 72	73 83
5	Ph-CH=CH-CO ₂ Ph	Ph-CH-Cyclopentane-CO ₂ Ph	-25	83	80
6	Ph-CH=CH-CO ₂ Ar	Ph-CH-Cyclopentane-CO ₂ Ar	a: -25 b: -25	73 80	72 74
7	Ph-CH=CH-CN	Ph-CH-Cyclopentane-CN	0	78	58

^a Isolated yields.

lactone. Use of electron-rich or electron-poor aromatic enones slightly lessened the enantioselectivity with respect to the parent chalcone. Nitriles were compatible functionalities and gave enantioselectivities comparable to those of esters (entry 7).

The reaction of **1** with various tetralone derivatives in the presence of Pd(dba)₂ and **L6** gave high yields and enantiomeric excesses of the corresponding *exo*-methylene-cyclopentanes. The reaction of benzylidene tetralone at 23 °C gave 99% yield and 85% ee (entry 1). Reducing the temperature to -25 °C gave 94% yield and 92% ee. Exchanging the phenyl group for six- and five-membered aromatics did not have a large effect on the reaction

Table 3. Palladium-Catalyzed [3 + 2] TMM Cycloaddition Reactions of Aryl- and Alkylidene Tetralones

entry	R	T (°C)	yield (%) ^a	ee (%)
1	Ph	23 -25	99 94	85 92
2	2-pyridyl	23 -25	78 87	83 86
3	2-furyl	23 -25	71 60	73 82
4	cyclopropyl	23 -25	95 70	79 87
5	cyclopentyl	0	53	78

^a Isolated yields.

(entries 2 and 3). Cycloalkyl-substituted tetralones were also good substrates (entries 4 and 5); however, cyclohexylidene tetralone failed to react under our conditions at room temperature.

In summary, we have developed conditions to effect an asymmetric palladium-catalyzed [3 + 2] cycloaddition reaction between in situ generated Pd-TMM intermediates and various olefins, despite the large distance between the chiral ligands and the asymmetric bond-forming event. Future work will focus on extending this methodology to include [4 + 3] and [6 + 3] cycloadditions, as well as developing catalysts that promote asymmetric [3 + 2*n*] cycloaddition reactions with substituted TMM precursors.

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Supporting Information Available: Experimental details for procedures and spectral data for all unknown compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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