

Communication

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*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • DOI: 10.1021/ja305717r • Publication Date (Web): 20 Jun 2012

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# Development of Diamidophosphite Ligands and their Application to the Palladium-catalyzed Vinyl-substituted Trimethylenemethane Asymmetric [3+2] Cycloaddition

Barry M. Trost\* and Tom M. Lam

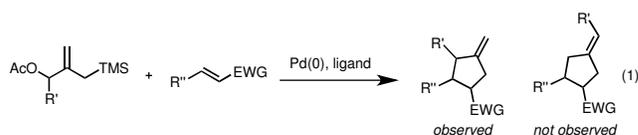
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Supporting Information Placeholder

**ABSTRACT:** A palladium-catalyzed asymmetric [3+2] cycloaddition of a vinyl-substituted trimethylenemethane (TMM) donor with  $\alpha,\beta$ -unsaturated acyl imidazoles is described. A newly designed bisdiazidophosphite ligand derived from (*S,S*)-*trans*-1,2-cyclohexanediamine and (*2R,4R*)-pentanediol has been instrumental for the development of this process. This transformation generates tetrasubstituted cyclopentanes bearing three contiguous stereocenters in high yields, with good diastereo- and enantioselectivity.

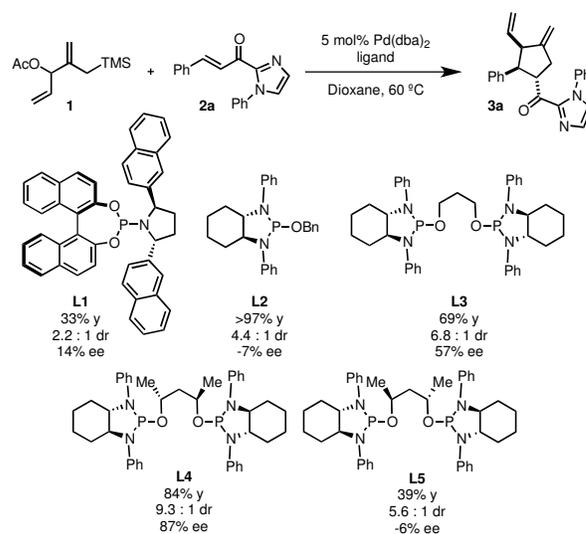
Cycloadditions remain powerful transformations in the synthesis of functionalized ring systems, achieving high levels of complexity and multiple bond formations in a single reaction. To that end, the palladium-catalyzed trimethylenemethane reaction has shown broad application in the formation of various five-, seven- and nine-membered ring systems.<sup>1</sup> Recently, the development of chiral phosphoramidite ligands has allowed our group to conduct these same reactions asymmetrically, generating various carbocycles,<sup>2</sup> tetrahydrofurans,<sup>3</sup> and pyrrolidines<sup>4</sup> in good yields and selectivities.

Due to the success of this process, we were eager to expand the donor scope of the transformation to substituted TMM donors. The placement of a substituent on the TMM species generates an additional stereocenter, forming tetrasubstituted cyclopentanes containing three contiguous stereocenters. The well recognized importance of cyclopentane<sup>5</sup> derived structures possessing important biological activity encourages the development of more facile asymmetric methods. The racemic variant of the substituted TMM reaction was first disclosed in 1985,<sup>6</sup> where various substituents, including vinyl, phenyl, acetoxy, and cyano groups formed five membered rings as a single regioisomer (eq 1). To date, only the cyano-TMM donor has been rendered asymmetric.<sup>7</sup> The difficulty in expanding the donor scope of the reaction lies in the loss of reactivity and selectivity whenever substitution other than cyano is used. Designing a ligand that would enable a broader tolerance of substituents is then required. Herein, we describe the development of such a ligand family and illustrate the process using the vinyl-substituted TMM donor because of its potential versatility for further synthetic elaboration. Such a substitution also raises the question of the effect of ligands on regioselectivity which could lead to [5+2] cycloadditions.



We were attracted to the use of acyl imidazoles<sup>8</sup> as ester surrogates due to their synthetic utility along with their tunability to impart yield and selectivity.<sup>9</sup> In our initial ligand screen, however, **L1**, which has performed well in our previous studies of the parent and cyano-TMM donor, led to only 33% yield of the desired product with low levels of diastereo- and enantioselectivity.

## Scheme 1. Initial Ligand Screen<sup>a</sup>



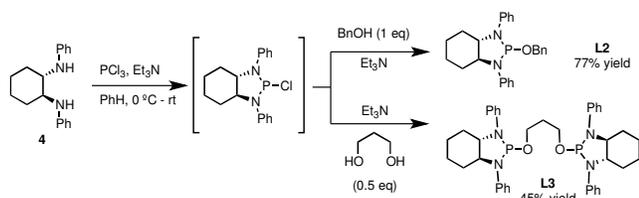
<sup>a</sup> All reactions were conducted for 18 h at 0.5 M in dioxane with 2.0 equiv of **1**, 5% Pd(dba)<sub>2</sub>, and 10% (for **L1** and **L2**) or 8% (for **L3**, **L4** and **L5**) ligand. Yields are combined isolated values; ee's were determined by HPLC with a chiral stationary phase column.

To increase the reactivity of the catalyst system, we investigated diamidophosphites as a new ligand system for the asymmetric TMM reaction. In earlier studies, we noted that the use of a phosphorus triamide significantly accelerated the cycloaddition compared to a phosphite,<sup>10</sup> presumably by increasing the nucleophilicity of the palladium-TMM complex. The substitution of one oxygen atom in the phosphoramidites for a nitrogen atom in the diamidophosphites should also increase the electron density on the phosphorus center, which

would hopefully increase the efficacy of the palladium-catalyzed TMM reaction.

Diamidophosphite ligands are an emerging class of ligands in asymmetric transition metal catalysis. These ligands have been applied to a limited range of asymmetric transition metal-catalyzed transformations, such as hydrovinylation, conjugate addition, and hydrogenation of substituted enoates.<sup>11</sup> Diamidophosphites have had limited success in palladium-catalyzed asymmetric allylic alkylations.<sup>12</sup> Quite interestingly, Pfaltz and co-workers have developed a bisdiamidophosphite ligand based on sulfonamides of *trans*-1,2-cyclohexanediamine and *trans*-1,2-stilbenediamines which led to a novel mass-spectroscopy study of palladium-catalyzed kinetic resolution of quasienantiomeric allyl species.<sup>12d</sup>

### Scheme 2. Synthesis of Diamidophosphite Ligands



In the design of our diamidophosphites, we pursued ligand structures that contained *N*-aryl motifs. We believed that the proximity of the aryl group to the phosphorus atom is important in enhancing the chiral space about the metal center.<sup>13</sup> Our synthesis begins with the Buchwald-Hartwig amination of commercially available (*S,S*)-*trans*-1,2-cyclohexane diamine with bromobenzene according to literature procedure, giving **4** (Scheme 2).<sup>14</sup> Treatment of diamine **4** with phosphorus trichloride in the presence of triethylamine generates the *P*-chlorodiazaphospholidine, which after filtration of the triethylammonium salts under argon is reacted with an equivalent of benzyl alcohol and triethylamine.<sup>12b</sup> The desired diamidophosphite ligand **L2** is isolated in good yields. Substitution of the benzyl alcohol for an alkyl diol in the final step of the ligand synthesis provided a dimeric diamidophosphite ligand **L3**, which could potentially be bidentate.

With the new synthesized ligands in hand, we tested their ability to perform the TMM cycloaddition (Scheme 1). Grati-fyingly, using **L2**, we were able to isolate the cycloaddition product in >97% yield as a single regioisomer. While the enantioselectivity remained low, employment of **L3** led to a jump from -7% to 57% ee. The clear dependence of the ligand system on the propanediol tether encouraged us to place a chiral element on the diol backbone in order to further define the chiral space generated by the ligand. Ligands **L4** and **L5** were thus synthesized using commercially available (*2R,4R*)-pentanediol and (*2S,4S*)-pentanediol, respectively. In the case of ligand **L4**, the cycloadduct was isolated in 84% yield, 9.3:1 dr and 87% ee. Both yield and selectivity dropped with ligand **L5**.

Following our ligand screen, we performed a solvent and palladium precatalyst screen (Table 1). Various solvents were tested but showed reduced yields and selectivities. Interestingly, THF led to a marked reduction in enantioselectivity with only 10% ee. Toluene, which has been successful in other TMM reactions, also led to diminished yield and selectivity. Switching from Pd(*dba*)<sub>2</sub> to CpPd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>) resulted in nearly quantitative yield with only slight erosion of selectivity. These conditions were selected as our standard conditions.

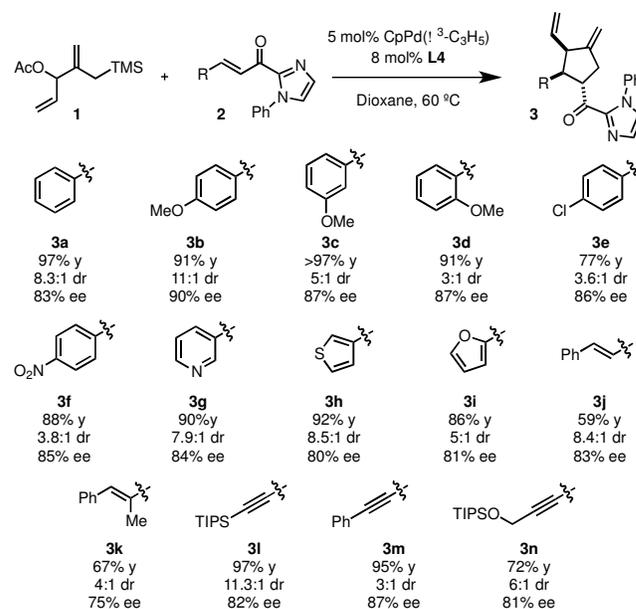
Table 1. Selected Optimization Studies<sup>a</sup>

entry	Pd	solvent	% yield	dr	% ee
1	Pd( <i>dba</i> ) <sub>2</sub>	Dioxane	84	9.3:1	87
2	Pd( <i>dba</i> ) <sub>2</sub>	DME	80	3:1	83
3	Pd( <i>dba</i> ) <sub>2</sub>	DCE	58	4.4:1	87
4	Pd( <i>dba</i> ) <sub>2</sub>	Toluene	76	6.9:1	82
5	Pd( <i>dba</i> ) <sub>2</sub>	THF	67	3.3:1	10
6	CpPd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )	Dioxane	97	8.3:1	83

<sup>a</sup> All reactions were conducted for 18 h at 0.5 M in solvent with 2.0 equiv of **1**, 5% palladium precatalyst, and 8% **L4**. Yields are combined isolated values; ee's were determined by HPLC with a chiral stationary phase column.

With the optimized conditions in hand, we explored the substrate scope of the reaction (Scheme 3).<sup>15</sup> *Ortho*-, *meta*- and *para*-substituents performed well in this transformation, providing products **3b-d** in good yields and selectivities. The highest selectivity was observed in the case of the *p*-methoxy substrate, where **3b** was isolated with 11:1 dr and 90% ee. Aryl chlorides were tolerated under the reaction conditions, along with electron-deficient aromatic rings. Five-membered heterocycles performed well, although with slightly reduced enantioselectivity. Importantly, nonaromatic groups were compatible with the reaction conditions. Unsaturated side-chains such as styrenyl and alkynyl groups could also be used in this transformation, with good regioselectivity for the  $\alpha,\beta$ -unsaturated products.<sup>16</sup>

### Scheme 3. Palladium-catalyzed [3+2] Reactions with Vinyl-TMM Donor<sup>a</sup>

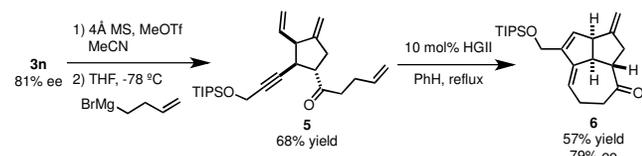


<sup>a</sup> All reactions were conducted for 18 h at 0.5 M in dioxane with 2.0 equiv of **1**, 5% CpPd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>), and 8% **L4**. Yields are com-

bined isolated values; ee's were determined by HPLC with a chiral stationary phase column.

These cycloadducts are highly versatile as chiral building blocks. The flexibility of the acyl imidazole group allows for easy manipulation to various functionalities.<sup>8</sup> Additionally, the proximal nature of the alkene and alkyne in **3l-n** led us to investigate ruthenium-catalyzed ring closing metathesis strategies toward the synthesis of tricyclic systems.<sup>17</sup> We posited that substitution of the imidazole with an alkyl chain bearing a terminal alkene would generate a triene-yne system, upon which exposure to Grubbs' catalyst would first effect an enyne metathesis reaction followed by second ring closure by the pendant alkene. To test this, activation of the imidazole with methyl triflate and subsequent alkylation with homoallyl-magnesium bromide resulted in the triene-yne **5** in 68% yield (Scheme 4).<sup>8c</sup> Using 10 mol% of Hoveyda-Grubbs II catalyst in benzene at reflux performed the desired ring closure to give **6** in 57% yield. This product possesses three chemically differentiated olefins with three stereocenters set during the TMM cycloaddition. The 5,5,7-fused tricyclic ring system of **6** also resembles the carbocyclic core of the *Daphnyphyllum* alkaloids.<sup>18</sup>

#### Scheme 4. Further Functionalization of Cycloadduct 3n



In summary, a palladium-catalyzed vinyl-substituted TMM asymmetric cycloaddition has been achieved. Tetrasubstituted cyclopentanes bearing three contiguous stereocenters are synthesized in good yields with good regio-, diastereo- and enantioselectivity. The realization of this process was due to the development of new bisdiamidophosphite ligands based on (*S,S*)-*trans*-1,2-cyclohexane diamine and (*2R,4R*)-pentanediol. These newly synthesized bisdiamidophosphite ligands bearing *N*-phenyl substituents represent a class of ligands not previously examined, allowing reactivity and selectivity that has not been observed prior to this work. Furthermore, these cycloadducts bearing a 1,4-diene and acyl imidazole have been subsequently functionalized, displaying the synthetic utility of such products. Expansion of the scope of the reaction in both donor and acceptor complexity is currently underway and will be reported in due course.

## ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental details, compound characterization data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## ACKNOWLEDGMENT

We thank the NSF for their generous support of our programs. We thank Dr. Allen Oliver from the University of Notre Dame for

the X-ray crystal structures and Johnson-Matthey for generous gifts of palladium salts

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- 26% of the  $\gamma,\delta$ -cycloadduct was observed in the case of **3j**. For **3k-n**, only the  $\alpha,\beta$ -cycloadduct was observed.
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