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Regio- and Enantioselective Synthesis of Pyrrolidines Bearing a Quaternary Center by Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of Trimethylenemethanes

Barry M. Trost,* Tom M. Lam, and Melissa A. Herbage†

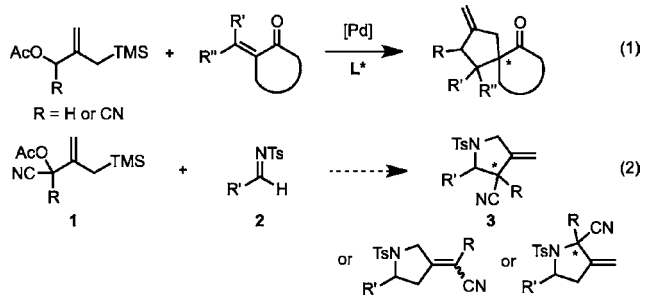
Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: Herein we describe the first use of disubstituted donors in the palladium-catalyzed trimethylenemethane (TMM) cycloaddition resulting in an enantioselective synthesis of highly substituted pyrrolidines. These cyanoalkyl donors **1** form all-carbon quaternary centers in a catalytic, asymmetric, and intermolecular manner uniquely using diamidophosphite ligands **L2** and **L3**, generating synthetically important chiral building blocks in good yields and selectivities.

The transition-metal-catalyzed trimethylenemethane (TMM) cycloaddition is a powerful tool in the synthesis of various ring systems. Since its inception, the method has shown its versatility in the synthesis of five-, seven-, and nine-membered rings.[1,2] In our efforts to develop asymmetric catalysts for the TMM reaction, our ligand designs simultaneously expanded the types of substitution tolerated in the acceptor. For example, using chiral phosphoramidite ligands[3] not only delivered good enantioselectivity but also allowed both aldimines and ketimines to be used as acceptors for cycloaddition.[3c,4a] To further expand this methodology, we have been interested in employing substituted-TMM donors. These donors, when performed in an asymmetric fashion, would allow us to generate highly substituted ring systems enantioselectively. We have found that the choice of ligands may be crucial to the success of these transformations from a reactivity point of view as well as an enantioselectivity perspective. For example, while the phosphoramidite ligand **L1** performed well for the cyano-substituted donor,[4,5] we had to turn to a new class of ligands, diamidophosphites such as **L2**, for success with vinyl substituted donors.[6]

We became intrigued by the possibility of generating quaternary stereocenters with the use of disubstituted-TMM donors, a process that heretofore has not been done. The synthesis of all-carbon quaternary stereocenters remains a challenge in organic chemistry.[7] The intrinsic steric bulk of this structural entity complicates its synthesis from both a reactivity and enantioselectivity standpoint. We have been able to synthesize quaternary stereocenters using the TMM methodology by reacting with tri- or tetrasubstituted π-system acceptors (eq 1).[3d,5] In those cases, the formation of the quaternary center resides on the acceptor, which limits the types of products formed. We envisioned that placement of the stereogenic center on the donor coupling partner (eq 2, **1**) would allow us to generate molecular complexity by varying the substituents on the donor, thereby increasing the generality of this methodology.[8] The difficulty of this prospect, however, lies in the donor−catalyst system, as increased substitution reduces both reactivity and selectivity. Herein, we describe the realization of such a process and its application to the synthesis of functionalized pyrrolidines. These products serve as useful chiral building blocks bearing stereodefined quaternary centers which can be further functionalized to complex structures.



We began our investigation by identifying the best coupling partners for the reaction. Tosyl imines were chosen as a substrate class due to their previous success in TMM cycloadditions as well as the importance of pyrrolidines in nature.[4a] Given the success of cyano-subsituted donors in the TMM methodology, we designed a disubstituted donor including this functional group to potentially increase the reactivity of the donor as well as to provide a functional handle for further elaborations of the cycloadducts. Our initial screen with phosphoramidite ligand **L1** and methylcyano donor **1a** led to trace amounts of product (Table 1). On the other hand, switching to **L2**, we were able to isolate the desired product in 66% yield, 6:1 dr, and 89% ee (entry 2). Increasing the steric bulk about the ligand from the (*S*,*S*)-cyclohexanediamine backbone in **L2** to the (*R*,*R*)-stilbene diamine in **L3** led to a slight increase in enantioselectivity (entry 3).[9] Extending the methyl group in the donor to an ethyl group **1b** increased the diastereoselectivity while retaining high levels of enantioselectivity. We decided to continue our exploration with the ethylcyano donor **1b** due to its superior selectivity.

During our substrate screen, we realized that the conditions set out in entry 4 led to good yields and selectivities for electron-poor tosyl imines. However, when a more electron-rich imine was employed (R′ = NMe_2), the reaction completely

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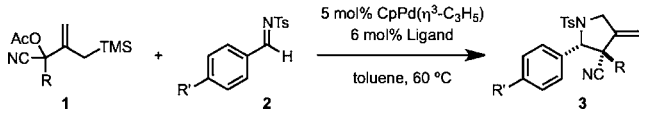
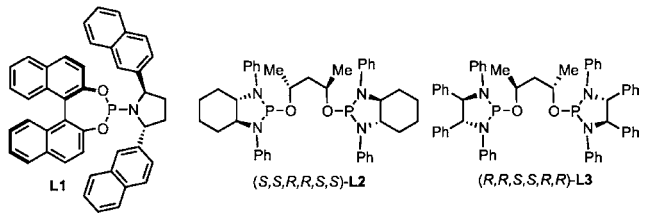
Table 1. Selected Optimization Studies[a]



entry	R	R′	Pd source	Ln	yield (%)	dr	ee (%)
1	Me (**1a**)	Cl	$Pd(dba)_2$	**L1**	trace		
2	Me	Cl	$Pd(dba)_2$	**L2**	66	6:1	89
3	Me	Cl	$Pd(dba)_2$	**L3**	74	4:1	−92
4	Et (**1b**)	Cl	$Pd(dba)_2$	**L3**	68	13:1	−93
5	Et	$N(Me)_2$	$Pd(dba)_2$	**L3**	NR		
6	Et	$N(Me)_2$	$Pd(dba)_2$	**L2**	45	9:1	75
7	Et	$N(Me)_2$	CpPd (η^3-C_3H_5)	**L2**	63	16:1	85
8[b]	Et	$N(Me)_2$	CpPd (η^3-C_3H_5)	**L2**	88	14:1	83
9[b]	Et	$N(Me)_2$	CpPd (η^3-C_3H_5)	**L3**	40	9:1	−73

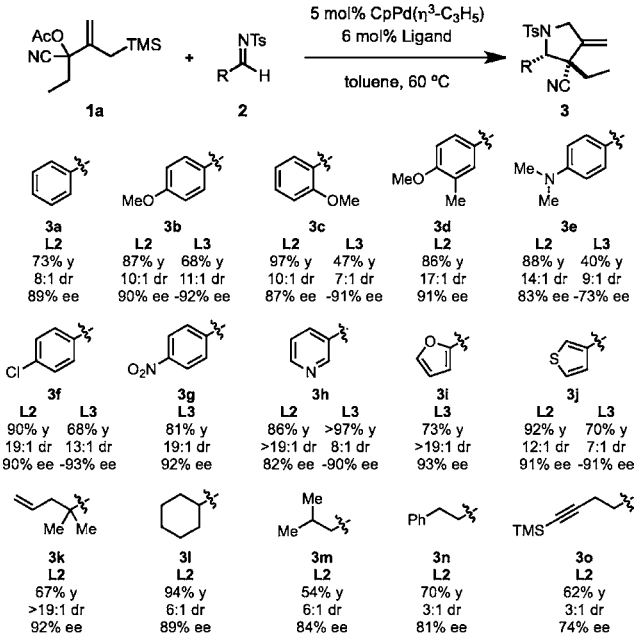
[a]All reactions were conducted for 18 h at 0.2 M in toluene with 1.4 equiv of **1**, 5% palladium precatalyst, and 6% ligand. Yields are combined isolated values; ee's were determined by HPLC with a chiral stationary phase column. [b]Concentration increased to 0.5 M.



shut down (Table 1, entry 5). Switching to **L2** provided the desired product, albeit in 45% yield (entry 6). Trying to increase this yield, we tested the more reactive palladium precatalyst CpPd(η^3-C_3H_5), and an increase in yield to 63% was observed (entry 7). The increased yield obtained from this precatalyst is likely due to the removal of dibenzylidene acetone from the system, which could act as a competitive ligand for the metal center. Increasing the concentration of the system from 0.2 to 0.5 M further increased the yield to 88% with 83% ee (entry 8). However, using these optimized conditions with **L3**, only 40% of the product was isolated with a decrease in selectivity (entry 9). While **L2** was selected as the optimal ligand for this transformation, **L3** sometimes performed better depending upon the exact acceptor.

With conditions in hand, we proceeded to evaluate the scope of the reaction (Scheme 1). Various pyrrolidines were synthesized in good yields and diastereo- and enantioselectivity. Assignment of the absolute and relative stereochemistry was achieved through both nOe analysis and X-ray crystallography.[10] Several aromatic groups are well tolerated (**3a**−**3j**), regardless of the position of substitution around the aromatic ring (**3b**−**3d**). Both electron-withdrawing and -donating groups serve well in the transformation, although, as mentioned before, **L2** is preferred for more electron-rich cases. Five-membered heterocycles show no significant difference in yield and selectivity as well (**3i**−**3j**). Gratifyingly, alkyl side chains also perform well in the cycloaddition (**3k**−**3o**).[11] With the alkyl variants, it was found that the steric bulk of the side chain affects the selectivity of the reaction. As the alkyl branching is further removed from the reaction center, both diastereo- and enantioselectivity drop from >19:1 dr and 92% ee in **3k** to 6:1

Scheme 1. Palladium-Catalyzed [3 + 2] Reactions of Ethylcyano-TMM Donor with Tosyl Imines[a]

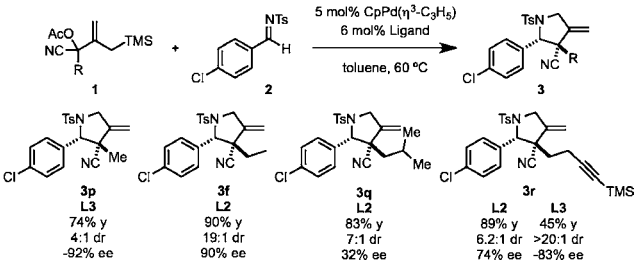


[a]All reactions were conducted for 18 h at 0.5 M in toluene with 1.4 equiv of **1a**, 5% CpPd(η^3- C_3H_5), and 6% ligand. Yields are combined isolated values; ee's were determined by HPLC with a chiral stationary phase column.

dr and 84% ee in **3m**. This decrease in enantioselectivity can also be observed in **3n** and **3o**, where the products are isolated in 81% and 74% ee, respectively.

Variations in the alkyl substituent on the donor are also tolerated. We have seen that methyl and ethyl groups function well in this cycloaddition (Scheme 2). Further extension of the

Scheme 2. Exploration of Other Alkyl Substituents on Donor 1



chain to an isobutyl group led to formation of **3q** in good yields and diastereoselectivity; however, the enantioselectivity was greatly reduced to 32% ee. Attaching an alkyne functionality to the ethyl chain restored the enantioselectivity of the donor catalyst system, although it was slightly reduced to 74% ee in **3r**. Again, using **L3** increases the enantioselectivity to 83% ee but with a drop in yield to 45%.

These pyrrolidines are versatile chiral building blocks that are easily elaborated to synthetically important structures. The cyano group can be reduced to both the aldehyde and free amine with no erosion of enantiopurity (Scheme 3, **4** and **5**). Desulfonylation with magnesium in methanol gave the unprotected pyrrolidine **6** as a single diastereomer. In our previous work using the cyano-substituted TMM donor,

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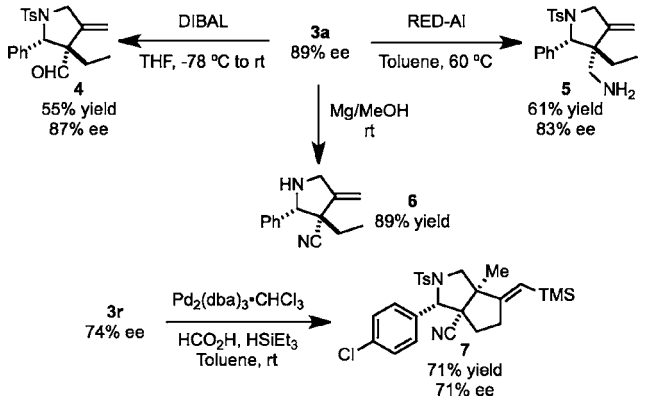
Scheme 3. Further Functionalizations of Cycloadducts 3



derivatization of the substrate was required prior to deprotection, which we proposed underwent base-catalyzed double bond isomerization which was responsible for producing multiple products.[4a] The current results, which proceeded quantitatively on the direct cycloadduct, support that contention. The alkynyl side chain in **3r** can also react with the exocyclic methylene using a palladium-catalyzed reductive ring closing reaction.[12] The reaction proceeds with catalytic palladium in the presence of formic acid and triethylsilane as a reducing agent. Diastereoselectivity of the C−C bond forming ring closure reaction is controlled by the nature of the substrate, forming the *cis*-fused [5,5] ring system **7** as a single olefin isomer with stereodefined vicinal quaternary centers, a synthetically challenging structural entity.[7b]

In summary, we have described the synthesis of substituted pyrrolidines bearing quaternary centers using a TMM cycloaddition. The reaction was made possible by the utility of diamidophosphite ligands **L2** and **L3**, allowing us to perform the cycloaddition with disubstituted-TMM donors for the first time. The products are formed in good yields and selectivities and are readily functionalized to diverse architectures. Further investigation into the full scope of the reaction is underway and will be reported in due time.

■ 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.

■ AUTHOR INFORMATION

Corresponding Author

bmtrost@stanford.edu

Present Address

[†]Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877-0368, United States

Notes

The authors declare no competing financial interest.

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(8) While disubstituted TMM donors have been successful previously using a cyclopropyl donor (see Trost, B. M.; Parquette, J. R.; Nubling, C. *Tetrahedron Lett.* **1995**, *36*, 2917) the quaternary center produced was not chiral, and the process was only carried out in a racemic fashion.

(9) Ligands **L2** and **L3** are derived from diamines of opposite chiralities; thus the products observed possess opposite enantioselectivities, as reflected in Table 1.

(10) All products were isolated as a single regioisomer. The absolute and relative stereochemistry of the product was determined by the crystal structure of **3d** (see Supporting Information). All other products were assigned by analogy.

(11) **L3** was not tested more broadly due to the lowered yields experienced by this ligand in these reactions.

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