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Enantioselective Construction of Highly Substituted Pyrrolidines by Palladium-Catalyzed Asymmetric [3+2] Cycloaddition of Trimethylenemethane with Ketimines

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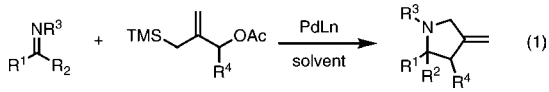
The transition-metal catalyzed [3+2] trimethylenemethane (TMM) cycloaddition reaction is a versatile method for the chemo-, regio-, and diastereoselective construction of highly substituted five-membered rings.[1] Utilization of Pd-TMM complexes derived from 3-acetoxy-2-trimethylsilylmethyl-1-propene has resulted in the efficient catalytic syntheses of carbocycles[2] and heterocycles.[3] Although this methodology was disclosed over 30 years ago by our laboratory,[4] a general asymmetric variant of the cycloaddition remained elusive until 2006.[5] Using a new class of chiral phosphoramidite ligands, we were able to affect the efficient syntheses of cyclopentanes,[5,6] pyrrolidines,[7] and bicyclo[4.3.1]decadienes[8] through reaction of olefins, aldimines, and tropones respectively.[9]

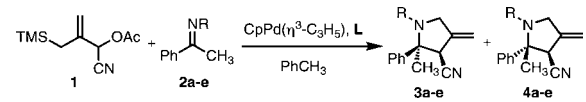
While catalytic, enantioselective addition of carbon nucleophiles to aldimines is well precedented, the corresponding additions to ketimines are rare.[10] The intrinsic lower reactivity of ketimines due to both electronic and steric factors undoubtedly plays a significant role. In addition to the opportunity for novel selectivity afforded by our phosphoramidite ligands, we also observed a significant increase in reactivity of various substrate classes. Many cycloadditions requiring elevated temperatures and high catalyst loading in the racemic reaction were found to proceed under milder conditions, requiring as little as 1 mol % metal at low temperatures. This enhanced reactivity inspired us to examine the asymmetric cycloaddition to ketimines, despite the relatively rare and specialized nature of reactive ketimines in the achiral TMM reaction.[3b] Such a reaction (eq 1, R^1, $R^2 \neq H$) would provide a novel route to highly substituted pyrrolidines containing a tetrasubstituted center.



(1)

We began our studies with the examination of the Pd-catalyzed [3+2] cycloaddition of our cyano-TMM donor **1** with a series of ketimines **2a**−**e** (Table 1). Using CpPd(η^3-C_3H_5) and Feringa ligand **L1** (Figure 1), we were discouraged by the fact that PMP-imine **2a** proved completely unreactive under the conditions utilized, as the corresponding aldimine class had performed well using our parent donor (eq 1, R^4 = H).[7] Equally frustrating, no reactivity was observed with benzyl imine **2b** or oxime ether **2c**. Diphenylphosphinoyl imine **2d** provided a complex mixture. Analysis of the crude mixture by NMR indicated the presence of the desired product **3d** and its tautomer containing an endocyclic olefin conjugated with the nitrile; however purification proved problematic. These results indicated that a strongly electron-withdrawing group was necessary for reactivity. Gratifyingly, using *N*-tosyl imine **2e** we observed formation of the desired cycloadduct, albeit as a mixture of **4e** and its endocyclic olefin tautomer. Reduction of the temperature prevented isomerization and increased the enantioselectivity, but the diastereoselectivity remained poor and it became

Table 1. Selected Optimization Studies[a]



entry	R	Ligand	*T*, °C	% yield	**3**/**4**	**3** % ee	**4** % ee
1	4-$MeOC_6H_4$ (**2a**)	**L1**	50	0			
2	Bn (**2b**)	**L1**	50	0			
3	OCH_3 (**2c**)	**L1**	50	0			
4	$P(O)Ph_2$ (**2d**)	**L1**	50	Complex			
5	Ts (**2e**)	**L1**	50	24[b]	0:1	−	53
6	Ts	**L1**	4	67	1:1.1	86	63
7	Ts	**L2**	4	79	2.2:1	95	89
8	Ts	**L3**	4	91	>20:1	>99	−

[a] All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, and 1.5 equiv of **1** and stirred for 4 h. Yields are isolated values; ee's were determined by chiral HPLC. [b] Mixture also contained 53% yield of the endocyclic double bond with a 41% ee.

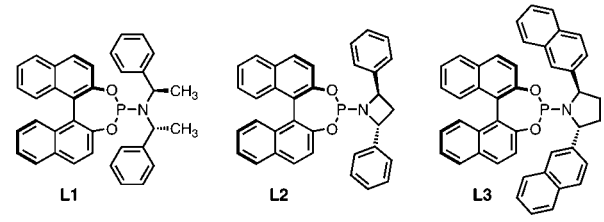


Figure 1. Phosphoramidite ligands examined.

clear that ligand optimization would be required. Azetidine ligand **L2** (Figure 1) provided a sizable increase in enantioselectivity, although the diastereoselectivity remained low. Our previously introduced bis-2-naphthyl phosphoramidite **L3** solved both the enantio- and diastereoselectivity issues, providing the desired product in excellent yield with a >20:1 dr and a >99% ee. Notably, while *N*-Boc imines derived from aromatic aldehydes performed admirably in previous studies, they were ineffective in this case due to their propensity to isomerize to the enamine tautomer.

We next wanted to examine the reaction scope with respect to the imine (Table 2). Gratifyingly, the reaction proved very general under the optimized conditions, performing well in every case examined. Yields and selectivities proved insensitive to the steric bulk of the aromatic substituent (entry 2), aliphatic substituent (entry 3), substitution pattern of the aromatic ring (entries 4−6), or electronic nature of the substituent. Spirocycles could be formed in good to excellent diastereoselectivity and excellent enantioselectivity (entries 7−8). Heterocycles were tolerated (entry 9), albeit with moderately decreased enantioselectivity, and equivalently substituted aliphatic ketimines performed well (entry 10). Conver-

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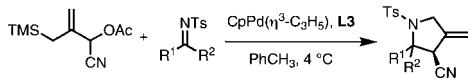
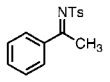
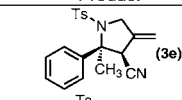
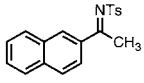
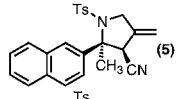
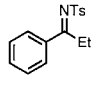
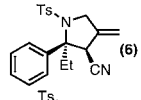
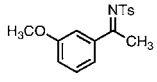
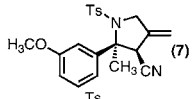
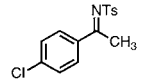
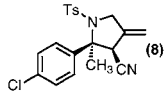
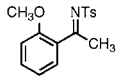
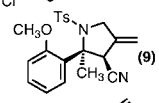
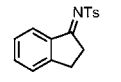
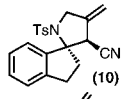
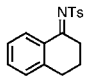
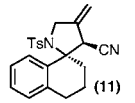
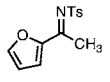
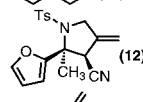
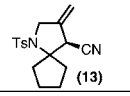
Table 2. Initial Scope of the Imine Cycloaddition[a]



entry	Substrate	Product	% yield	dr	% ee
1		 (3e)	91	>20:1	>99
2		 (5)	77	>20:1	98
3		 (6)	99	>20:1	99
4		 (7)	89	>20:1	99
5		 (8)	90	>20:1	>99
6		 (9)	99	10:1	98
7[b]		 (10)	99	7:1	99 96[c]
8		 (11)	99	>20:1	>99
9		 (12)	99	15:1	81
10		 (13)	86	—	95

[a] All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, and 1.5 equiv of **1** and stirred for 2−4 h. Yields are combined, isolated values; ee's were determined by chiral HPLC. [b] Reaction performed at −15 °C. [c] Minor diastereomer.

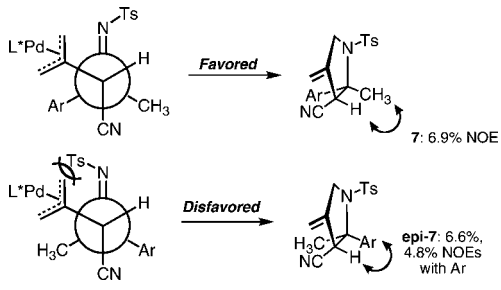
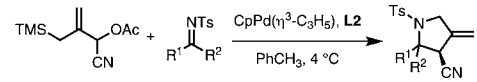


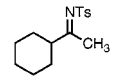
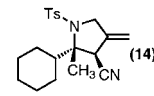
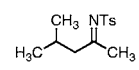
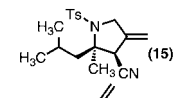
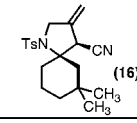
Figure 2. Proposed model for reaction diastereoselectivity.

sion remained high at low temperatures, in some cases as low as −15 °C (entry 7). An X-ray crystal structure analysis of **9** (entry 6) unambiguously allowed the determination of absolute stereochemistry.

Our proposed model for the diastereoselectivity of the reaction is shown in Figure 2 and is based on the imine geometry. We suggest that the initial bond forming event occurs as depicted from the top conformer, leading to the observed, thermodynamically less favored diastereomer.[11] The other diastereomer would arise from the bottom conformer, which is highly disfavored due to severe steric interactions between the tosyl group and bulky π-allyl.

Table 3. Scope of the Aliphatic Imine Cycloaddition[a]



entry	Substrate	Product	% yield	dr	% ee
1		 (14)	86[b]	1:1	99, 96
2			50[c]	12:1	84
3			83	10:1	95
4		 (15)	99	5:1	95
5		 (16)	77	>20:1	88

[a] All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, and 1.5 equiv of **1** and stirred for 2−4 h. Yields are combined, isolated values; ee's were determined by chiral HPLC. [b] Using Ligand **L3**. [c] Using Ligand **L1**.

Nonequivalently substituted aliphatic ketimines presented a selectivity problem when subjected to the standard conditions (Table 3, entry 1). Using **L3** conversion remained high with the cyclohexyl imine, but the diastereoselectivity dropped below acceptable levels. Ligand **L1** (entry 2) restored the diastereoselectivity, albeit at the cost of conversion and enantioselectivity. Ligand **L2** provided a nice compromise, providing the desired product in good yield, 10:1 diastereoselectivity, and restored enantioselectivity. A more remote branch point could be tolerated while maintaining selectivity as shown by the isobutyl and cyclohexyl imines (entries 4−5).

In summary, we have demonstrated a palladium-catalyzed asymmetric addition of a carbon nucleophile to ketimines in the context of a [3+2] TMM cycloaddition, providing highly substituted pyrrolidines. This transformation showcases novel reactivity and selectivity that has not been previously observed. We have been able to affect high enantio- and diastereomeric excesses by matching substrate classes with the appropriate ligand. Investigations into the full imine scope and further transformations are ongoing and will be reported in due course.

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

References

(1) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (b) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Yamago, S.; Nakamura, E. *Org. React.* **2002**, *61*, 1.
(2) Chan, D. M. T. Recent Advances in Palladium-Catalyzed Cycloadditions Involving Trimethylenemethane and its Analogs. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 57−83.
(3) (a) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902. (b) Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636.
(4) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.
(5) Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328 Hayashi reported a single account of an asymmetric

TMM reaction: Yamamoto, A.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 375.
(6) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.
(7) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398.
(8) Trost, B. M.; McDougall, P. J.; Hartmann, O.; Wathen, P. T. *J. Am. Chem. Soc.* **2008**, *130*, 14960.
(9) Marquand, P. L.; Tam, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 2926.
(10) (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 873. (b) Shibasaki, M.; Motomu, K. *Chem. Rev.* **2008**, *108*, 2853.
(11) Semiempirical AM1 calculations performed using Spartan indicate an energy difference of 1.09 kcal/mol with **epi-7** being the more stable isomer.

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