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

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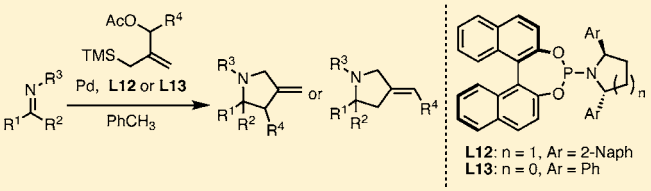
Supporting Information

ABSTRACT: A protocol for the enantioselective [3 + 2] cycloaddition of trimethylenemethane (TMM) with imines has been developed. Central to this effort were the novel phosphoramidite ligands developed in our laboratories. The conditions developed to effect an asymmetric TMM reaction using 2-trimethylsilylmethyl allyl acetate were shown to be tolerant of a wide variety of imine acceptors to provide the corresponding pyrrolidine cycloadducts with excellent yields and selectivities. Use of a bis-2-naphthyl phosphoramidite allowed the successful cycloaddition of the parent TMM with *N*-Boc imines, and has further permitted the reaction of substituted donors with *N*-tosyl aldimines and ketimines in high regio-, diastereo-, and enantioselectivity. Use of a diphenylazetidine ligand allows the complementary synthesis of the exocyclic nitrile product shown, and we demonstrate control of the regioselectivity of the product based on manipulation of the reaction parameters.

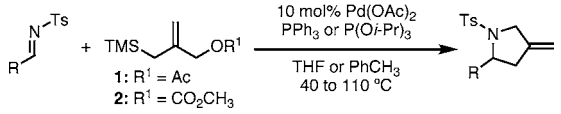


INTRODUCTION

Pyrrolidines are ubiquitous structures in organic chemistry, appearing routinely in nature in the form of primary and secondary metabolites as well as in other biomolecules and non-naturally occurring pharmaceuticals.[1] Reported pyrrolidine syntheses date back to the early twentieth century with some of the first methods accounted as part of synthetic efforts to the tropane ring system by Richard Willstätter in 1903 and Sir Robert Robinson in 1917.[2] Classical methods of pyrrolidine synthesis include alkylations and condensations, reductions of succinimides, cyclic enamines and pyrroles, Overman's Aza-Cope Mannich cascade, and numerous others.[3] The stereoselective synthesis of functionalized pyrrolidines is a topic of longstanding interest due to the abundance of this structural unit in natural products and pharmaceuticals, as well as in chiral ligands[4] and organocatalysts.[5] A number of enantioselective pyrrolidine syntheses have been reported in the literature; some recent examples include methods such as the reduction of cyclic enamines,[6] hydroamination,[7] and reductive cyclization.[8]

Dipolar cycloadditions also represent a well-studied approach toward the synthesis of pyrrolidines. The most extensively studied method involves the reaction of olefins with azomethine ylides.[9,10] Methods have been developed to control absolute stereochemistry using chiral auxiliaries[11] and through asymmetric catalysis.[12] The complementary cycloaddition of olefins with α-amino aldehydes has also been demonstrated,[13] but methods in which an all carbon 1,3-dipole is used in the cycloaddition are rare. The Lewis acid-catalyzed ring-opening of cyclopropanes and subsequent addition to imines has been effected,[14,15] but the most general method is the metal-catalyzed [3 + 2] cycloaddition of trimethylenemethane with imines. A limited account of the nickel-catalyzed cycloaddition of 2-((trimethylsilyl)methyl) allyl mesylate with imines was disclosed by Kremmit and Jones.[16] In 1993, the Trost group disclosed the palladium-catalyzed reaction of 2-((trimethylsilyl)methyl) allyl acetate (and the methyl carbonate) with aromatic and aliphatic imines (Scheme 1).[17] The

Scheme 1. Achiral TMM Reaction of Donors 1 and 2 with Tosyl Imines



reaction was conducted in toluene or THF at elevated temperatures using triphenylphosphine or triisopropylphosphite as a ligand. Aromatic and aliphatic aldimines were tolerated, though ketimine examples were scarce. Phenyl and nitrile-substituted donors were also effective in the cycloaddition.

Due to the prevalence of this heterocycle in many molecules of interest, its formation in an enantioselective manner is highly desirable. The proposed process would extend the scope of our previously developed cycloaddition with olefin substrates[18] to imines, thereby providing a new method for the generation of chiral pyrrolidines. Prior to this work, the asymmetric reaction had been studied in the Trost group. It was discovered that the BPPFA ligand shown could catalyze the reaction (Scheme 2), generating the pyrrolidine depicted in good yield and 35%

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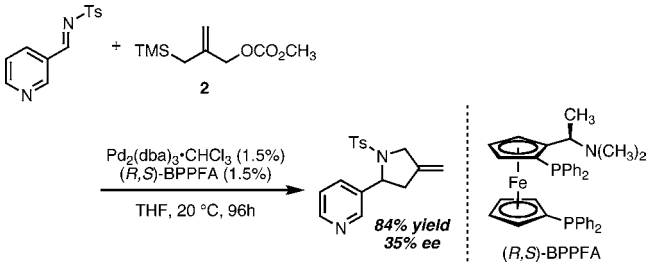
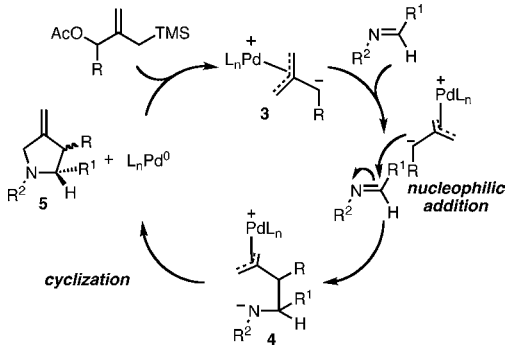
Scheme 2. Marrs' Catalytic, Asymmetric Pyrrolidine Synthesis



enantiomeric excess.[19] However, despite extensive efforts, higher ee could not be obtained.

The catalytic cycle for this process is shown in Scheme 3. The reaction is believed to proceed through the zwitterionic

Scheme 3. Catalytic Cycle for the Palladium-Catalyzed [3 + 2] TMM Cycloaddition with Imines



Pd-TMM intermediate **3** (Scheme 3), generated in situ by ionization of the donor followed by acetate promoted desilylation. Addition of the nucleophilic Pd-TMM complex to the imine followed by collapse of the zwitterionic intermediate **4** via attack of the nitrogen nucleophile onto the π-allylpalladium species gives the desired product **5**. In general, the cycloaddition is believed to be stepwise in nature. The product can subsequently undergo base-promoted isomerization to give an endocyclic olefin.

The catalytic cycle illustrates the inherent difficulty in the development of an asymmetric variant of the TMM reaction. Nucleophilic addition is almost certainly the enantiodiscriminating step. The coordinated chiral ligands on the palladium are distal to the reaction center, and this distance likely decreases the ability of chiral ligands to transfer stereochemical information during the addition. Accordingly, attempts to induce asymmetry into the TMM reaction have largely been limited to the use of chiral auxiliaries;[20] chiral catalysis has been largely unsuccessful.[21] No reports of catalytic asymmetric cycloadditions to imines have appeared prior to our work.

RESULTS AND DISCUSSION

Palladium-Catalyzed Reaction of 3-Acetoxy-2-trimethylsilylmethyl-1-propene with Aldimines. Our initial studies focused on the phosphoramidite ligands which had enjoyed success in the olefin cycloaddition.[18] We chose benzylidene aniline (**6**) as a test substrate as it had been successfully utilized in the racemic reaction, and employed conditions which mimicked the cyclopentane synthesis (5 mol % $Pd(dba)_2$, 10 mol % ligand, 1.6 equivalents TMM donor, toluene). Our choice to use excess donor was based on the fact that it undergoes slow polymerization under the reaction conditions. Running the reaction at 45 °C for 4 h with a variety of ligands, we immediately observed that both conversions and selectivities were inferior to those observed in the olefin cycloaddition (Scheme 4). Feringa ligand **L1**[22] gave a reasonable 71% conversion but a disappointing 3% ee. Alexakis observed that minor alterations to the amine portion of the phosphoramidite had beneficial effects on the reactivity and selectivity of iridium-catalyzed asymmetric allylic alkylation reactions.[23] On the basis of these studies, we tested **L2**-**L7**. Variants of **L1** with the (*R,R,R*) motif all gave fairly low ee values. Naphthyl derivative **L2** gave a similar result to the

Scheme 4. Performance of Phosphoramidite Ligands in the Reaction with Benzylidene Aniline

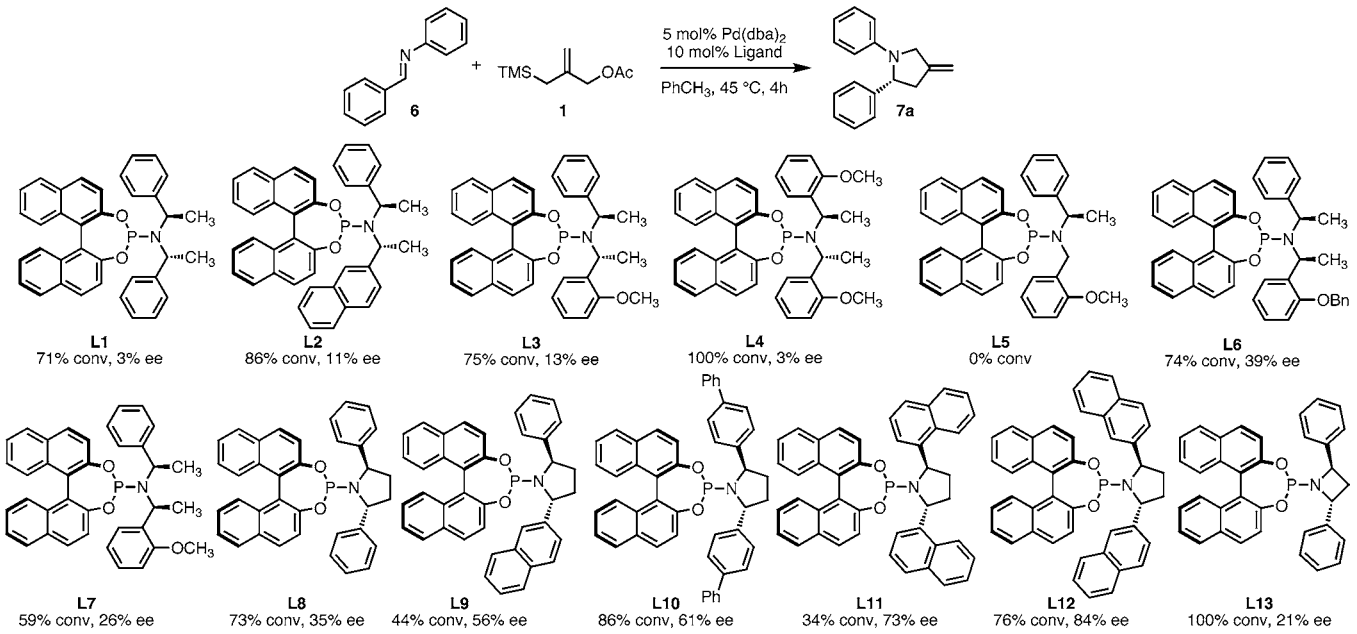


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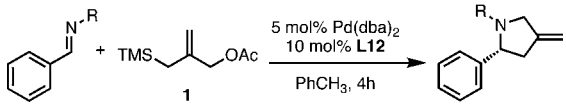
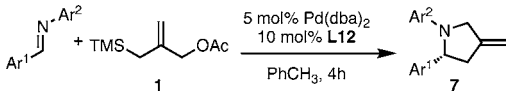
Table 1. Imine Optimization Study[a]

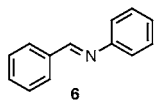
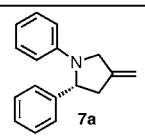
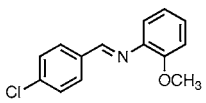
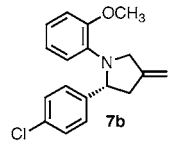
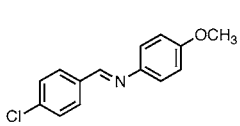
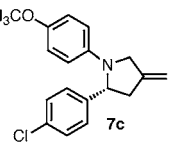
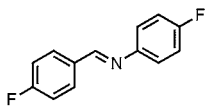
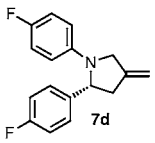
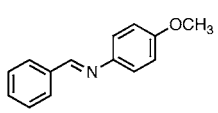
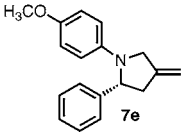


entry	R	temp (°C)	% yield	% ee
1	Ph (**6**)	45	76[b]	84
2	Ts	45	98	45
3	Bn	45	0[c]	
4	$P(O)Ph_2$	23	0[c]	
5	Boc	45	98	87
6	Fmoc	23	0[d]	
7	Cbz	23	0[d]	

[a]All reactions were performed at 0.2 M in toluene and used 1.6 equivalents **1**. [b]Conversion. [c]Recovered starting material. [d]Complex mixture.

Table 2. Palladium-Catalyzed [3 + 2] Reactions of *N*-Aryl Imines[a]



entry	substrate	product	temp (°C)	% yield	% ee
1[b]	 **6**	 **7a**	45	80	82
2		 **7b**	45	87	83
3		 **7c**	45	80	84
4		 **7d**	4	83	83
5		 **7e**	45	35[c]	78

[a]All reactions were performed at 0.2 M in toluene with 5% $Pd(dba)_2$, 10% ligand, 1.6 equiv **1**, and stirred for 4 h. Yields are isolated values; ee's were determined by chiral HPLC or chiral GC. [b]Reaction performed with 2.5 equivalents **1**. [c]Conversion.

Feringa ligand with only a small increase in enantioselectivity. Similar to what was observed in the alkene reaction, installation of an *ortho*-methoxy group (**L3**) increased conversion levels, and substitution at both *ortho*-positions (**L4**) increased it further. Removal of a methyl group as in **L5** provided an inactive catalyst. Inverting a stereocenter to provide ligands of an (*R,R,S*) motif **L6**-**L7** improved the ee values, but they still remained below 40%. We next turned to pyrrolidine-based phosphoramidites. The catalyst formed from **L8** gave the product in 35% ee and 73% conversion. Adjusting the nature of the chiral space by substituting a 2-naphthyl group for a phenyl (**L9**) increased the ee of the cycloadduct to 56%, though the conversion dropped slightly. Substitution with 4-biphenyl groups (**L10**) gave still higher ee and conversion (61% and 86% respectively), and the bis-1-naphthyl ligand (**L11**) boosted the ee to 73%. Bis-2-naphthyl ligand **L12** gave the best results with a 76% conversion and 84% ee. In order to examine the effects of ring size, we turned to azetidine ligand **L13**. A very facile reaction was observed with full conversion being achieved in less than an hour, but to our disappointment, it was discovered that the highly active catalyst generated from this system gave a significantly lower ee.

Having determined that **L12** provided the most suitable catalyst system for our reaction, we turned our focus to optimization of the imine type (Table 1). Ideally, we wanted a group which would not only provide products in high enantiomeric excess, but could also be easily removed. While the use of a tosyl group (entry 2) gave a very facile reaction, providing essentially quantitative desired product within minutes, the material obtained was of low ee. Benzyl and diphenylphosphinoyl imines (entries 3−4) showed no reactivity. Use of an *N*-Boc imine (entry 5) gave excellent results with the protected pyrrolidine being obtained in 98% yield and 87% ee. Other carbamates were not successful (entries 6−7) as neither the fluorenylmethyl or benzyl carbonates gave significant amounts of desired product, instead yielding only complex mixtures.

The reaction of both *N*-aryl and *N*-Boc imines was examined. A short assessment of substituted benzylidene anilines is shown in Table 2. The reaction worked well when the *N*-bound aryl ring bore electron donating groups (entries 2−3) or withdrawing groups (entry 4). On the *C*-bound ring, electron withdrawing groups significantly enhanced reactivity as reflected in reduced amounts of silyl acetate needed to reach full conversion (2.5 equivalents in entry 1 versus 1.6 in entries 2−4), as well as the lower temperature required (entry 4). Lowering the temperature to 4 °C failed to produce significant (>10%) product from more electron rich imines (entries 1−3). Electron rich aniline **7e** showed a high level of instability, both under the reaction conditions and during purification attempts. Highly electron poor imines of this class, such as those derived from nitroaniline, were unstable to the reaction conditions. Use of a Lewis acidic additive such as $In(acac)_3$ did not improve the results for this substrate class.

The use of *N*-Boc imines provided a broader reaction scope (Table 3). This class proved more reactive than the substituted benzylidene anilines. The temperature could be reduced

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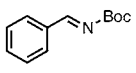
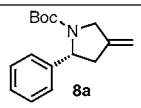
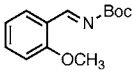
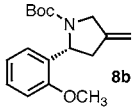
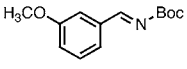
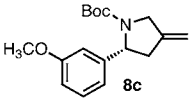
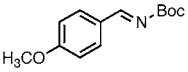
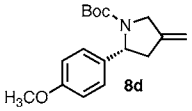
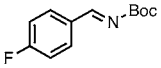
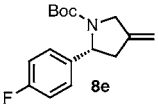
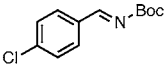
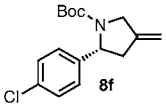
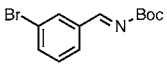
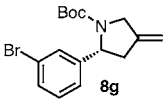
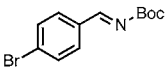
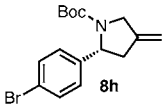
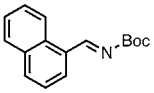
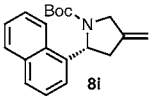
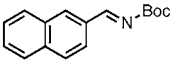
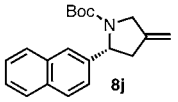
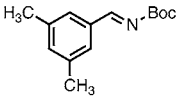
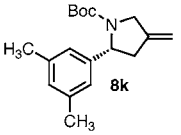
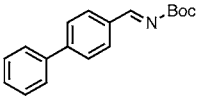
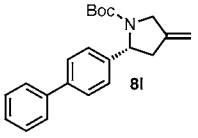
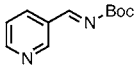
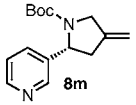
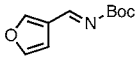
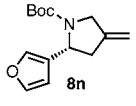
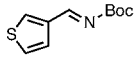
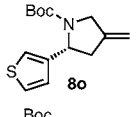
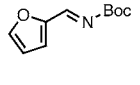
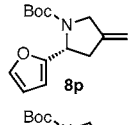
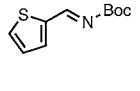
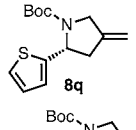
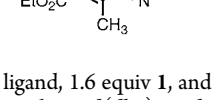
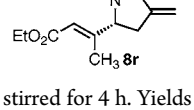
Table 3. Palladium-Catalyzed [3 + 2] Reactions of *N*-Boc imines[a]

entry	substrate	product	temp (°C)	% yield	% ee
1		 8a	45	98	87
			4	84	91
2		 8b	4	80	92
3		 8c	4	83	86
			-15	73	90
4		 8d	4	94	93
5		 8e	4	91	90
6		 8f	4	96	91
7		 8g	4	93	85
			-15	94	86
8		 8h	4	73	84
9		 8i	4	86	84
10[b]		 8j	4	86	85
11		 8k	4	71	88
			-15	65	90
12		 8l	4	81	83
13		 8m	4	75	86
14		 8n	4	71	91
15		 8o	4	74	88
			-15	60	90
16		 8p	4	74	70
17		 8q	4	88	72
18		 8r	4	43	22

[a]All reactions were performed at 0.2 M in toluene with 5 mol % $Pd(dba)_2$, 10 mol % ligand, 1.6 equiv **1**, and stirred for 4 h. Yields are isolated values; ee's were determined by chiral HPLC or chiral GC. [b]Reaction performed with 2.5 mol % $Pd(dba)_2$ and 5 mol % **L12**.

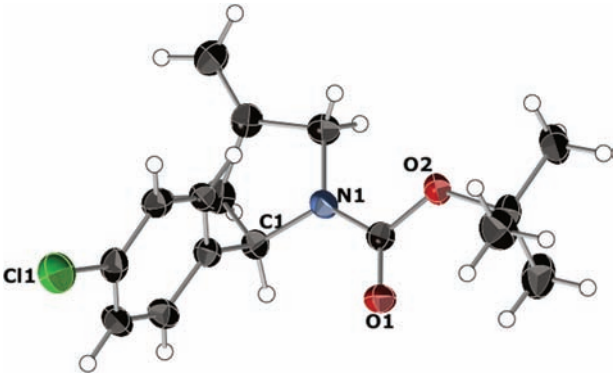
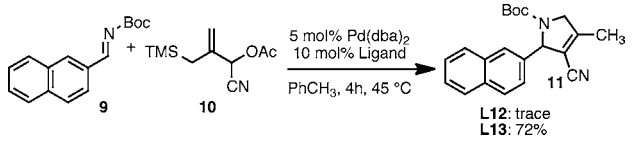


Figure 1. ORTEP illustration of (*R*)-*tert*-butyl 2-(4-chlorophenyl)-4-methylenepyrrolidine-1-carboxylate (**8f**) with thermal ellipsoids drawn at the 50% probability level.

Scheme 5. Initial Reaction of Donor 10 with *N*-Boc Imine 9



considerably, as low as −15 °C in some cases (entries 3, 7, 11, 15), and conversion remained high with moderate increases in enantioselectivity observed. The reaction proved insensitive to the nature of the aromatic substitutent with similar results obtained regardless of substitution pattern (entries 2−4) or electronic nature of the substitutent (entries 2−8). Steric bulk was tolerated as well (entries 9−12). Heterocycles performed well in the reaction as can be seen by the pyridyl (entry 13), furyl (entry 14), and thiophenyl (entry 15) substituents. The pyridyl example is particularly interesting as **8m** constitutes a

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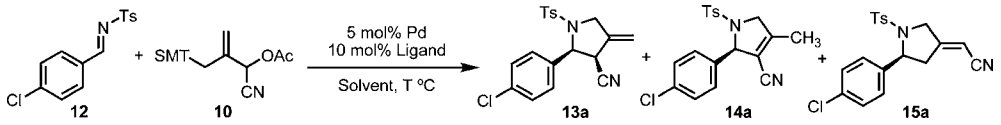
Table 4. Initial Study of the Reaction of Cyano Donor 10 with Tosyl Imine 12



entry	Pd	ligand	temp (°C)	solvent	conc (M)	yield (%)	**13a** (ee)	**14a** (ee)	**15a** (ee)
1	CpPd(η^3-C_3H_5)	**L13**	50	$PhCH_3$	0.2	88	0	0.7	1
2	CpPd(η^3-C_3H_5)	**L13**	4	$PhCH_3$	0.2	100	0.2 (49%)	0	1 (27%)
3	$Pd(dba)_2$	**L13**	4	$PhCH_3$	0.2	100	0.2	0	1
4	CpPd(η^3-C_3H_5)	**L14**	4	$PhCH_3$	0.2	97	0	0.4 (66%)	1 (42%)
5	CpPd(η^3-C_3H_5)	**L15**	4	$PhCH_3$	0.2	100	0.7 (3.5:1, 79%, ND)	0.7 (77%)	1 (15%)
6	CpPd(η^3-C_3H_5)	**L16**	4	$PhCH_3$	0.2	43	12 (1.4:1, −30%, −56%)	0	1 (ND)
7	CpPd(η^3-C_3H_5)	**L12**	4	$PhCH_3$	0.2	80	0.2 (92%)	0.2 (90%)	1 (32%)
8	CpPd(η^3-C_3H_5)	**L17**	4	$PhCH_3$	0.2	64	9 (1.2:1, 63%, 25%)	0	1 (69%)
9	CpPd(η^3-C_3H_5)	**L18**	4	$PhCH_3$	0.2	79	5.2 (1.8:1, 52%, 32%)	0	1 (30%)
10	CpPd(η^3-C_3H_5)	**L2**	4	$PhCH_3$	0.2	78	6 (1:1, 73%, 45%)	0	1 (33%)
11	CpPd(η^3-C_3H_5)	**L19**	4	$PhCH_3$	0.2	100	0.5 (45%)	0	1 (10%)
12	CpPd(η^3-C_3H_5)	**L20**	4	$PhCH_3$	0.2	100	0.3 (39%)	0	1 (31%)
13	CpPd(η^3-C_3H_5)	**L21**	4	$PhCH_3$	0.2	79	0	3 (27%)	1 (33%)
14	CpPd(η^3-C_3H_5)	**L22**	4	$PhCH_3$	0.2	0			
15	CpPd(η^3-C_3H_5)	**L12**	50	$PhCH_3$	0.2	93	0	0.8 (90%)	1 (43%)
16	CpPd(η^3-C_3H_5)	**L12**	80	$PhCH_3$	0.2	100	0	1.1 (70%)	1 (46%)
17	$Pd(dba)_2$	**L12**	50	$PhCH_3$	0.2	100	0	0.5 (82%)	1 (41%)
18	$Pd(OAc)_2$	**L12**	4	$PhCH_3$	0.2	100	0.2 (96%)	0.1 (92%)	1 (33%)
19	CpPd(η^3-C_3H_5)	**L12**	40	CH_2Cl_2	0.2	83	0	0.9 (53%)	1 (12%)
20	CpPd(η^3-C_3H_5)	**L12**	4	THF	0.2	100	0.2 (95%)	0.3 (91%)	1 (35%)
21	CpPd(η^3-C_3H_5)	**L12**	4	dioxane	0.2	100	0.2 (92%)	0.1 (91%)	1 (21%)
22	CpPd(η^3-C_3H_5)	**L12**	4	Et_2O	0.2	complex	0	0.5	1
23	CpPd(η^3-C_3H_5)	**L12**	4	$PhCH_3$	0.01	35	1.25 (95%)	0	1 (37%)
24	CpPd(η^3-C_3H_5)	**L12**	4	THF	0.01	46	2.5 (95%)	0	1 (48%)
25	CpPd(η^3-C_3H_5)	**L12**	4	THF	0.02	100	1.8 (95%)	1.7 (92%)	1 (50%)
26[a]	CpPd(η^3-C_3H_5)	**L12**	4	THF	0.02	90	2 (90%)	0	1 (50%)
27[b]	CpPd(η^3-C_3H_5)	**L12**	4	THF	0.02	100	0.3 (86%)	3.3 (82%)	1 (50%)
28	CpPd(η^3-C_3H_5)	**L12**	23	THF	0.02	100	0	4 (81%)	1 (52%)
29	CpPd(η^3-C_3H_5)	**L12**	50	THF	0.02	100	0	10 (81%)	1
30	CpPd(η^3-C_3H_5)	**L12**	4	PhCl	0.02	48	0.5 (92%)	0	1 (33%)
31	CpPd(η^3-C_3H_5)	**L12**	4	DME	0.02	100	2 (90%)	0.6 (85%)	1 (39%)
32[c]	CpPd(η^3-C_3H_5)	**L12**	4	$PhCH_3$	0.02	0			

[a] $In(acac)_3$ (10 mol %) was added. [b] DMSO (1 vol%) was added. [c] n-Hex_4NCl (10 mol %) was added.

formal total synthesis of nicotine.[17] The enantiomeric excess was reduced in the cases examined where the heterocycle was substituted adjacent to the heteroatom (entries 16−17), presumably because of lower steric congestion; the corresponding 3-substituted isomers gave significantly higher ee's (entries 14−15). The unsaturated system (entry 18) gave material with low yield and ee. The catalyst loading could be lowered (entry 10) with little change in results. The absolute configuration of the cycloadducts was shown to be as depicted via X-ray crystallographic analysis (Figure 1).

Palladium-Catalyzed Asymmetric Cycloaddition Reactions of Substituted Donors with Aldimines. Having developed a practical route to the synthesis of disubstituted *N*-Boc and *N*-aryl pyrrolidines, we turned our attention to substituted donors with the goal of preparing more complex systems. Due to the success of nitrile substituted donor **10** in our cyclopentane synthesis, we chose this as a starting point. Using *tert*-butyl naphthalen-2-ylmethylenecarbamate (**9**, Scheme 5), the only identifiable material was trace amounts of the dihydropyrrole **11**, which results from the facile isomerization of the exocyclic olefin to the more stable internal double bond isomer. Because of the sluggish nature of the reaction, we turned to azetidine ligand **L13** as we had previously observed it to promote very rapid cycloaddition. Gratifyingly, at 45 °C we obtained a 72% yield of the product. Attempts to lower the temperature gave only complex mixtures. Use of CpPd(η^3-C_3H_5) as a precatalyst[24] gave similar results. Complex mixtures were also obtained using a phenyl-substituted donor.

Because of the facile reaction observed with tosyl imines when studying the parent donor, we decided to reexamine this substrate class. We reasoned that the increased steric bulk of a substituted donor could serve to increase enantiodiscrimination and provide the desired product with a higher ee than what had been observed previously. To this end, we subjected tosyl imine **12** to the reaction conditions (Table 4). We were excited to observe a quick reaction leading to a high yield of the anticipated, albeit isomerized, TMM cycloadduct (entry 1). However, analysis of the mixture indicated that in addition to **14a**, it contained exocyclic cyano product **15a** in a 0.7:1 mixture with **15a** slightly favored. Decreasing the temperature and reducing the reaction time provided a mixture containing a greater proportion of **15a** (entry 2). No isomerization was observed at this temperature. The anticipated cycloadduct **13a**

dx.doi.org/10.1021/ja210981a | J. Am. Chem. Soc. 2012, 134, 4941−4954

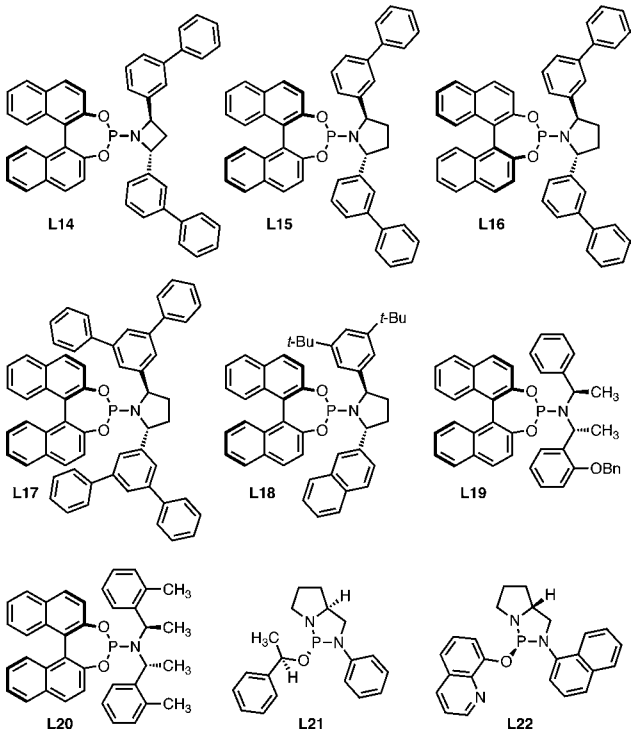


Figure 2. Structures of additional ligands studied in the reaction of cyano donor **10** with tosyl imine **12**.

was obtained as a single diastereomer; the ee values observed for both products were low. Lowering the temperature to −15 °C did not change the ratio. Switching to $Pd(dba)_2$ (entry 3) had no effect on the product distribution. We did observe that the amount of isomerized product increased over time, and accordingly, reactions were quenched immediately after disappearance of starting material, generally less than two hours.

We next studied ligand effects on the cycloaddition, and immediately found that the enhanced reactivity of this imine class proved differential; a variety of ligands promoted the reaction. Additional ligands tested are depicted in Figure 2. Increasing the steric bulk of the azetidine component with **L14** (entry 4) decreased the regioselectivity. Furthermore, this ligand seemed more prone to promote isomerization of **13a** to **14a**. Less isomerization was observed with the corresponding pyrrolidine **L15** (entry 5) and the endocyclic cyano products were obtained in good ee. We varied the ligand diastereomer using (*S,R,R*)-**L16** (entry 6) and found that **13a** was strongly favored, but the yield, diastereoselectivity, and enantioselectivity were low. Our previously studied naphthyl ligand **L12** gave good conversion to a mixture of cycloadducts (entry 7), with the anticipated product **13a** and its tautomer **14a** being obtained with excellent enantioselectivities. Increasing the steric bulk of the pyrrolidine moiety provided mixtures significantly favoring **13a** (entries 8–9), but selectivity dropped. Switching to acyclic amine-derived phosphoramidites, use of the Feringa ligand **L1** also gave a mixture favoring **13a** (entry 10). No isomerization was observed, but the enantio- and diastereoselectivities were poor. More bulky acyclic amine phosphoramidite ligands gave mixtures favoring **15a** and enantioselectivity was low (entries 11–12). In both of these cases, **13a** was obtained as a single diastereomer and no isomerization was observed. We also tested known diaminophosphite ligands in order to determine how a more electron rich phosphorus species would affect selectivity. Ligand **L21** gave a mixture favoring the isomerized product **14a** but the selectivity was low (entry 13). Ligand **L22** formed an unreactive catalyst system (entry 14).

Using **L12**, we observed that increasing the reaction temperature (entries 15–16) increased the proportion of isomerized product **14a**. The enantioselectivity remained high at 50 °C, but decreased sharply when the temperature was increased further. Variation of the palladium source did not drastically alter the product proportions (entries 17–18). A brief solvent study was also conducted. While the reaction proceeded quickly in dichloromethane at 40 °C (entry 19), the product ratio was similar to the reaction in toluene and the ee was reduced. Use of tetrahydrofuran and dioxane (entries 20–21) had only a marginal effect on the relative product amounts. The reaction in diethyl ether gave a complex mixture with no improvement in selectivity (entry 22).

Scheme 6. Expanded Catalytic Cycle Depicting the Mechanism of Formation of Exocyclic Cycloadduct 15

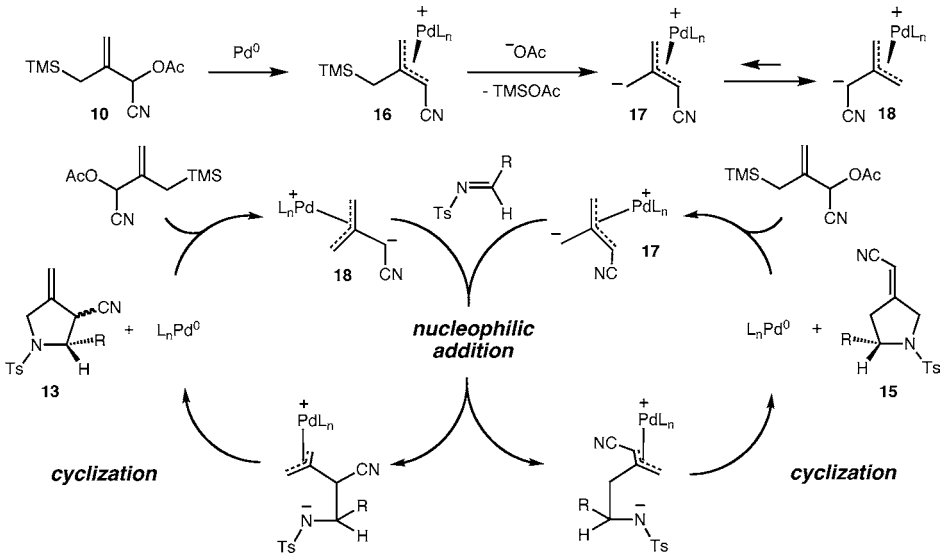


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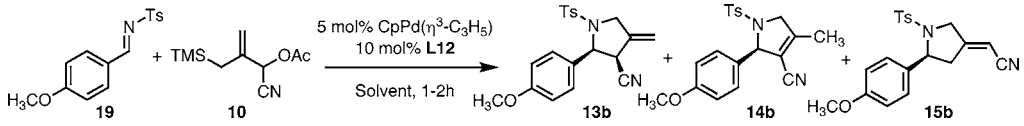
Table 5. Study of the Reaction of Cyano Donor 10 with Electron-Rich Tosyl Imine 19



entry	temp (°C)	solvent	time (h)	conc (M)	% yield	**13b** (dr, ee)	**14b** (ee)	**15b**
1	50	THF	2	0.02	100	1.5 (6:1 dr)	1	0
2	4	$PhCH_3$	2	0.02	40	1	0	0
3	4	$PhCH_3$	1	0.2	100	8 (>10:1 dr)	0	1
4	4	$PhCH_3$	1.5	0.08	100	10 (>20:1 dr, 96%)	0	1

Exocyclic nitrile **15** had not been previously reported to occur in significant quantities. Its formation can be explained by the modified catalytic cycle shown in Scheme 6. In an analogous fashion to the parent donor, insertion of palladium(0) into **10** gives π-allyl species **16**. The displaced acetate serves to remove the silyl group, giving reactive species **17**. In the racemic reaction and previously studied asymmetric variants, isomerization of **17** to **18** occurs more quickly than addition to the π-system of the acceptor. Active donor **18** proceeds in the catalytic cycle shown on the left, giving the anticipated TMM product **13**, which may isomerize to **14** depending on the reaction conditions. Donor **18** is favored on both steric and electronic grounds. Due to the highly nucleophilic character of the palladium-phosphoramide-donor system and the activated nature of the tosyl imine acceptor, the addition of **17** to the imine occurs at a competitive rate with the isomerization (right cycle). Assuming that ring closure occurs by attack at the unsubstituted end of the syn π-allyl, this path would lead to product **15**.

The above data can be rationalized by this explanation. Any modification of the reaction conditions that increases the rate of $\pi-\sigma-\pi$ isomerization transforming **17** to the more stable **18** favors production of **13** and **14**. Conversely, any modification that slows the rate of the $\pi-\sigma-\pi$ interconversion leads to increased proportions of **15**. Lowering the reaction temperature decreases the unimolecular isomerization rate by a greater amount than the bimolecular addition rate, leading to increased **15** at lower temperatures (entry 1 versus entry 2 or entry 7 versus entry 15). Use of a more coordinating solvent such as tetrahydrofuran stabilizes palladium during isomerization, thereby accelerating it, and products **13** and **14** are observed in increased proportions.

The observed ligand effects can also be rationalized by this mechanism. Use of sterically less demanding ligands such as azetidine **L13** allows for a faster rate of TMM addition to the imine relative to the isomerization. There is a clear trend observed when moving to very bulky ligands. Use of ligands **L17** and **L18** slows the addition significantly allowing time for the $\pi-\sigma-\pi$ isomerization to occur and accordingly, larger proportions of **13** are observed. In fact, the mismatched case of **L16** slows the addition such that the highest ratio of **13** to **15** is observed.

The appearance of significant quantities of product **15** when only trace quantities of this type of product were observed in the racemic reaction may be justified in terms of the nature of the palladium-ligand complex. In the racemic case, two phosphorus ligands are present on palladium during the catalytic cycle, but ^{31}P NMR suggests that only a single phosphoramidite is present in the asymmetric reaction. In addition to the electronic factors that favor the isomerization of **17** to **18**, steric factors also favor **18** as interactions between the R substituent and bulky palladium-ligand complex are reduced. With only a single ligand on the palladium however, steric factors are mitigated.

Additionally, this mechanism provides a justification for the high enantiomeric excess of **13** and **14**, and the low enantioselectivity observed in the formation of **15**. In the case of the parent donor, we observed low enantioselectivity when a tosyl imine was tested (Table 1, entry 2). In the case of the substituted donor, we felt that the increased steric bulk would allow for a more effective enantiodiscriminating event. This result is what is generally observed in the pathway leading to **13** and **14**. However, the nucleophilic attack leading to **15** does not have the benefit of this added steric bulk and is more similar to the case of the parent donor and indeed, similar levels of enantioselectivity are observed.

In order to find conditions that minimized formation of **15**, we next explored concentration effects. By decreasing the concentration, we hoped to slow the rate of TMM addition to the imine to allow for complete equilibration of the donor. Decreasing the concentration to 0.01 M (entries 23−24) gave product ratios favoring **13a** with high diastereo- and enantioselectivity, but the reactions did not go to completion. Increasing the concentration to 0.02 M restored the yield to quantitative levels (entries 25−32). The amount of product arising from the left cycle in Scheme 6 remained proportionally high, as did the enantioselectivity. Only a single diastereomer was observed but isomerization was a persistent problem. Use of an indium additive (entry 26) mitigated this, but also decreased the amount of **13a** formed. DMSO promoted isomerization (entry 27). Increasing the temperature (entries 28−29) led to complete isomerization, but greatly increased the proportion of product arising from the left catalytic cycle, giving a 10:1 ratio at 50 °C. Switching the solvent to chlorobenzene (entry 30) reversed the regioselectivity and use of DME (entry 31) gave results similar to THF. Addition of n-Hex_4NCl, known to facilitate $\pi-\sigma-\pi$ isomerization, stopped the reaction entirely (entry 32).

With optimized conditions in hand, we turned our attention to expansion of the substrate scope. Using the conditions in Table 4, entry 29 on the more electron-rich tosyl imine **19**, we observed complete conversion to a mixture of **13b** and **14b**. Interestingly, no exocyclic nitrile **15b** was observed (Table 5, entry 1). As THF had been observed to facilitate isomerization, we switched the solvent to toluene, to mitigate this and observed exclusively **13b**, albeit in low yield. Increasing the concentration (entry 3) restored the yield and gave the product with good regioselectivity. An intermediate concentration of 0.08 M (entry 4) provided the optimal balance of yield and regioselectivity. Clearly the reduced rate of attack of the TMM complex on the more electron-rich imine decreased the amount of **15b** formed.

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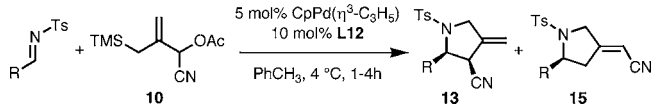
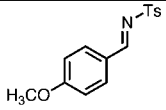
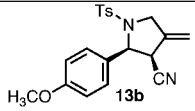
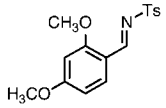
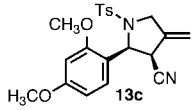
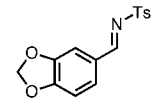
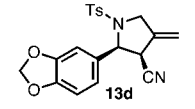
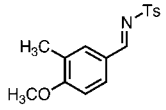
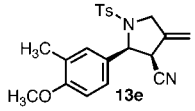
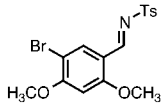
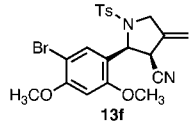
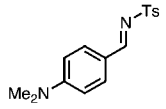
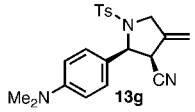
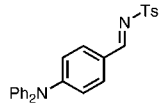
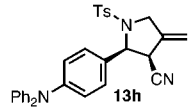
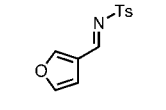
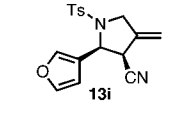
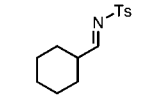
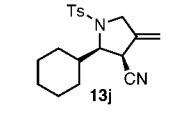
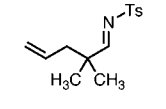
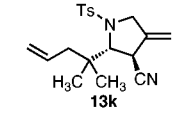
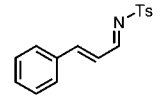
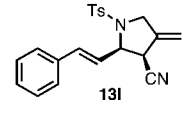
Table 6. Scope of the Reaction of Cyano Donor 10 with Electron-Rich Tosyl Imines



entry	substrate	major product	conc	% yield	13 : 15	13 dr	13 % ee
1		 13b	0.08M	100	10:1	>20:1	96
2		 13c	0.08M	93	>20:1	>20:1	94
3		 13d	0.08M 0.04M	100 99	5.5:1 10:1	14:1 20:1	96 97
4		 13e	0.04M	98	>20:1	17:1	96
5		 13f	0.04M	88	>20:1	>20:1	93
6		 13g	0.08M	86	>20:1	>20:1	97
7		 13h	0.04M	100	7.5:1	>10:1	97
8		 13i	0.08M 0.04M	100 94	5:1 10:1	15:1 >20:1	ND 96
9		 13j	0.2M 0.04M	84[b] 99	>20:1 >20:1	3:1 3.5:1	96, 86 97
10		 13k	0.2M	100	>20:1	3:1	97, 93
11		 13l	0.04M	62	3:1	3:1	ND

[a]All reactions were performed at the stated concentration in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, 1.5 equiv **10**, and stirred until complete consumption of starting imine was achieved as monitored by GC. Yields are combined isolated values; ee values were determined by chiral HPLC. Product ratios are determined by crude NMR. [b]Remaining material consisted of **14j**.

Using the further optimized conditions, we were able to explore the scope of the cycloaddition of *N*-tosyl aldimines with our cyano donor (Table 6). The reaction scope was broad and included oxygenated aromatic (entries 1−5), aniline-derived (entries 6−7), electron-rich heterocyclic (entry 8), and aliphatic imines (entries 9−10). An electron-withdrawing group was tolerated as long as the ring remained sufficiently electron-rich (entry 5). This product type is important as it should allow subsequent transformation using cross-coupling reactions. In some cases (entries 3−5, 7−8), optimal conditions were observed when concentration was further reduced to 0.04M; this tended to improve both the endo:exo selectivity as well as the diastereoselectivity of the major product. In the case where a *para*-diphenylaminobenzaldehyde derived imine was used (entry 7), we observed a drop in endo:exo selectivity, even at 0.04M. This is understandable as the electron density is more distributed in this system and therefore the imine is less electron-rich. Aliphatic imines performed very well in this

dx.doi.org/10.1021/ja210981a | J. Am. Chem. Soc. 2012, 134, 4941−4954

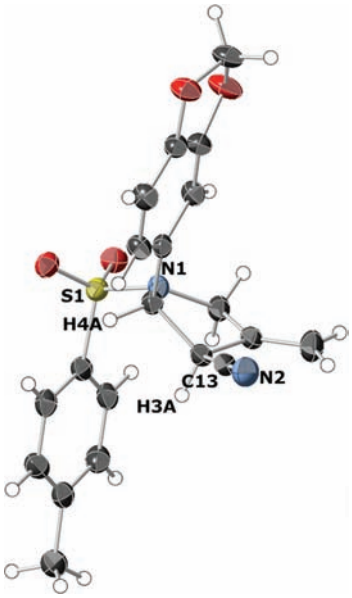
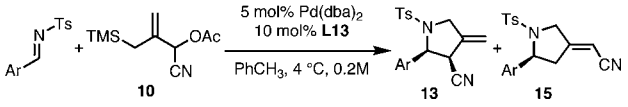
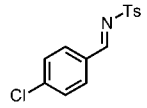
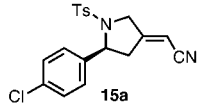
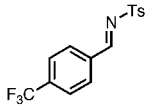
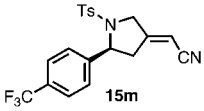
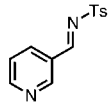
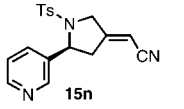
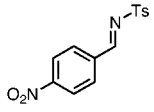
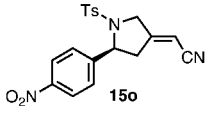
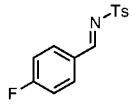
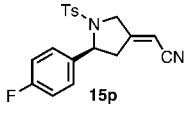
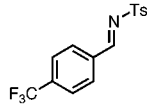
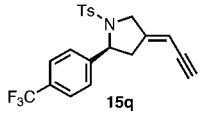


Figure 3. ORTEP illustration of (2*S*,3*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-4-methylene-1-tosylpyrrolidine-3-carbonitrile (**13d**) with thermal ellipsoids drawn at the 50% probability level.

reaction with consistently high yields being obtained at concentrations ranging from 0.04 M to 0.2M. Even at increased concentrations (entry 10), no trace of products of type **15** were observed for saturated systems. A bulky imine containing an adjacent quaternary center performed superbly, but interestingly, the sense of diastereoselectivity was reversed from what had been previously observed and the more stable *trans*-pyrrolidine was obtained. This may indicate a reversible initial addition step. In this case, ring closure to the sterically hindered pyrrolidine is likely slowed and the thermodynamically favored system is ultimately the major product. The cinnamaldehyde imine (entry 11) gave a mixture of both products in decreased yield. Relative stereochemistry was determined by NOE analysis. Additionally, the relative and absolute stereochemistry was confirmed through single crystal X-ray analysis of **13d** (Figure 3)

Table 7. Selective Preparation of Exocyclic Product



entry	substrate	major product	% yield	13 : 15
1		 **15a**	100	1:5
2		 **15m**	98	<1:20
3		 **15n**	100	<1:20
4		 **15o**	100	1:4
5		 **15p**	100	1:5
6[a]		 **15q**	95	<1:20

[a]Using CpPd(η^3-C_3H_5) with corresponding alkyne donor

In addition to the development of conditions that led to the anticipated TMM cycloadduct in high chemo-, diastereo-, and enantioselectivity, our optimization studies also elucidated conditions that allowed for the chemoselective preparation of exocyclic cyano-type products. This is novel reactivity, as this product has been observed only in trace quantities previously. Using conditions developed during these studies, we were able to prepare a series of these cycloadducts in excellent yields and good chemoselectivity (Table 7). An alkyne donor could even be used in the reaction to prepare enyne **15q** (entry 6).

Through developing a mechanistic understanding of the reaction and appropriate manipulation of reaction parameters, we were able to exhibit significant control over the identity of the product formed in the TMM reaction of aldimines with nitrile donor **10** (Scheme 7). Using electron-rich imines and dilute conditions, we could obtain "normal" cycloadducts such as **13b** with high chemo-, diastereo-, and enantioselectivity. With electron-poor aldimines, we also could selectively form the normal, albeit isomerized, product **14a** in good yield and high enantioselectivity using THF, dilute conditions, and elevated temperature. Careful selection of reaction parameters also gave us the opportunity to demonstrate novel reactivity. Using our active azetidine ligand **L13** and cold, concentrated conditions, we could form **15a** in good yield and chemoselectivity.

Palladium-Catalyzed Asymmetric Cycloaddition Reactions of a Cyano Substituted Donor with Ketimines. We have shown that the transition metal catalyzed [3 + 2] TMM cycloaddition is a versatile method for the regio-, diastereo-, and enantioselective construction of pyrrolidines. While the catalytic, enantioselective addition of carbon nucleophiles to aldimines is well precedented, the corresponding additions to ketimines are rare.[25] 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 have also observed a significant increase in reactivity of various substrate classes. 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. Such a reaction would provide a novel route to highly substituted pyrrolidines containing a tetrasubstituted center.

We felt that the reduced reactivity of ketimines could prove advantageous in one regard. Because the addition of a nucleophile to a ketimine is expected to be considerably slower than the corresponding aldimine, the occurrence of the exocyclic product discussed above could be avoided.Our initial studies began with examination of the Pd-catalyzed [3 + 2] cycloaddition of cyano-TMM donor **10** with a series of ketimines **20a**–**g** (Table 8). Using CpPd(η^3-C_3H_5) and Feringa

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Scheme 7. Control over TMM Reaction Chemoselectivity by Selection of Reaction Parameters

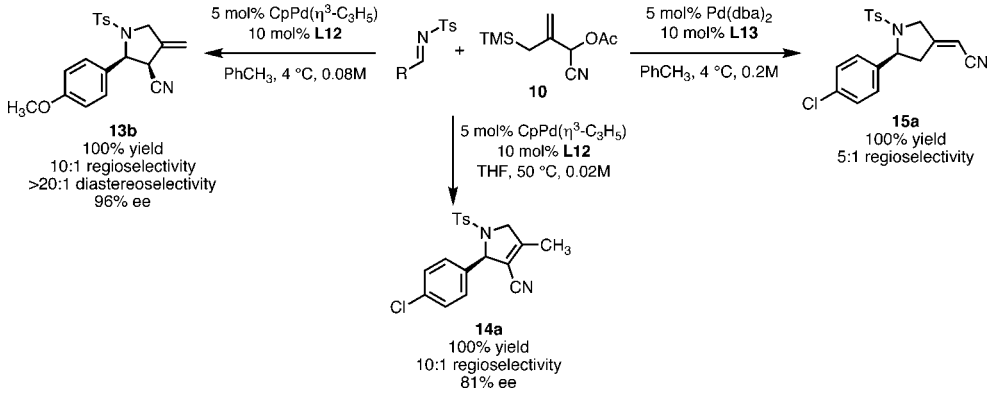
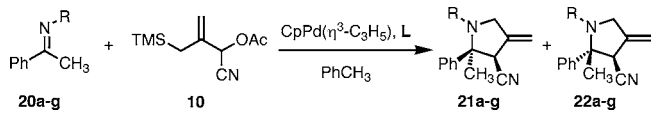


Table 8. Initial Studies of the Reaction of Donor 10 with Ketimine Substrates[a]



entry	R	ligand	temp (°C)	% yield[b]	21/22	21 % ee	22 % ee
1	4-MeOC$_6$H$_4$ (**20a**)	**L1**	50	0			
2	Bn (**20b**)	**L1**	50	0			
3	OCH$_3$ (**20c**)	**L1**	50	0			
4	P(O)Ph$_2$ (**20d**)	**L1**	50	complex			
5	Ns (**20e**)	**L1**	50	77 (16)	0.17: 1	ND	ND
6	Ts (**20f**)	**L1**	50	24 (53[c])	0: 1		53
7	Ts	**L1**	4	67	1: 1.1	86	63
8	Ts	**L13**	4	79	2.2: 1	95	89
9	Ts	**L12**	4	91	>20: 1	>99	
10	Ts	**L12**	50	0 (87[d])			
11	MBS (**20g**)	**L12**	50	0 (100[e])			

[a]All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C$_3$H$_5$), 10% ligand, 1.5 equiv **10**, and stirred for 4 h. Yields are isolated values; ee's were determined by chiral HPLC. [b]Value in parentheses represents additional yield of tautomerized product of type **14**. [c]41% ee. [d]96% ee. [e]92% ee.

ligand **L1**, we were initially discouraged by the fact that PMP-imine **20a** proved completely unreactive under the conditions utilized (entry 1), as the corresponding aldimine class had performed well using our parent donor (Table 2). Equally frustrating, no reactivity was observed with benzyl imine **20b** or oxime ether **20c**. Diphenylphosphinoyl imine **20d** provided a complex mixture (entry 4). Analysis of the crude mixture by NMR indicated the presence of the desired product **21d** and its tautomer containing an endocyclic olefin conjugated with the nitrile. Unfortunately, efforts to purify the products proved problematic. These results indicated that a strongly electron-withdrawing group was necessary for reactivity. We tested *N*-nosyl imine **20e** which proved to be superior to the phosphinoyl imine from a reactivity standpoint (entry 5). Disappearance of the imine was observed within a short time, but the mixture contained a complex mixture consisting of both diastereomers as well as the endocyclic tautomer. Using *N*-tosyl imine **20f** we observed formation of the desired cycloadduct, albeit as a mixture of **22f** and its endocyclic olefin tautomer. Reduction of the temperature prevented isomerization and increased the enantioselectivity, but the diastereoselectivity remained poor and it became clear that ligand optimization would be required (entry 7). Azetidine ligand **L13** provided a sizable increase in enantioselectivity, although the diastereoselectivity remained low (entry 8). Our previously utilized bis-2-naphthyl phosphoramidite **L12** solved both the enantio- and diastereoselectivity issues, providing the desired product in excellent yield with a >20:1 dr and a >99% ee (entry 9). The tautomerization event appeared to be entirely temperature dependent with ligand **L12**. Using either tosyl imine **20f** or 4-methoxybenzenesulfonyl imine **20g** (entries 10−11), complete tautomerization was observed when the reaction was conducted at 50 °C, providing the tetrasubstituted olefins in 96% and 92% ee, respectively. 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 examined the reaction scope with respect to the imine (Table 9). Gratifyingly, the reaction proved very general under the optimized conditions (Table 8, entry 9), performing well in nearly every case examined. Yields and selectivities proved insensitive to the steric bulk of the aromatic substituent (entry 2). The steric bulk of the aliphatic substituent could be increased (entry 3), but conversion dropped when it became too sterically demanding (entry 4). Increasing the temperature of this reaction only resulted in decomposition. The reaction was insensitive to substitution pattern of the aromatic ring (entries 5−7) or electronic nature of the substituent. Spirocycles could be formed in good to excellent diastereoselectivity and excellent enantioselectivity (entries 8−10),

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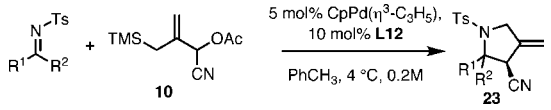
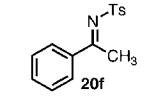
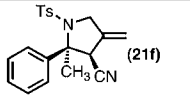
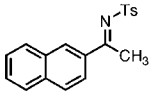
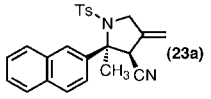
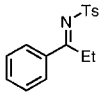
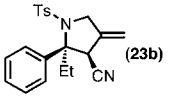
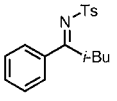
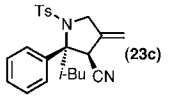
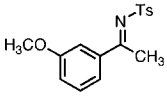
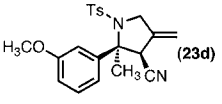
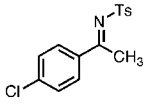
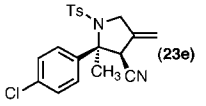
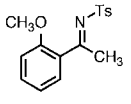
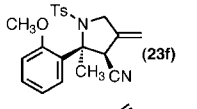
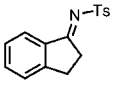
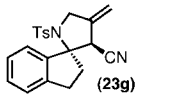
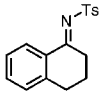
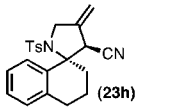
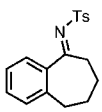
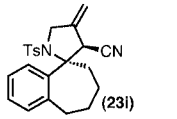
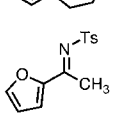
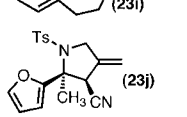
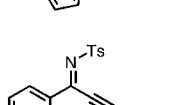
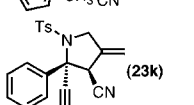
Table 9. Initial Scope of the Reaction of Cyano Donor 10 with Ketimines[a]



entry	substrate	product	% yield	dr	% ee
1[b]		 (21f)	94	>20:1	>99
2		 (23a)	77	>20:1	98
3		 (23b)	99	>20:1	99
4		 (23c)	24	>20:1	ND
5		 (23d)	89	>20:1	99
6		 (23e)	90	>20:1	>99
7		 (23f)	99	10:1	98
8[c]		 (23g)	99	7:1	99, 96[d]
9		 (23h)	99	>20:1	>99
10		 (23i)	26	>20:1	ND
11		 (23j)	99	15:1	81
12		 (23k)	0		

[a]All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, 1.5 equiv **10**, and stirred for 2−4 h. Yields are combined, isolated values; ee's were determined by chiral HPLC. [b]1.0 mmol scale. [c]Reaction performed at −15 °C. [d]Minor diastereomer.

though the [6.7.5] system was obtained in low yield. It appeared that the substrate itself was unstable, as decomposition was observed by ^{1}H NMR over very short periods of time. Heterocycles were tolerated (entry 11), albeit with moderately decreased enantioselectivity. Unfortunately, an

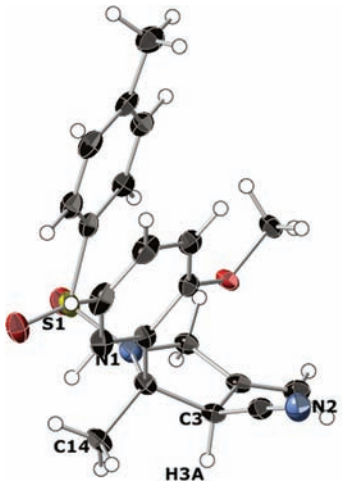


Figure 4. ORTEP illustration of (2*S*,3*R*)-2-(2-methoxyphenyl)-2-methyl-4-methylene-1-tosylpyrrolidine-3-carbonitrile (**23f**) with thermal ellipsoids drawn at the 50% probability level.

yneimine was not tolerated at 4 or 50 °C (entry 12). Conversion remained high at low temperatures, in some cases as low as −15 °C (entry 8). The reaction could be successfully scaled to 1.0 mmol using 5% CpPd(η^3-C_3H_5) and 7.5% ligand with no loss in yield or selectivity, as was shown in the case of substrate **20f**. An X-ray crystal structure analysis of **23f** (entry 7) unambiguously allowed the determination of absolute and relative stereochemistry (Figure 4).

Our proposed model for the diastereoselectivity of the reaction is shown in Figure 5, and is based on the imine geometry. NOE studies show that the ketimines adopt the geometry which places the sulfonyl group *syn* to the methyl or methylene group. In fact, none of the other isomer was observed by ^{1}H NMR in any case. We suggest that the initial bond forming event occurs as depicted in the top right scenario, leading to the observed, thermodynamically less favored diastereomer[26] containing the nitrile and aryl group on the same face of the pyrrolidine ring. The other diastereomer would arise from the top left conformer, which is highly disfavored due to severe steric interactions between the tosyl group and bulky π-allyl. Interestingly, the only example in Table 9 in which significant quantities of the minor diastereomer were observed is entry 8. In this case, the methylene group is constrained such that it is spatially closer to the aryl group; the 120° angle depicted cannot be attained. This allows the π-allyl to rotate away from the tosyl group, mitigating the steric interactions and understandably, this pathway becomes more prevalent.

In order to test the validity of this model, we needed to constrain the imine in such a manner that the sulfonyl group would be *syn* to the aryl group. An imine derived from saccharin met this criterion. Our hypothesis for this imine class is shown in the bottom row of Figure 5. Because the sulfone is constrained in such a manner that it is *syn* to the aryl group, the most favorable conformer becomes the one shown on the bottom left in which the opposite face of the imine approaches the donor. This places the π-allyl away from the sulfone and leads to the product depicted with the nitrile and the methyl group on the same face of the pyrrolidine. The conformer leading to the other isomer is shown in the lower right and places the allyl close to the sulfone. This pathway is disfavored on steric grounds. The results of the TMM reaction shown in

dx.doi.org/10.1021/ja210981a | *J. Am. Chem. Soc.* 2012, 134, 4941−4954

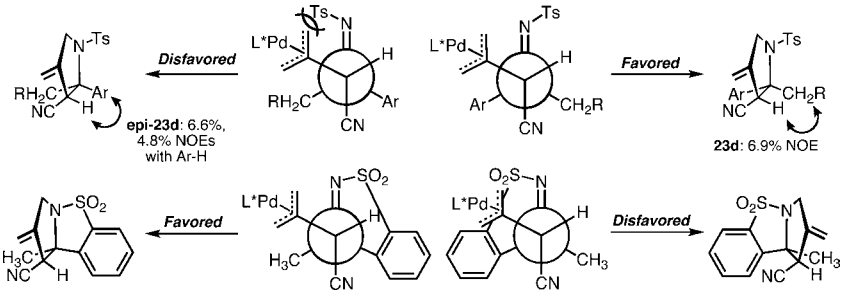
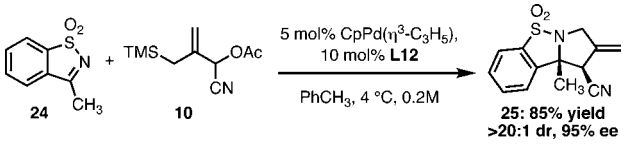


Figure 5. Proposed stereochemical model for diastereoselectivity of ketimine TMM reaction.

Scheme 8. Reaction of Cyano Donor 10 with Saccharin-Derived Imine 24



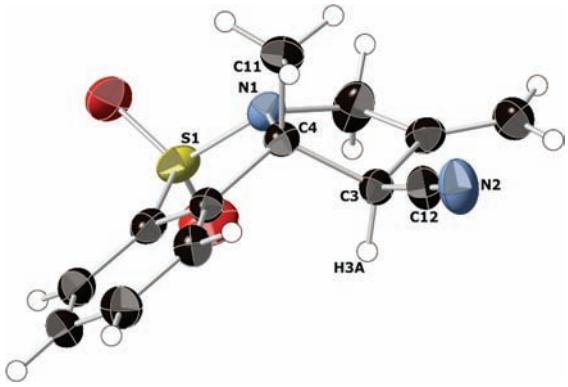
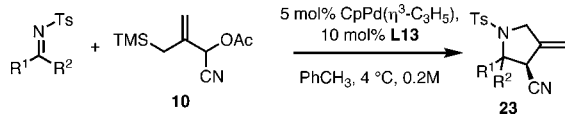


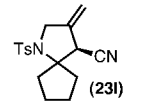
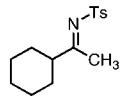
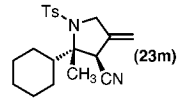
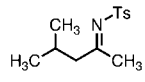
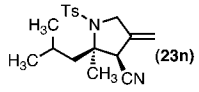
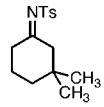
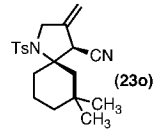
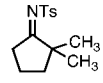
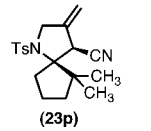
Figure 6. Crystal structure of saccharine imine derived cycloadduct **25**.

Scheme 8 support this interpretation. The relative stereochemistry was confirmed through single crystal X-ray analysis (Figure 6). Use of this class of cyclic imine provides a method to control the diastereoselectivity of the reaction. After removal of the sulfone, the opposite diastereomer of that shown in Table 9 would be obtained.

The reaction could also be conducted with aliphatic ketimines containing multiple enolizable sites. Equivalently substituted aliphatic ketimines performed well (Table 10, entry 1). Nonequivalently substituted aliphatic ketimines presented a selectivity problem when subjected to the standard conditions (entry 2). When **L12** was employed, conversion remained high with the cyclohexyl imine, but the diastereoselectivity dropped below acceptable levels. Ligand **L1** (entry 3) restored the diastereoselectivity, albeit at the cost of conversion and enantioselectivity. Azetidine ligand **L13** provided a compromise, giving the desired product in good yield, 10:1 diastereoselectivity, and restored enantioselectivity (entry 4). Interestingly, the diastereoselectivity in this system was reversed relative to the less bulky substrates. As discussed above (Table 6, entry 10), this may indicate a reversible addition step. A more remote branch point could be tolerated while maintaining selectivity as shown by the isobutyl and cyclohexyl imines (entries 5–6). Interestingly, the cyclohexyl imine also gave excellent diastereoselectivity with ligand **L12** with a jump in enantioselectivity (entry 7), likely due to the rigidity of the system. The reaction remained moderately tolerant of sterics, as seen by these substrates. However, a tetrasubstituted center adjacent to the imine shut down the reaction (entry 8). All product diastereselectivities were confirmed by NOE analysis.

Table 10. Scope of the Aliphatic Ketimine Cycloaddition[a]



entry	substrate	product	% yield	dr	% ee
1[b]		 (23l)	86	—	95
2[b]		 (23m)	86	1:1	99, 96
3[c]			50	12:1	84
4			83	10:1	95
5		 (23n)	99	5:1	95
6		 (23o)	77	>20:1	88
7[b]			100	>20:1	99
8		 (23p)	0		

[a]All reactions were performed at 0.2 M in toluene with 5% CpPd(η^3-C_3H_5), 10% ligand, 1.5 equiv **10**, and stirred for 2–4 h unless otherwise noted. Yields are combined, isolated values; ee's were determined by chiral HPLC. [b]Using **L12**. [c]Using **L1**.

It should be noted that no exocyclic nitrile was observed in the examples above, even at concentrations of 0.2 M and low temperatures due to the slow rate of attack of the TMM intermediate on the ketimine relative to π–σ-π isomerization. However, we were able to observe significant quantities of this product through use of a nosyl ketimine. Under our standard conditions, quantitative yield of a mixture favoring exocyclic cycloadduct **27** was obtained, due to the faster rate of attack of the TMM intermediate on the more electron-deficient imine (Scheme 9).

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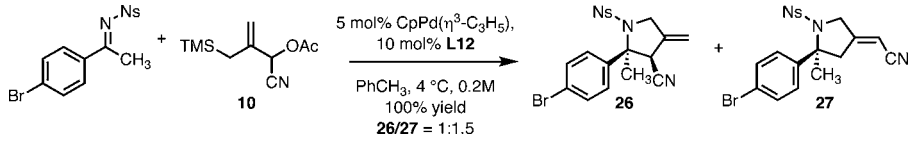
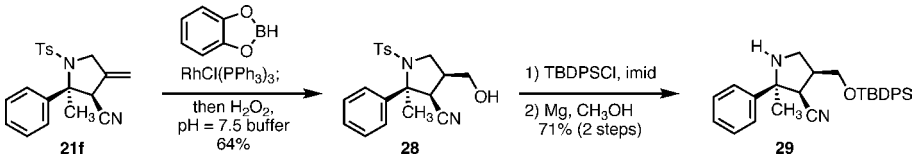
Scheme 9. Formation of exo Product through Cycloaddition of TMM Donor 10 with Nosyl Ketimine



Scheme 10. Functionalization and Removal of the Tosyl Protecting Group from Ketimine Cycloadduct 21f



To show the utility of the pyrrolidine cycloadducts, we wanted to demonstrate that the sulfonyl protecting group could be removed (Scheme 10). Initial attempts to remove the tosyl group using a variety of conditions (SmI_2, sodium naphthalide, lithium naphthalide) resulted in significant decomposition, likely arising from reduction of the endocyclic double bond tautomer of the cycloadduct. Use of magnesium in methanol effectively removed the sulfonyl group in quantitative yield, but concomitant olefin tautomerization and reduction afforded a mixture of pyrrolidine diastereomers. Accordingly, we felt that prior removal of the exocyclic olefin was necessary. From cycloadduct **21f**, Rh-catalyzed hydroboration provided the desired alcohol **28** as a single diastereomer after oxidation. The product was silylated and subsequently treated with magnesium in methanol to easily remove the tosyl group, providing the anticipated pyrrolidine **29** under mild conditions. The relative stereochemistry was confirmed by NOE analysis.

Both the exocyclic double bond and nitrile provide handles for further functionalization in complex molecule synthesis. In this case, we show that the olefin can be hydroborated with complete regio- and diastereoselectivity. Subsequent removal of the tosyl group gives the free pyrrolidine which we envision will be useful in a variety of further transformations.

CONCLUSION

We have developed a successful catalytic, asymmetric [3 + 2] TMM cycloaddition reaction with imine acceptors that affords pyrrolidine products. The methodology described herein showcases the enantioselective addition of a carbon nucleophile to an imine. This challenging transformation is expected to be of great synthetic utility. The ketimine additions especially stand out, as catalytic, asymmetric additions of any nucleophile to these systems are rare. We have accomplished this with high levels of chemo-, diastereo- and enantioselectivity, and generated a tetrasubstituted center in the process. The reaction scope is broad with respect to acceptor, tolerating a variety of aromatic and aliphatic imines. We have also demonstrated that the reaction conditions can be tailored to favor specific reaction pathways to afford unique products. The nitrile donor provides access to a variety of synthetically useful intermediates after functional group interconversion, some of which we have demonstrated. Investigations toward further expansion of the donor scope are ongoing and will be reported in due course. Applications of the novel TMM reactivity showcased here in the synthesis of complex molecules are highly anticipated.

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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Notes

The authors declare no competing financial interest.

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