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Palladium-Catalyzed Asymmetric [3+2] Cycloaddition of Trimethylenemethane with Imines

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Pyrrolidines are ubiquitous structural units in the chemical literature, with numerous applications seen throughout the pharmaceutical industry as well as among natural products.[1] As such, much attention has been devoted toward their synthesis. While cycloaddition strategies to form pyrrolidines are well documented, they are largely based on the reaction of azomethine ylides with two carbon units.[2] Complementary strategies involving the addition of imines to suitable three carbon units have received less attention. The transition metal-catalyzed [3+2] trimethylenemethane (TMM) cycloaddition is a highly efficient process that provides a direct route to five-, seven-, and nine-membered ring systems.[3] Though this venerable reaction has been primarily studied in the construction of carbocycles, there have been few accounts detailing TMM cycloaddition reactions of imines to form pyrrolidines.[4] Further, asymmetric syntheses of this moiety are highly desirable. Our recent disclosure of an asymmetric variant of the TMM reaction between 3-acetoxy-2-trimethylsilylmethyl-1-propene and olefins[5] prompted us to investigate the enantioselective synthesis of pyrrolidines using this methodology.

Initial studies focused on the reaction of benzylidene aniline under the previously developed conditions (5 mol % $Pd(dba)_2$, 10 mol % ligand, 1.6 equiv TMS propenyl acetate) at 45 °C (Scheme 1). Ligand **L1**[6] gave only 3% ee at 71% conversion. On the basis of a report detailing the beneficial effects that minor alterations of phosphoramidite ligands have on the selectivity of iridium-catalyzed AAA reactions,[7] we tested **L2** and **L3**. Unfortunately, enantiomeric excesses remained low, though increased conversion was observed. Further variations of this segment that may affect conformation such as inverting the stereochemistry of the methyl group (**L4**) increased the ee, but removal of a methyl group (**L5**) provided an inactive catalyst. The previously utilized asymmetric palladium catalyst for the TMM reaction of olefins (**L6**)[5,8] provided the desired product in only 35% ee and 73% conversion. Adjusting the nature of the chiral space by increasing the size of the aryl groups led initially to replacement of one phenyl group with a 2-naphthyl group (**L7**), which did increase the ee. Substitution with 4-biphenyl groups (**L8**) or even better, the bis-1-naphthyl ligand (**L9**) boosted the ee. Bis-2-naphthyl ligand **L10** gave the best results with a 76% conversion and 84% ee. To examine the effects of ring size, we turned to azetidine ligand **L11**, which gave significantly lower ee.

Scheme 1

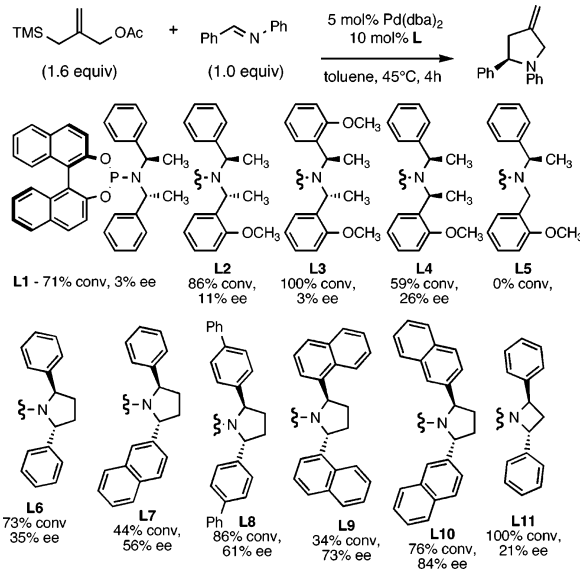
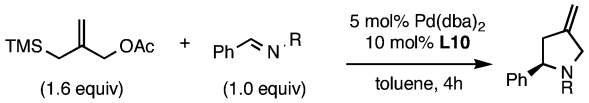


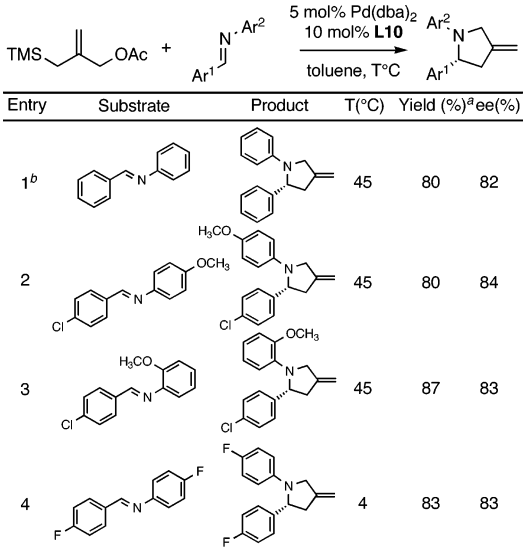
Table 1. Imine Optimization Study



Entry	R	Temp (°C)	Yield (%)	ee (%)
1	Ph	45	76[a]	84
2	Ts	45	98	45
3	Bn	45	0	ND
4	$P(O)Ph_2$	23	0	ND
5	Boc	45	98	87
6	Fmoc	23	0	ND
7	Cbz	23	0	ND

[a] Conversion. [b] ND = Not determined.

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



Entry	Substrate	Product	T(°C)	Yield (%)[a]	ee(%)
1[b]			45	80	82
2			45	80	84
3			45	87	83
4			4	83	83

[a] Isolated yields. [b] Reaction performed with 2.5 equiv propenyl acetate.

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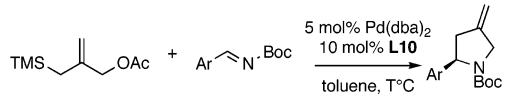
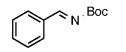
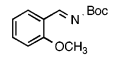
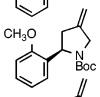
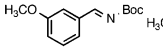
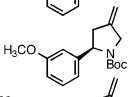
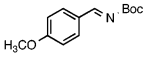
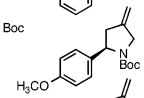
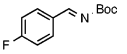
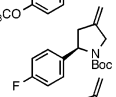
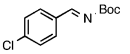
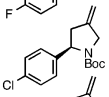
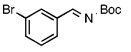
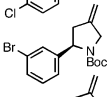
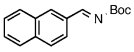
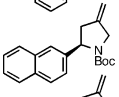
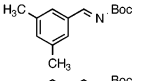
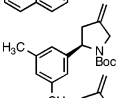
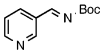
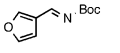
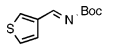
Table 3. Palladium-Catalyzed [3+2] Reactions of *N*-Boc Imines



Entry	Substrate	Product	T(°C)	Yield (%)[a]	ee(%)
1			4	84	91
2			4	80	92
3			-15	73	90
4			4	94	93
5			4	91	90
6			4	96	91
7			-15	94	86
8[b]			4	86	85
9			-15	65	90
10			4	75	86
11			4	71	91
12			-15	60	90

[a] Isolated yields. [b] Reaction performed with 2.5% $Pd(dba)_2$ and 5% **L10**.

Using the optimized ligand **L10**, we next determined the best class of imine for this reaction (Table 1). Ideally, we wanted a group that would not only provide high enantiomeric excess, but could also be easily removed. While the use of a tosyl group (entry 2) provided a good yield, the ee was low. No reaction was observed with benzyl or phosphonyl imines (entries 3−4) and complex mixtures were obtained with Fmoc and Cbz imines (entries 6−7). However, the use of the *N*-Boc imine (entry 5) gave excellent results with the protected pyrrolidine being obtained in 98% yield and 87% ee.

The reaction using both *N*-Boc and *N*-aryl imines was examined. A short assessment of substituted benzylidene anilines is shown in Table 2.[8] 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 equiv in entry 1 versus 1.6 equiv in entries 2−4) and lower temperature required (entry 4).

The use of Boc-imines provided a broader reaction scope (Table 3). This class proved more reactive than the substituted benzylidene anilines. The temperature could be reduced considerably, as low as −15 °C in some cases (entries 3, 7, 9, 12), and conversion remained high with moderate increases in enantioselectivity observed. Unfortunately, further reduction to −25 °C failed to provide desired product in any case studied. The reaction proved insensitive to the nature of the aromatic substituent with similar results obtained regardless of substitution pattern (entries 2−4) or electronic nature of the substituent. Heterocycles presented no problems (entries 10−12) with ee values remaining high, though slightly reduced yield was observed. While the standard conditions utilized 5 mol % Pd and 10 mol % ligand to ensure complete conversion, catalyst loading could often be lowered (entry 8) with little change in results. The absolute configuration was determined by X-ray crystallographic analysis, as shown in Figure 1.

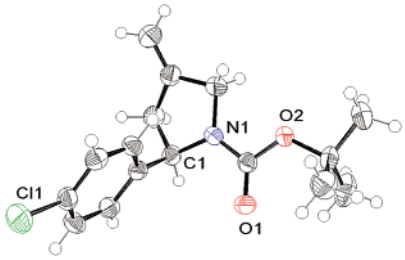


Figure 1. ORTEP illustration of (*R*)-*tert*-butyl 2-(4-chlorophenyl)-4-methylenepyrrolidine-1-carboxylate (Table 3, entry 6) with thermal ellipsoids drawn at the 50% probability level.

In summary, we have reported a new phosphoramidite ligand that effects the palladium-catalyzed asymmetric TMM reaction of imines to form substituted pyrrolidines in high ee. Investigations into the scope of this reaction, as well as the use of substituted TMM donors are currently underway 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.

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(9) Our initial studies of TMM reactions of aliphatic *N*-aryl imines afforded complex mixtures of products. Work in this area is ongoing.

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