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Palladium-Catalyzed Diastereo- and Enantioselective Synthesis of Substituted Cyclopentanes via a Dynamic Kinetic Asymmetric Formal [3+2]-Cycloaddition of Vinyl Cyclopropanes Alkylidene Azlactones**

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The development of new enantioselective methods for the formation of cyclopentane rings containing multiple stereocenters is of importance both in organic and medicinal chemistry.^[1] A powerful approach would be a metal catalyzed asymmetric formal [3+2]-cycloaddition between a 1,3-dipole and an olefin; it would allow for the construction of the cyclopentane and form multiple stereocenters in a single synthetic step. Additionally development of this methodology would identify new “three-carbon-atom” precursors for asymmetric cycloadditions, beyond the relatively small number that currently exist in the literature.^[2]

Vinyl epoxides, aziridines, and cyclopropanes bearing electron withdrawing groups are known to open into 1,3-dipoles in the presence of palladium(0) catalysts. The resulting Pd(II) complexes add across olefins,^[3] isocyanates,^[4,5] carbodiimides,^[6] and aldehydes^[7] to afford five-membered rings. We hypothesized that we could use 1,3-dipoles generated from vinyl cyclopropanes as a novel three carbon fragment to generate cyclopentanes in an asymmetric fashion via palladium catalysis.

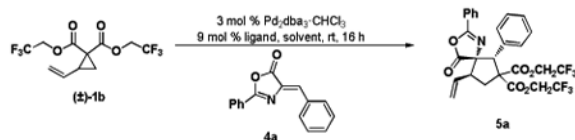
Tsuji has reported that vinylcyclopropane **1a** adds across methyl vinyl ketone in the presence of Pd₂dba₃ and bis(diphenylphosphino)ethane to afford vinylcyclopentane **3** (Scheme 1).^[3] Later, Johnson demonstrated the Pd-catalyzed additions of the vinyl cyclopropane **1a** to aldehydes.^[7] However, he needed to employ an alternative strategy using chiral Lewis acid catalysts to achieve asymmetric induction, a process that has not been expanded to electron poor olefins.^[8,9]

Previously, the class of chiral ligands, developed in our laboratory (**L1-L4**) for the Pd-catalyzed asymmetric allylic alkylation, have been employed to induce asymmetry at both the prochiral nucleophile and/or at the carbon of the π -allyl which is being attacked.^[10a,b,c] However, it has not been demonstrated for these ligands to be able to control stereochemistry in a bond forming event distal to the π -allyl Pd-complex. Our proposed Pd-catalyzed formal [3+2]-cycloaddition is a new challenge for these chiral ligands, in that it is requisite for them to control the stereochemistry of the Michael addition by the malonate carbanion, in addition to the stereochemistry at the nucleophile and the allyl center.

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To explore the prospect of this new class of asymmetric 1,3-dipole donors, we chose alkylidene azlactones as acceptors since these olefins should represent a reactive and useful class that would generate an interesting family of conformationally constrained α -amino acids.^[11] Promisingly, when **1a** and **4a** were combined with Pd₂(dba)₃·CHCl₃ (3 mol %) and **L1** (9 mol %) in toluene at room temperature, the desired [3+2]-cycloadduct was observed, albeit in only a 16% yield with a 10:1 dr and 60% ee.

Attributing the low reactivity of the dipole **2** derived from precursor **1a** to its low lifetime, we speculated that the trifluoroester **1b** might possess sufficiently greater stability to increase its lifetime, while at the same time maintaining reactivity.^[12] Indeed, by combining our more reactive vinyl cyclopropane **1b** and Michael acceptor **4a**, we were able to observe the desired product in 64% yield, 19:1 dr and 96% ee (Table 1, entry 1). Notably, only two of four possible diastereomers were observed, one of which was heavily favored. Furthermore, the reactions proceeded well at room temperature.



Further ligand (Table 1, entries 2-4) and solvent (Table 1, entries 5-8) optimization confirmed that ligand **L1** was differential, and the highest selectivities were observed with toluene. Dioxane provided higher yields at only a modest decrease in stereoselectivity (Table 1, entry 8). We also found the catalyst loading could be reduced from 6% to 4%.

We then sought to evaluate the scope of the reaction with a variety of aryl-substituted azlactones, using the conditions for optimal diastereoselectivity (Table 2). Moderately electron-withdrawing substituents in the *meta*- and *para*- positions (entries 1-3) were well tolerated, maintaining high levels of enantioselectivity and diastereoselectivity. However, when a substituent was introduced in the *ortho*-position (entry 4), no product was obtained, presumably due to the additional steric bulk. The moderately electron rich 2-naphthyl system was also well tolerated (entry 5). A substrate bearing a highly electron withdrawing substituent (entry 6) proved slightly detrimental to the enantioselectivity and diastereoselectivity, while electron rich furan (entry 7) gave excellent diastereoselectivity, enantioselectivity and yield.

Next, we examined non-aromatic substituents on the azlactone electrophile (Table 3). The cinnamyl derivative (entry 1) gave excellent selectivities, albeit in a slightly reduced yield. Notably, only 1,4-addition was observed. The *n*-hexyl derivative (entry 2) reacted well, affording a 63% yield of the desired product, with somewhat reduced diastereo- and enantioselectivity. Increasing the steric bulk to cyclohexyl led to no product formation (entry 3), suggesting sensitivity to steric effects on the electrophile, similar to the *ortho*-methoxyphenyl group (Table 2, entry 4). Finally, both a protected alcohol in the alkyl chain (entry 4) and a heteroatom were well tolerated, with no elimination products observed in the latter case (entry 5). Those azlactones which are more reactive for steric (**6b**) or electronic reasons (**4g**), gave reduced diastereo- and enantioselectivities, while those with increased steric bulk (**6c**) or with electron donating (**6a**) substituents appeared gave good selectivity but reduced (or no) yield.

To rationalize the observed stereoselectivity, we propose a modification of our previously reported “wall and flap” model (Scheme 2).^[10b,13] Both the matched and mismatched ionization of the starting vinyl cyclopropane ((*R*)-**1b**, (*S*)-**1b**) occur to give complexes **8** and **9**. By π - σ - π equilibration, **8** and **9** can interconvert to the thermodynamically-favored **8**,

where the malonate sits under the “flap,” in order to avoid the steric bulk of the “wall” in **9**. The malonate anion attacks the alkylidene azlactone, when the aryl group on the alkylidene is oriented away from the back “wall” of the ligand (**10**). Finally, attack of the azlactone anion onto the π -allyl-palladium (**11**) provides the observed major diastereomer **5a**.

In order to determine the stereochemistry of **5b**, it was treated with sodium methoxide in methanol (Scheme 3) to afford trimethyl ester **12** in quantitative yield as a crystalline solid. Single crystal X-ray diffraction analysis secured the relative and absolute stereochemistry of **12**.^[14] Interestingly, our method provides a *trans* relationship between the vinyl and aryl groups, rather than the thermodynamically more favored *cis* diastereomer.^[15]

The juxtaposition of functionality allows for ready structural modification (Scheme 4). For example, treatment of **5f** with dicyclohexyl borane in THF, followed by *m*-CPBA oxidation of the trialkylborane gives the primary alcohol *in situ*, which cyclizes onto the azlactone to give lactone **13**.

In conclusion, we have developed a new palladium-catalyzed enantioselective formal [3+2] cycloaddition between vinyl cyclopropanes and prochiral Michael acceptors. The use of the bis(2,2,2-trifluoroethyl)malonate vinylcyclopropanes allows for much higher yields and selectivities. Using alkylidene azalactones as the acceptor for this reaction provides access to highly functionalized chiral amino acid derivatives, a method which simultaneously sets three stereogenic centers in excellent enantio- and diastereoselectivities. This represents the first time this class of chiral ligands has been used to induce asymmetry in conjugate addition reactions, as well as the first time racemic vinyl cyclopropanes have been utilized in a formal [3+2] cycloaddition to form carbocycles in an asymmetric fashion. Work continues in our laboratory towards expanding the scope of this reaction towards a range of other acceptors.

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 15. The heats of formation of **5b** and epi-**5b** were calculated using SPARTAN 06 Essential 1.0.1. Epi-**5b** was found to be 11.6 kJ/mol more stable. For details, see supporting information.

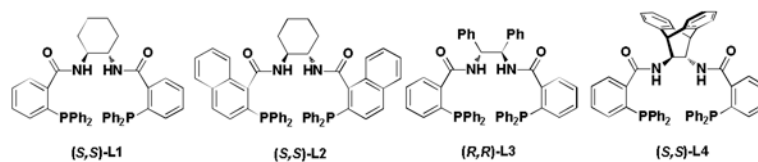
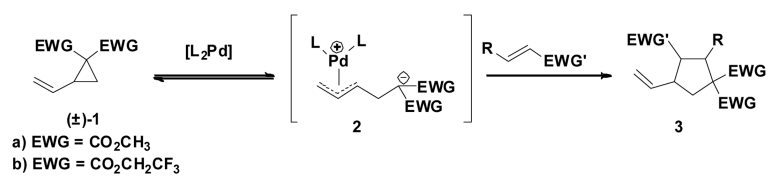
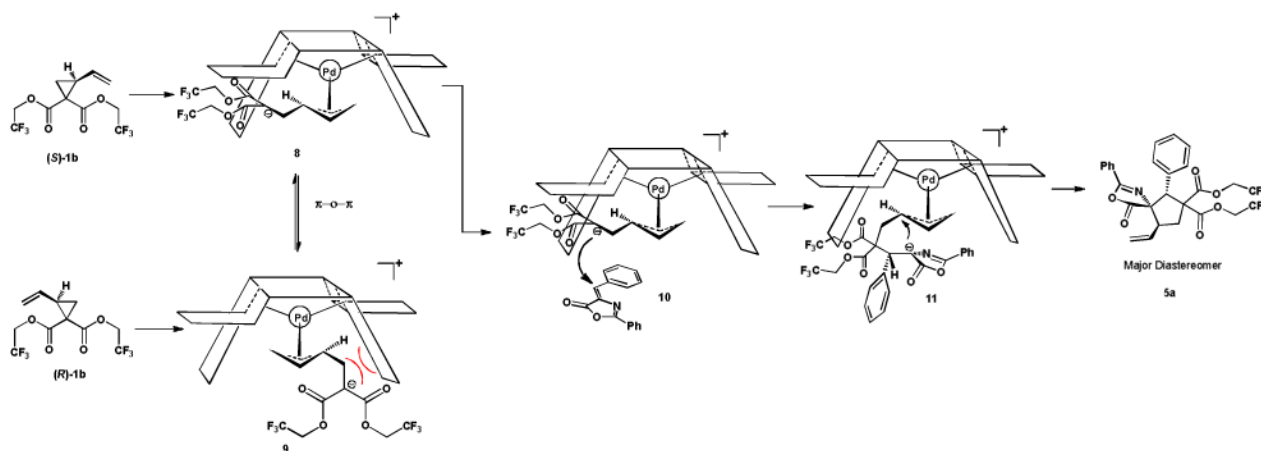


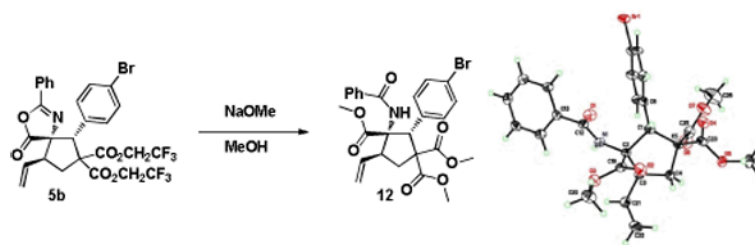
Figure 1. Trost asymmetric allylic alkylation ligands

**Scheme 1.**

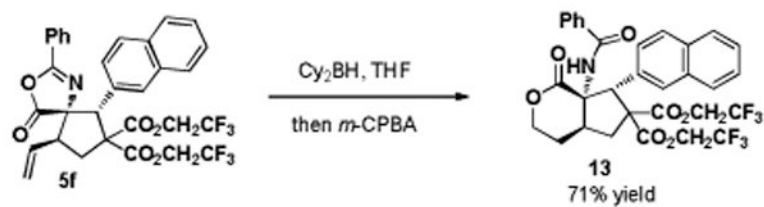
Palladium-catalyzed addition of vinyl cyclopropanes **1** to electron poor olefins.



Scheme 2. Mechanistic rationale



Scheme 3.
Functionalization of cycloadduct for crystallographic analysis.



Scheme 4.
One step functionalization to bicyclic system.

Table 1

Selected optimization results

Entry	Ligand	Solvent	Yield ^[a]	dr ^[b]	ee ^[c]
1	L1	Toluene	64%	19:1	96%
2	L2	Toluene	61%	19:1	92%
3	L3	Toluene	66%	15:1	-87%
4	L4	Toluene	21%	4:1	23%
5	L1	α,α,α -Trifluorotoluene	69%	4:1	83%
6	L1	THF	14%	15:1	89%
7	L1	CH ₂ Cl ₂	77%	8:1	91%
8	L1	Dioxane	82%	14:1	94%

^[a] Isolated yields.

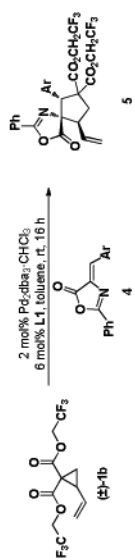
^[b] Diastereomeric ratios determined by ¹H NMR spectroscopy.

^[c] Determined by chiral HPLC.

Table 2

Cycloaddition of vinyl cyclopropanes with aryl alkylidene azlactones.

Entry	Substrate	Product	Yield[a]	dr[b]	ee[c]
1			78%	19:1	98%
2			70%	>19:1	93%
3			83%	19:1	94%
4			0%	n.d.	n.d.
5			84%	>19:1	94%



Entry	Substrate	Product	Yield ^[a]	dr ^[b]	ee ^[c]
6			72%	8:1	85%
7			87%	>19:1	95%

^[a] Isolated yields.

^[b] Diastereomeric ratios determined by ¹H NMR spectroscopy.

^[c] Determined by chiral HPLC.

Table 3

Cycloaddition of vinyl cyclopropanes with non-aryl alkylidene azlactones.

Entry	Substrate	Product	Yield ^[a]	dr ^[b]	ee ^[c]
1			51%	>19:1	94%
2			63%	8:1	74%
3			0%	n.d.	n.d.
4			64%	3:1 ^[d]	77% ^[e]
5			73%	10:1	63%

^[a] Isolated yields.

[b] Diastereomeric ratios determined by ^1H NMR spectroscopy.

[c] Determined by chiral HPLC.

[d] A 3:1 mixture of the E/Z isomers of **6d** was used.

[e] Determined on a derivative of this compound.